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1 **Title: An individual-based model to assess the spatial and individual heterogeneity of**
2 ***Brucella melitensis* transmission in Alpine ibex**

3

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26 **Highlights (3-5 bullet points, maximum 85 characters/point, including spaces):**

- 27 • Individual-based models are powerful tools to assess heterogeneity of transmission
- 28 • Transmission of brucellosis in ibex is highly heterogeneous
- 29 • Females generate the vast majority of new cases of brucellosis infection ($\geq 90\%$)
- 30 • Males spread over the infection when moving between subpopulations
- 31 • Our findings have important implications for disease management strategies

32

33 **Abstract:** Heterogeneity of infectious disease transmission can be generated by individual
34 differences in the frequency of contacts with susceptible individuals, in the ability to transmit
35 the infectious agent or in the duration of infection, and by spatial variation in the distribution,
36 density or movements of hosts. Identifying spatial and individual heterogeneity can help
37 improving management strategies to eradicate or mitigate infectious diseases, by targeting the
38 individuals or areas that are responsible for most transmissions. Individual-based models
39 allow quantifying the respective role of these sources of heterogeneity by integrating potential
40 mechanisms that generate heterogeneity and then by tracking transmissions caused by each
41 infected **individual**. In this study, we provide an individual-based model of **endemic**
42 **brucellosis *Brucella melitensis* transmission in the population of Alpine ibex (*Capra ibex*) of**
43 **the Bargy massif (France)** by taking advantage of detailed information available on ibex
44 population dynamics, behaviour, and habitat use, and on epidemiological surveys. This host-
45 pathogen system is expected to be subject of both individual and spatial heterogeneity. We
46 first estimated the transmission probabilities, hitherto unknown, of the two main transmission
47 routes of the infection (i.e., exposure to infectious births/abortions and venereal transmission).
48 Then, we quantified heterogeneity at both individual and spatial levels. We found that both
49 transmission routes are not negligible to explain the data, and that there is a high amount of
50 heterogeneity of the host-pathogen system at the individual level, with females generating

51 around 90% of the new cases of brucellosis infection. Males transmit infection at a lesser
52 extent but still play a non-negligible role because they move between subpopulations and
53 thereby create opportunities for spreading the infection spatially by venereal transmission.
54 Two particular socio-spatial units are hotspots of transmission, and act as sources of
55 transmission for the other units. These results may have important implications for disease
56 management strategies.

57

58 **Keywords (maximum 6):** wildlife disease; epidemiology; disease ecology; metapopulation;
59 superspreading; transmission routes

60 **1. Introduction**

61 Heterogeneity in the transmission of infectious agents occurs when a small proportion of an
62 animal population is responsible for the majority of transmission, whereas the rest of the
63 population only generates few secondary cases. The '20-80' rule emerged from empirical data
64 for several sexually-transmitted and vector-borne diseases, where 20% of cases contributed to
65 at least 80% of transmission (Woolhouse et al., 1997). When comparing several directly-
66 transmitted diseases, Lloyd-smith et al. (2005) found support for this pattern, but nonetheless
67 found evidence for high variation in the amount of heterogeneity, with 20% of cases
68 contributing to 40% up to around 90% of transmission depending on the disease considered.
69 Such substantial levels of heterogeneities are common in infectious diseases of both humans
70 and animals (Brooks-Pollock et al., 2014; Galvani and May, 2005; Matthews et al., 2006).
71 Individuals responsible for the majority of transmission are referred to as “superspreaders”
72 (Lloyd-Smith et al., 2005). Their high success in transmission of infectious agents is related
73 either to a high contact rate with susceptible individuals, to a long duration of infection, or to
74 an especially high infectiousness, i.e., ability to transmit the infectious agent (VanderWaal
75 and Ezenwa, 2016). These three components of transmission can be influenced by various
76 traits such as age, sex, behaviour, immunity or genetics (Cross et al., 2009; VanderWaal and
77 Ezenwa, 2016).

78 Heterogeneous transmission can also occur when areas with a particularly high pathogen
79 prevalence or transmission rate are responsible for the transmission to other areas (Paull et al.,
80 2012). This spatial heterogeneity can arise from various environmental factors that promote
81 the transmission or persistence of the disease, but also from the distribution, density and
82 movement patterns of hosts (Conner and Miller, 2004). Spatial heterogeneity can also be
83 related to individual heterogeneity, as superspreaders are likely to enhance transmission
84 around them more than in other areas (Paull et al., 2012). Identifying spatial and individual

85 heterogeneity can help improving management strategies to eradicate or mitigate infectious
86 diseases, by targeting the individuals or areas that are responsible for most transmissions
87 (Lloyd-Smith et al., 2005; Woolhouse et al., 1997).

88 In the present study, we built an individual-based model of *Brucella melitensis* transmission
89 in the wild population of Alpine ibex (*Capra ibex*) of the Bargy massif in the French Alps, the
90 first reported case of persistence of brucellosis in European wild ungulates. France is
91 officially free of Brucellosis in domestic ruminants, a major zoonosis due to *B. abortus* and
92 *B. melitensis* that causes economic and public health issues worldwide, the last cases having
93 been reported in 2003 (Perrin et al., 2016a, 2016b). However, in 2012-2013, a high
94 seroprevalence was found in the Alpine ibex population of the Bargy massif (Hars et al.,
95 2013). *B. melitensis* probably spilled over from domestic animals to ibex before disease
96 eradication in the domestic compartment, and probably spilled back from ibex to cattle
97 (ANSES, 2015), and then from cattle to humans in 2012 (Mailles et al., 2012).

98 The persistence of brucellosis in a wildlife population raises serious public health and
99 economic concerns. Effective disease management options would therefore be desirable to
100 mitigate the risk to livestock and humans. Moreover, brucellosis in Alpine ibex raises a
101 conservation issue because ibex have been restored in the Alps during the last decades, after
102 being close to extinction at the beginning of the 20th century, and is now protected. The
103 sanitary management of brucellosis usually operated in domestic herds, which involves
104 culling both infected and exposed individuals, is hardly applicable to a wildlife population,
105 especially in the case of a species with a protection status. Targeting individuals or areas that
106 are responsible for most transmissions allows sparing other individuals and could be a
107 relevant option for a more effective and more **ethically acceptable** management strategy to
108 eradicate brucellosis.

109 This host-pathogen system is expected to be subject of both individual and spatial
110 heterogeneity. First, five socio-spatial units were identified in the population, associated with
111 marked differences in seroprevalence, ranging from <15% up to ~70% depending on the unit
112 considered (Marchand et al., 2017). Second, individual heterogeneity could arise from sex and
113 age differences, as typically observed in vertebrate populations (e.g., Plard et al. (2015)).
114 Indeed, four transmission routes have been demonstrated in domestic ruminants for
115 brucellosis: horizontal transmission after abortion or parturition when *Brucella* is shed in
116 genital fluids, venereal transmission, congenital transmission and pseudo-vertical
117 transmission (Diaz-Aparicio, 2013). Bacteriological data on necropsied seropositive ibex
118 suggest that the same four routes may also exist in ibex (Lambert et al., 2018). All routes
119 relate to reproduction, and thus involve specific age- and sex-classes. In this highly socially-
120 structured species, contact rates vary between sex- and age-classes because of differences in
121 terms of [social behaviour](#) (Bon et al., 2001), space use (Marchand et al., 2017) but also mating
122 behaviour (Willisch and Neuhaus, 2009). Moreover, the proportion of active infection is
123 higher in young individuals than in old ones (Lambert et al., 2018).

124 We had two main objectives when building our model: (i) to determine the relative
125 importance of the various transmission routes, which is currently unknown in this species, and
126 (ii) to quantify transmission heterogeneity among individuals, classes of individuals and
127 socio-spatial units in the ibex Bargy population. Based on general knowledge on brucellosis
128 transmission in livestock and wildlife (European Commission, 2001; FAO and WHO, 1986;
129 Godfroid et al., 2013) and on preliminary studies on the Bargy case study (Lambert et al.,
130 2018; Marchand et al., 2017), we formulated two [hypotheses](#):

131 - First, due to their distinct patterns of space use, males and females should play
132 different epidemiological roles. Males, which are more [likely](#) to move across the
133 whole study area than females (especially during the mating period), should mostly

134 spread the infection between socio-spatial units through venereal transmission. By
135 **contrast**, females, which are more sedentary and usually stay within their spatial unit,
136 should maintain the infection inside each socio-spatial unit through bacterial shedding
137 following abortion or birth.

138 - Second, units with the highest seroprevalences, which also occupy central positions in
139 the Massif, were the first areas colonised by ibex and **corresponded** to the largest
140 socio-spatial units. These socio-spatial units should act as sources of infection,
141 whereas the more peripheral units with both lower seroprevalence and lower
142 abundance, should be sinks.

143 Understanding and quantifying these heterogeneities is a necessary preliminary step towards
144 designing and evaluating disease management strategies for Alpine ibex.

145

146 **2. Material and methods**

147 **2.1 Study site and population monitoring**

148 Our model was built on the kinetics of the Alpine ibex population of the Bargy massif in the
149 French Alps (46°N, 6.5°E; elevation: 600-2348 m; area: *ca.* 7000 ha). The brucellosis
150 outbreak was detected in 2012, and since **then**, the ibex population has been closely monitored
151 by Capture-Mark-Recapture, allowing estimating the pre-breeding Alpine ibex population
152 size to 567 individuals (95% Confidence Interval: [487-660]) in 2013, 310 [275-352] in 2014,
153 277 [220-351] in 2015, 272 [241-312] in 2016 and 291 [262-327] in 2017 (Marchand et al.
154 (2017); C. Toïgo, unpubl. data).

155 During captures, Test-and-Remove (TR) operations were implemented on the basis of
156 serological tests performed according to requirements of the European Union (EU) for
157 diagnosis of brucellosis in small ruminants and following standards of the World Organisation
158 for Animal Health (OIE) – see Marchand et al. (2017) and Lambert et al. (2018) for details. In

159 addition, a rapid serological test was used in the field to screen the sanitary status of captured
160 animals during their handling, and take the decision of removal or release (ANSES, 2014;
161 Corde et al., 2014). Between 2012 and 2018, 319 individuals were captured at least once.
162 Among them, 115 were seropositive and removed, while 204 were seronegative and were
163 marked and released. Fifty marked individuals were recaptured, sometimes several times, and
164 among them, four were found positive and then removed. For each individual, sex, age (by
165 counting horn growth annuli, Michallet et al. (1988)) and spatial location of capture were
166 systematically recorded.

