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Population dynamics of wild rodents induce
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Running headline: Stochastic fadeouts of Hantavirus in rodents

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Keywords

Dobrava-Belgrade virus; *Apodemus flavicollis*; Agent Based Model; stochastic fadeout; zoonotic spillover;

Abstract

- 1) Stochastic processes play an important role in the infectious disease dynamics of wildlife, especially in species subject to large population oscillations.
- 2) Here we study the case of a free ranging population of yellow-necked mice (*Apodemus flavicollis*) in northern Italy, where circulation of Dobrava-Belgrade hantavirus (DOBV) has been detected intermittently since 2001, until an outbreak emerged in 2010.
- 3) We analyzed the transmission dynamics of the recent outbreak using a computational model that accounts for seasonal changes of the host population and territorial behavior. Model parameters were informed by capture-mark-recapture data collected over 14 years and longitudinal seroprevalence data from 2010 to 2013.
- 4) The intermittent observation of DOBV before 2010 can be interpreted as repeated stochastic fadeouts after multiple introductions of infectious rodents migrating from neighboring areas. We estimated that only 20% of introductions in a naïve host population results in sustained transmission after two years, despite an effective reproduction number well above the epidemic threshold (mean 4.5, 95% credible intervals, CI: 0.65-15.8). Following the 2010 outbreak, DOBV has become endemic in the study area, but we predict a constant probability of about 4.7% per year that infection dies out, following large population drops in winter. In the absence of stochastic fadeout, viral prevalence is predicted to continue its growth to an oscillating equilibrium around a value of 24% (95% CI: 3-57%).
- 5) We presented an example of invasion dynamics of a zoonotic virus where stochastic fadeout have played a major role and may induce future extinction of the endemic infection.

Introduction

Stochastic fadeouts are spontaneous extinctions of an infection circulating in a population, due to random fluctuations in the epidemiological processes (Anderson & May 1991). Fadeouts are common when a pathogen is newly introduced in a population, even when transmission potential is above the epidemic threshold, because the few infectious individuals in the initial phase of invasion may all die or lose their infectiousness before passing on the pathogen (“epidemic” stochastic fadeout). However, spontaneous extinctions may also occur after a pathogen has established in a community, especially when the population size is small or if it is subject to large fluctuations because of its intrinsic vital dynamics (“endemic” stochastic fadeouts) (Lloyd-Smith et al. 2005).

Here, we study the potential impact of stochastic fadeouts on the transmission of Dobrava-Belgrade virus (DOBV) in a population of wild yellow-necked mice (*Apodemus flavicollis*) in northern Italy (Rizzoli et al, 2015) that was monitored from 2000 to 2013. In this rodent community, DOBV infection was detected for the first time in 2001 and recorded intermittently at low seroprevalence (around 2%) until 2009. Between 2010 and 2013 a rapid upsurge was observed, with about 12.5% of the rodents found infected by 2013 (Rizzoli et al. 2015).

DOBV belongs to the hantavirus genus (Bunyaviridae family), whose members chronically infect several rodent species without obvious symptoms or effects on mortality (Jonsson, Figueiredo & Valpalhti 2010). Hantaviruses are of high public health relevance because occasional spillover to humans, caused by rodent bites or by the inhalation of aerosolized excreta, may lead to the development of potentially lethal zoonoses such as hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS) (Jonsson, Figueiredo & Valpalhti 2010). In particular, DOBV is the most pathogenic hantavirus in Europe, with a case-fatality rate in humans of up to 12% (Papa 2012). Since DOBV was first isolated and genetically characterized in Slovenia in 1992 (Avsic-Zupanc et al. 1992), human and animal cases have been reported in 17 European countries to date

(Heyman et al. 2011; Vaheri et al. 2013). In our study region, no humans have reported symptoms of hantaviral disease so far, but two serosurveys on humans conducted a decade apart found a prevalence of 0.2% (1/488) in 2002 (Kallio-Kokko et al. 2006) and 4.3% (13/300) in 2015 (V. Tagliapietra et al., unpublished data). Therefore, the recent outbreak may pose concerns for public health and makes it important to establish epidemiological mechanisms in wild rodents and possible infection hazards for humans.

