



**HAL**  
open science

# Combining seroprevalence and capture-mark-recapture data to estimate the force of infection of brucellosis in a managed population of Alpine ibex

Sébastien Lambert, Emmanuelle Gilot-Fromont, Carole Toïgo, Pascal Marchand, Elodie Petit, Sophie Rossi, Anne Thébault

## ► To cite this version:

Sébastien Lambert, Emmanuelle Gilot-Fromont, Carole Toïgo, Pascal Marchand, Elodie Petit, et al.. Combining seroprevalence and capture-mark-recapture data to estimate the force of infection of brucellosis in a managed population of Alpine ibex. *Epidemics*, 2022, 38, pp.100542. 10.1016/j.epidem.2022.100542 . anses-03597873

**HAL Id: anses-03597873**

<https://anses.hal.science/anses-03597873v1>

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Title: Combining seroprevalence and capture-mark-recapture data to estimate the force**  
2 **of infection of brucellosis in a managed population of Alpine ibex**

3

4 **Author names and affiliations:**

5 Sébastien Lambert <sup>a\*</sup>, Emmanuelle Gilot-Fromont <sup>b</sup>, Carole Toïgo <sup>c</sup>, Pascal Marchand <sup>d</sup>,

6 Elodie Petit <sup>b,e</sup>, Sophie Rossi <sup>f\*\*</sup>, Anne Thébault <sup>g</sup>

7

8 <sup>a</sup> Université de Lyon, Université Lyon 1, CNRS, Laboratoire de Biométrie et Biologie

9 Évolutive UMR 5558, Villeurbanne, France

10 <sup>b</sup> Université de Lyon, VetAgro Sup, CNRS, Laboratoire de Biométrie et Biologie Évolutive

11 UMR 5558, Villeurbanne, France

12 <sup>c</sup> Office Français de la Biodiversité (OFB), Unité Ongulés Sauvages, Gières, France

13 <sup>d</sup> Office Français de la Biodiversité (OFB), Unité Ongulés Sauvages, Juvignac, France

14 <sup>e</sup> Office Français de la Biodiversité (OFB), Unité Sanitaire de la Faune, Sévrier, France

15 <sup>f</sup> Office Français de la Biodiversité (OFB), Unité Sanitaire de la Faune, Gap, France

16 <sup>g</sup> Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement et du travail

17 (Anses), Direction de l'Évaluation des Risques, Maisons-Alfort, France

18 <sup>\*</sup> Present address: Centre for Emerging, Endemic and Exotic Diseases, Department of

19 Pathobiology and Population Sciences, Royal Veterinary College, University of London,

20 Herts, UK

21 <sup>\*\*</sup> The authors wish to dedicate this work to the beloved memory of Dr Sophie Rossi, who

22 sadly passed away during the preparation of this manuscript. She dedicated her career to

23 further the understanding of wildlife diseases and improve wildlife health, and her passionate

24 work will remain an inspiration to us all.

25

26 **Corresponding author:** Dr Sébastien Lambert, Department of Pathobiology and Population

27 Sciences, Royal Veterinary College, University of London, Hertfordshire, AL9 7TA, United

28 Kingdom, selambert@rvc.ac.uk

29

30 **Abstract:** In wildlife, epidemiological data are often collected using cross-sectional surveys  
31 and antibody tests, and seroprevalence is the most common measure used to monitor the  
32 transmission dynamics of infectious diseases. On the contrary, the force of infection, a  
33 measure of transmission intensity that can help understand epidemiological dynamics and  
34 monitor management interventions, remains rarely used. The force of infection can be  
35 derived from age-stratified cross-sectional serological data, or from longitudinal data  
36 (although less frequently available in wildlife populations). Here, we combined  
37 seroprevalence and capture-mark-recapture data to estimate the force of infection of  
38 brucellosis in an Alpine ibex (*Capra ibex*) population followed from 2012 to 2018. Because  
39 the seroprevalence of brucellosis was 38% in this population in 2012, managers conducted  
40 two culling operations in 2013 and 2015, as well as captures every year since 2012, where  
41 seronegative individuals were marked and released, and seropositive individuals were  
42 removed. We obtained two estimates of the force of infection and its changes across time, by  
43 fitting (i) a catalytic model to age-seroprevalence data obtained from unmarked animals  
44 (cross-sectional), and (ii) a survival model to event time data obtained from recaptures of  
45 marked animals (longitudinal). Using both types of data allowed us to make robust inference  
46 about the temporal dynamics of the force of infection: indeed, there was evidence for a  
47 decrease in the force of infection between mid-2014 and late 2015 in both datasets. The force  
48 of infection was estimated to be reduced from  $0.115 \text{ year}^{-1}$  [0.074–0.160] to  $0.016 \text{ year}^{-1}$   
49 [0.001–0.057]. These results confirm that transmission intensity decreased during the study  
50 period, probably due to management interventions and natural changes in infection dynamics.  
51 Estimating the force of infection could therefore be a valuable complement to classical  
52 seroprevalence analyses to monitor the dynamics of wildlife diseases, especially in the  
53 context of ongoing disease management interventions.

54

55 **Keywords (5):** wildlife disease management; force of infection; seroprevalence; catalytic  
56 model; survival analysis

## 57 INTRODUCTION

58 Recent outbreaks of wildlife diseases in Europe such as Chronic Wasting Disease or African  
59 Swine Fever have brought to light the need for effective, science-based disease management  
60 strategies in the wild (Mysterud and Rolandsen, 2018; Vicente et al., 2019). Depending on  
61 the host species and infectious disease considered, interventions such as culling, fencing, test-  
62 and-remove or vaccination have been implemented with various success in wild populations  
63 (le Roex et al., 2015; McDonald et al., 2008; Müller et al., 2015; Mysterud and Rolandsen,  
64 2019). The first step in the choice of an appropriate management intervention is a sound  
65 evaluation of the epidemiological situation, in order to optimize strategies before any action  
66 is implemented (Artois et al., 2009). Then, ongoing management interventions should be  
67 accompanied by a close monitoring of both the infection and the population dynamics to  
68 assess their effectiveness (Joseph et al., 2013; Vicente et al., 2019). However, the  
69 management of wildlife diseases is often hampered by our limited knowledge of population  
70 and infection dynamics, and management actions are often implemented before a full picture  
71 of the situation has been drawn. It would therefore be desirable to extract the most  
72 information out of the available data to inform management decisions.

73 Incidence, i.e. the number of new infections in a population at risk over a given period of  
74 time, and prevalence, the proportion of infected individuals at a given point in time or over a  
75 certain period of time, are two common measures used to describe epidemiological dynamics  
76 of infections (Keiding, 1991). In wildlife populations, the collection of epidemiological data  
77 is often performed using cross-sectional surveys and serological (antibody) tests (Gilbert et  
78 al., 2013). Therefore, the prevalence of individuals positive to antibody tests (called  
79 seroprevalence) is often the only measure used to monitor the dynamics of infections in  
80 managed populations (Gilbert et al., 2013). However, the variation of seroprevalence over  
81 time provides only limited information on transmission dynamics, as the presence of

82 antibodies does not necessarily reflect active infections or inform on the timing of infection,  
83 especially in long-lived species. Unfortunately, incidence is rarely available for wildlife  
84 populations, because it requires longitudinal samplings of individual animals which are often  
85 logistically difficult (Gilbert et al., 2013). The force of infection (FOI), on the other hand, is a  
86 measure of transmission intensity related to incidence that can be obtained from age-  
87 seroprevalence data collected during cross-sectional surveys (Heisey et al., 2006) and that  
88 can help planning and optimizing management interventions (Lewis et al., 2014).

89 The FOI is the rate at which susceptible individuals become infected, and combines the  
90 contact rate, the probability of transmission given contact, and the number of infectious  
91 individuals in the population (Begon et al., 2002). Classical methods for estimating the FOI  
92 are based on the fact that the proportion of individuals who have ever been infected increases  
93 with age as a result of increased time of exposure to the infection (Heisey et al., 2006; Hens  
94 et al., 2010). These methods, also described as catalytic models (Muench, 1934), have been  
95 widely used for life-long immune infections in humans (Farrington, 1990; Keiding, 1991;  
96 Papoz et al., 1986). A common assumption in these models is that the FOI is constant over  
97 time, or at least constant on average (Hens et al., 2010), which is often not the case for  
98 diseases that are emerging or under management. Nonetheless, several studies were able to  
99 estimate time-varying FOI in humans (Katzelnick et al., 2018) and animals (Courtejoie et al.,  
100 2018). Estimating the FOI from age-seroprevalence data also has the additional advantage of  
101 assessing for infection-related mortality (Heisey et al., 2006; Reynolds et al., 2019).

102 The aim of this study was to estimate the FOI of brucellosis (*Brucella melitensis*) in Alpine  
103 ibex (*Capra ibex*) in the Bargy Massif (French Alps). This is the first reported example of  
104 self-sustained brucellosis infection in European wild-living ungulates, with a seroprevalence  
105 level as high as 38% at the beginning of monitoring in 2012-2013 (Garin-Bastuji et al., 2014;  
106 Hars et al., 2013). As France has been declared officially free of *Brucella melitensis* and

107 *Brucella abortus* in domestic ruminants since 2005 (Perrin et al., 2016a, 2016b), the  
108 persistence of *B. melitensis* in a wildlife population raises serious public health and economic  
109 concerns. This led the French authorities to undertake several management interventions  
110 since the discovery of the outbreak in 2012 (Lambert et al., 2018; Marchand et al., 2017).  
111 Among these, two massive culling operations were carried out in autumn 2013-spring 2014  
112 ( $n=251$  individuals culled, estimated population size before culling: 567, 95% CI [487-660])  
113 and in autumn 2015 ( $n=70$  individuals culled, estimated population size before culling: 344,  
114 95% CI [290-421]). In parallel, the population was monitored by Capture-Mark-Recapture  
115 (CMR) to collect demographic and epidemiological data every year. During captures ( $n=387$   
116 between 2012 and 2018), a test-and-remove program was implemented where seropositive  
117 individuals were removed ( $n=119$ ), while seronegative individuals were marked and released.  
118 The 2015 test-and-remove campaign was particularly intense with 38 individuals removed  
119 among the 125 captured.

120 As a consequence, cross-sectional data are available from unmarked animals, whereas the  
121 follow up of marked animals can be seen as data of a cohort study of seronegative animals.  
122 Contrary to the seroprevalence (Calenge et al., 2021; Marchand et al., 2017), the FOI has  
123 never been studied in the population before, although Calenge et al., 2021 estimated the FOI  
124 exerted on susceptible marked animals only, and assuming that it was proportional to the  
125 proportion of the total ibex population being seropositive, unmarked and actively infected.  
126 Therefore, we were interested in estimating the FOI from the available datasets to get a  
127 complementary picture of the epidemiological dynamics in the study population.