167 Culling operations were also conducted as part of the disease management strategy conducted
168 by the French Authorities. In autumn 2013 and spring 2014, respectively, 233 and 18
169 individuals older than 5 years were culled, as apparent seroprevalence was the highest for this
170 age class (Hars et al., 2013). In autumn 2015, autumn 2017 and spring 2018, 70, 5 and 5
171 unmarked individuals were culled respectively, because they were considered as having a
172 higher risk of being seropositive than marked individuals (which were all seronegative when
173 released).

174 Finally, among marked and released ibex, 51 females and 39 males were equipped with GPS
175 collars. We recorded hourly locations that provided information on ibex space use and
176 movements. In particular, the locations of 27 females, which were followed for at least six
177 months, revealed a spatial structuration including five socio-spatial units – Fig. 1A, see
178 Marchand et al. (2017) for further details.

179

180 **2.2 Individual-based model**

181 We describe the individual-based model we built following the updated ODD protocol
182 (“Overview”, “Design concepts”, “Details”) of Grimm et al. (2010, 2006). [We present a](#)
183 [concise and narrative ODD in the main text below, while the full description of the ODD and](#)

184 the complete system of mathematical equations are provided in Appendix A. All simulations
185 and further analyses were performed using R 3.4.1 (R Core Development Team, 2017).

186

187 2.2.1 Purpose

188 We developed an individual-based, spatially implicit SEIR (Susceptible, Exposed, Infectious,
189 Recovered) model to represent the ibex brucellosis dynamics in the Bargy massif. The
190 purpose of the model was to quantify transmission of brucellosis among ibex, and to
191 determine whether heterogeneity of transmission arises from differences among individuals in
192 terms of social behaviour, space use, mating behaviour, transmission routes or active
193 infection. We used an individual-based model for this purpose because it offers the possibility
194 to take into account numerous individual specificities that can impact the infection dynamics
195 (Keeling and Rohani, 2008), and has the ability to track the number of secondary cases caused
196 by each infected individuals (VanderWaal and Ezenwa, 2016). This approach was also
197 practicable in a timely manner because the overall size of the population was small (several
198 hundreds). The individual-based model was also chosen in previous models of *Brucella*
199 *abortus* in bison in the Yellowstone area (Treanor et al., 2010).

200

201 2.2.2 Entities, state variables, and scales

202 The only entities in the model were ibex individuals. To track information on each individual
203 at each time step, the model included several state variables: individual ibex identity, sex, age
204 in weeks, socio-spatial unit, health status (susceptible: *S*; exposed: *E*; actively infected: *I*; or
205 non-actively infected, i.e., non-shedder: *R*), year of infection, year of recovery and
206 reproductive status (sexually receptive, pregnant, abortion, birth, parity).

207 The population is structured into five socio-spatial units, with contrasting seroprevalences.
208 Units 1 and 2 had seroprevalence less than 15%, vs. 54% for Unit 3, 70% for Unit 4 and 35%
209 for Unit 5 (Fig. 1A – Marchand et al. (2017)). Within each socio-spatial unit, ibex have the
210 tendency to form groups, but they experience very loose bonds (Villaret and Bon, 1998):
211 groups are not stable and split and merge frequently (fission-fusion dynamics; C. Calenge,
212 pers. comm.). To account for this structure in the model, we used a spatial metapopulation
213 model (Fig. 1B), often applied to populations naturally subdivided into spatial units, with
214 homogeneous contacts within subpopulations (Keeling and Rohani, 2008). At birth, each
215 individual was attributed to the socio-spatial unit of its mother (permanent socio-spatial unit).
216 All individuals living in the same socio-spatial unit constituted a subpopulation, each
217 subpopulation being characterised by its name and its own relative carrying capacity, defined
218 as a proportion of the carrying capacity of the whole population. The five subpopulations
219 constituted the overall metapopulation (Fig. 1B).
220 The model was developed to represent the evolution of brucellosis transmission and
221 population dynamics between December 1, 2012 and November 30, 2018 with a discrete
222 weekly time step.

223

224 2.2.3 Process overview and scheduling

225 Simulated years began on December 1st, and were split into two periods: the mating period,
226 which lasts from early December to mid-January in ibex (Couturier, 1962; Gauthier et al.,
227 1991; Willisich and Neuhaus, 2009) and was therefore fixed at 7 weeks in the model; and the
228 non-mating period for the remaining 45 weeks (Fig. 2). During the mating period, the events
229 occurring successively at each discrete time step were mortality, spatial movements,
230 reproduction, venereal transmission, incubation and recovery (Appendix A; Fig. A.1). During
231 the non-mating period, the events occurring successively at each discrete time step were

232 surveillance and management strategies, mortality, spatial movements, abortions or births,
233 congenital/pseudo-vertical transmission, horizontal transmission, incubation and recovery
234 (Appendix A; Fig. A.1). Such an order is artificial but is required to apply probabilities of
235 dying or getting infected to the correct numbers of individuals. For each event, individuals
236 were processed simultaneously.

237 *Alpine ibex* show a strong seasonal pattern of reproduction, and thus of brucellosis
238 transmission. The mating period is short, from early December to mid-January, and *ca.* 70%
239 of mating associations between males and females occur during the first 2 weeks (Willisch
240 and Neuhaus, 2009), which produces a seasonal peak of births of susceptible individuals. The
241 social structure is also subject to seasonal variation, because of progressive sexual segregation
242 (Bon et al., 2001; Villaret and Bon, 1995) with consequences on the patterns of contacts that
243 are relevant for transmission. These seasonal patterns were important to take into account
244 because of their expected impacts on disease dynamics (Altizer et al., 2006).

245 Gestation in ibex lasts 167 days (Stüwe and Grodinsky, 1987), which leads births to take
246 place from the end of May to mid-July, i.e., 24 weeks after the mating period (Fig. 2).
247 Abortions caused by brucellosis occur during the last third of gestation (Diaz-Aparicio, 2013),
248 i.e., 16 weeks after the beginning of gestation for an ibex. In domestic ruminants, shedding of
249 *Brucella* through placenta, foetal fluids and vaginal discharges when a female aborts or gives
250 birth may last *ca.* three weeks (European Commission, 2001), and we assumed a similar
251 duration for ibex in the model. Therefore, horizontal transmission of *Brucella* through
252 abortions is possible from early April to the end of May. However, after parturition, an ibex
253 female tends to isolate itself in cliffs and rocky areas with its newborn for two weeks (Bon et
254 al., 2001; Couturier, 1962; Villaret et al., 1997). Thus, other individuals were assumed to be
255 in contact with a female only the third week after its parturition, reducing the period of
256 exposure to this transmission route (Fig. 2).

257

258 *2.2.4 Design concepts*

259 The model considers ibex demography, transmission of infection within- and between-unit,
260 and surveillance and management strategies. Population dynamics emerge from individual
261 reproduction and mortality, which parameters depend on age, sex and density (Appendix A).

262 Infection dynamics emerge from contacts between susceptible and actively infected
263 individuals and from probabilities of successful transmission given those contacts for each
264 transmission routes. For venereal transmission, contacts emerge from male mating tactic and
265 from female sexual receptivity, described by empirical rules and probabilities. Thus, venereal
266 transmission depended only on the mating system of the host and not on population size, and
267 can thus be labelled as frequency-dependent (McCallum et al., 2001). For horizontal
268 transmission of *Brucella* through infectious abortions or births, contacts were considered as
269 homogeneous inside a socio-spatial unit, i.e., all individuals could contact each other. Thus,
270 this horizontal transmission increases with the size of the population (i.e., positive density-
271 dependence, McCallum et al. (2001)). For transmission between subpopulations, we used a
272 mechanistic model that explicitly represented movements of individuals, representing
273 opportunities of contacts and transmission between individuals from different subpopulations
274 (Jesse et al., 2008). Heterogeneity of transmission can emerge from age- and sex-specific
275 variation in these contact and transmission patterns.

276 For the model analysis, individual statuses were used to derive population-level variables such
277 as population size, prevalence or annual incidence (i.e., number of new cases) in the
278 population. For the model fitting, data on the number of individuals captured and the number
279 of seropositive individuals found among them was used, to match how data were collected in
280 the field.

281 Transitions between states were modelled as stochastic flows assuming demographic
282 stochasticity. Each transition was the outcome of a Bernoulli process.

283

284 *2.2.5 Initialisation*

285 The initial state was established from field-data of 2013 and the assumption that the
286 population was then close to saturation ((ANSES, 2015) – Appendix A).

287

288 *2.2.6 Input data*

289 The model does not use input data or an external model to represent time series of driving
290 environmental variables. The simulation period is short (6 years) and no relevant
291 environmental change was documented during the period of study.

292

293 *2.2.7 Submodels*

294 **Density-dependence**

295 Density-dependence of survival and reproduction is a common process in populations of large
296 herbivores (Bonenfant et al., 2009). Density-dependent responses of population parameters
297 were shaped to reproduce a logistic population growth, where the population size stabilises
298 around the carrying capacity in the absence of management interventions (Appendix A;
299 Eq. A.1-3 and Fig. A.2). Indeed, previous studies of population dynamics of ibex have shown
300 that the logistic model may be appropriate to describe the density regulation in ibex
301 populations (Sæther et al., 2007, 2002). Density-dependent processes play a crucial role in
302 disease ecology because it can interact with transmission, for example by increasing the
303 number of births and therefore the pool of susceptible individuals after population size
304 reduction (Choisy and Rohani, 2006). In the case of brucellosis, density-dependence of

305 reproduction is also critical because all transmission routes are related to reproduction
306 processes.

307

308 **Surveillance and management strategies:** Test-and-remove operations implemented
309 between 2012 and 2018 on the Alpine ibex population of the Bargy massif were integrated in
310 the model. The model reproduced the number of ibex captured and recaptured in each age-
311 and sex-class and each socio-spatial unit, sampling individuals at random inside each
312 category. Seropositive individuals were removed, whereas seronegative ones were marked
313 and released. The sensitivity and specificity of serological tests were assumed to be 95% and
314 100%, respectively (ANSES, 2015).

