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

**Author names and affiliations:**

Sébastien Lambert a*, Emmanuelle Gilot-Fromont b, Carole Toïgo c, Pascal Marchand d, Elodie Petit e, Bruno Garin-Bastuji f, Dominique Gauthier g, Jean-Michel Gaillard a, Sophie Rossi h, Anne Thébault i.

a University of Lyon1, UMR CNRS 5558 Biometry and Evolutionary Biology laboratory (LBBE), Villeurbanne, France

b University of Lyon, University of Lyon1, CNRS, VetAgro Sup, UMR CNRS 5558 Biometry and Evolutionary Biology laboratory (LBBE), Villeurbanne, France

c French Biodiversity Agency (OFB), Wild Ungulates Unit, Gières, France

d French Biodiversity Agency (OFB), Wild Ungulates Unit, Juvignac, France

e French Biodiversity Agency (OFB), Wild Ungulates Unit, Sévrier, France

f French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Strategy and Programmes Department, Maisons-Alfort, France

g Departmental Veterinary Laboratory of Hautes-Alpes (LDVHA 05), Gap, France

h French Biodiversity Agency (OFB), Wildlife Diseases Unit, Gap, France

i French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Risk Assessment Department, Maisons-Alfort, France

* Present address: University of London, Royal Veterinary College, Department of Pathobiology and Population Sciences, Hatfield, United Kingdom

**Corresponding author:** Sébastien Lambert, selambert@rvc.ac.uk

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

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

Abstract: Heterogeneity of infectious disease transmission can be generated by individual differences in the frequency of contacts with susceptible individuals, in the ability to transmit the infectious agent or in the duration of infection, and by spatial variation in the distribution, density or movements of hosts. Identifying spatial and individual heterogeneity can help improving management strategies to eradicate or mitigate infectious diseases, by targeting the individuals or areas that are responsible for most transmissions. Individual-based models allow quantifying the respective role of these sources of heterogeneity by integrating potential mechanisms that generate heterogeneity and then by tracking transmissions caused by each infected individual. In this study, we provide an individual-based model of endemic brucellosis *Brucella melitensis* transmission in the population of Alpine ibex (*Capra ibex*) of the Bargy massif (France) by taking advantage of detailed information available on ibex population dynamics, behaviour, and habitat use, and on epidemiological surveys. This host-pathogen system is expected to be subject of both individual and spatial heterogeneity. We first estimated the transmission probabilities, hitherto unknown, of the two main transmission routes of the infection (i.e., exposure to infectious births/abortions and venereal transmission). Then, we quantified heterogeneity at both individual and spatial levels. We found that both transmission routes are not negligible to explain the data, and that there is a high amount of heterogeneity of the host-pathogen system at the individual level, with females generating
around 90% of the new cases of brucellosis infection. Males transmit infection at a lesser extent but still play a non-negligible role because they move between subpopulations and thereby create opportunities for spreading the infection spatially by venereal transmission.

Two particular socio-spatial units are hotspots of transmission, and act as sources of transmission for the other units. These results may have important implications for disease management strategies.

Keywords (maximum 6): wildlife disease; epidemiology; disease ecology; metapopulation; superspreading; transmission routes
1. Introduction

Heterogeneity in the transmission of infectious agents occurs when a small proportion of an animal population is responsible for the majority of transmission, whereas the rest of the population only generates few secondary cases. The '20-80' rule emerged from empirical data for several sexually-transmitted and vector-borne diseases, where 20% of cases contributed to at least 80% of transmission (Woolhouse et al., 1997). When comparing several directly-transmitted diseases, Lloyd-Smith et al. (2005) found support for this pattern, but nonetheless found evidence for high variation in the amount of heterogeneity, with 20% of cases contributing to 40% up to around 90% of transmission depending on the disease considered. Such substantial levels of heterogeneities are common in infectious diseases of both humans and animals (Brooks-Pollock et al., 2014; Galvani and May, 2005; Matthews et al., 2006).

Individuals responsible for the majority of transmission are referred to as “superspreaders” (Lloyd-Smith et al., 2005). Their high success in transmission of infectious agents is related either to a high contact rate with susceptible individuals, to a long duration of infection, or to an especially high infectiousness, i.e., ability to transmit the infectious agent (VanderWaal and Ezenwa, 2016). These three components of transmission can be influenced by various traits such as age, sex, behaviour, immunity or genetics (Cross et al., 2009; VanderWaal and Ezenwa, 2016).

Heterogeneous transmission can also occur when areas with a particularly high pathogen prevalence or transmission rate are responsible for the transmission to other areas (Paull et al., 2012). This spatial heterogeneity can arise from various environmental factors that promote the transmission or persistence of the disease, but also from the distribution, density and movement patterns of hosts (Conner and Miller, 2004). Spatial heterogeneity can also be related to individual heterogeneity, as superspreaders are likely to enhance transmission around them more than in other areas (Paull et al., 2012). Identifying spatial and individual
heterogeneity can help improving management strategies to eradicate or mitigate infectious diseases, by targeting the individuals or areas that are responsible for most transmissions (Lloyd-Smith et al., 2005; Woolhouse et al., 1997).