128 In ruminants, brucellosis is considered to produce lifelong infections, in particular in goats  
129 (European Commission, 2001; Schlafer and Miller, 2007), a species closely related to ibex.  
130 *Brucella* infection induces both humoral and cellular immune responses (Carvalho Neta et  
131 al., 2010; European Commission, 2001), which remains detectable over long periods of time



132 (Godfroid et al., 2010). The characteristics of brucellosis are therefore compatible with the  
133 use of catalytic models.

134 The presence of antibodies detected by serologic tests is used to detect previous exposure to  
135 *Brucella* (Godfroid et al., 2010). However, a potential issue with using antibodies as a proxy  
136 of past exposure is that infected individuals could be missed if antibody levels wane over  
137 time and decrease below detectable levels (Benavides et al., 2017). In elk (*Cervus*  
138 *canadensis*) infected with *B. abortus*, evidence suggest lifelong protective immunity but a  
139 progressive antibody loss after some years, which explains the decline in seroprevalence in  
140 older individuals (Benavides et al., 2017). In bison (*Bison bison*), a similar decline in  
141 seroprevalence in older individuals is observed (Treanor et al., 2011). This could be  
142 explained by the finding that active infections, which can be reactivated on favourable  
143 occasions such as oestrus or pregnancy (European Commission, 2001; Schlafer and Miller,  
144 2007) and are associated with increased antibody levels (Durán-Ferrer et al., 2004), decreases  
145 with age in seropositive bison (Treanor et al., 2011).

146 In ibex, similar patterns have been found with a decline of seroprevalence in older individuals  
147 (Marchand et al., 2017) and a decrease of the probability of active infection with age  
148 (Lambert et al., 2018). Therefore, a partial antibody loss cannot be excluded; however, in the  
149 absence of relevant data to estimate this process, we assumed life-long infection and  
150 seropositivity in our study.

151 Infection-related mortality is another mechanism that could explain a decrease of  
152 seroprevalence with age (Benavides et al., 2017; Heisey et al., 2006). Therefore, one aim of  
153 the present study was to look for evidence of infection-related mortality, which can be  
154 estimated at the same time as the FOI (Heisey et al., 2006; Reynolds et al., 2019). Although  
155 there is currently no evidence for brucellosis-related mortality in the Alpine ibex population  
156 of the Bargy massif, it remains a possibility, e.g. because of brucellosis-related lesions such

157 as arthritis (Freycon et al., 2017). In other wild species, evidence for brucellosis-related  
158 mortality were found in moose (*Alces alces*) and African buffalo (*Syncerus caffer*) (Forbes et  
159 al., 1996; Gorsich et al., 2015), but not in bison or elk (Benavides et al., 2017; Fuller et al.,  
160 2007; Joly and Messier, 2005).

161 Our study also aimed at evaluating temporal changes in the FOI between October 2012 and  
162 June 2018. The seroprevalence did not change between 2012 and 2015 (Marchand et al.,  
163 2017), when management interventions were dominated by massive culling operations.  
164 However, a recent study demonstrated that it then decreased between 2015 and 2016, before  
165 getting roughly stable from 2016 to 2018 (Calenge et al., 2021). Management interventions in  
166 this second period were mainly based on test-and-remove during captures, especially in 2015  
167 when 125 captures were achieved, followed by around 30-50 captures each following year.  
168 Given this information, we hypothesized that the FOI also decreased between 2015 and 2016,  
169 at the same time as the seroprevalence and following changes in the management  
170 interventions. Alternatively, if individuals remain immune lifelong after infection, test-and-  
171 remove of seropositive individuals could also increase the FOI by specifically removing  
172 immune individuals (Ebinger et al., 2011). We also hypothesized that the FOI could change  
173 in 2012, as there was no management in the study population before brucellosis was detected.  
174 We therefore expected three periods, one before 2012, and two others between 2012 and  
175 2018.

176

## 177 **MATERIAL AND METHODS**

### 178 **Population management and monitoring**

179 The study area, ibex population and discovery of *B. melitensis* infection have been described  
180 previously (ANSES, 2015; Garin-Bastuji et al., 2014; Hars et al., 2013; Mailles et al., 2012;  
181 Marchand et al., 2017; Mick et al., 2014).

182 The estimates of the population size were: 567 individuals (95% Confidence Interval: [487-  
183 660]) in 2013, 310 [275-352] in 2014, 347 [290-421] in 2015, 272 [241-312] in 2016, 291  
184 [262-327] in 2017 and 374 [326-435] in 2018 (Calenge et al., 2021; Marchand et al., 2017).  
185 Between the beginning of the monitoring by CMR in October 2012 and summer 2018 (see  
186 Figure 1 for the timing of captures and recaptures), a total of 387 captures and recaptures  
187 have been performed (2012: 24, 2013: 57, 2014: 71, 2015: 125, 2016: 35, 2017: 27 and 2018:  
188 48 – Lambert et al., 2020, 2018; Marchand et al., 2017). For each individual, information on  
189 age (in years, by counting horn growth annuli, Michallet et al., 1988), sex, date of sampling  
190 and spatial location of capture were systematically recorded. Captured animals were blood-  
191 sampled by trained technical staff and serological tests were performed on serum samples.  
192 The serological antibody tests were performed according to requirements of the European  
193 Union for diagnosis of brucellosis in small ruminants and following standards of the World  
194 Organization of Animal Health (OIE). Four serological tests were performed in parallel in  
195 laboratory conditions: the Rose Bengal Test, the Complement Fixation Test, and the indirect  
196 and the competitive Enzyme Linked ImmunoSorbent Assays. Individuals were considered as  
197 seropositive when at least two of the tests were positive. Sensitivities and specificities of  
198 these four tests for the diagnosis of *B. melitensis* in small domestic ruminants are generally  
199 high: 75-100% and 97.6-100%, respectively (Blasco et al., 1994b, 1994a; Ferreira et al.,  
200 2003; Nielsen et al., 2004). Although they remain unknown in ibex, the sensitivity and  
201 specificity of the diagnosis protocol in ibex are considered high because of the use of  
202 multiple tests in parallel and few cases of inconsistent results (ANSES, 2015). As part of a  
203 test-and-remove program, captured individuals were either euthanized when they were  
204 seropositive, or marked and released if they were seronegative at the time of sampling. Since  
205 2015, the decision to euthanize ibex was based on the results of a rapid Lateral Flow  
206 Immune-chromatographic Assay (LFIA), available for direct use in the field before

207 confirmation by the other tests in the laboratory. The LFIA had been validated on ibex samples  
208 by the EU/OIE/FAO and National reference laboratory for animal brucellosis, showing very good  
209 correlation with the four laboratory tests (ANSES, 2014; Corde et al., 2014).

210 In addition to CMR monitoring and test-and-remove operations, culling operations were also  
211 implemented as part of the disease management strategy conducted by the French Authorities  
212 (Figure 1). In spring 2013, four individuals showing clinical signs (e.g., lameness or presence  
213 of visible gross lesions of the joints or the testes) were culled. In autumn 2013 and spring  
214 2014, 233 and 18 individuals estimated to be older than 5 years were culled, based on the  
215 observation that seroprevalence was significantly higher for this age class (Hars et al., 2013).

216 Non-selective culling of individuals that were never captured was also performed in autumn  
217 2015 ( $n=70$ ), autumn 2017 ( $n=5$ ) and spring 2018 ( $n=5$ ). The same antibody tests as in  
218 captured animals were performed on culled ones whenever blood samples of good quality  
219 were available. Among the 42 culled individuals for which results of serological tests were  
220 available, the serological status of culled animals was based on a single LFIA test in a few  
221 cases ( $n=12$ ). This was also the case for one captured animal in 2015, and two marked  
222 animals recaptured (all three with negative test results).

223

#### 224 **Cross-sectional and longitudinal datasets**

225 In total, cross-sectional serological data were available from 363 unmarked individuals tested  
226 between 2012 and 2018 (320 captured individuals, one found-dead individual and 42 culled  
227 individuals– 129 seropositive and 234 seronegative results; Table S1). The first dataset we  
228 used was therefore age-seroprevalence data from these unmarked individuals (Figure 2A,  
229 Table S1 and Figure S1).

230 Among the seronegative individuals that were marked and released, 50 were recaptured at  
231 least once during the study period and were tested again for antibodies against brucellosis.

232 The second dataset we used was therefore the follow up time (in days) between the first  
233 capture and the last recapture of marked animals. Because these animals were seronegative at  
234 the first capture, they either remained seronegative ( $n=46$ ) or became seropositive in the  
235 interval ( $n=4$  – Figure 2B and Figure S1). This type of data is also called “event time” data,  
236 where the event here would be the seroconversion from negative to positive. Individuals that  
237 seroconverted are “interval censored”, i.e., the event of interest occurred between the last  
238 negative test and the positive test, but the exact time is not known (Kleinbaum and Klein,  
239 2005). Conversely, individuals that remained seronegative at the last recapture are “right  
240 censored”, i.e., the event of interest did not occur yet and may or may not occur in the future  
241 (Kleinbaum and Klein, 2005).

242 The longitudinal event time dataset covered the period 2012-2018, from first captures to last  
243 recaptures (Figure 2B), while the cross-sectional age-seroprevalence dataset covered the  
244 period from 1998 to 2018 (see below and Figure S1). The sample size for the longitudinal  
245 dataset ( $n=50$ ) was also much smaller than for the cross-sectional dataset ( $n=363$ ), because in  
246 the study population, most captures targeted unmarked individuals, in an attempt to test new  
247 individuals and maximise chances to remove infected individuals (Calenge et al., 2021).  
248 Indeed, marked ibex have more chances to be seronegative, as they already were during their  
249 last capture in a more or less recent past (Calenge et al., 2021).

250

### 251 **Estimating the FOI using cross-sectional age-seroprevalence data**

252 The FOI  $\lambda(t)$  represents the rate at which susceptible individuals become infected per unit of  
253 time, at time  $t$  (Vynnycky and White, 2010), and can be calculated using the equation:  $\lambda(t) =$   
254  $c\nu \frac{I(t)}{N(t)}$ , where  $c$  is the contact rate,  $\nu$  is the probability that the contact leads to infection, and  
255  $\frac{I(t)}{N(t)}$  is the proportion of infectious individuals in the population at time  $t$  (Begon et al., 2002).