315 In addition to captures, management strategies implemented by the French Authorities, were
316 also integrated in the model. In autumn 2013 and spring 2014, the model reproduced the
317 number of culled individuals of each sex class and socio-spatial unit, by sampling individuals
318 for removal at random among individuals over five years old. It also considered younger
319 individuals culled because of erroneous age estimation (Appendix A). In autumn 2015,
320 autumn 2017 and spring 2018, the model reproduced the number of unmarked individuals of
321 each sex class and socio-spatial unit that were culled, sampling individuals for removal at
322 random.

323

324 **Mortality:** We used a complete age-dependent model, with a mortality estimate for each age
325 and sex (Toïgo et al. (2007) – Table 1 and Appendix A). Males lived up to 16 years and
326 females up to 19 years (Toïgo et al., 2007). In our model, we assumed no brucellosis-related
327 mortality, as there is currently no evidence for it (no important mortality detected, no
328 seropositive individuals detected in the few individuals found dead).

329

330 **Spatial movements:** Movements of males between units during the mating period and the
331 abortion period, when they can transmit or acquire infection, were derived from [hourly](#)
332 [locations](#) collected by GPS collars (Appendix A). The probability and direction of movements
333 were estimated separately for the two periods, because males are especially [likely](#) to visit
334 other units during the mating period (Fig. 1B and Appendix A; Fig. A.3). We considered all
335 movements to be temporary, as the model randomly sampled a new temporary socio-spatial
336 unit at each time step based on the movement probabilities [and on permanent socio-spatial](#)
337 [unit](#).

338

339 **Reproduction:** In the model, reproductive success of females was the outcome of two
340 processes: sexual receptivity during mating, and the probability to give birth to a [live](#)
341 newborn. In ibex, most mature females are sexually receptive only once during the mating
342 period (Couturier, 1962; Willisch and Neuhaus, 2009). We considered that a mature female
343 could become sexually receptive during mating only once every year with probabilities
344 depending on age (starting at 1.5 years old – (Couturier, 1962; Gauthier et al., 1991)).
345 Males, on the other hand, are sexually mature at 2.5 years of age and active every year
346 throughout the mating period (Couturier, 1962; Willisch et al., 2012).
347 [In ibex, only one male succeeds in engaging sexual intercourse with a given female](#)
348 [\(Tettamanti, 2015; Willisch and Neuhaus, 2009\). Dominant males that monopolise access to](#)
349 [the female by using the “tending” tactic are more successful in engaging sexual intercourse](#)
350 [and have higher reproductive success than subordinate males adopting the “coursing” tactic](#)
351 [\(Willisch et al., 2012\). Younger males \(2-7 years\) mainly adopt the coursing tactic while older](#)
352 [males \(\$\geq 8\$ years\) mainly engage in tending \(Willisch et al., 2012; Willisch and Neuhaus,](#)
353 [2009\). Accordingly, in the model, we made the simple assumption that all males aged 2-7](#)
354 [years were coursing while all males aged 8-14 years were considered as tending. Each](#)

355 sexually receptive female was associated to one tending and several coursing males
356 (Appendix A). Consequently, offspring were sired by a small fraction of males, mainly
357 dominant males engaging in the tending tactic.
358 Every **receptive** female who engaged in sexual intercourse with a male became pregnant. In
359 our model, we assumed that *Brucella* infection decreased sexual receptivity during mating,
360 thus leading to a lower probability of gestation (Table 2) **based on data from the study**
361 **population (unpubl. data) and by analogy with domestic ruminant infection** (ANSES, 2015).

362

363 **Venereal transmission:** High amounts of bacteria were found in testes of seropositive males
364 (Freycon, 2015; Lambert et al., 2018). It was therefore hypothesised that venereal
365 transmission could play a role in brucellosis transmission in the Alpine ibex population of the
366 Bargy massif (Hars et al., 2013; Lambert et al., 2018). The model thus assumed the existence
367 of this transmission route for ibex; however, the corresponding transmission probability was
368 unknown and thus had to be estimated using Approximate Bayesian Computation (see 2.3).

369

370 **Abortions or births:** In domestic ruminants, 80% of infectious females abort and most of
371 them do so only once, during the first pregnancy post-infection (FAO and WHO, 1986;
372 Godfroid et al., 2004). If abortion does not occur, invasion of the uterus leads to *Brucella*
373 shedding in genital fluids at the time of parturition (European Commission, 2001). In the
374 model, we assumed that **infected** pregnant females could abort only during their first
375 pregnancy following infection with a probability of 80% (Table 2). When abortion does not
376 occur, females give birth to a live newborn. In both cases, females shed *Brucella* in genital
377 fluids for *ca.* three weeks.

378 For other pregnant females, and for actively infected females that already went through their
379 first pregnancy following infection, the probability to give birth to a live newborn that

380 survives until winter depends on their parity (Table 1). We also assumed that active *Brucella*
381 infection decreases the probability to give birth to a live newborn (Table 2 – unpubl. data).
382 Actively infected females that give birth to a live newborn shed *Brucella* in genital fluids for
383 three weeks. The sex-ratio at birth was expected to be 1.

384

385 **Congenital/pseudo-vertical transmission:** Congenital transmission from infected mothers to
386 their offspring *in utero* is demonstrated in domestic ruminants (Lapraik et al., 1975; Plommet
387 et al., 1973; Renoux, 1962) and happens in *ca.* 5% of kids born from infectious mothers (FAO
388 and WHO, 1986; Godfroid et al., 2013). Pseudo-vertical transmission from infectious mothers
389 to kids can also happen through colostrum or milk consumption in all gestation events
390 (European Commission, 2001; Philippon et al., 1971), but this transmission only concerns a
391 small proportion of kids (Grilló et al., 1997). Both transmission routes are suspected in Alpine
392 ibex (Lambert et al., 2018). Therefore, we included both transmissions in the model, with
393 fixed low probabilities of 5% by analogy with domestic ruminants (ANSES, (2015) –
394 Table 2). During the two weeks following parturition, we considered that an actively infected
395 female that shed *Brucella* in genital fluids could only transmit infection to its newborn, which
396 we considered as a special case of pseudo-vertical transmission because ibex females isolate
397 themselves with their newborns during the parturition time.

398

399 **Horizontal transmission:** In domestic ruminants, excretion of the *Brucella* in female genital
400 discharges through infectious abortions or births is considered as the main route of
401 transmission to other individuals (European Commission, 2001). For this transmission route,
402 contacts were not modelled explicitly. An individual was exposed to all abortions or births
403 caused by brucellosis within the same socio-spatial unit. We assumed that at a given time
404 step, the probability of an individual coming into effective contact (i.e., coming into a contact

405 that leads to infection) with one infectious abortion or with one infectious birth was the same
406 (Table 2). This probability had to be estimated using Approximate Bayesian Computation (see
407 2.3).

408 In ibex, males over 5 years of age segregate from females both socially and spatially soon
409 after the rut, whereas segregation is more gradual for males 5 years of age and under, which
410 are still associated to females during spring (Bon et al., 2001; Villaret and Bon, 1995). Thus,
411 we assumed in the model that males under 5 were less exposed than females to *Brucella* shed
412 following infectious abortions, and males over 6 even less (Table 2). After being isolated for
413 two weeks following parturition, females and kids gather to form nurseries (Gauthier et al.,
414 1991), and have different space use than males older than 1 year old and females without kids
415 (Grignolio et al., 2007b, 2007a). Thus, we considered that mothers began to gather in
416 nurseries three weeks after parturition. Horizontal transmission through infectious births was
417 assumed to occur only in nurseries, from infected mothers to non-infected mothers and
418 susceptible newborns.

419

420 **Incubation and recovery:** Transmission of *Brucella* to a susceptible ibex S led to an
421 incubation (state E) of three weeks (Table 2), which is the duration of the incubation period
422 after which seroconversion generally occurs in domestic ruminants (European Commission,
423 2001). For kids born after congenital transmission, the incubation ends only at abortion or
424 parturition after their first pregnancy for females or at the age of sexual maturity for males
425 (Plommet et al., 1973). After incubation, we considered that infected individuals first entered
426 the I class, characterised by an active infection and therefore the ability to shed the bacteria.
427 Bacteriological analyses revealed that the probability of active infection decreases with
428 increasing age (Lambert et al., 2018). Therefore, we assumed that I individuals could transit
429 to the R class, i.e. infected but without active infection and unable to shed the bacteria, based

430 on the probability of recovery. We derived the probability of recovery from these
431 bacteriological data (see Table 2 and Appendix A for details).

432

433 **2.3 Simulation experiments**

434 The model was parameterised using Approximate Bayesian Computation (ABC) rejection
435 algorithm (Beaumont et al., 2002), based on the abc R package (Csilléry et al., 2012). This
436 approach has the advantage to approximate the likelihood by running the model a large
437 number of times and comparing simulated outputs to the observed data (Toni et al., 2009).

438 *However, this is a computationally intensive approach which was possible in our case because*
439 *of access to highly performant computing facilities and because of the small population size*
440 *of the investigated system.*

441 The algorithm is fully described in Appendix B. We first determined the parameters to be
442 estimated based on (i) identifying the most uncertain parameters, from literature survey and
443 field data, and (ii) performing a sensitivity analysis to determine which parameters have the
444 strongest influence on model outputs. These steps led us to estimate K , the carrying capacity;
445 $\beta_{IA}^{\circ} = \beta_{IB}$, the per-capita probability of one female coming into effective contact with one
446 infectious abortion (IA) or birth (IB) due to *Brucella*; and $\nu_{ven.}^{T\circ}$, the probability of successful
447 venereal transmission from tending males to females given contact, which were both the most
448 influential and uncertain parameters (Appendix B). For the ABC parameterisation, we fitted
449 the model to two types of available data: the population size over time, and the results of test-
450 and-remove operations in each sex- and age-class and in each socio-spatial unit (number of
451 captured and recaptured animals during test-and-remove operations, and seroprevalence in
452 captured and recaptured animals – Appendix B). For model fitting, we chose to distinguish
453 two age classes, individuals 5 years of age and under and individuals over 5 years of age,
454 because it was the criterion used in the field during management interventions, especially

455 culling operations, and because in males, these age classes corresponded to different levels of
456 exposure to *Brucella* shed following infectious abortions.