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

The persistence of brucellosis in a wildlife population raises serious public health and economic concerns. Effective disease management options would therefore be desirable to mitigate the risk to livestock and humans. Moreover, brucellosis in Alpine ibex raises a conservation issue because ibex have been restored in the Alps during the last decades, after being close to extinction at the beginning of the 20th century, and is now protected. The sanitary management of brucellosis usually operated in domestic herds, which involves culling both infected and exposed individuals, is hardly applicable to a wildlife population, especially in the case of a species with a protection status. Targeting individuals or areas that are responsible for most transmissions allows sparing other individuals and could be a relevant option for a more effective and more ethically acceptable management strategy to eradicate brucellosis.
This host-pathogen system is expected to be subject of both individual and spatial heterogeneity. First, five socio-spatial units were identified in the population, associated with marked differences in seroprevalence, ranging from <15% up to ~70% depending on the unit considered (Marchand et al., 2017). Second, individual heterogeneity could arise from sex and age differences, as typically observed in vertebrate populations (e.g., Plard et al. (2015)). Indeed, four transmission routes have been demonstrated in domestic ruminants for brucellosis: horizontal transmission after abortion or parturition when *Brucella* is shed in genital fluids, venereal transmission, congenital transmission and pseudo-vertical transmission (Diaz-Aparicio, 2013). Bacteriological data on necropsied seropositive ibex suggest that the same four routes may also exist in ibex (Lambert et al., 2018). All routes relate to reproduction, and thus involve specific age- and sex-classes. In this highly socially-structured species, contact rates vary between sex- and age-classes because of differences in terms of social behaviour (Bon et al., 2001), space use (Marchand et al., 2017) but also mating behaviour (Willisch and Neuhaus, 2009). Moreover, the proportion of active infection is higher in young individuals than in old ones (Lambert et al., 2018).

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

- First, due to their distinct patterns of space use, males and females should play different epidemiological roles. Males, which are more likely to move across the whole study area than females (especially during the mating period), should mostly
spread the infection between socio-spatial units through venereal transmission. By contrast, females, which are more sedentary and usually stay within their spatial unit, should maintain the infection inside each socio-spatial unit through bacterial shedding following abortion or birth.

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

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

2. Material and methods

2.1 Study site and population monitoring

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

During captures, Test-and-Remove (TR) operations were implemented on the basis of serological tests performed according to requirements of the European Union (EU) for diagnosis of brucellosis in small ruminants and following standards of the World Organisation for Animal Health (OIE) – see Marchand et al. (2017) and Lambert et al. (2018) for details. In
addition, a rapid serological test was used in the field to screen the sanitary status of captured animals during their handling, and take the decision of removal or release (ANSES, 2014; Corde et al., 2014). Between 2012 and 2018, 319 individuals were captured at least once. Among them, 115 were seropositive and removed, while 204 were seronegative and were marked and released. Fifty marked individuals were recaptured, sometimes several times, and among them, four were found positive and then removed. For each individual, sex, age (by counting horn growth annuli, Michallet et al. (1988)) and spatial location of capture were systematically recorded.

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

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

2.2 Individual-based model

We describe the individual-based model we built following the updated ODD protocol (“Overview”, “Design concepts”, “Details”) of Grimm et al. (2010, 2006). We present a concise and narrative ODD in the main text below, while the full description of the ODD and
the complete system of mathematical equations are provided in Appendix A. All simulations and further analyses were performed using R 3.4.1 (R Core Development Team, 2017).

2.2.1 Purpose

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

2.2.2 Entities, state variables, and scales

The only entities in the model were ibex individuals. To track information on each individual at each time step, the model included several state variables: individual ibex identity, sex, age in weeks, socio-spatial unit, health status (susceptible: *S*; exposed: *E*; actively infected: *I*; or non-actively infected, i.e., non-shedder: *R*), year of infection, year of recovery and reproductive status (sexually receptive, pregnant, abortion, birth, parity).
The population is structured into five socio-spatial units, with contrasting seroprevalences. Units 1 and 2 had seroprevalence less than 15%, vs. 54% for Unit 3, 70% for Unit 4 and 35% for Unit 5 (Fig. 1A – Marchand et al. (2017)). Within each socio-spatial unit, ibex have the tendency to form groups, but they experience very loose bonds (Villaret and Bon, 1998): groups are not stable and split and merge frequently (fission-fusion dynamics; C. Calenge, pers. comm.). To account for this structure in the model, we used a spatial metapopulation model (Fig. 1B), often applied to populations naturally subdivided into spatial units, with homogeneous contacts within subpopulations (Keeling and Rohani, 2008). At birth, each individual was attributed to the socio-spatial unit of its mother (permanent socio-spatial unit). All individuals living in the same socio-spatial unit constituted a subpopulation, each subpopulation being characterised by its name and its own relative carrying capacity, defined as a proportion of the carrying capacity of the whole population. The five subpopulations constituted the overall metapopulation (Fig. 1B). The model was developed to represent the evolution of brucellosis transmission and population dynamics between December 1, 2012 and November 30, 2018 with a discrete weekly time step.

2.2.3 Process overview and scheduling

Simulated years began on December 1st, and were split into two periods: the mating period, which lasts from early December to mid-January in ibex (Couturier, 1962; Gauthier et al., 1991; Willisch and Neuhaus, 2009) and was therefore fixed at 7 weeks in the model; and the non-mating period for the remaining 45 weeks (Fig. 2). During the mating period, the events occurring successively at each discrete time step were mortality, spatial movements, reproduction, venereal transmission, incubation and recovery (Appendix A; Fig. A.1). During the non-mating period, the events occurring successively at each discrete time step were
surveillance and management strategies, mortality, spatial movements, abortions or births, congenital/pseudo-vertical transmission, horizontal transmission, incubation and recovery (Appendix A; Fig. A.1). Such an order is artificial but is required to apply probabilities of dying or getting infected to the correct numbers of individuals. For each event, individuals were processed simultaneously.

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

Gestation in ibex lasts 167 days (Stüwe and Grodinsky, 1987), which leads births to take place from the end of May to mid-July, i.e., 24 weeks after the mating period (Fig. 2).