256 The FOI changes over time, although its average value remains unchanged over time in  
257 endemic situations.

258 If we were to follow over time a cohort of individuals born the same year, we would observe  
259 that, as the cohort ages, the proportion of individuals who have ever been infected increases  
260 (in our case, the proportion of seropositive individuals as we are using seropositivity as a  
261 proxy of past infection). A cross-sectional sample would produce a similar pattern, as animals  
262 would be of different ages and therefore would have experienced various exposure times  
263 (Heisey et al., 2006). This has led to the development of the ‘catalytic model’ (Muench,  
264 1934), that can be written as:

$$265 \quad z(a) = 1 - e^{-\lambda a}$$

266 where  $z(a)$  is the proportion ever infected at age  $a$  (in years), and  $\lambda$  is the average FOI (in  
267 years<sup>-1</sup>). The main assumptions are that the average FOI  $\lambda$  is independent of age and year,  
268 that infection is lifelong or confers lifelong immunity, that all individuals are born without  
269 infection, and that susceptible and infected animals have the same mortality rate (i.e., no  
270 infection-related mortality experienced by infected animals).

271 When antibodies remain detectable lifelong, this model can be fitted to observed age-  
272 seroprevalence data to estimate the average FOI. However, the limitations related to the  
273 model assumptions led to new developments over the years, dealing for instance with age-  
274 dependent FOI (see Hens et al., 2010 for a review).

275 In this study, we used the general FOI model developed by Heisey et al. (2006) that allows  
276 for the existence of infection-related mortality in infected animals and the influence of  
277 covariates  $X_1, \dots, X_n$  on the FOI  $\lambda$ , leading to the new equation:

$$278 \quad z(a) = \frac{1 - e^{-(\lambda-\mu)a}}{1 - \frac{\mu}{\lambda} e^{-(\lambda-\mu)a}}$$

279 where  $z(a)$  is the proportion of seropositive at age  $a$ ,  $\mu$  is the infection-related mortality  
280 (infection being brucellosis in our case) and  $\lambda$  is the average FOI with  $\lambda = \lambda_0 e^{\beta_1 X_1 + \dots + \beta_n X_n}$ ,  
281 where  $\lambda_0$  is the baseline FOI which is constant over age and time. Note that when  $\mu = 0$ , the  
282 equation simplifies to Muench's model:  $z(a) = 1 - e^{-\lambda a}$ . The model still assumes that all  
283 animals are born without infection, but can immediately leave this state and become positive  
284 (Heisey et al., 2006).

285 We tested for the existence of infection-related mortality by fitting this general FOI model to  
286 our age-seroprevalence data using a maximum likelihood approach and the R function  
287 `currentstatus.1` provided in Heisey et al. (2006). We took into account the effects of sex and  
288 socio-spatial unit, which were demonstrated to play a major role in explaining variation in  
289 brucellosis seroprevalence in the study ibex population (Lambert et al., 2020; Marchand et  
290 al., 2017). Indeed, it has been highlighted that females transmit the infection in ~90% of  
291 cases (Lambert et al., 2020) and that they are spatially structured in five subpopulations with  
292 contrasted seroprevalence levels, the units at the centre of the massif ("core area") having the  
293 highest seroprevalence levels (Marchand et al., 2017).

294 We also tested the assumption that  $\lambda$  is independent of age. First, we added age (as a  
295 quantitative variable) among the covariates (Table 1), even though, in this case, the function  
296 for  $z(a)$  would be incorrect, as it was obtained under the hypothesis that  $\lambda_0$  was independent  
297 of age. However, this step is useful as a diagnostic tool, as if age or a function of age as  
298 covariate improves the model fit, it means that this assumption should be revised and  
299 functions other than constant with age should be explored for the baseline FOI (Heisey et al.,  
300 2006). Second, we used the piecewise constant hazards approach developed by Heisey et al.  
301 (2006) to enable the use of age-varying models for the baseline FOI  $\lambda_0$  such as the Weibull,  
302 the Gompertz or the log-logistic models (Table S2).

303 Similarly, we added year of sampling (as a categorical variable) among the variables  
304 (Table 1), to test if the time-independence assumption holds (Heisey et al., 2006).  
305 For each type of model (constant FOI, diagnostic model with covariate year – YEAR,  
306 diagnostic model with covariate age – AGE, diagnostic model with covariate quadratic age –  
307 AGE<sup>2</sup>, diagnostic model with both AGE or AGE<sup>2</sup> and YEAR, Weibull, Log-logistic, Pareto,  
308 Gompertz), we fitted submodels including infection-related mortality ( $\mu$ ) or not, taking into  
309 account socio-spatial unit (UNIT) and sex (SEX) (Table 1 and Table S2). For each model, the  
310 number of parameters (degrees of freedom), the log-likelihood, the Akaike Information  
311 Criterion corrected for small sample sizes (AICc), and the difference between the AICc and  
312 the lowest AICc value ( $\Delta$ AICc) were computed. The Akaike Weights, which are relative  
313 model likelihoods normalized over the likelihoods of all possible submodels, were computed  
314 using the function `aictabCustom` of the *AICcmodavg* R package (Mazerolle, 2019). The  
315 Akaike weight can be regarded as the conditional probability given the data of being the best  
316 model among the set of possible submodels (Wagenmakers and Farrell, 2004). We selected a  
317 set of models for which the  $\Delta$ AICc was below two (Burnham et al., 2011; Burnham and  
318 Anderson, 2002).

319 Given that the selected models included the covariate year, we further explored the existence  
320 of temporal variation in the annual FOI by assuming a constant FOI with age but estimating  
321 different baseline FOI  $\lambda_0$  for one, two or three periods of time to test our hypothesis. We  
322 therefore assumed that the FOI could be considered as time-independent on average for  
323 several years. This remains an approximation, but it allowed us to estimate temporal changes  
324 in the FOI while staying in the framework of the general FOI model.

325 Because births in ibex take place between the end of May and the beginning of July, we  
326 considered FOI of year  $n$  to start from July 1<sup>st</sup> year  $n-1$  up to July 1<sup>st</sup> year  $n$ . Based on age and  
327 years of sampling, individuals were born between 1998 and 2017. Because the monitoring



328 and management interventions started in 2012, the years 1998-2012 were always included in  
329 the first period. We compared all possible models with two or three periods, using all  
330 possible threshold years or couple of threshold years between 2012 and 2018 to obtain  
331 different periods.

332 For each explanatory variable of the final model, results were expressed as Hazard Ratios  
333 (HR). The hazard function is expressed as  $\lambda = \lambda_0 e^{\beta_1 X_1 + \dots + \beta_n X_n}$ . For a single qualitative  
334 covariate  $X$  that is either present ( $X = 1$ ) or absent ( $X = 0$ ), the hazard (FOI) is  $\lambda = \lambda_0 e^\beta$  for  
335  $X = 1$ , and  $\lambda = \lambda_0$  for  $X = 0$ . Therefore, the hazard ratio is  $HR = \lambda_0 e^\beta / \lambda_0 = e^\beta$ . Similarly,  
336 hazard ratios can be expressed for qualitative covariates with multiple categories, and for an  
337 increase in one unit of a quantitative covariate. Hazard ratios have a similar interpretation as  
338 odds ratios (Dohoo et al., 2009). Profile likelihood 95% confidence interval around each  
339 estimated coefficient were computed (Therneau and Grambsch, 2000).

340

#### 341 **Estimating the FOI using longitudinal event time data**

342 As we were interested in the time until the occurrence of infection (“survival time”), we  
343 analysed our longitudinal event time dataset using survival models. We note  $T$  the random  
344 variable representing the time between the first capture and the infection event, in days. The  
345 survival function is the probability that infection has not yet occurred by time  $t$  (follow up  
346 time):  $Surv(t) = P(T \geq t)$ . Note that in our data, animals were captured for the first time at  
347 different dates, meaning that the follow up time had different origins and therefore was not  
348 equivalent to the calendar time (Figure S1).

349 The survival function can be related to the hazard function  $\lambda(t)$ , i.e., the rate at which the  
350 event occurs per unit time, at time  $t$ , using the following equation (Kleinbaum and Klein,  
351 2005):

$$352 \quad Surv(t) = e^{-\int_0^t \lambda(u) du}$$

353 In our case, the event of interest is infection, and therefore the hazard function is the FOI.  
354 Note that if we assume a constant hazard risk (FOI) with follow up time, the hazard function  
355 is  $\lambda(t) = \lambda$ , and the corresponding survival function is  $Surv(t) = e^{-\lambda t}$  (exponential model).  
356 We tested the assumption that the hazard function is independent of age and calendar time,  
357 using the exponential model from the function *flexsurvreg* of the *flexsurv* R package  
358 (Jackson, 2016). We tested for the effects of age at last recapture (as a continuous variable,  
359 calculated as the age at first capture incremented by the number of years between first capture  
360 and last recapture) and year of recapture (as a categorical variable). Because of small sample  
361 sizes, we had to group years 2014 and 2015 on the one hand and 2016 to 2018 on the other  
362 hand. We were not able to take into account the effects of sex and socio-spatial unit because  
363 of small sample sizes.

364 Given the results of the exponential model, we also explored the existence of variations with  
365 calendar time, fitting models assuming two periods between 2012 and 2018 characterised by  
366 two different FOI (independent of age and follow up time – Figure 2B). We fitted models  
367 considering two periods, using all possible monthly threshold dates between November 2012  
368 and June 2018, and compared them to the model considering a constant FOI.