457 We used 10^6 simulations of the model, using uniform prior distributions, and we kept the 10^3
458 sets of parameter values that produced the closest simulated outputs to the observed data to
459 approximate the posterior distributions. To determine if the ABC approach was able to
460 estimate accurately the parameters, we used cross-validation (Csilléry et al., 2012). This
461 procedure uses a subset of simulated outputs as “pseudo-data”, performing ABC on the
462 remaining outputs. As the parameter values chosen to generate the pseudo-data are known, it
463 is possible to check if ABC is accurately estimating them (see Appendix B for details).

464

465 **2.4 Model analysis**

466 The model allowed us to describe the main life events of each individual (i.e., birth, death,
467 reproductive events and movements between units) as well as its epidemiological status at
468 each step. These crude predictions allowed us to reconstruct population size over time from
469 2012 to 2018, also with the demographic, spatial and epidemiological distribution of the
470 population.

471 For each susceptible individual that acquired infection, the year it got infected, the
472 transmission route by which it was infected, and whether transmission was between- or
473 within-unit was recorded. We defined between-unit transmission as a transmission that
474 occurred between a male and a female that do not share the same permanent socio-spatial unit
475 (regardless of the direction of transmission, i.e., from male to female or vice versa), which is
476 possible when a male is temporarily visiting another unit. From this information, we derived
477 the annual incidence (i.e., number of new cases) in the population, and the proportion of these
478 new cases in each age- and sex-class and in each socio-spatial unit, for each transmission
479 route.

480 We also recorded the number of secondary cases caused by each actively infected individual,
481 written as Z (Lloyd-Smith et al., 2005). Z represents an individual equivalent of the
482 population parameter R_n , the net or effective reproductive number, which is defined as the
483 average number of secondary infections caused by an infected individual over the course of
484 its infectious period in a given population (Vynnycky and White, 2010). However, due to the
485 relatively short period considered in our model (6 years, compared to a maximum lifespan
486 >20 years in ibex), we could not compute the total number of secondary cases caused by each
487 infected individual during all its infectious life. We thus computed the number of secondary
488 cases caused by each infectious individual every year, keeping track of the transmission route
489 and whether it corresponded to within- or between-unit transmission. When it was not
490 possible to attribute a secondary case to a single source case, the secondary case was shared
491 uniformly between all possible source cases involved.

492 Thus, the number and proportion of these actively infected individuals that caused secondary
493 cases, called “source cases”, were calculated. Moreover, we computed the number of
494 secondary cases that originated from each age- and sex-class as well as each socio-spatial
495 unit, and their respective proportions.

496

497 **3. Results**

498 **3.1 Parameter estimation and model predictions**

499 The estimated parameter values were (median and 95% credible interval): $K =$
500 564 [535 – 591] for the carrying capacity; $\beta_{IA}^{\varnothing} = \beta_{IB} = 0.026$ [0.001 – 0.128] for the per-
501 capita probability of one female to come into effective contact with one infectious abortion or
502 birth per week; and $\nu_{ven}^{T \rightarrow \varnothing} = 0.168$ [0.005 – 0.682] for the probability of successful venereal
503 transmission from tending males to females given contact. The posterior distributions of the
504 parameter values are provided in Appendix B. We evaluated the correlations between the

505 accepted parameter values (Appendix B), and we found a correlation of 0.018 between K and
506 $\nu_{ven}^{T \rightarrow \varnothing}$, of about -0.14 between $\beta_{IA}^{\varnothing} = \beta_{IB}$ and K and of -0.25 between $\nu_{ven}^{T \rightarrow \varnothing}$ and $\beta_{IA}^{\varnothing} = \beta_{IB}$.
507 The cross-validation procedure revealed that K was the most accurately estimated parameter,
508 followed by $\beta_{IA}^{\varnothing} = \beta_{IB}$ and then by $\nu_{ven}^{T \rightarrow \varnothing}$ (Appendix B).
509 Simulations with 1000 iterations, each iteration using a set of parameter values from the 1000
510 best simulations from the ABC, produced predictions in accordance with observations both
511 qualitatively and quantitatively (Fig. 3 and Appendix B). The population size decreased
512 drastically after massive culling and to a much lesser extent due to birth and death processes
513 (Figure 3A). Similarly, the number of actively infected individuals dropped after the massive
514 culling of 2013, especially in Unit 3, which was the largest subpopulation and concentrated
515 most of the culling operations (Fig. 4A). It then decreased more gradually in 2014 and 2015,
516 before stabilising at a roughly constant level during the last three years. The number of new
517 cases per year decreased down to a minimum of 5.6 individuals on average in 2016, followed
518 by a slight increase since 2016 (Fig. 4.B).

519

520 **3.2 Importance of transmission routes**

521 New cases were in majority (95%) caused by within-unit transmission, while between-unit
522 transmission caused less than 5% (see Fig. 5A). Among the few cases of between-unit
523 transmission, more than 75% on average were due to venereal transmission, while the
524 remaining cases were due to horizontal transmission through abortions (i.e., susceptible males
525 that visited other units and were infected by females there, before returning to their original
526 unit – Fig. 5B and Appendix C; Fig. C.1).

527 Among the cases due to within-unit transmission, horizontal transmission through infectious
528 abortions and births were predominant (more than 58% on average of within-unit new cases),
529 followed by vertical transmission (congenital and pseudo-vertical transmission) and then by

530 venereal transmission (Fig. 5C and Appendix C; Fig. C.1). We did not detect any variation in
531 these proportions during the study period (Appendix C; Fig. C.1).

532

533 **3.3 Quantification of heterogeneity**

534 *3.3.1 Individual-level heterogeneity*

535 We first considered heterogeneity of transmission at the individual level. For each infectious
536 individual, we recorded the number of secondary cases generated each year. Fig. 6A shows
537 the cumulative contribution of infectious individuals to the total transmission during one year.
538 Each year, only *ca.* 20% of infectious individuals (i.e., so called **source** cases) were
539 responsible for all secondary cases. Among these **source** cases, the majority generated one or
540 two secondary cases (Fig. 6B), but a few **source** cases were responsible of some extremely
541 high numbers of secondary cases that sometimes occurred (the maximal annual number of
542 secondary cases was 57, with a median maximum of 2 [0-12]).

543

544 *3.3.2 Heterogeneity between demographic classes*

545 Fig. 7A shows the distribution of secondary cases by age- and sex-classes and by age- and
546 sex-classes they originated from. In accordance with the previous result on heterogeneity, we
547 show that the distribution of **source** and secondary cases differs in term of age- and sex-
548 classes, with **source** cases (20% of infectious individuals each year) having specific
549 demographic characteristics. In particular, females generated 89% on average of the new
550 cases resulting from within-unit transmission (Fig. 7A and Appendix C; Fig. C.3). Females
551 over 5 years of age generated on average 56% of these new cases, especially through
552 horizontal transmission following births, congenital/pseudo-vertical transmission and venereal
553 transmission (Fig. 7A and Appendix C; Figs. C.3-4-6-7), while younger mature females (2-5

554 years old) generated on average 33% of them but mainly through abortions (Fig. 7A and
555 Appendix C; Fig. C.5).

556 Secondary cases resulting from within-unit transmission occurred mostly in newborns and
557 yearlings of both sexes (average proportion of around 27% for each sex) through horizontal
558 transmission following births and through congenital and pseudo-vertical transmission
559 (Fig. 7A and Appendix C; Figs. C.6-7). Females 2-5 years old were also often infected
560 (around 23% of new cases) mostly through indirect transmission following abortions (Fig. 7A
561 and Appendix C; Fig. C.5), while older age- and sex-classes were less concerned and mostly
562 contaminated through venereal transmission (Fig. 7A and Appendix C; Fig. C.4).

563 As regards between-unit transmission, which as a reminder occurs mainly through venereal
564 transmission, females contaminated males slightly more often than the other way around (*ca.*
565 60 versus 40% – Fig. 7A and Appendix C; Fig. C.4). Contrary to what was observed within-
566 unit, the older age classes were the most represented in both **source** and secondary cases in
567 both sexes for the between-unit transmission (Fig. 7A and Appendix C; Fig. C.4).

568

569 3.3.3 Socio-spatial units

570 Fig. 7B shows the spatial distribution of where the secondary cases occurred and where the
571 **source** cases came from. Within-unit transmission mostly occurred in Unit 3 (Figs. 7B and 8
572 and Appendix C; Fig. C.8), where 58.5% of within-unit new cases arose, followed by
573 decreasing order by Units 4 (14.9%), 5 (13.2%), 1 (7.6%) and 2 (5.8%). Between-unit
574 transmissions mostly originated from both central Units 3 (49.4% of between-unit new cases)
575 and 4 (36.1%), which were mostly responsible for new cases in Units 2 (18.3%) and 5 (56.6%)
576 – Fig. 7B and Appendix C; Fig. C.8). Units 3 and 4 generated more new cases of between-unit
577 transmission than they received, while it was the opposite for Units 1, 2 and 5 (Figure 8).

578

579 **4. Discussion**

580 We built an individual-based model of *Brucella melitensis* transmission in the wild population
581 of Alpine ibex (*Capra ibex*) of the Bargy massif in the French Alps, the first reported case of
582 persistence of brucellosis in European wild ungulates. Our results revealed (i) an extremely
583 high heterogeneity with only 20% of individuals which are responsible for new cases each
584 year, (ii) a predominant role of females which are the most frequent source of brucellosis
585 infection and (iii) source-sink metapopulation dynamics of infection between the five socio-
586 spatial units in the population. In the following sections, we will discuss each of the results
587 provided by our model on heterogeneity at the different levels and compare them to existing
588 knowledge on this system and others, before discussing the potential implications of our work
589 for disease management.

590

591 **4.1 A highly heterogeneous system**

592 Our model allowed us to track the annual number of secondary cases produced by each
593 individual. We revealed an extremely high heterogeneity. Each year, only 20% of individuals
594 are responsible for most new cases (Fig. 6). However, this result is not strictly comparable to
595 the proportion of transmission due to the most infectious 20% of cases reported by
596 Woolhouse et al. (1997) and Lloyd-Smith et al. (2005), since we considered in the present
597 study the number of secondary cases caused by an infectious individual each year instead of
598 summing them over the course of the individual infectious period. Therefore, the contribution
599 of an individual to the proportion of transmission could vary between years, and we could
600 reasonably expect that on longer periods more than 20% of infectious individuals would
601 contribute to the infection transmission. It is also important to stress out that this high
602 individual heterogeneity could be enhanced by disease management measures (Lloyd-Smith
603 et al., 2005) implemented in the population during our study period. Indeed, removing an

604 infectious individual a given year reduced its number of secondary cases that year, while
605 infectious individuals that were not the subject to measures or were wrongly diagnosed as
606 seronegative could continue to infect other individuals.