Abortions caused by brucellosis occur during the last third of gestation (Diaz-Aparicio, 2013), i.e., 16 weeks after the beginning of gestation for an ibex. In domestic ruminants, shedding of Brucella through placenta, foetal fluids and vaginal discharges when a female aborts or gives birth may last ca. three weeks (European Commission, 2001), and we assumed a similar duration for ibex in the model. Therefore, horizontal transmission of Brucella through abortions is possible from early April to the end of May. However, after parturition, an ibex female tends to isolate itself in cliffs and rocky areas with its newborn for two weeks (Bon et al., 2001; Couturier, 1962; Villaret et al., 1997). Thus, other individuals were assumed to be in contact with a female only the third week after its parturition, reducing the period of exposure to this transmission route (Fig. 2).
2.2.4 Design concepts

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

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

For the model analysis, individual statuses were used to derive population-level variables such as population size, prevalence or annual incidence (i.e., number of new cases) in the population. For the model fitting, data on the number of individuals captured and the number of seropositive individuals found among them was used, to match how data were collected in the field.
Transitions between states were modelled as stochastic flows assuming demographic

stochasticity. Each transition was the outcome of a Bernoulli process.

2.2.5 Initialisation

The initial state was established from field-data of 2013 and the assumption that the

population was then close to saturation (ANSES, 2015 – Appendix A).

2.2.6 Input data

The model does not use input data or an external model to represent time series of driving

environmental variables. The simulation period is short (6 years) and no relevant

environmental change was documented during the period of study.

2.2.7 Submodels

Density-dependence

Density-dependence of survival and reproduction is a common process in populations of large

herbivores (Bonenfant et al., 2009). Density-dependent responses of population parameters

were shaped to reproduce a logistic population growth, where the population size stabilises

around the carrying capacity in the absence of management interventions (Appendix A;

Eq. A.1-3 and Fig. A.2). Indeed, previous studies of population dynamics of ibex have shown

that the logistic model may be appropriate to describe the density regulation in ibex

populations (Sæther et al., 2007, 2002). Density-dependent processes play a crucial role in

disease ecology because it can interact with transmission, for example by increasing the

number of births and therefore the pool of susceptible individuals after population size

reduction (Choisy and Rohani, 2006). In the case of brucellosis, density-dependence of
reproduction is also critical because all transmission routes are related to reproduction processes.

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

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

**Mortality:** We used a complete age-dependent model, with a mortality estimate for each age and sex (Toïgo et al. (2007) – Table 1 and Appendix A). Males lived up to 16 years and females up to 19 years (Toïgo et al., 2007). In our model, we assumed no brucellosis-related mortality, as there is currently no evidence for it (no important mortality detected, no seropositive individuals detected in the few individuals found dead).
Spatial movements: Movements of males between units during the mating period and the abortion period, when they can transmit or acquire infection, were derived from hourly locations collected by GPS collars (Appendix A). The probability and direction of movements were estimated separately for the two periods, because males are especially likely to visit other units during the mating period (Fig. 1B and Appendix A; Fig. A.3). We considered all movements to be temporary, as the model randomly sampled a new temporary socio-spatial unit at each time step based on the movement probabilities and on permanent socio-spatial unit.

Reproduction: In the model, reproductive success of females was the outcome of two processes: sexual receptivity during mating, and the probability to give birth to a live newborn. In ibex, most mature females are sexually receptive only once during the mating period (Couturier, 1962; Willisch and Neuhaus, 2009). We considered that a mature female could become sexually receptive during mating only once every year with probabilities depending on age (starting at 1.5 years old – (Couturier, 1962; Gauthier et al., 1991)). Males, on the other hand, are sexually mature at 2.5 years of age and active every year throughout the mating period (Couturier, 1962; Willisch et al., 2012).

In ibex, only one male succeeds in engaging sexual intercourse with a given female (Tettamanti, 2015; Willisch and Neuhaus, 2009). Dominant males that monopolise access to the female by using the “tending” tactic are more successful in engaging sexual intercourse and have higher reproductive success than subordinate males adopting the “coursing” tactic (Willisch et al., 2012). Younger males (2-7 years) mainly adopt the coursing tactic while older males (≥ 8 years) mainly engage in tending (Willisch et al., 2012; Willisch and Neuhaus, 2009). Accordingly, in the model, we made the simple assumption that all males aged 2-7 years were coursing while all males aged 8-14 years were considered as tending. Each
sexually receptive female was associated to one tending and several coursing males (Appendix A). Consequently, offspring were sired by a small fraction of males, mainly dominant males engaging in the tending tactic. Every receptive female who engaged in sexual intercourse with a male became pregnant. In our model, we assumed that *Brucella* infection decreased sexual receptivity during mating, thus leading to a lower probability of gestation (Table 2) based on data from the study population (unpubl. data) and by analogy with domestic ruminant infection (ANSES, 2015).

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

**Abortions or births:** In domestic ruminants, 80% of infectious females abort and most of them do so only once, during the first pregnancy post-infection (FAO and WHO, 1986; Godfroid et al., 2004). If abortion does not occur, invasion of the uterus leads to *Brucella* shedding in genital fluids at the time of parturition (European Commission, 2001). In the model, we assumed that infected pregnant females could abort only during their first pregnancy following infection with a probability of 80% (Table 2). When abortion does not occur, females give birth to a live newborn. In both cases, females shed *Brucella* in genital fluids for ca. three weeks. For other pregnant females, and for actively infected females that already went through their first pregnancy following infection, the probability to give birth to a live newborn that
survives until winter depends on their parity (Table 1). We also assumed that active *Brucella* infection decreases the probability to give birth to a live newborn (Table 2 – unpubl. data). Actively infected females that give birth to a live newborn shed *Brucella* in genital fluids for three weeks. The sex-ratio at birth was expected to be 1.