369

## 370 **RESULTS**

### 371 **Force of infection estimated from cross-sectional age-seroprevalence data**

372 Among the twelve diagnostic models taking into account the effect of SEX and UNIT, all  
373 models with  $\Delta AICc < 2$  included the variable year, which suggests that the assumption of a  
374 time-independent FOI is not appropriate (Table 1; see also parameter estimates in Table S3).  
375 Models 9, 11 and 12 also included an age effect (Table 1). However, the effect sizes of linear  
376 or quadratic age were small, and adding these effects to model 3 including the variable year  
377 did not significantly improve model fit (Likelihood Ratio Tests:  $p=0.10$  and  $p=0.09$ ,

378 respectively). For completeness, we fitted several models of age-varying FOI using a  
379 piecewise constant hazards approach (models 13-20, Table S2). None of these models had a  
380 better AICc than model 3, which does not support variation of the FOI with age.  
381 Two models (4 and 12) with  $\Delta\text{AICc} < 2$  included infection-related mortality (Table 1). The  
382 effect sizes of the infection-related mortality in models 4 and 12 were small (Table S3), and  
383 adding infection-related mortality  $\mu$  to model 3 or to model 11 did not significantly improve  
384 model fit (Likelihood Ratio Test:  $p=0.13$  and  $p=0.52$ , respectively).  
385 Given that all models with  $\Delta\text{AICc} < 2$  included the variable year, we further explored the  
386 existence of temporal variation in the annual FOI by assuming a constant FOI with age and  
387 no infection-related mortality, but estimating different baseline FOI  $\lambda_0$  for one (as a reference  
388 for no temporal variation), two or three periods of time.  
389 The model with the lowest AICc (374.96; model 10 in Table S4) was obtained when  
390 considering three periods, with 2012 and 2015 as threshold years (Figure 3A and Table S4),  
391 and improved model fit compared to the model without temporal variation (AICc = 33.09,  
392  $\Delta\text{AICc} = 8.13$  with model 10). Baseline FOI estimates and hazard ratios for the effects of  
393 SEX and UNIT are provided in Table S5: the FOI was highest in the second period, and  
394 lowest in the third period; it was higher for females than males, and for the socio-spatial units  
395 at the centre of the massif, where the seroprevalence levels are the highest. The average FOI  
396 over the whole population (from the same model with three periods but without effects of  
397 SEX and UNIT) was estimated to be  $0.069 \text{ year}^{-1}$  [0.046–0.097] for the period 1998-2012,  
398  $0.115 \text{ year}^{-1}$  [0.074–0.160] for the period 2012-2015 and  $0.016 \text{ year}^{-1}$  [0.001–0.057] for the  
399 period 2015-2018 (Figure 3B). A very similar model was obtained when considering three  
400 periods but with 2012 and 2014 as threshold years (Tables S4 and S5, Figure S2).

401

402 **Force of infection estimated from longitudinal event time data**

403 Using the exponential model (constant baseline hazard) to fit our event time data collected on  
404 marked animals, we found no significant effect of the variable AGE ( $HR_{\text{per year}} = 0.81$  [0.54-  
405 1.20],  $p=0.28$ ), but a significant effect of the variable YEAR ( $HR_{2014-2015 \text{ vs } 2016-2018} = 0.095$   
406 [0.009-0.92],  $p=0.043$ ).

407 These results did not support variation of the FOI with age. However, given the significance  
408 of the variable YEAR, we further explored the existence of temporal variations in the FOI by  
409 fitting a model with two different periods on the calendar time, where individuals were  
410 submitted to different constant FOI before and after threshold dates. Among models  
411 considering all possible monthly threshold dates between November 2012 and June 2018, the  
412 best models ( $\Delta AICc < 2$ ) were obtained when considering two periods with a threshold date  
413 between July 2014 and December 2015 (Figure 3C). The model with the lowest AICc was  
414 obtained when considering a threshold date in March 2015 ( $AICc = 30.72$  – Figure 3C) and  
415 improved the model fit compared to the simple exponential model without temporal  
416 variations ( $AICc = 34.30$ ,  $\Delta AICc = 3.58$ ). The FOI was estimated to be higher for the first  
417 period ( $0.086 \text{ year}^{-1}$  [0.015–0.193]) than for the second period ( $0$  [0–0.030] – Figure 3D).

418

## 419 **DISCUSSION**

420 The aim of this study was to estimate the FOI of brucellosis in the wild Alpine ibex  
421 population of the Bargy massif (France) between 2012 and 2018. This measure of  
422 transmission intensity could help assess changes in transmission dynamics after management  
423 interventions started in 2012, as a complement to existing seroprevalence studies (Calenge et  
424 al., 2021; Marchand et al., 2017). Two massive culling operations were implemented in the  
425 population in 2013 and 2015. In addition, test-and-remove operations were performed during  
426 captures every year since 2012, with particularly high number of captures in 2015. We used  
427 two different datasets: age-seroprevalence data obtained from culling or first captures

428 operations ( $n=363$ ), and event time data, derived from recaptures of marked animals ( $n=50$ ).  
429 In both datasets, the model selection process supported an effect of time on the FOI, and  
430 returned estimates supporting a potential decrease of the FOI between mid-2014 and late  
431 2015. The force of infection was estimated to be reduced from  $0.115 \text{ year}^{-1}$  [0.074–0.160] to  
432  $0.016 \text{ year}^{-1}$  [0.001–0.057] in the age-seroprevalence data.  
433 Longitudinal samplings are difficult to obtain in wild populations and are therefore often not  
434 available (Gilbert et al., 2013). In our case, data from recaptured animals were available, but  
435 the sample size remained relatively low (only four seropositive among 50 recaptured  
436 animals), leading to large confidence intervals in the estimates of the FOI (e.g. [0.015–0.193]  
437  $\text{year}^{-1}$  for 2012-2015). Although a higher number of recaptures may have provided a more  
438 complete dataset, it would have had negative impact in terms of disease management. The  
439 total number of captures each year being constrained for logistical reasons, focusing captures  
440 on already marked animals would have led to less animals being captured for the first time,  
441 and thus less seropositive animals being removed from the population. When management  
442 actions and disease surveillance both rely on the same field actions, a compromise has to be  
443 found between both objectives that may lead to gather less relevant surveillance data. In such  
444 cases where longitudinal data are absent or scarce because of practical or management  
445 reasons, the derivation of the FOI from cross-sectional serological data, more frequently  
446 collected in wildlife, is a useful complementary approach to gain insights into the  
447 epidemiological dynamics as we illustrated in our study.

448

#### 449 **Model assumptions and infection-related mortality**

450 In both FOI models of cross-sectional and longitudinal data, the main assumption is the  
451 independence of the FOI with age. We did not find any support for age-dependency in our  
452 datasets (Table 1).

453 Estimating the FOI from age-prevalence data also had the advantage of bringing insights on  
454 brucellosis-related mortality, for which we did not find strong evidence (Table 1). Our results  
455 did not detect brucellosis-induced mortality in ibex, similar to studies in bison (Fuller et al.,  
456 2007; Joly and Messier, 2005) or elk (Benavides et al., 2017).

457 We also postulated that the serological test has perfect sensitivity and specificity: due to the  
458 use of multiple serological assays, previous studies estimated the sensitivity of diagnosis  
459 protocol to be around 95%, with perfect specificity (expert assumption in ANSES, 2015;  
460 Lambert et al., 2020). Test failure thus does not appear to be a high source of bias, however,  
461 in the case of lower quality tests, other modelling approaches could be investigated (Bollaerts  
462 et al., 2012; Buzdugan et al., 2017). A few individuals in our datasets only had results from  
463 the rapid LFIA test used in the field (see Material and Methods). The analyses produced  
464 qualitatively and quantitatively similar results when using reduced datasets without these  
465 individuals (not shown).

466 In a former study, seroprevalence was found to decrease in old individuals, especially in  
467 males (Marchand et al., 2017). It was hypothesized that this phenomenon could be explained  
468 either by a lower survival rates or by lower probabilities to test positive in older individuals  
469 infected by brucellosis (Marchand et al., 2017). We did not find strong evidence for  
470 infection-related mortality, but we cannot exclude a decrease of antibody levels under  
471 detectable levels as the animals age, which is difficult to reveal using seroprevalence data  
472 (Heisey et al., 2006) (but see Benavides et al., 2017). Indeed, antibody titres measured by the  
473 Complement Fixation Test appeared to decrease with age (Figure S3) (Lambert et al., 2018).  
474 However, as high Complement Fixation Test titres are associated with active infections  
475 (Durán-Ferrer et al., 2004), which are less often observed in old ibex (Lambert et al., 2018),  
476 this may not reflect the antibody levels measured by the other serological tests used in the  
477 study population. Unfortunately, the data for these other tests was not readily available.

478 Therefore, further studies investigating antibodies persistence with age or age-related  
479 variation in test performance is needed to firmly conclude about these results. Moreover,  
480 acquiring knowledge on antibody kinetics in ibex could have the additional advantage of  
481 developing alternative approaches that improve the derivation of the FOI by estimating the  
482 time since infection using individual data on antibody titres (Borremans et al., 2016; Pepin et  
483 al., 2017).

484 Finally, we also assumed, as classically done in catalytic models, that all individuals are born  
485 without infection. In domestic ruminants, congenital transmission of brucellosis exists but is  
486 rare, i.e., in only ca. 5% of kids born from infectious mothers (FAO and WHO, 1986;  
487 Godfroid et al., 2013). This transmission route is also suspected in ibex (Lambert et al.,  
488 2018), but is probably as uncommon as in domestic ruminants. Moreover, individuals  
489 congenitally infected seroconvert and become infectious only at the age of sexual maturity  
490 (Plommet et al., 1973). Therefore, we assumed that the effects would be negligible on our  
491 results.

492

### 493 **Temporal variation of the force of infection**

494 In Marchand et al. (2017), statistical analyses of seroprevalence data from 2012 to 2015 did  
495 not detect changes in seroprevalence before and after the mass culling of autumn 2013. Using  
496 a Bayesian approach to estimate seroprevalence, Calenge et al. (2021) found a strong  
497 decrease in the overall seroprevalence between 2015 and 2016. In the present study, both  
498 datasets suggest that the FOI decreased between mid-2014 and late 2015 (Figure 3), which  
499 could explain the seroprevalence drop also observed. Our results support a decrease in  
500 transmission during the study period, probably due to management interventions and natural  
501 changes in the infection dynamics. Quantitatively, seroprevalence was halved between 2015

502 and 2016 (Calenge et al., 2021), while FOI as estimated using age-seroprevalence data was  
503 divided by approximately ten at the same period ( $0.115 \text{ year}^{-1}$  vs.  $0.016 \text{ year}^{-1}$ ).

504 In the process of estimating the seroprevalence in marked animals, Calenge et al. (2021) also  
505 estimated the FOI exerted on marked females in the core area, assuming it was proportional  
506 to the proportion of seropositive unmarked ibex with an active infection among the  
507 population of females in the core area. This analysis showed a decrease between 2015 and  
508 2016, with estimates that were consistent with the values obtained with our longitudinal event  
509 time dataset where we did not make such assumptions on the relation between the FOI and  
510 active infections in the population (Calenge et al., 2021). Finally, an individual-based,  
511 stochastic SEIR mechanistic model, also showed a decrease in incidence between 2013 and  
512 2016 in the whole population, and a low increase of new cases between 2016 and 2018.

513 However, this increase in new cases was associated with a similar increase of population size  
514 which could indicate a constant incidence rate (Lambert et al., 2020). Therefore, the temporal  
515 dynamics appear to be consistent between the different approaches. The approach developed  
516 here has the advantage of being much simpler than the mechanistic model, and of bringing  
517 complementary information to previous seroprevalence analyses which can inform  
518 management decisions.