607 Even if individual heterogeneity may not be as marked as suggested by Fig. 6, our work
608 suggests that disease management targeting the most infectious individuals could be more
609 efficient than that based on population-wide strategies. This is especially expected for low or
610 intermediate control efforts (Lloyd-Smith et al., 2005), and therefore would be particularly
611 relevant in the study case. However, although we were able to identify the individuals most
612 responsible for infection using our model, doing so in the field would prove quite challenging.
613 This is the reason why we focused on identifying the classes of individuals most responsible
614 for infection rather than the individuals themselves (VanderWaal and Ezenwa, 2016), using
615 traits associated with transmission that are identifiable in the field, such as sex, age or socio-
616 spatial unit in our case.

617

618 **4.2 Brucellosis dynamics in ibex: asymmetric roles for males and females**

619 Several years ago, a review of host-pathogen systems in mammals suggested that males play a
620 critical role in diseases transmission compared to females, and proposed that disease
621 dynamics was “all caused by males” (Skorping and Jensen, 2004). To explain this pattern, the
622 authors proposed either a biased prevalence or shedding intensity towards males (Poulin,
623 1996; Schalk and Forbes, 1997), or differences in behaviour (such as movements of males
624 over large range) leading to biased exposure even in the absence of prevalence or shedding
625 differences (Ferrari et al., 2003; Skorping and Jensen, 2004). In contrast with this general rule,
626 we found that females are the most frequent source of brucellosis infection for ibex, as for
627 brucellosis in other species of domestic and wild ruminants (European Commission, 2001;
628 Rhyan, 2013). In our study system, there were no or few differences between males and

629 females in terms of seroprevalence (Marchand et al., 2017) or probability of active infection
630 (Lambert et al., 2018). However, we expected sex differences in disease transmission because
631 mating behaviour (Willisch and Neuhaus, 2009), social behaviour (Bon et al., 2001) and space
632 use (Marchand et al., 2017) all markedly differ between sexes.

633 The different transmission routes potentially involved in males and females (Lambert et al.,
634 2018) could also be a potential driver of sex differences in transmission (Zuk and McKean,
635 1996). Indeed, males can only be involved in venereal transmission, which is frequency-
636 dependent, whereas females also have the ability to transmit the infection horizontally by
637 shedding *Brucella* in genital fluids. Females could therefore infect more individuals, because
638 horizontal transmission route follows a positive density-dependence. The posterior
639 distributions of horizontal and venereal transmission parameters were both narrower than their
640 prior distributions, which suggests that available data are informative for both transmission
641 routes, although uncertainty remains high especially for venereal transmission.

642 According to the socio-spatial behaviour of ibex and the transmission routes of brucellosis,
643 we would have expected female-to-female transmission through bacterial shedding following
644 abortion or birth to be predominant within units, and male-to-female transmission through
645 venereal transmission to play a critical role between units. Instead, we found that bacterial
646 shedding following abortion or birth was indeed the predominant transmission route within
647 units (Fig. 5), but was not restricted to female-to-female transmission. In particular, female-
648 to-male transmission occurred frequently after birth, when susceptible newborn males were in
649 contact with shedding females (Appendix C; Figs. C.6-7). Vertical transmission also played a
650 significant role, and overall, as within-unit transmission was largely predominant, our results
651 demonstrated a critical role of females in the studied system.

652 As regards between-unit transmission, venereal transmission was the predominant
653 transmission route, but contrary to our expectation, again, transmission occurred slightly more

654 often from female to male than from male to female (Fig. 7A and Appendix C; Fig. C.4). This
655 means that males got infected from females of other units almost as much as they transmitted
656 infection to females. Therefore, females represent also an important source of transmission
657 between units, which was counterintuitive given their sedentary behaviour. However, it is
658 important to stress out that males are the only individuals that move between units in the ibex
659 population and are thus essential for the spatial spread of brucellosis. In bison, venereal
660 transmission was assumed to play a negligible role compared to *Brucella* shedding in females
661 following abortion or birth (Ebinger et al., 2011; Treanor et al., 2010). In our study, although
662 the uncertainty around the venereal transmission parameter remains high, most **transmissions**
663 between units were accounted for by the venereal route. Our result suggest that this
664 transmission route **plays** a critical role for the spatial spread of brucellosis in ibex, and thus
665 has to be taken into account.

666 The critical role of within-unit transmission, and especially through shedding following
667 infectious birth, could explain the maintenance of the differences in seroprevalence among
668 socio-spatial units, and the fact that males present the same spatial structuration in
669 seroprevalence as females, despite their movements between units (Marchand et al., 2017).
670 Indeed, if there was a majority of between-unit transmissions, we would expect a
671 homogenisation of seroprevalences in the different units.

672

673 **4.3 The role of old individuals**

674 For males, the age class that is both a source and a victim of transmission (through venereal
675 transmission) clearly appears to be the individuals over 5 years old, even when compared to
676 the proportion of males of this age class in the whole population (Fig. 7A and Appendix C;
677 Figs. C.2-3). This result is in accordance with the hypothesis made by Hars et al. (2013) based
678 on serological data. This occurs because older males are more frequently in contact with

679 females (“tending” mating tactic) and have thus a higher probability of effective contact than
680 younger males. This pattern still held after the massive culling operation in autumn 2013,
681 even though males over 5 years old were specifically targeted. Although the number of older
682 males in the population decreased (Appendix C; Figs. C.2-3), we did not detect a strong
683 increase of the proportion of younger males (≤ 5 years old) involved in venereal transmission
684 (Appendix C; Fig. C.4), contrarily to what was suggested in Hars et al. (2015).
685 In contrast, females 5 years old and under were responsible for most new cases through
686 infectious abortions (Appendix C; Fig. C.5), whereas older females were accountable for the
687 majority of new cases through infectious births as well as congenital/pseudo-vertical
688 transmission (Appendix C; Figs. C.6-7). Thus, despite the fact that young seropositive
689 females have a higher probability of being actively infected (Lambert et al., 2018), young
690 females play a major role through abortion during their first gestation post-infection, but
691 transmission through shedding after birth in the following gestations (i.e. in older females)
692 also plays a determinant role. This could be explained, although less categories of individuals
693 are exposed to this route and for shorter duration than for abortions, by the fact that most of
694 exposed individuals are newborns, fully susceptible to the infection. Therefore, ecological
695 data in combination with epidemiological data on seroprevalence structure and shedding
696 pattern suggest that brucellosis transmission is not limited to young age classes in ibex, in
697 contrast to what is suggested by shedding patterns alone (Lambert et al., 2018). This result is
698 similar to the pattern of transmission in domestic ruminants facing endemic brucellosis
699 (ANSES, 2015; European Commission, 2001).

700

701 **4.4 Source, sink and metapopulation dynamics of brucellosis**

702 As regards our second hypothesis, we expected that units with the highest seroprevalence and
703 the largest sub-population, that also occupy a central positions in the Massif (Marchand et al.,

704 2017), would act as sources of infection to the other units. We used explicit movements of
705 animals, quantified through the use of GPS data, to model transmission between units, rather
706 than a phenomenological model that links units between them without specifying any
707 mechanism (Jesse et al., 2008). Therefore, transmission between units was the result of both
708 movement pathways of animals and characteristics of each unit such as abundance and
709 seroprevalence.

710 Our prediction was supported by the outcome of the model (Figs. 7B and 8), with both
711 Units 3 and 4 (with high seroprevalence) being the main sources of between-unit new cases,
712 while Units 2 (with low seroprevalence) and 5 (with intermediate level of seroprevalence)
713 were the main units where new cases occurred from between-unit transmission. During the
714 mating period, movements of males from Unit 3 mostly occurred towards Unit 2
715 (Appendix A; Fig. A.3). Therefore, transmission between these units was mostly accounted
716 for by movement of infectious males from Unit 3 and contamination of susceptible females of
717 Unit 2. As for Unit 4, it acted as a source through two main mechanisms: through movements
718 of infectious males from Unit 4 and contamination of susceptible females of Unit 5; but also
719 from movements of susceptible males from Unit 5, which got infected by infectious females
720 from Unit 4.

721 We therefore confirmed the role of transmission source of the two central socio-spatial units
722 in our population, which mainly infected the two peripheral socio-spatial units. The last socio-
723 spatial unit, more isolated than the others (Fig. 1B and Appendix A), also received the
724 infection from the two sources, but relatively less so. To attribute to the peripheral units the
725 role of sink, in the context of metapopulation dynamics, would require confirming that
726 infection would eventually fade-out from these units without movements and transmission
727 from the sources (Pulliam, 1988), which was not explored by our model.

728

729 **4.5 Potential consequences for disease management**

730 Our study, although not aiming to analyse explicitly the relative relevance of different
731 management scenarios, **suggests** that management interventions implemented so far have
732 decreased brucellosis transmission, even if *Brucella* was still persistent in all 1000 simulations
733 at the end of the study period. However, we could not disentangle the effects of each
734 intervention or combination of interventions, as we did not compare our results to other
735 management scenarios. Our results also offer first insights on how to improve disease
736 management. For example, previous studies suggested that disease management targeted
737 towards a subset of units in a metapopulation, based on their position in the configuration of
738 the metapopulation and their contribution to transmission, could be more effective (Fulford et
739 al., 2002; Haydon et al., 2006; Hess, 1996). In our case, targeting the three units acting as
740 hotspots of transmission could be a possible way of improving the cost/benefit ratio of disease
741 management.

742 Targeting specific age- or sex-classes could be an alternative (Fenichel and Horan, 2007;
743 Ferrari et al., 2003). In the ibex case, management strategies should probably focus on
744 females, as they are responsible for the vast majority of new cases in the system. Predicting
745 which female age class to target appears difficult because younger females are more often
746 actively infected and abort, while older females play an important role as well through
747 shedding at birth and vertical transmission. In a model of brucellosis infection in bison from
748 the Yellowstone National Park, test-and-remove was more effective when targeting pre-
749 reproductive seropositive females rather than targeting all females regardless of age (Ebinger
750 et al., 2011). This selective strategy allowed to remove seropositive females before they could
751 even shed bacteria following abortion or birth (Ebinger et al., 2011). In ibex, individuals
752 under two years of age are seldom captured, which would make this strategy difficult to
753 apply.