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

**Horizontal transmission:** In domestic ruminants, excretion of the *Brucella* in female genital discharges through infectious abortions or births is considered as the main route of transmission to other individuals (European Commission, 2001). For this transmission route, contacts were not modelled explicitly. An individual was exposed to all abortions or births caused by brucellosis within the same socio-spatial unit. We assumed that at a given time step, the probability of an individual coming into effective contact (i.e., coming into a contact
that leads to infection) with one infectious abortion or with one infectious birth was the same (Table 2). This probability had to be estimated using Approximate Bayesian Computation (see 2.3).

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

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

2.3 Simulation experiments

The model was parameterised using Approximate Bayesian Computation (ABC) rejection algorithm (Beaumont et al., 2002), based on the abc R package (Csilléry et al., 2012). This approach has the advantage to approximate the likelihood by running the model a large number of times and comparing simulated outputs to the observed data (Toni et al., 2009). However, this is a computationally intensive approach which was possible in our case because of access to highly performant computing facilities and because of the small population size of the investigated system.

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

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

### 2.4 Model analysis

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

For each susceptible individual that acquired infection, the year it got infected, the transmission route by which it was infected, and whether transmission was between- or within-unit was recorded. We defined between-unit transmission as a transmission that occurred between a male and a female that do not share the same permanent socio-spatial unit (regardless of the direction of transmission, i.e., from male to female or vice versa), which is possible when a male is temporarily visiting another unit. From this information, we derived the annual incidence (i.e., number of new cases) in the population, and the proportion of these new cases in each age- and sex-class and in each socio-spatial unit, for each transmission route.
We also recorded the number of secondary cases caused by each actively infected individual, written as \( Z \) (Lloyd-Smith et al., 2005). \( Z \) represents an individual equivalent of the population parameter \( R_e \), the net or effective reproductive number, which is defined as the average number of secondary infections caused by an infected individual over the course of its infectious period in a given population (Vynnycky and White, 2010). However, due to the relatively short period considered in our model (6 years, compared to a maximum lifespan >20 years in ibex), we could not compute the total number of secondary cases caused by each infected individual during all its infectious life. We thus computed the number of secondary cases caused by each infectious individual every year, keeping track of the transmission route and whether it corresponded to within- or between-unit transmission. When it was not possible to attribute a secondary case to a single source case, the secondary case was shared uniformly between all possible source cases involved.

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

3. Results

3.1 Parameter estimation and model predictions

The estimated parameter values were (median and 95% credible interval): \( K = 564 \) \([535 – 591]\) for the carrying capacity; \( \beta_{I_A}^Q = \beta_{I_B} = 0.026 \) \([0.001 – 0.128]\) for the per-capita probability of one female to come into effective contact with one infectious abortion or birth per week; and \( \nu_{ven}^{T\rightarrow F} = 0.168 \) \([0.005 – 0.682]\) for the probability of successful venereal transmission from tending males to females given contact. The posterior distributions of the parameter values are provided in Appendix B. We evaluated the correlations between the
accepted parameter values (Appendix B), and we found a correlation of 0.018 between $K$ and
$\nu_{\text{ven}}^{T=0}$, of about $-0.14$ between $\beta_{IA}^q = \beta_{IB}$ and $K$ and of $-0.25$ between $\nu_{\text{ven}}^{T=0}$ and $\beta_{IA}^q = \beta_{IB}$.

The cross-validation procedure revealed that $K$ was the most accurately estimated parameter,
followed by $\beta_{IA}^q = \beta_{IB}$ and then by $\nu_{\text{ven}}^{T=0}$ (Appendix B).

Simulations with 1000 iterations, each iteration using a set of parameter values from the 1000
best simulations from the ABC, produced predictions in accordance with observations both
qualitatively and quantitatively (Fig. 3 and Appendix B). The population size decreased
drastically after massive culling and to a much lesser extent due to birth and death processes
(Figure 3A). Similarly, the number of actively infected individuals dropped after the massive
culling of 2013, especially in Unit 3, which was the largest subpopulation and concentrated
most of the culling operations (Fig. 4A). It then decreased more gradually in 2014 and 2015,
before stabilising at a roughly constant level during the last three years. The number of new
cases per year decreased down to a minimum of 5.6 individuals on average in 2016, followed
by a slight increase since 2016 (Fig. 4.B).

### 3.2 Importance of transmission routes

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

Among the cases due to within-unit transmission, horizontal transmission through infectious
abortions and births were predominant (more than 58% on average of within-unit new cases),
followed by vertical transmission (congenital and pseudo-vertical transmission) and then by
venereal transmission (Fig. 5C and Appendix C; Fig. C.1). We did not detect any variation in these proportions during the study period (Appendix C; Fig. C.1).

3.3 Quantification of heterogeneity

3.3.1 Individual-level heterogeneity

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

3.3.2 Heterogeneity between demographic classes

Fig. 7A shows the distribution of secondary cases by age- and sex-classes and by age- and sex-classes they originated from. In accordance with the previous result on heterogeneity, we show that the distribution of source and secondary cases differs in term of age- and sex-classes, with source cases (20% of infectious individuals each year) having specific demographic characteristics. In particular, females generated 89% on average of the new cases resulting from within-unit transmission (Fig. 7A and Appendix C; Fig. C.3). Females over 5 years of age generated on average 56% of these new cases, especially through horizontal transmission following births, congenital/pseudo-vertical transmission and venereal transmission (Fig. 7A and Appendix C; Figs. C.3-4-6-7), while younger mature females (2-5...
years old) generated on average 33% of them but mainly through abortions (Fig. 7A and Appendix C; Fig. C.5).