519 The FOI did not decrease between 2012 and mid-2014, even though the population size was  
520 halved due to massive culling operations in autumn 2013-spring 2014. On the contrary, our  
521 results showed that the FOI increased in 2012, which could be related to management  
522 interventions or undetermined natural changes in infection dynamics, such as abortion events  
523 that play a critical role in brucellosis transmission. We also demonstrated a decrease in the  
524 FOI in 2014 or 2015, which is probably related to management interventions. At the same  
525 time, test-and-remove during captures replaced massive culling as the main component of  
526 management strategies. However, our analyses cannot disentangle the effects of each



527 management intervention that were implemented between 2012 and 2015, and the intense  
528 test-and-remove operation of 2015 could have benefited from cumulative effects from the  
529 previous years. These hypothesis could be tested in the future using the stochastic SEIR  
530 mechanistic model developed in Lambert *et al.* (2020).

531 Unfortunately, we could not test for differences in temporal variation in the FOI between  
532 socio-spatial units (interactions between calendar time and spatial unit), due to low sample  
533 sizes. In a context where the FOI increases, such interactions could help to identify hotspots  
534 of infection, i.e., spatial units where the FOI increases faster, or simply different course of  
535 epidemics in the different spatial units (Heisey et al., 2010). Conversely, in a context of  
536 decreasing FOI such as in our study, interactions between calendar time and spatial units  
537 could reveal socio-spatial units with the sharpest decrease of FOI, which could correspond to  
538 areas where the management interventions are the most effective. In particular, management  
539 interventions since 2016 have been targeted towards the socio-spatial units at the centre of  
540 the massif, where the seroprevalence levels (and the FOI as demonstrated here) are the  
541 highest. It would therefore be interesting in the future to see if the FOI decreased faster in  
542 those units, and to test whether the FOI keeps decreasing in the units with less management  
543 interventions.

544

#### 545 **Force of infection in marked and unmarked animals**

546 Our study aimed to compare the FOI between marked and unmarked animals. Most captures  
547 targeted unmarked individuals to maximise chances to remove seropositive individuals  
548 (Calenge et al., 2021). As a result, only a small number of marked animals were recaptured  
549 and a few cases of seroconversion were observed, leading to high uncertainty around the  
550 estimates of the FOI from the longitudinal event time dataset. Despite this uncertainty, the  
551 estimates from both datasets are comparable in each period (2012-2015 and 2015-2018) and

552 support a potential decrease of the FOI of similar magnitude. These results indicate that the  
553 FOI is similar in susceptible individuals from both groups, and therefore that marked  
554 individuals have similar patterns of exposure as unmarked individuals. Assuming similar  
555 FOI, a unified framework, using marked and unmarked animals, could be then further  
556 investigated to gain in precision of FOI estimates, even with relatively small longitudinal  
557 sample sizes, and better evaluate the requested sampling size of the monitoring (Gamble et  
558 al., 2020). An integrated framework combining cross sectional and longitudinal capture-  
559 recapture setups would also decrease the needed sample size in comparison with separate  
560 approaches (Gamble et al., 2020). It is worth noting that both our cross-sectional and  
561 longitudinal datasets are interval censored event time dataset: from birth to the positive test  
562 for the age-seroprevalence data or from negative to positive test for the longitudinal data.  
563 Therefore, future research could use both datasets in the same analyses, which will allow to  
564 increase the statistical power and to use more complex models of time-varying FOI.

565

## 566 **CONCLUSIONS**

567 In conclusion, using two distinct methods and datasets, our analyses revealed a decrease in  
568 the FOI between mid-2014 and late 2015, possibly as a result of the successive management  
569 operations implemented since 2012. Estimating the FOI can therefore provide valuable  
570 insights on the epidemiological dynamics, as a complement to classical seroprevalence  
571 analyses. This is especially the case in the context of ongoing disease management  
572 interventions in wildlife populations, where the FOI is expected to change. Insights on the  
573 effect of managing on transmission dynamics can be obtained using rather simple models as  
574 we did here, provided that there is no strong evidence that the basic assumptions are violated.  
575 Comparing two different sources of data, cross-sectional and cohort studies, with appropriate  
576 models may contribute to provide robust inference about the FOI. Nonetheless, it is possible

577 to derive FOI estimates from cross-sectional serological data only, which are the most  
578 commonly available in wild populations.

579

## 580 **Acknowledgments**

581 The authors thank the two anonymous reviewers whose comments helped improve and  
582 clarify this manuscript. The authors warmly thank all the field staff who performed  
583 monitoring and management of the Alpine ibex population. They also thank the scientific  
584 experts of the ANSES working groups on brucellosis of Alpine ibex in the Bargy massif, as  
585 well as Charlotte Dunoyer (ANSES; UERSABA’s chief unit) and Jean Hars (ONCFS). This  
586 study was coordinated by the French Biodiversity Agency (Office Français de la Biodiversité,  
587 OFB, formerly Hunting and Wildlife Agency, Office National de la Chasse et de la Faune  
588 Sauvage, ONCFS). This work was performed within the framework of the LABEX  
589 ECOFECT (ANR-11-LABX-0048) of Université de Lyon and of the program  
590 “Investissements d’Avenir” (ANR- 11-IDEX-0007) operated by the French National  
591 Research Agency (ANR).

592

## 593 **Funding**

594 This work was co-supported by the French Ministry of Research, the French Biodiversity  
595 Agency (Office Français de la Biodiversité, OFB, formerly Hunting and Wildlife Agency,  
596 Office National de la Chasse et de la Faune Sauvage, ONCFS), ANSES, and VetAgroSup  
597 Lyon. The funders of the study had no role in the study design, the collection, analysis and  
598 interpretation of data, the writing of the report, or the decision to submit the article for  
599 publication.

600

601 **Data availability statement:** The raw data required to reproduce the above findings are  
602 available from the authors on reasonable request.

603

604 **Declarations of interest:** none

605 **CRedit author statement**

606 **Sébastien Lambert:** Conceptualisation, Methodology, Software, Formal Analysis, Data  
607 Curation, Writing – Original Draft, Writing – Review & Editing, Visualisation. **Emmanuelle**  
608 **Gilot-Fromont, Anne Thébault:** Conceptualisation, Methodology, Writing – Review &  
609 Editing, Supervision. **Carole Toïgo, Sophie Rossi:** Conceptualisation, Investigation, Writing  
610 – Review & Editing, Supervision. **Pascal Marchand, Elodie Petit:** Investigation, Data  
611 Curation, Writing – Review & Editing.

612

## 613 **LITERATURE CITED**

- 614 ANSES, 2015. Mesures de maîtrise de la brucellose chez les bouquetins du Bargy. Rapport  
615 ANSES.
- 616 ANSES, 2014. Note d'appui scientifique et technique de l'ANSES relatif au dépistage des  
617 bouquetins infectés de brucellose sur le terrain. Rapport ANSES.
- 618 Artois, M., Bengis, R., Delahay, R.J., Duchêne, M.-J., Duff, J.P., Ferroglia, E., Gortázar, C.,  
619 Hutchings, M.R., Kock, R., Leighton, F.A., Mörner, T., Smith, G.C., 2009. Wildlife  
620 disease surveillance and monitoring, in: Management of Disease in Wild Mammals.  
621 pp. 187–214.
- 622 Begon, M., Bennett, M., Bowers, R.G., French, N.P., Hazel, S.M., Turner, J., 2002. A  
623 clarification of transmission terms in host-microparasite models: numbers, densities  
624 and areas. *Epidemiol. Infect.* 129, 147–153.
- 625 Benavides, J.A., Caillaud, D., Scurlock, B.M., Maichak, E.J., Edwards, W.H., Cross, P.C.,  
626 2017. Estimating loss of *Brucella abortus* antibodies from age-specific serological  
627 data in elk. *EcoHealth* 14, 234–243. <https://doi.org/10.1007/s10393-017-1235-z>
- 628 Blasco, J.M., Garin-Bastuji, B., Marin, C.M., Gerbier, G., Fanlo, J., Jimenez de Bagues,  
629 M.P., Cau, C., 1994a. Efficacy of different Rose Bengal and complement fixation  
630 antigens for the diagnosis of *Brucella melitensis* infection in sheep and goats. *Vet.*  
631 *Rec.* 134, 415–420. <https://doi.org/10.1136/vr.134.16.415>
- 632 Blasco, J.M., Marin, C.M., Jiménez-de-Bagués, M., Barberán, M., Hernández, A., Molina, L.,  
633 Velasco, J., Diaz, R., Moriyon, I., 1994b. Evaluation of allergic and serological tests  
634 for diagnosing *Brucella melitensis* infection in sheep. *J. Clin. Microbiol.* 32, 1835–  
635 1840.