754 Males play a less important role quantitatively, but qualitatively they connect socio-spatial
755 units together and create opportunities for between-unit transmission. Therefore, if the aim of
756 the management strategy is to reduce or prevent transmission between socio-spatial units, then
757 males, especially older ones, should be targeted.

758 Future studies about the efficacy of disease strategies in our population are therefore required
759 and could be improved by the new insights we provided in this work. The model we proposed
760 could be expanded for predictions on the future dynamics of the population, with and without
761 disease management, so as to evaluate theoretically the relative efficacy of various strategies
762 that could then be implemented in the field.

763

764 **4.6 Conclusion**

765 By integrating information issued from population demography, [space](#) use, management
766 strategies and epidemiological surveys to build a realistic model, we provide an accurate
767 picture of the population dynamics of ibex in the Bargy massif, which faced a brucellosis
768 outbreak. This [model](#) allows unravelling the mechanisms involved in [these](#) dynamics.

769 Considering the specific features of this population, particularly the management measures
770 implemented since 2012, extrapolating our conclusions to other cases (if these arise), should
771 be done with caution. In particular, the outcome of infection would have likely been different
772 if management options had been different. Nonetheless, our results suggest that brucellosis in
773 ibex is epidemiologically similar to *B. melitensis* and *B. abortus* infection in other species of
774 domestic and wild ruminants, with mature females playing a predominant role of transmission
775 through *Brucella* shedding in genital fluids (Diaz-Aparicio, 2013; European Commission,
776 2001; Rhyan, 2013). Our findings demonstrate that our general framework using individual-
777 based models is suitable for the study of transmission heterogeneity in wild populations and
778 could be applied to other host-pathogen systems.

779

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- 1036

1038 **Table 1: Definition and value of demographic parameters included in the model of**
 1039 **population dynamics of ibex facing a brucellosis outbreak in the Bargy massif, France.**

	Description (dimension)	Value	References
k	Threshold for density-dependent effect	131	†
K	Carrying capacity of the metapopulation		‡
μ_0^{min}	Probability of winter mortality of newborns, minimum (over the duration of winter)	0	†
μ_0^{max}	Probability of winter mortality of newborns, maximum (over the duration of winter)	0.60	†
$\mu_{X\text{♀}}$	Probability of mortality of X-years old females (annual)	App. A	*
$\mu_{X\text{♂}}$	Probability of mortality of X-years old males (annual)	App. A	*
τ_X^{max}	Sexual receptivity probability of X-years old females, maximum	App. A	†
τ_X^{min}	Sexual receptivity probability of X-years old females, minimum	App. A	†
p'_{ij}	Probability for a male whose permanent unit is i to visit the unit j during one time step (per week)		
p_1	Proportion of associations during the first 2 weeks of the mating period	0.70	(Willisch and Neuhaus, 2009)
p_2	Proportion of associations during the rest of the mating period	0.30	(Willisch and Neuhaus, 2009)
n_T	Number of tending males per female (over the duration of mating)	1	(Willisch and Neuhaus, 2009)
n_C	Number of coursing males per female (over the duration of mating)	3	(Willisch and Neuhaus, 2009)
p_{C1}	Proportion of coursing males 2-5 years old associated to females	1/3	(Willisch et al., 2012)
p_{C2}	Proportion of coursing males 6-7 years old associated to females	2/3	(Willisch et al., 2012)
τ_T	Copulation probability of tending males (8-14 years old)	6/7	(Willisch et al., 2012)
τ_C	Copulation probability of coursing males (2-7 years old)	1/7	(Willisch et al., 2012)
n^{max}	Maximal number of partners for males (per week)	3	(Willisch and Neuhaus, 2009)
η_1	Probability of giving birth for primiparous females	0.70	†
η_2	Probability of giving birth for multiparous females	0.90	†
δ	Sex ratio	0.50	†
d_{rut}	Duration of mating period (weeks)	7	(Willisch and Neuhaus, 2009)
d_{gest}	Duration of gestation (weeks)	24	(Gauthier et al., 1991)
d_{isol}	Duration of postpartum isolation of the mother-offspring couple (weeks)	2	(Gauthier et al., 1991)

1040 App. A: see Appendix A
 1041 * Calibrated using field data
 1042 † Experts knowledge
 1043 ‡ Approximate Bayesian Computation
 1044

1045 **Table 2: Definition and value of epidemiological parameters included in the model of**
 1046 **population dynamics of ibex facing a brucellosis outbreak in the Bargy massif, France.**

	Description (dimension)	Value	References
d_{inc}	Duration of <i>Brucella</i> incubation (weeks)	3	(European Commission, 2001)
d_{shed}	Duration of shedding of <i>Brucella</i> in genital fluids when a female aborts or gives birth (weeks)	3	(European Commission, 2001)
d_{abo}	Delay between mating and abortion due to <i>Brucella</i> (weeks)	16	(Diaz-Aparicio, 2013)
Se	Sensitivity of serologic tests	0.95	(ANSES, 2015)
ρ	Probability of abortion during the first pregnancy following infection	0.80	(Godfroid et al., 2004)
γ	Probability of recovery (annual)	0.16	*
β_{IA}^{\varnothing}	Per capita probability of one female coming into effective contact with one infectious abortion due to <i>Brucella</i> (per week)		‡
σ	Reduction in the number of contacts with infectious abortion for males ≤ 5 years old	0.27	*
$\beta_{IA}^{\sigma \leq 5}$	Per capita probability of one male ≤ 5 years old coming into effective contact with one infectious abortion (per week)	$\sigma \times \beta_{IA}^{\varnothing}$	
ϕ	Reduction in the number of contacts with infectious abortion for males > 5 years old	0.06	*
$\beta_{IA}^{\sigma > 5}$	Per capita probability of one male > 5 years old coming into effective contact with one infectious abortion (per week)	$\phi \times \beta_{IA}^{\varnothing}$	
β_{IB}	Per capita probability of one female or one newborn coming into effective contact with one infectious birth (per week)		‡
$v_{ven}^{T \rightarrow \varnothing}$	Probability of successful venereal transmission from tending males to females given contact		‡
κ	Relative efficacy of coursing male-to-female transmission	0.45	(Willisch and Neuhaus, 2009)
$v_{ven}^{C \rightarrow \varnothing}$	Probability of successful venereal transmission from coursing males to females given contact	$\kappa \times v_{ven}^{T \rightarrow \varnothing}$	
ω	Relative efficacy of female-to-male transmission	0.60	(Augustine, 1998)
$v_{ven}^{\varnothing \rightarrow T}$	Venereal transmission coefficient from females to tending males	$\omega \times v_{ven}^{T \rightarrow \varnothing}$	
$v_{ven}^{\varnothing \rightarrow C}$	Venereal transmission coefficient from females to coursing males	$\omega \times v_{ven}^{C \rightarrow \varnothing}$	
β_{cong}	Congenital transmission coefficient by <i>in utero</i> infection	0.05	(FAO and WHO, 1986; Godfroid et al., 2013)
β_{pseu}	Pseudo-vertical transmission coefficient by milk ingestion	0.05	†
ζ_{τ}	Impact of brucellosis on sexual receptivity probability of infectious females	0.80	†
ζ_{η}	Impact of brucellosis on probability of giving birth of infectious females in subsequent pregnancies	0.90	†