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

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

3.3.3 Socio-spatial units

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

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

4.1 A highly heterogeneous system

Our model allowed us to track the annual number of secondary cases produced by each individual. We revealed an extremely high heterogeneity. Each year, only 20% of individuals are responsible for most new cases (Fig. 6). However, this result is not strictly comparable to the proportion of transmission due to the most infectious 20% of cases reported by Woolhouse et al. (1997) and Lloyd-Smith et al. (2005), since we considered in the present study the number of secondary cases caused by an infectious individual each year instead of summing them over the course of the individual infectious period. Therefore, the contribution of an individual to the proportion of transmission could vary between years, and we could reasonably expect that on longer periods more than 20% of infectious individuals would contribute to the infection transmission. It is also important to stress out that this high individual heterogeneity could be enhanced by disease management measures (Lloyd-Smith et al., 2005) implemented in the population during our study period. Indeed, removing an
infectious individual a given year reduced its number of secondary cases that year, while infectious individuals that were not the subject to measures or were wrongly diagnosed as seronegative could continue to infect other individuals. Even if individual heterogeneity may not be as marked as suggested by Fig. 6, our work suggests that disease management targeting the most infectious individuals could be more efficient than that based on population-wide strategies. This is especially expected for low or intermediate control efforts (Lloyd-Smith et al., 2005), and therefore would be particularly relevant in the study case. However, although we were able to identify the individuals most responsible for infection using our model, doing so in the field would prove quite challenging. This is the reason why we focused on identifying the classes of individuals most responsible for infection rather than the individuals themselves (VanderWaal and Ezenwa, 2016), using traits associated with transmission that are identifiable in the field, such as sex, age or socio-spatial unit in our case.

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

Several years ago, a review of host-pathogen systems in mammals suggested that males play a critical role in diseases transmission compared to females, and proposed that disease dynamics was “all caused by males” (Skorping and Jensen, 2004). To explain this pattern, the authors proposed either a biased prevalence or shedding intensity towards males (Poulin, 1996; Schalk and Forbes, 1997), or differences in behaviour (such as movements of males over large range) leading to biased exposure even in the absence of prevalence or shedding differences (Ferrari et al., 2003; Skorping and Jensen, 2004). In contrast with this general rule, we found that females are the most frequent source of brucellosis infection for ibex, as for brucellosis in other species of domestic and wild ruminants (European Commission, 2001; Rhyan, 2013). In our study system, there were no or few differences between males and
females in terms of seroprevalence (Marchand et al., 2017) or probability of active infection (Lambert et al., 2018). However, we expected sex differences in disease transmission because mating behaviour (Willisch and Neuhaus, 2009), social behaviour (Bon et al., 2001) and space use (Marchand et al., 2017) all markedly differ between sexes.

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

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

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

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

### 4.3 The role of old individuals

For males, the age class that is both a source and a victim of transmission (through venereal
transmission) clearly appears to be the individuals over 5 years old, even when compared to
the proportion of males of this age class in the whole population (Fig. 7A and Appendix C;
Figs. C.2-3). This result is in accordance with the hypothesis made by Hars et al. (2013) based
on serological data. This occurs because older males are more frequently in contact with
females (“tending” mating tactic) and have thus a higher probability of effective contact than younger males. This pattern still held after the massive culling operation in autumn 2013, even though males over 5 years old were specifically targeted. Although the number of older males in the population decreased (Appendix C; Figs. C.2-3), we did not detect a strong increase of the proportion of younger males (≤5 years old) involved in venereal transmission (Appendix C; Fig. C.4), contrarily to what was suggested in Hars et al. (2015).

In contrast, females 5 years old and under were responsible for most new cases through infectious abortions (Appendix C; Fig. C.5), whereas older females were accountable for the majority of new cases through infectious births as well as congenital/pseudo-vertical transmission (Appendix C; Figs. C.6-7). Thus, despite the fact that young seropositive females have a higher probability of being actively infected (Lambert et al., 2018), young females play a major role through abortion during their first gestation post-infection, but transmission through shedding after birth in the following gestations (i.e. in older females) also plays a determinant role. This could be explained, although less categories of individuals are exposed to this route and for shorter duration than for abortions, by the fact that most of exposed individuals are newborns, fully susceptible to the infection. Therefore, ecological data in combination with epidemiological data on seroprevalence structure and shedding pattern suggest that brucellosis transmission is not limited to young age classes in ibex, in contrast to what is suggested by shedding patterns alone (Lambert et al., 2018). This result is similar to the pattern of transmission in domestic ruminants facing endemic brucellosis (ANSES, 2015; European Commission, 2001).

4.4 Source, sink and metapopulation dynamics of brucellosis

As regards our second hypothesis, we expected that units with the highest seroprevalence and the largest sub-population, that also occupy a central positions in the Massif (Marchand et al.,
would act as sources of infection to the other units. We used explicit movements of animals, quantified through the use of GPS data, to model transmission between units, rather than a phenomenological model that links units between them without specifying any mechanism (Jesse et al., 2008). Therefore, transmission between units was the result of both movement pathways of animals and characteristics of each unit such as abundance and seroprevalence.