- 636 Bollaerts, K., Aerts, M., Shkedy, Z., Faes, C., Van der Stede, Y., Beutels, P., Hens, N., 2012.  
637 Estimating the population prevalence and force of infection directly from antibody  
638 titres. *Stat. Modelling* 12, 441–462. <https://doi.org/10.1177/1471082X12457495>
- 639 Borremans, B., Hens, N., Beutels, P., Leirs, H., Reijnders, J., 2016. Estimating time of  
640 infection using prior serological and individual information can greatly improve  
641 incidence estimation of human and wildlife infections. *PLOS Comput. Biol.* 12,  
642 e1004882. <https://doi.org/10.1371/journal.pcbi.1004882>
- 643 Burnham, K.P., Anderson, D.R., 2002. *Model selection and multimodel inference: a practical  
644 information-theoretic approach*, 2nd ed. ed. Springer, New York.
- 645 Burnham, K.P., Anderson, D.R., Huyvaert, K.P., 2011. AIC model selection and multimodel  
646 inference in behavioral ecology: some background, observations, and comparisons.  
647 *Behav. Ecol. Sociobiol.* 65, 23–35. <https://doi.org/10.1007/s00265-010-1029-6>
- 648 Buzdugan, S.N., Vergne, T., Grosbois, V., Delahay, R.J., Drewe, J.A., 2017. Inference of the  
649 infection status of individuals using longitudinal testing data from cryptic  
650 populations: towards a probabilistic approach to diagnosis. *Sci. Rep.* 7, 1–11.  
651 <https://doi.org/10.1038/s41598-017-00806-4>
- 652 Calenge, C., Lambert, S., Petit, E., Thébault, A., Gilot-Fromont, E., Toïgo, C., Rossi, S.,  
653 2021. Estimating disease prevalence and temporal dynamics using biased capture  
654 serological data in a wildlife reservoir: the example of brucellosis in Alpine ibex  
655 (*Capra ibex*). *Prev. Vet. Med.* 187, 1–12.  
656 <https://doi.org/10.1016/j.prevetmed.2020.105239>
- 657 Carvalho Neta, A.V., Mol, J.P.S., Xavier, M.N., Paixão, T.A., Lage, A.P., Santos, R.L., 2010.  
658 Pathogenesis of bovine brucellosis. *Vet. J.* 184, 146–155.  
659 <https://doi.org/10.1016/j.tvjl.2009.04.010>
- 660 Corde, Y., Drapeau, A., Game, Y., Maucci, E., Hars, J., Jaÿ, M., Garin-Bastuji, B., 2014. A  
661 rapid test for evaluating *B. melitensis* infection prevalence in an Alpine ibex (*Capra  
662 ibex*) reservoir in the French Alps. Presented at the Brucellosis 2014 International  
663 Research Conference, including the 67th Annual Brucellosis Research Meeting,  
664 Berlin, Germany, p. 221.
- 665 Courtejoie, N., Salje, H., Durand, B., Zanella, G., Cauchemez, S., 2018. Using serological  
666 studies to reconstruct the history of bluetongue epidemic in French cattle under  
667 successive vaccination campaigns. *Epidemics* 25, 54–60.  
668 <https://doi.org/10.1016/j.epidem.2018.05.005>
- 669 Dohoo, I., Martin, W., Stryhn, H., 2009. *Veterinary epidemiologic research*, 2. ed. ed. VER  
670 Inc, Charlottetown, Canada: University of Prince Edward Island.
- 671 Durán-Ferrer, M., León, L., Nielsen, K., Caporale, V., Mendoza, J., Osuna, A., Perales, A.,  
672 Smith, P., De-Frutos, C., Gómez-Martín, B., Lucas, A., Chico, R., Delgado, O.D.,  
673 Escabias, J.C., Arrogante, L., Díaz-Parra, R., Garrido, F., 2004. Antibody response  
674 and antigen-specific gamma-interferon profiles of vaccinated and unvaccinated  
675 pregnant sheep experimentally infected with *Brucella melitensis*. *Vet. Microbiol.* 100,  
676 219–231. <https://doi.org/10.1016/j.vetmic.2004.02.008>
- 677 Ebinger, M., Cross, P., Wallen, R., White, P.J., Treanor, J., 2011. Simulating sterilization,  
678 vaccination, and test-and-remove as brucellosis control measures in bison. *Ecol. Appl.*  
679 21, 2944–2959. <https://doi.org/10.1890/10-2239.1>
- 680 European Commission, 2001. *Brucellosis in sheep and goats (Brucella melitensis)* (No.  
681 SANCO.C.2/AH/R23/2001). Health & Consumer Protection Directorate-General,  
682 Brussels, Belgium.
- 683 Farrington, C.P., 1990. Modelling forces of infection for measles, mumps and rubella. *Stat.  
684 Med.* 9, 953–967. <https://doi.org/10.1002/sim.4780090811>

- 685 Ferreira, A.C., Cardoso, R., Travassos Dias, I., Mariano, I., Belo, A., Rolão Preto, I.,  
686 Manteigas, A., Pina Fonseca, A., Corrêa De Sá, M.I., 2003. Evaluation of a modified  
687 Rose Bengal test and an indirect Enzyme-Linked Immunosorbent Assay for the  
688 diagnosis of *Brucella melitensis* infection in sheep. *Vet. Res.* 34, 297–305.  
689 <https://doi.org/10.1051/vetres:2003005>
- 690 Forbes, L.B., Tessaro, S.V., Lees, W., 1996. Experimental studies on *Brucella abortus*  
691 in moose (*Alces alces*). *J. Wildl. Dis.* 32, 94–104. [https://doi.org/10.7589/0090-3558-](https://doi.org/10.7589/0090-3558-32.1.94)  
692 [32.1.94](https://doi.org/10.7589/0090-3558-32.1.94)
- 693 Freycon, P., Game, Y., Hars, J., Gilot-Fromont, E., 2017. Lesional aspects of *Brucella*  
694 *melitensis* in *Capra ibex*. *Bull. Acad. Vét. France* 170, 1–5.  
695 <https://doi.org/10.4267/2042/62276>
- 696 Fuller, J.A., Garrott, R.A., White, P.J., Aune, K.E., Roffe, T.J., Rhyan, J.C., 2007.  
697 Reproduction and survival of Yellowstone bison. *J. Wildl. Manage.* 71, 2365–2372.  
698 <https://doi.org/10.2193/2006-201>
- 699 Gamble, A., Garnier, R., Chambert, T., Gimenez, O., Boulinier, T., 2020. Next-generation  
700 serology: integrating cross-sectional and capture–recapture approaches to infer  
701 disease dynamics. *Ecology* 101, e02923. <https://doi.org/10.1002/ecy.2923>
- 702 Garin-Bastuji, B., Hars, J., Drapeau, A., Cherfa, M.-A., Game, Y., Le Horgne, J.M.,  
703 Rautureau, S., Maucci, E., Pasquier, J.J., Jaÿ, M., Mick, V., 2014. Reemergence of  
704 *Brucella melitensis* in wildlife, France. *Emerg. Infect. Dis* 20, 1570–1571.  
705 <https://doi.org/10.3201/eid2009.131517>
- 706 Gilbert, A.T., Fooks, A.R., Hayman, D.T.S., Horton, D.L., Müller, T., Plowright, R., Peel,  
707 A.J., Bowen, R., Wood, J.L.N., Mills, J., Cunningham, A.A., Rupprecht, C.E., 2013.  
708 Deciphering serology to understand the ecology of infectious diseases in wildlife.  
709 *EcoHealth* 10, 298–313. <https://doi.org/10.1007/s10393-013-0856-0>
- 710 Godfroid, J., Nielsen, K., Saegerman, C., 2010. Diagnosis of brucellosis in livestock and  
711 wildlife. *Croat. Med. J.* 51, 296–305. <https://doi.org/10.3325/cmj.2010.51.296>
- 712 Gorsich, E.E., Ezenwa, V.O., Cross, P.C., Bengis, R.G., Jolles, A.E., 2015. Context-  
713 dependent survival, fecundity and predicted population-level consequences of  
714 brucellosis in African buffalo. *J. Anim. Ecol.* 84, 999–1009.  
715 <https://doi.org/10.1111/1365-2656.12356>
- 716 Hars, J., Rautureau, S., Jaÿ, M., Game, Y., Gauthier, D., Herbaux, J.P., Le Horgne, J.M.,  
717 Maucci, E., Pasquier, J.J., Vaniscotte, A., Mick, V., Garin-Bastuji, B., 2013. Un foyer  
718 de brucellose chez les ongulés sauvages du massif du Bargy en Haute-Savoie. *Bull.*  
719 *Epidémiol. Santé Anim. Alim.* 60, 2–7.
- 720 Heisey, D.M., Joly, D.O., Messier, F., 2006. The fitting of general force-of-infection models  
721 to wildlife disease prevalence data. *Ecology* 87, 2356–2365.  
722 [https://doi.org/10.1890/0012-9658\(2006\)87\[2356:TFOGFM\]2.0.CO;2](https://doi.org/10.1890/0012-9658(2006)87[2356:TFOGFM]2.0.CO;2)
- 723 Heisey, D.M., Osnas, E.E., Cross, P.C., Joly, D.O., Langenberg, J.A., Miller, M.W., 2010.  
724 Linking process to pattern: estimating spatiotemporal dynamics of a wildlife epidemic  
725 from cross-sectional data. *Ecol. Monogr.* 80, 221–240. [https://doi.org/10.1890/09-](https://doi.org/10.1890/09-0052.1)  
726 [0052.1](https://doi.org/10.1890/09-0052.1)
- 727 Hens, N., Aerts, M., Faes, C., Shkedy, Z., Lejeune, O., Van Damme, P., Beutels, P., 2010.  
728 Seventy-five years of estimating the force of infection from current status data.  
729 *Epidemiol. Infect.* 138, 802–812. <https://doi.org/10.1017/S0950268809990781>
- 730 Jackson, R., 2016. Flexsurv: a platform for parametric survival modeling in R. *J. Stat. Softw.*  
731 70, 1–33. <https://doi.org/10.18637/jss.v070.i08>
- 732 Joly, D.O., Messier, F., 2005. The effect of bovine tuberculosis and brucellosis on  
733 reproduction and survival of wood bison in Wood Buffalo National Park. *J. Anim.*  
734 *Ecol.* 74, 543–551. <https://doi.org/10.1111/j.1365-2656.2005.00953.x>