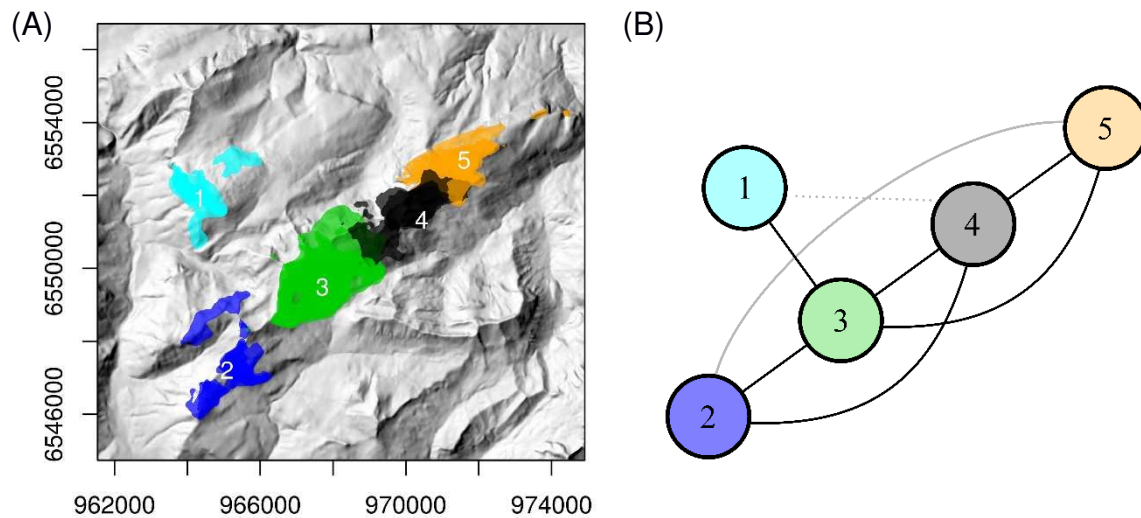
1047 * Calibrated using field data

1048 † Experts knowledge

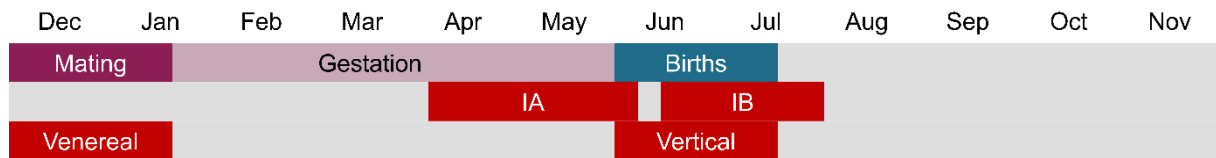
1049 ‡ Approximate Bayesian Computation

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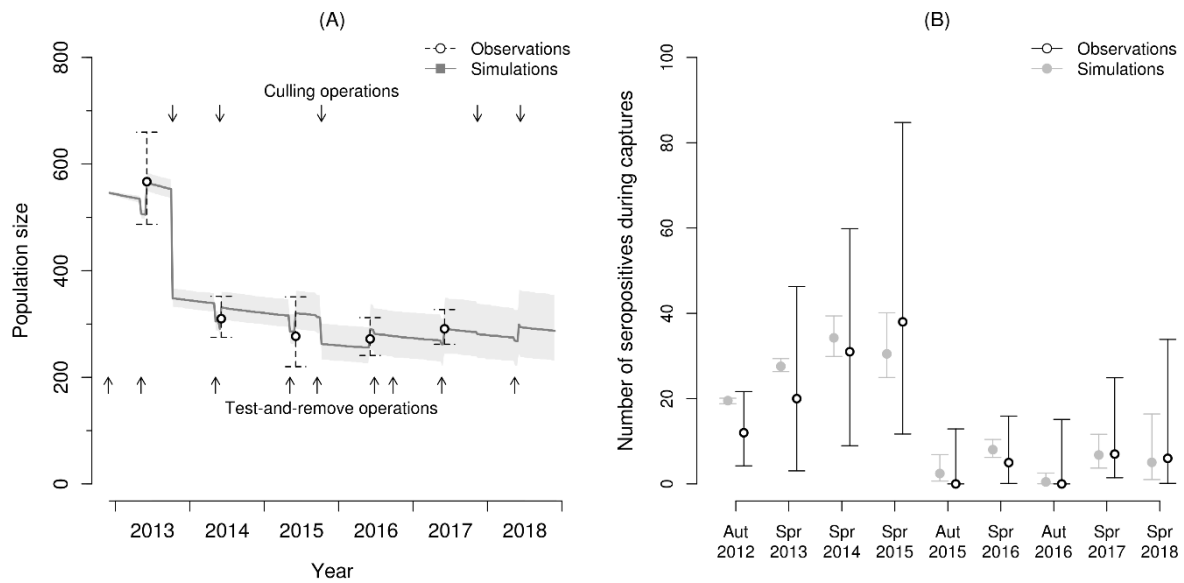


1052 **Figure 1: The five socio-spatial units of the Bargy massif and representation of the**
 1053 **associated conceptual metapopulation model.** A (left): identification of the five socio-
 1054 spatial units. Unit 1 is called “Leschaux-Andey”, Unit 2 “Charmieux-Buclon”, Unit 3
 1055 “Jallouvre-Peyre”, Unit 4 “Grand Bargy” and Unit 5 “Petit Bargy”. This is an updated version
 1056 of Figure 2 in (Marchand et al., 2017), using new data of GPS-collared Alpine ibex (*Capra*
 1057 *ibex*), corroborating the socio-spatial structure of the population. See Marchand et al. (2017)
 1058 for details on the method. B (right): configuration of the associated conceptual
 1059 metapopulation model. Circles represent the five socio-spatial units. Females always stay in
 1060 their unit, whereas male can make temporary visits to other units. Solid black lines represent
 1061 between-unit movements of males that are possible during both mating and abortion period.
 1062 The solid grey line represents movements of males that exist only during mating period. The
 1063 dashed grey line represents movements of males that exist only during abortion period.
 1064 Seroprevalence varied between units (Marchand et al., 2017): <15% for Units 1 and 2, 54%
 1065 for Unit 3, 70% for Unit 4 and 35% for Unit 5. See Appendix A for more details.
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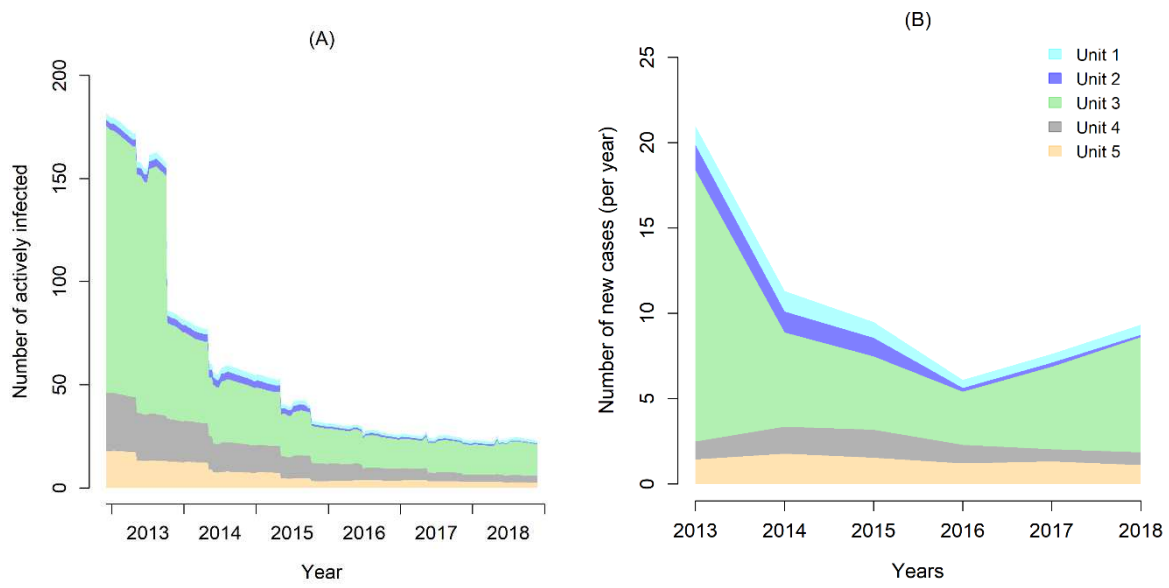
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1068 **Figure 2: Seasonal reproduction of the Alpine ibex and periods of potential *Brucella***
 1069 **shedding.** Mating season lasts from early December to mid-January (purple rectangle),
 1070 leading to births from the end of May to mid-July (blue rectangle). *Brucella* shedding after an
 1071 infectious abortion (IA) or birth (IB) lasts three weeks. Therefore, horizontal transmission by
 1072 IA is possible from early April to the end of May. After parturition, a female is not in contact
 1073 with other individuals for two weeks, therefore the beginning of horizontal transmission by IB
 1074 is delayed for two weeks compared to the start of the birth period. Venereal transmission is
 1075 possible during the entire mating period, and vertical transmission (congenital and pseudo-
 1076 vertical) happens during the entire birth period.
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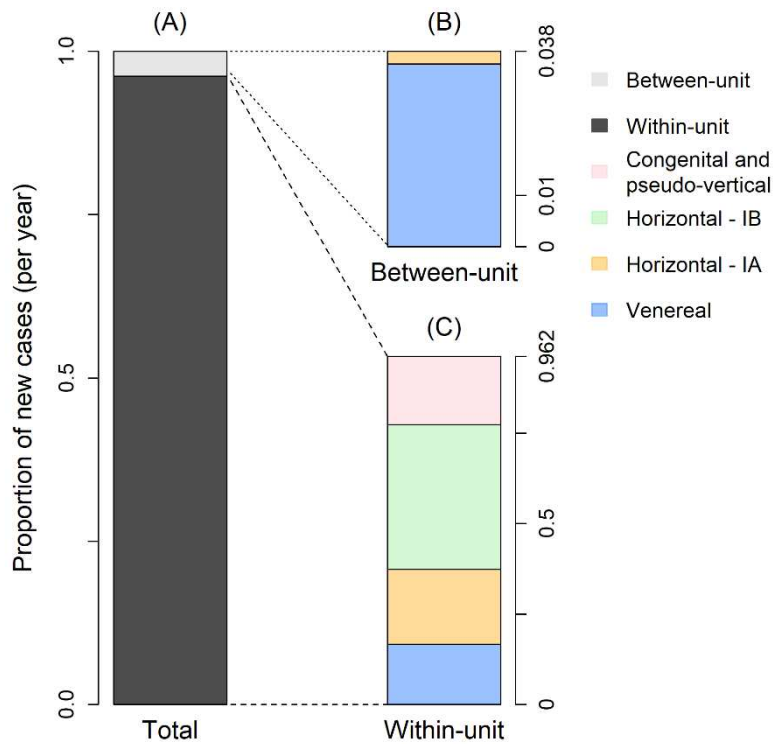
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Figure 3: Fit of the model to observed data. A: Fit of the model to the estimated pre-breeding population size, also with capture, test-and-remove operations (bottom arrows) and culling operations (top arrows). B: Fit of the model to the expected number of seropositive animals during captures and recaptures. The open black circles and black lines are the observed data and the 95% confidence interval, respectively. Similarly, the grey line (left) or the grey points (right) represent the median of the simulated outputs over the 1000 iterations, while the grey area (left) or the grey lines (right) represent the 95% credible interval. See Appendix B for more details.



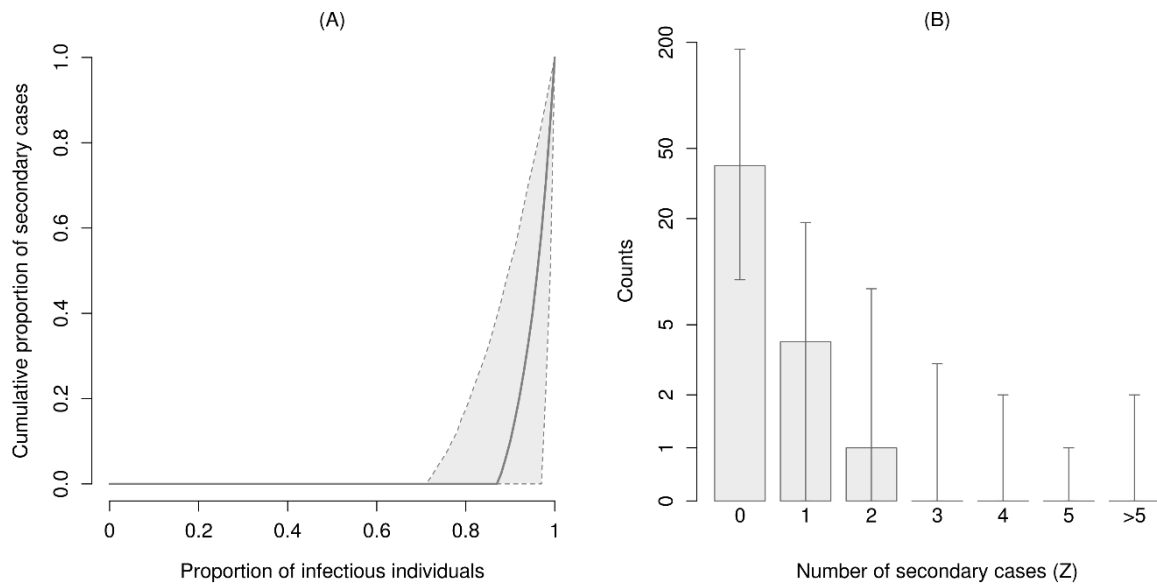
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Figure 4: Model predictions for the spatio-temporal dynamics of brucellosis infection in the wild population of Alpine ibex (*Capra ibex*) of the Bargy massif. A: evolution of the average number of actively infected (I) individuals in the model at each time step (weeks). B: evolution of the average number of new cases per annum in each socio-spatial unit.