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

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

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

Targeting specific age- or sex-classes could be an alternative (Fenichel and Horan, 2007; Ferrari et al., 2003). In the ibex case, management strategies should probably focus on females, as they are responsible for the vast majority of new cases in the system. Predicting which female age class to target appears difficult because younger females are more often actively infected and abort, while older females play an important role as well through shedding at birth and vertical transmission. In a model of brucellosis infection in bison from the Yellowstone National Park, test-and-remove was more effective when targeting pre-reproductive seropositive females rather than targeting all females regardless of age (Ebinger et al., 2011). This selective strategy allowed to remove seropositive females before they could even shed bacteria following abortion or birth (Ebinger et al., 2011). In ibex, individuals under two years of age are seldom captured, which would make this strategy difficult to apply.
Males play a less important role quantitatively, but qualitatively they connect socio-spatial units together and create opportunities for between-unit transmission. Therefore, if the aim of the management strategy is to reduce or prevent transmission between socio-spatial units, then males, especially older ones, should be targeted.

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

4.6 Conclusion

By integrating information issued from population demography, space use, management strategies and epidemiological surveys to build a realistic model, we provide an accurate picture of the population dynamics of ibex in the Bargy massif, which faced a brucellosis outbreak. This model allows unravelling the mechanisms involved in these dynamics. Considering the specific features of this population, particularly the management measures implemented since 2012, extrapolating our conclusions to other cases (if these arise), should be done with caution. In particular, the outcome of infection would have likely been different if management options had been different. Nonetheless, our results suggest that brucellosis in ibex is epidemiologically similar to *B. melitensis* and *B. abortus* infection in other species of domestic and wild ruminants, with mature females playing a predominant role of transmission through *Brucella* shedding in genital fluids (Diaz-Aparicio, 2013; European Commission, 2001; Rhyan, 2013). Our findings demonstrate that our general framework using individual-based models is suitable for the study of transmission heterogeneity in wild populations and could be applied to other host-pathogen systems.
Declarations of interest: none.

CRedit author statement

Sébastien Lambert: Conceptualisation, Methodology, Software, Formal Analysis, Data Curation, Writing – Original Draft, Visualisation. Emmanuelle Gilot-Fromont:

Conceptualisation, Methodology, Writing – Review & Editing, Supervision. Carole Toïgo,

Sophie Rossi: Conceptualisation, Investigation, Writing – Review & Editing. Carole Toïgo,

Pascal Marchand: Investigation, Data Curation, Writing – Review & Editing, Visualisation.


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Literature cited:


The ibex reservoir in the French Alps. Presented at the Brucellosis 2014 International
Research Conference, including the 67th Annual Brucellosis Research Meeting,
Berlin, Germany, p. 221.

Grenoble.

population structure and parasite transmission: implications for disease management,
in: Delahay, R.J., Smith, G.C., Hutchings, M.R. (Eds.), Management of Disease in

Csilléry, K., François, O., Blum, M.G.B., 2012. abc: an R package for approximate Bayesian
210X.2011.00179.x

Diaz-Aparicio, E., 2013. Epidemiology of brucellosis in domestic animals caused by Brucella
melitensis, Brucella suis and Brucella abortus. Rev. Sci. Tech. Off. Int. Epizoot. 32,
43–51.

Ebinger, M., Cross, P., Wallen, R., White, P.J., Treanor, J., 2011. Simulating sterilization,
vaccination, and test-and-remove as brucellosis control measures in bison. Ecol. Appl.
21, 2944–2959. https://doi.org/10.1890/10-2239.1

SANCO.C.2/AH/R23/2001). Health & Consumer Protection Directorate-General,
Brussels, Belgium.


Am. J. Agric. Econ. 89, 904–920. https://doi.org/10.1111/j.1467-8276.2007.01025.x

sex in parasite dynamics: field experiments on the yellow-necked mouse Apodemus

Freycon, P., 2015. Rôle du bouquetin Capra ibex dans l’épidémiologie de la brucellose à
Brucella melitensis en Haute-Savoie (Th. Méd. Vét.). Université Claude Bernard -
Lyon I.

https://doi.org/10.1006/tpbi.2001.1553

293–295. https://doi.org/10.1038/438293a


J.A.W., Tustin, R.C. (Eds.), Infectious Diseases of Livestock. Oxford University


Grignolio, S., Rossi, I., Bassano, B., Apollonio, M., 2007a. Predation risk as a factor affecting
https://doi.org/10.1644/06-MAMM-A-351R.1

on space use and habitat selection of female Alpine ibex. J. Wildl. Manag. 71, 713–