735 Joseph, M.B., Mihaljevic, J.R., Arellano, A.L., Kueneman, J.G., Preston, D.L., Cross, P.C.,  
736 Johnson, P.T.J., 2013. Taming wildlife disease: bridging the gap between science and  
737 management. *J. Appl. Ecol.* 50, 702–712. <https://doi.org/10.1111/1365-2664.12084>  
738 Katzelnick, L.C., Ben-Shachar, R., Mercado, J.C., Rodriguez-Barraquer, I., Elizondo, D.,  
739 Arguello, S., Nuñez, A., Ojeda, S., Sanchez, N., Mercado, B.L., Gresh, L., Burger-  
740 Calderon, R., Kuan, G., Gordon, A., Balsmeda, A., Harris, E., 2018. Dynamics and  
741 determinants of the force of infection of dengue virus from 1994 to 2015 in Managua,  
742 Nicaragua. *PNAS* 115, 10762–10767. <https://doi.org/10.1073/pnas.1809253115>  
743 Keiding, N., 1991. Age-specific incidence and prevalence: a statistical perspective. *J. R. Stat.*  
744 *Soc. Ser. A Stat. Soc.* 154, 371–412. <https://doi.org/10.2307/2983150>  
745 Kleinbaum, D.G., Klein, M., 2005. *Survival analysis: a self-learning text*, 2. ed. ed, Statistics  
746 for biology and health. Springer, New York, NY.  
747 Lambert, S., Gilot-Fromont, E., Freycon, P., Thébault, A., Game, Y., Toïgo, C., Petit, E.,  
748 Barthe, M.-N., Reynaud, G., Jaÿ, M., Garin-Bastuji, B., Ponsart, C., Hars, J., Rossi,  
749 S., 2018. High shedding potential and significant individual heterogeneity in  
750 naturally-infected Alpine ibex (*Capra ibex*) with *Brucella melitensis*. *Front.*  
751 *Microbiol.* 9, 1–15. <https://doi.org/10.3389/fmicb.2018.01065>  
752 Lambert, S., Gilot-Fromont, E., Toïgo, C., Marchand, P., Petit, E., Garin-Bastuji, B.,  
753 Gauthier, D., Gaillard, J.-M., Rossi, S., Thébault, A., 2020. An individual-based  
754 model to assess the spatial and individual heterogeneity of *Brucella melitensis*  
755 transmission in Alpine ibex. *Ecol. Modell.* 425, 109009.  
756 <https://doi.org/10.1016/j.ecolmodel.2020.109009>  
757 le Roex, N., Cooper, D., van Helden, P.D., Hoal, E.G., Jolles, A.E., 2015. Disease control in  
758 wildlife: evaluating a test and cull programme for bovine tuberculosis in African  
759 buffalo. *Transbound. Emerg. Dis.* [Epub ahead of print].  
760 <https://doi.org/10.1111/tbed.12329>  
761 Lewis, F.I., Otero-Abad, B., Hegglin, D., Deplazes, P., Torgerson, P.R., 2014. Dynamics of  
762 the force of infection: insights from *Echinococcus multilocularis* infection in foxes.  
763 *PLoS Negl. Trop. Dis.* 8, e2731. <https://doi.org/10.1371/journal.pntd.0002731>  
764 Mailles, A., Rautureau, S., Le Horgne, J.M., Poignet-Leroux, B., d'Arnoux, C., Denetière,  
765 G., Faure, M., Lavigne, J.P., Bru, J.P., Garin-Bastuji, B., 2012. Re-emergence of  
766 brucellosis in cattle in France and risk for human health. *Euro Surveill.* 17, 1–3.  
767 Marchand, P., Freycon, P., Herbaux, J.P., Game, Y., Toïgo, C., Gilot-Fromont, E., Rossi, S.,  
768 Hars, J., 2017. Sociospatial structure explains marked variation in brucellosis  
769 seroprevalence in an Alpine ibex population. *Sci. Rep.* 7, 15592.  
770 <https://doi.org/10.1038/s41598-017-15803-w>  
771 Mazerolle, M.J., 2019. AICcmodavg: model selection and multimodel inference based on  
772 (Q)AIC(c). R package version 2.2-2.  
773 McDonald, R.A., Delahay, R.J., Carter, S.P., Smith, G.C., Cheeseman, C.L., 2008. Perturbing  
774 implications of wildlife ecology for disease control. *Trends Ecol. Evol.* 23, 53–56.  
775 <https://doi.org/10.1016/j.tree.2007.10.011>  
776 Michallet, J., Grand, B., Bonardi, J., 1988. La population de bouquetins des Alpes du massif  
777 de Belledonne-Sept Laux (département de l'Isère). *Bull. Mens. ONC* 19–24.  
778 Mick, V., Le Carrou, G., Corde, Y., Game, Y., Jaÿ, M., Garin-Bastuji, B., 2014. *Brucella*  
779 *melitensis* in France: persistence in wildlife and probable spillover from Alpine ibex  
780 to domestic animals. *PLoS ONE* 9, e94168.  
781 <https://doi.org/10.1371/journal.pone.0094168>  
782 Muench, H., 1934. Derivation of rates from summation data by the catalytic curve. *J. Am.*  
783 *Stat. Assoc.* 29, 25–38. <https://doi.org/10.2307/2278457>

784 Müller, T., Freuling, C.M., Wysocki, P., Roumiantzeff, M., Freney, J., Mettenleiter, T.C.,  
785 Vos, A., 2015. Terrestrial rabies control in the European Union: historical  
786 achievements and challenges ahead. *Vet. J.* 203, 10–17.  
787 <https://doi.org/10.1016/j.tvjl.2014.10.026>

788 Mysterud, A., Rolandsen, C.M., 2019. Fencing for wildlife disease control. *J. Appl. Ecol.* 56,  
789 519–525. <https://doi.org/10.1111/1365-2664.13301>

790 Mysterud, A., Rolandsen, C.M., 2018. A reindeer cull to prevent chronic wasting disease in  
791 Europe. *Nat. Ecol. Evol.* 1–3. <https://doi.org/10.1038/s41559-018-0616-1>

792 Nielsen, K., Gall, D., Smith, P., Balsevicius, S., Garrido, F., Durán-Ferrer, M., Biancifiori, F.,  
793 Dajer, A., Luna, E., Samartino, L., Bermudez, R., Moreno, F., Renteria, T., Corral,  
794 A., 2004. Comparison of serological tests for the detection of ovine and caprine  
795 antibody to *Brucella melitensis*. *Rev. Sci. Tech. Off. Int. Epizoot.* 23, 979–987.

796 Papoz, L., Simondon, F., Saurin, W., Sarmini, H., 1986. A simple model relevant to  
797 toxoplasmosis applied to epidemiologic results in France. *Am. J. Epidemiol.* 123,  
798 154–161. <https://doi.org/10.1093/oxfordjournals.aje.a114210>

799 Pepin, K.M., Kay, S.L., Golas, B.D., Shriner, S.S., Gilbert, A.T., Miller, R.S., Graham, A.L.,  
800 Riley, S., Cross, P.C., Samuel, M.D., Hooten, M.B., Hoeting, J.A., Lloyd-Smith, J.O.,  
801 Webb, C.T., Buhnerkempe, M.G., 2017. Inferring infection hazard in wildlife  
802 populations by linking data across individual and population scales. *Ecol. Lett.* 20,  
803 275–292. <https://doi.org/10.1111/ele.12732>

804 Perrin, J.-B., Rautureau, S., Bronner, A., Hosteing, S., Dufour, B., Garin-Bastuji, B., Jaÿ, M.,  
805 2016a. Absence of bovine brucellosis confirmed in 2014, but vigilance must be  
806 maintained. *Bull. Epidémiol. Santé Anim. Alim.* 71, 12–16.

807 Perrin, J.-B., Rautureau, S., Bronner, A., Hosteing, S., Jaÿ, M., Garin-Bastuji, B., Dufour, B.,  
808 2016b. Brucellosis in small ruminants in 2014: 95 départements of metropolitan  
809 France are now officially disease-free. *Bull. Epidémiol. Santé Anim. Alim.* 71, 17–21.

810 Reynolds, J.J.H., Carver, S., Cunningham, M.W., Logan, K.A., Vickers, W., Crooks, K.R.,  
811 VandeWoude, S., Craft, M.E., 2019. Feline immunodeficiency virus in puma:  
812 estimation of force of infection reveals insights into transmission. *Ecol. Evol.* 9,  
813 11010–11024. <https://doi.org/10.1002/ece3.5584>

814 Schlafer, D.H., Miller, R.B., 2007. Female genital system, in: Maxie, M.G. (Ed.), Jubb,  
815 Kennedy & Palmer’s Pathology of Domestic Animals (Fifth Edition). Elsevier,  
816 Edinburgh, pp. 429–431. <https://doi.org/10.1016/B978-070202823-6.50174-3>

817 Therneau, T.M., Grambsch, P.M., 2000. Modeling survival data: extending the Cox model,  
818 Statistics for biology and health. Springer, New York.

819 Treanor, J.J., Geremia, C., Crowley, P.H., Cox, J.J., White, P.J., Wallen, R.L., Blanton,  
820 D.W., 2011. Estimating probabilities of active brucellosis infection in Yellowstone  
821 bison through quantitative serology and tissue culture. *J. Appl. Ecol.* 48, 1324–1332.  
822 <https://doi.org/10.1111/j.1365-2664.2011.02058.x>

823 Vicente, J., Apollonio, M., Blanco-Aguiar, J.A., Borowik, T., Brivio, F., Casaer, J., Croft, S.,  
824 Ericsson, G., Ferroglio, E., Gavier-Widen, D., Gortázar, C., Jansen, P.A., Keuling, O.,  
825 Kowalczyk, R., Petrovic, K., Plhal, R., Podgórski, T., Sange, M., Scandura, M.,  
826 Schmidt, K., Smith, G.C., Soriguer, R., Thulke, H.H., Zanet, S., Acevedo, P., 2019.  
827 Science-based wildlife disease response. *Science* 364, 943.2–944.  
828 <https://doi.org/10.1126/science.aax4310>

829 Vynnycky, E., White, R.G., 2010. An introduction to infectious disease modelling. Oxford  
830 University Press, New York.

831 Wagenmakers, E.J., Farrell, S., 2004. AIC model selection using Akaike weights. *Psychon.*  
832 *Bull. Rev.* 11, 192–196. <https://doi.org/10.3758/BF03206482>

833



834 **Table 1:** Model selection table to analyse the age-seroprevalence data using a constant force  
835 of infection with age and time, and testing for the effect of infection-related mortality  $\mu$ , year  
836 and age (linear or quadratic), taking into account the effect of sex and socio-spatial unit.

N°	Year	Age	Age <sup>2</sup>	$\mu$	Unit	Sex	DF	LL	AICc	$\Delta$ AICc	W
<b>11</b>	+		+		+	+	<b>12</b>	<b>-176.91</b>	<b>378.73</b>	<b>0.00</b>	<b>0.20</b>
<b>9</b>	+	+			+	+	<b>12</b>	<b>-176.99</b>	<b>378.89</b>	<b>0.16</b>	<b>0.19</b>
<b>4</b>	+			+	+	+	<b>12</b>	<b>-177.16</b>	<b>379.24</b>	<b>0.50</b>	<b>0.16</b>
<b>3</b>	+				+	+	<b>11</b>	<b>-178.31</b>	<b>379.38</b>	<b>0.65</b>	<b>0.15</b>
<b>12</b>	+		+	+	+	+	<b>13</b>	<b>-176.71</b>	<b>380.48</b>	<b>1.75</b>	<b>0.09</b>
10	+	+		+	+	+	13	-176.99	381.04	2.31	0.06
7			+		+	+	7	-183.68	381.69	2.96	0.05
5		+			+	+	7	-184.20	382.73	3.99	0.03
2				+	+	+	7	-184.34	383.01	4.27	0.02
1					+	+	6	-185.42	383.09	4.35	0.02
8			+	+	+	+	8	-183.60	383.62	4.88	0.02
6		+		+	+	+	8	-184.20	384.82	6.09	0.01

837 *For each model, the table gives the number of Degrees of Freedom (DF), the Log-Likelihood (LL),*  
838 *the Akaike Information Criterion corrected for small sample sizes (AICc), the difference between their*  
839 *AICc and the lowest AICc value ( $\Delta$ AICc), and the Akaike Weights (W), which are relative model*  
840 *likelihoods normalized over the likelihoods of all possible submodels. The models with  $\Delta$ AICc < 2 are*  
841 *in bold.*  
842

843 **Figure legends**

844

845 **Figure 1: Timing of the monitoring and management operations during which ibex of**  
846 **the Bargy massif (France) were sampled for serological tests between 2012 and 2018.**

847 In green: months during which captures were performed; in yellow: months during which  
848 recaptures were performed; in blue: months during which culling operations were performed.  
849 The number of individuals captured, recaptured or culled is indicated for each operation.