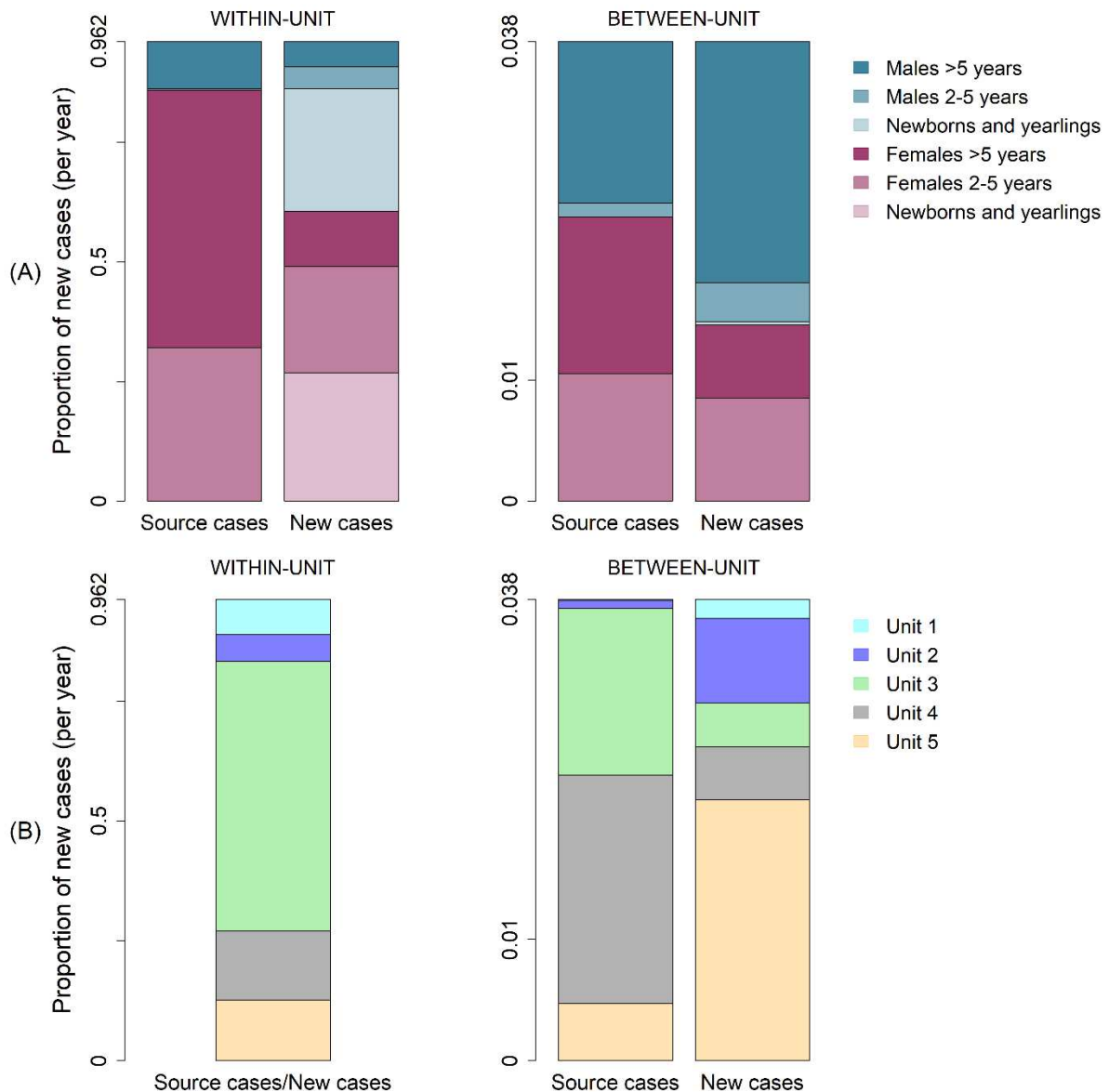


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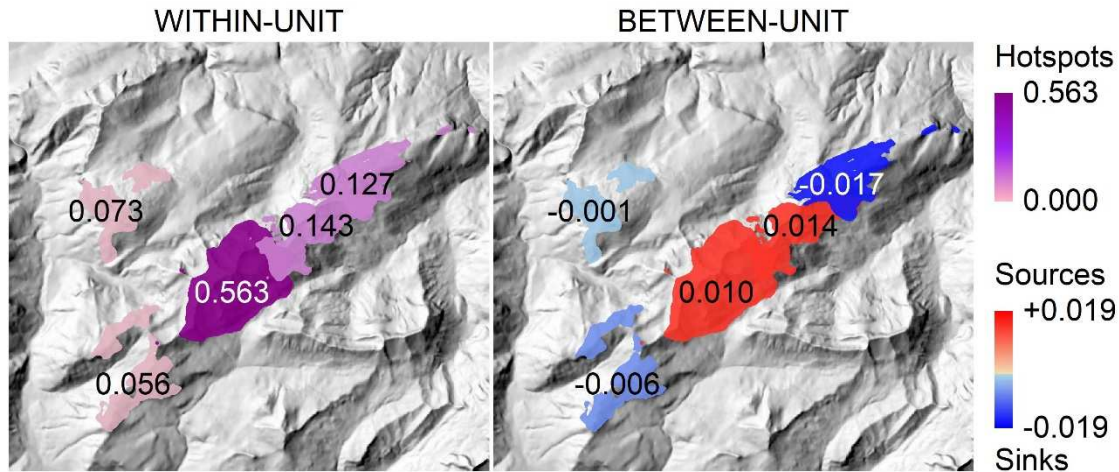
Figure 5: Proportion of new cases caused by each transmission route. A: Average proportion of new cases caused by between-unit (light grey) or within-unit (dark grey) transmission. B: Average proportion of new cases caused by each transmission route for between-unit transmission. C: Average proportion of new cases caused by each transmission route for within-unit transmission. Vertical transmission (congenital and pseudo-vertical) is in light pink, horizontal transmission through infectious births (IB) is in green, horizontal transmission through infectious abortions due to *Brucella* (IA) is in orange, and venereal transmission is in blue.



1103
 1104 **Figure 6: Contribution of infectious individuals to the yearly number of secondary cases.**
 1105 A: Cumulative contribution to transmission vs. proportion of infectious individuals, sorted by
 1106 increasing contribution of secondary cases. The solid grey line represents the median of the
 1107 output over the 1000 simulations and the six years of study, while the light grey area
 1108 represents the 95% credible interval. B: absolute frequency of Z, the number of secondary
 1109 cases caused by each infectious individual. Bars represent the median of the output over the
 1110 1000 simulations and the six years of study, while the grey lines represent the 95% credible
 1111 interval.
 1112



1113
 1114 **Figure 7: Distribution of secondary cases of brucellosis transmission according to their**
 1115 **age- and sex-classes and their socio-spatial unit, and according to the age- and sex-**
 1116 **classes and socio-spatial unit they originated from.** A: average proportion of secondary
 1117 cases that originated from **source** cases of each age- and sex-class (“Source cases”), and
 1118 average proportion of secondary cases that occurred in each age- and-sex class (“New cases”).
 1119 For the sake of example, consider a situation where one actively infected female caused two
 1120 secondary cases in females and one in males, and one actively infected male caused two
 1121 secondary cases in females. Then, a proportion of 60% (3/5) of secondary cases originated
 1122 from females and 40% (2/5) from males (“Source cases”), while the proportion of secondary
 1123 cases would be 80% (4/5) in females and 20% (1/5) in males (“New cases”). We separated
 1124 within-unit (left, 96.2% of new cases – Fig. 5A) and between-unit (right, 3.8% of new cases)
 1125 transmission. B: average proportion of secondary cases that originated from **source** cases of
 1126 the five socio-spatial units of the population (“Source cases”) and average proportion of
 1127 secondary cases that occurred in each socio-spatial unit (“New cases”). For within-unit
 1128 transmission (left), the socio-spatial unit of the secondary case and the socio-spatial unit it
 1129 originated from were necessarily the same as transmission occurred between two individuals
 1130 of the same unit; on the contrary, between-unit transmission (right) always occurred between
 1131 two individuals from different units.



1132
 1133 **Figure 8: Spatial transmission heterogeneity of brucellosis in the five socio-spatial units**
 1134 **of the Alpine ibex population of the Bargy massif.** To the left, socio-spatial units are ranked
 1135 according to the average proportion of secondary cases that occurred in each socio-spatial unit
 1136 by within-unit transmission (96.2% of new cases), to identify hotspots of transmission.
 1137 Proportions are the same than in Figure 7B. To the right, each unit is ranked according to the
 1138 difference between the proportion of new cases that originated from it and the proportion of
 1139 new cases that occurred in it because of the other units (between-unit transmission, 3.8% of
 1140 new cases). This corresponds to making the difference between the “source cases” column
 1141 and the “new cases” column in Figure 7B. If the difference is positive, the unit was
 1142 considered as a source of transmission, because more cases were generated than received. In
 1143 the case of a negative difference, the unit was considered as a sink of transmission, because
 1144 more cases were received than generated. The differences were calculated as: $0-0.001=-0.001$
 1145 for Unit 1, $0.001-0.007=-0.006$ for Unit 2, $0.014-0.004=0.010$ for Unit 3, $0.018-0.004=0.014$
 1146 for Unit 4 and $0.005-0.022=-0.017$ for Unit 5.