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

<table>
<thead>
<tr>
<th>Description (dimension)</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k$ Threshold for density-dependent effect</td>
<td>131</td>
<td>†</td>
</tr>
<tr>
<td>$K$ Carrying capacity of the metapopulation</td>
<td></td>
<td>‡</td>
</tr>
<tr>
<td>$p_0^{\text{min}}$ Probability of winter mortality of newborns, minimum (over the duration of winter)</td>
<td>0</td>
<td>†</td>
</tr>
<tr>
<td>$p_0^{\text{max}}$ Probability of winter mortality of newborns, maximum (over the duration of winter)</td>
<td>0.60</td>
<td>†</td>
</tr>
<tr>
<td>$\mu_{kQ}$ Probability of mortality of $X$-years old females (annual)</td>
<td>App. A</td>
<td>*</td>
</tr>
<tr>
<td>$\mu_{\kappa\sigma}$ Probability of mortality of $X$-years old males (annual)</td>
<td>App. A</td>
<td>*</td>
</tr>
<tr>
<td>$r_{X}^{\text{max}}$ Sexual receptivity probability of $X$-years old females, maximum</td>
<td>App. A</td>
<td>†</td>
</tr>
<tr>
<td>$r_{X}^{\text{min}}$ Sexual receptivity probability of $X$-years old females, minimum</td>
<td>App. A</td>
<td>†</td>
</tr>
<tr>
<td>$p_{ij}$ Probability for a male whose permanent unit is $i$ to visit the unit $j$ during one time step (per week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p_1$ Proportion of associations during the first 2 weeks of the mating period</td>
<td>0.70</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$p_2$ Proportion of associations during the rest of the mating period</td>
<td>0.30</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$n_T$ Number of tending males per female (over the duration of mating)</td>
<td>1</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$n_C$ Number of coursing males per female (over the duration of mating)</td>
<td>3</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$p_{C1}$ Proportion of coursing males 2-5 years old associated to females</td>
<td>1/3</td>
<td>(Willisch et al., 2012)</td>
</tr>
<tr>
<td>$p_{C2}$ Proportion of coursing males 6-7 years old associated to females</td>
<td>2/3</td>
<td>(Willisch et al., 2012)</td>
</tr>
<tr>
<td>$\tau_T$ Copulation probability of tending males (8-14 years old)</td>
<td>6/7</td>
<td>(Willisch et al., 2012)</td>
</tr>
<tr>
<td>$\tau_C$ Copulation probability of coursing males (2-7 years old)</td>
<td>1/7</td>
<td>(Willisch et al., 2012)</td>
</tr>
<tr>
<td>$n_{\text{max}}$ Maximal number of partners for males (per week)</td>
<td>3</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$\eta_1$ Probability of giving birth for primiparous females</td>
<td>0.70</td>
<td>†</td>
</tr>
<tr>
<td>$\eta_2$ Probability of giving birth for multiparous females</td>
<td>0.90</td>
<td>†</td>
</tr>
<tr>
<td>$\delta$ Sex ratio</td>
<td>0.50</td>
<td>†</td>
</tr>
<tr>
<td>$d_{\text{mat}}$ Duration of mating period (weeks)</td>
<td>7</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$d_{\text{gest}}$ Duration of gestation (weeks)</td>
<td>24</td>
<td>(Gauthier et al., 1991)</td>
</tr>
<tr>
<td>$d_{\text{isol}}$ Duration of postpartum isolation of the mother-offspring couple (weeks)</td>
<td>2</td>
<td>(Gauthier et al., 1991)</td>
</tr>
</tbody>
</table>

* Calibrated using field data
† Experts knowledge
‡ Approximate Bayesian Computation

App. A: see Appendix A
Table 2: Definition and value of epidemiological parameters included in the model of population dynamics of ibex facing a brucellosis outbreak in the Bargy massif, France.

<table>
<thead>
<tr>
<th>Description (dimension)</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_{inc}$ Duration of <em>Brucella</em> incubation (weeks)</td>
<td>3</td>
<td>(European Commission, 2001)</td>
</tr>
<tr>
<td>$d_{shed}$ Duration of shedding of <em>Brucella</em> in genital fluids when a female aborts or gives birth (weeks)</td>
<td>3</td>
<td>(European Commission, 2001)</td>
</tr>
<tr>
<td>$d_{abo}$ Delay between mating and abortion due to <em>Brucella</em> (weeks)</td>
<td>16</td>
<td>(Diaz-Aparicio, 2013)</td>
</tr>
<tr>
<td>$Se$ Sensitivity of serologic tests</td>
<td>0.95</td>
<td>(ANSES, 2015)</td>
</tr>
<tr>
<td>$\rho$ Probability of abortion during the first pregnancy following infection</td>
<td>0.80</td>
<td>(Godfroid et al., 2004)</td>
</tr>
<tr>
<td>$\gamma$ Probability of recovery (annual)</td>
<td>0.16 *</td>
<td></td>
</tr>
<tr>
<td>$\beta_{IA}$ Per capita probability of one female coming into effective contact with one infectious abortion due to <em>Brucella</em> (per week)</td>
<td>‡</td>
<td></td>
</tr>
<tr>
<td>$\sigma$ Reduction in the number of contacts with infectious abortion for males ≤5 years old</td>
<td>0.27 *</td>
<td></td>
</tr>
<tr>
<td>$\beta_{IA}^{\leq5}$ Per capita probability of one male ≤5 years old coming into effective contact with one infectious abortion (per week)</td>
<td>$\sigma \times \beta_{IA}^{\leq5}$</td>
<td></td>
</tr>
<tr>
<td>$\phi$ Reduction in the number of contacts with infectious abortion for males &gt;5 years old</td>
<td>0.06 *</td>
<td></td>
</tr>
<tr>
<td>$\beta_{IB}$ Per capita probability of one female or one newborn coming into effective contact with one infectious birth (per week)</td>
<td>‡</td>
<td></td>
</tr>
<tr>
<td>$\nu_{ven}^{I\rightarrow F}$ Probability of successful venereal transmission from tending males to females given contact</td>
<td>‡</td>
<td></td>
</tr>
<tr>
<td>$\kappa$ Relative efficacy of coursing male-to-female transmission</td>
<td>0.45</td>
<td>(Willisch and Neuhaus, 2009)</td>
</tr>
<tr>
<td>$\nu_{ven}^{C\rightarrow F}$ Probability of successful venereal transmission from coursing males to females given contact</td>
<td>$\kappa \times \nu_{ven}^{I\rightarrow F}$</td>
<td></td>
</tr>
<tr>
<td>$\omega$ Relative efficacy of female-to-male transmission</td>
<td>0.60</td>
<td>(Augustine, 1998)</td>
</tr>
<tr>
<td>$\nu_{ven}^{F\rightarrow C}$ Venereal transmission coefficient from females to tending males</td>
<td>$\omega \times \nu_{ven}^{I\rightarrow F}$</td>
<td></td>
</tr>
<tr>
<td>$\nu_{ven}^{F\rightarrow C}$ Venereal transmission coefficient from females to coursing males</td>
<td>$\omega \times \nu_{ven}^{C\rightarrow F}$</td>
<td></td>
</tr>
<tr>
<td>$\beta_{cong}$ Congenital transmission coefficient by <em>in utero</em> infection</td>
<td>0.05</td>
<td>(FAO and WHO, 1986; Godfroid et al., 2013)</td>
</tr>
<tr>
<td>$\beta_{pseu}$ Pseudo-vertical transmission coefficient by milk ingestion</td>
<td>0.05 †</td>
<td></td>
</tr>
<tr>
<td>$\zeta_{f}$ Impact of brucellosis on sexual receptivity probability of infectious females</td>
<td>0.80 †</td>
<td></td>
</tr>
<tr>
<td>$\zeta_{g}$ Impact of brucellosis on probability of giving birth of infectious females in subsequent pregnancies</td>
<td>0.90 †</td>
<td></td>
</tr>
</tbody>
</table>