850

851 **Figure 2: Serological datasets for brucellosis between 2012 and 2018 in the Bargy massif**  
852 **(France)**

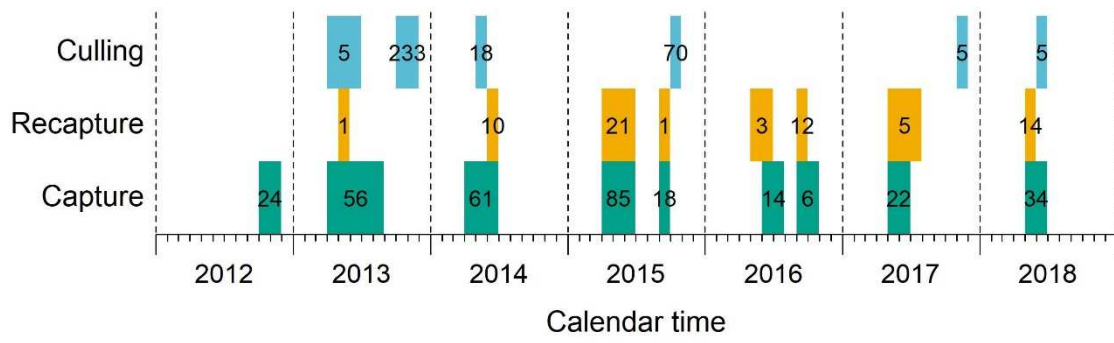
853 (A) Age-seroprevalence data, for ibex culled or captured for the first time, with black points  
854 representing the observed seroprevalence for each age, with the size of the points  
855 proportional to the sample taken ( $n=363$ ). (B) Distribution of the duration between the first  
856 capture (where the individuals were seronegative, marked and released) and the last  
857 recapture, where the ibex either tested seronegative, or converted to seropositive (the event of  
858 interest), for ibex that were recaptured at least once ( $n=50$ ). (B) Dates of first capture and last  
859 recapture of marked individuals, for ibex that were recaptured at least once ( $n=50$ ). The solid  
860 horizontal lines represent the life of marked animals between the date of their first capture,  
861 where they tested seronegative (white dots), and their last recapture, where they either tested  
862 seronegative or seropositive (black dots). The dashed vertical line represents a possible  
863 threshold date that separates the first period where individuals are exposed to a certain force  
864 of infection (FOI 1) from the second period where individuals are exposed to a different force  
865 of infection (FOI 2).

866

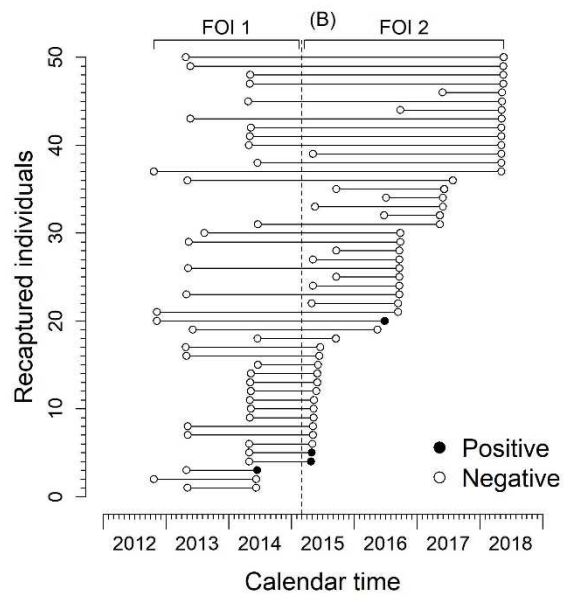
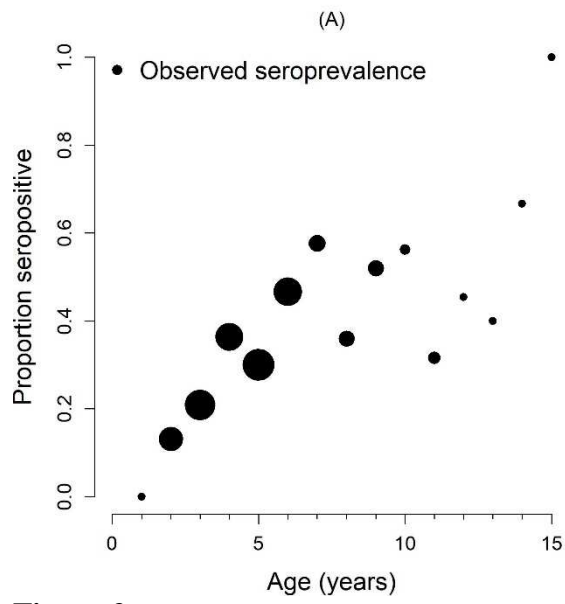
867 **Figure 3: Estimates of time-varying forces of infection.**

868 (A) AICc of the models considering different forces of infection for three periods on the  
869 calendar time for the cross-sectional age-seroprevalence dataset, comparing all possible pairs  
870 of threshold years between 2012 and 2017 to divide the 1998-2018 period into three. (C)  
871 AICc of the models considering different forces of infection for two periods on the calendar  
872 time for the longitudinal event time dataset, comparing all possible threshold months to  
873 divide the 2012-2018 period into two. In (A) and (C), the grey areas represents the AICc  
874 values where the difference between the AICc and the lowest AICc value ( $\Delta AICc$ ) were  
875 below two. (B) and (D) Estimates of the FOI ( $\text{year}^{-1}$ ) for the best model considering time-  
876 varying forces of infection for the age-seroprevalence and the event time datasets,  
877 respectively, without effects of sex and unit. The lines represent the means, and the areas  
878 represent the 95% confidence intervals. The dashed vertical lines represent the threshold  
879 dates that separate the different periods corresponding to different forces of infection in the  
880 models with the lowest AICc values.

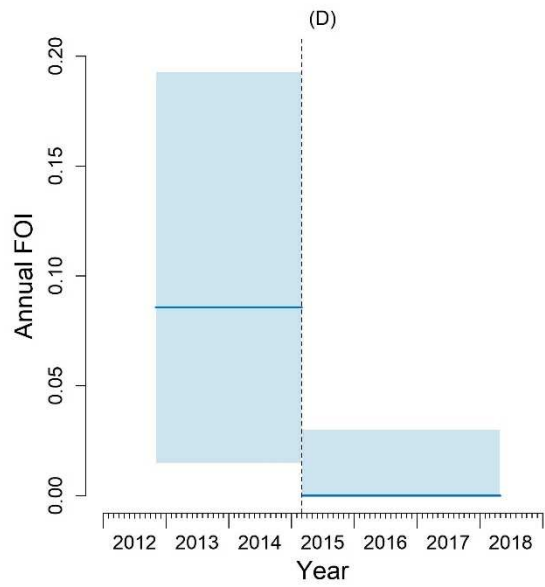
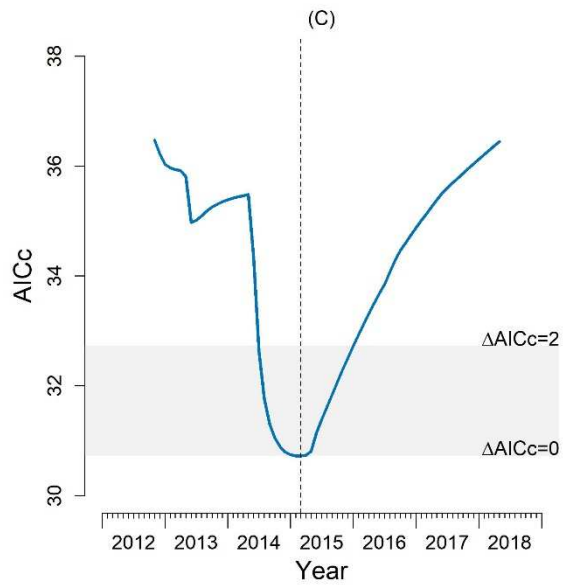
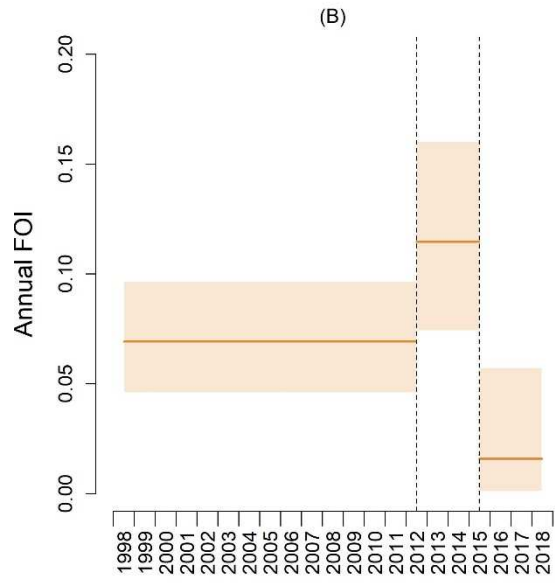
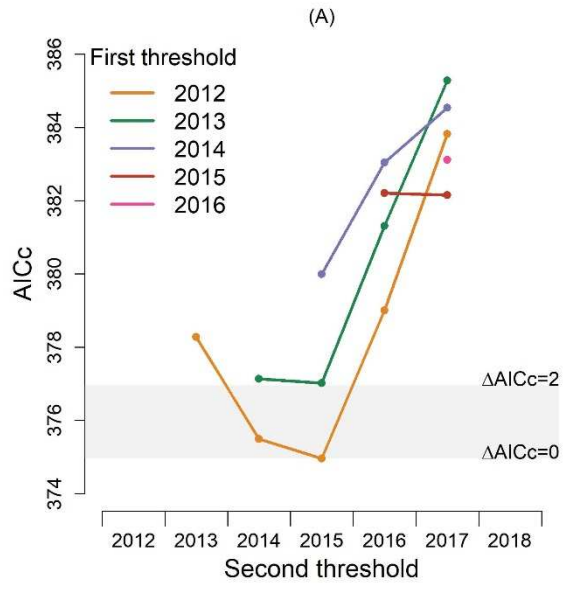
881



882  
883 **Figure 1**



884  
885 **Figure 2**  
886



887

888  
889

**Figure 3**