* Calibrated using field data
† Experts knowledge
‡ Approximate Bayesian Computation
Figure 1: The five socio-spatial units of the Bargy massif and representation of the associated conceptual metapopulation model. A (left): identification of the five socio-spatial units. Unit 1 is called “Leschaux-Andey”, Unit 2 “Charmieux-Buclon”, Unit 3 “Jallouvre-Peyre”, Unit 4 “Grand Bargy” and Unit 5 “Petit Bargy”. This is an updated version of Figure 2 in (Marchand et al., 2017), using new data of GPS-collared Alpine ibex (*Capra ibex*), corroborating the socio-spatial structure of the population. See Marchand et al. (2017) for details on the method. B (right): configuration of the associated conceptual metapopulation model. Circles represent the five socio-spatial units. Females always stay in their unit, whereas male can make temporary visits to other units. Solid black lines represent between-unit movements of males that are possible during both mating and abortion period. The dashed grey line represents movements of males that exist only during abortion period. Seroprevalence varied between units (Marchand et al., 2017): <15% for Units 1 and 2, 54% for Unit 3, 70% for Unit 4 and 35% for Unit 5. See Appendix A for more details.
Figure 2: Seasonal reproduction of the Alpine ibex and periods of potential Brucella shedding. Mating season lasts from early December to mid-January (purple rectangle), leading to births from the end of May to mid-July (blue rectangle). Brucella shedding after an infectious abortion (IA) or birth (IB) lasts three weeks. Therefore, horizontal transmission by IA is possible from early April to the end of May. After parturition, a female is not in contact with other individuals for two weeks, therefore the beginning of horizontal transmission by IB is delayed for two weeks compared to the start of the birth period. Venereal transmission is possible during the entire mating period, and vertical transmission (congenital and pseudo-vertical) happens during the entire birth period.
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.
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.
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.
**Figure 6: Contribution of infectious individuals to the yearly number of secondary cases.**

A: Cumulative contribution to transmission vs. proportion of infectious individuals, sorted by increasing contribution of secondary cases. The solid grey line represents the median of the output over the 1000 simulations and the six years of study, while the light grey area represents the 95% credible interval. B: absolute frequency of Z, the number of secondary cases caused by each infectious individual. Bars represent the median of the output over the 1000 simulations and the six years of study, while the grey lines represent the 95% credible interval.
Figure 7: Distribution of secondary cases of brucellosis transmission according to their age- and sex-classes and their socio-spatial unit, and according to the age- and sex-classes and socio-spatial unit they originated from. A: average proportion of secondary cases that originated from source cases of each age- and sex-class (“Source cases”), and average proportion of secondary cases that occurred in each age- and-sex class (“New cases”). For the sake of example, consider a situation where one actively infected female caused two secondary cases in females and one in males, and one actively infected male caused two secondary cases in females. Then, a proportion of 60% (3/5) of secondary cases originated from females and 40% (2/5) from males (“Source cases”), while the proportion of secondary cases would be 80% (4/5) in females and 20% (1/5) in males (“New cases”). We separated within-unit (left, 96.2% of new cases – Fig. 5A) and between-unit (right, 3.8% of new cases) transmission. B: average proportion of secondary cases that originated from source cases of the five socio-spatial units of the population (“Source cases”) and average proportion of secondary cases that occurred in each socio-spatial unit (“New cases”). For within-unit transmission (left), the socio-spatial unit of the secondary case and the socio-spatial unit it originated from were necessarily the same as transmission occurred between two individuals of the same unit; on the contrary, between-unit transmission (right) always occurred between two individuals from different units.
Figure 8: Spatial transmission heterogeneity of brucellosis in the five socio-spatial units of the Alpine ibex population of the Bargy massif. To the left, socio-spatial units are ranked according to the average proportion of secondary cases that occurred in each socio-spatial unit by within-unit transmission (96.2% of new cases), to identify hotspots of transmission. Proportions are the same than in Figure 7B. To the right, each unit is ranked according to the difference between the proportion of new cases that originated from it and the proportion of new cases that occurred in it because of the other units (between-unit transmission, 3.8% of new cases). This corresponds to making the difference between the “source cases” column and the “new cases” column in Figure 7B. If the difference is positive, the unit was considered as a source of transmission, because more cases were generated than received. In the case of a negative difference, the unit was considered as a sink of transmission, because more cases were received than generated. The differences were calculated as: 0-0.001=-0.001 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 for Unit 4 and 0.005-0.022=-0.017 for Unit 5.