The yellow-necked mouse has been recognized as the most competent sylvatic reservoir host for DOBV in Europe (Avsic-Zupanc et al. 1992). It is widely distributed in forested areas, extending from Great Britain across continental Europe to the Urals (Amori et al. 2008). Transmission is thought to occur horizontally via direct contact during mating and fighting, or indirectly via virus-contaminated excreta in the environment (Clay et al. 2009), with no vertical transmission (Schmaljohn & Hjelle 1997). Populations of yellow-necked mice are characterized by strong seasonal oscillations, mainly caused by the restriction of the breeding season to the warmer months of the year (usually between March and September) (Macdonald & Tattersall 2001): during the winter, large population drops occur because there are no newborns compensating the natural mortality. Seasonal breeding has an important impact on transmission, as it imposes a temporal structure to the replenishment of susceptible individuals, which is a major driver of infectious disease dynamics (Anderson & May 1991; Keeling & Grenfell 1997). Another relevant ecological aspect of yellow-necked mice is their tendency to occupy a limited territory, where each individual adjusts its space use to best suit its own survival and reproductive strategies. Spatial confinement of rodents within their territory may exacerbate the role of stochasticity by reducing the susceptible population at risk of infection, compared to homogeneous mixing where all individuals in a population have the same likelihood of being infected (Keeling 1999). In order to investigate the role of stochastic effects on the rise in DOBV circulation in our study area in 2010-2013, we developed a spatially explicit stochastic model of DOBV transmission. The model is informed with data from a long-term observational study (Rizzoli et

al. 2015) on the local rodent population dynamics and home range, and calibrated to longitudinal seroprevalence data from the same study.

Materials and Methods

Wild rodent sampling

The rodent population was monitored in a permanent study site in the province of Trento, Italy (municipality of Cavedine: 50°56'15"N, 16°31'13.8"E, 750 m a.s.l.), as a part of a long-term study on zoonotic rodent-borne pathogens (Rizzoli et al. 2015; Tagliapietra et al. 2009). The trapping area is an isolated calcareous ridge covered with mature coppice woodland (Figure 1). Four trapping grids (labeled A, C, E and F) were continuously monitored in 2000-2013, with the exception of 2009 when no sampling was done. Each trapping grid consisted of an 8×8 square array of trap stations set 15 m apart (for a total grid surface of 1.1ha). Data collected in these grids were complemented by data from an extra grid of 18×18 traps (covering an area of 6.5 ha), labeled 'SG', set for a parallel project during 2005 and 2006. One standard Ugglan Multiple Live Trap (model 2, Granhab, Sweden) was set on the ground at each station and standard capture-mark-recapture techniques (CMR) were adopted (Pollock et al. 1990; Armstrup, McDonald & Manly 2005). Overall, one hundred and eighty five capture sessions (3 days/2 nights) were carried out, every 2 weeks from 2000 to 2008 (including the SG grid) and every month from 2010 to 2013.

At first capture, rodents were identified to species and individually marked with a subcutaneous-implanted Passive Integrated Transponder (PIT) tag, which can be read on subsequent captures by passing a PIT tag reader over the animal's body (Trovan Ltd., UK). At each sampling session, date, grid, trap station, and the PIT tag number were recorded and a blood sample was collected from the retro orbital sinus using a hematocrit microcapillary tube (100 µl). Animals were released unharmed at the site of capture. Captures, and all procedures were approved by the Wildlife Committee of the Autonomous Province of Trento. All blood samples collected were centrifuged (10,000 rpm for 12

min) in the laboratory to separate serum from blood. Serum samples were tested for immunoglobulin G against DOBV by using an indirect immunofluorescent antibody assay test (IFAT) on spot slides containing Vero E6 cells infected with the Dobrava/Ano-Poroja strain, as described in (Kallio-Kokko et al. 2006). Average population density and survival rates were estimated using the Jolly-Seber model (Jolly 1965; Seber 1965) for open populations as implemented within the Rcapture package for R statistical software (Baillargeon & Rivest 2007), using constant capture probabilities (see Supplementary Materials for details).

Estimation of rodent home range

We adopted the definition of home range as the probability of locating a given animal in a particular point in space (McNab 1963) and we estimated it using CMR data from 2000-2013. For each rodent, we considered all the traps in which the animal had been caught and defined the center of a rodent's territory (hereafter referred to as the rodent's "reference location") as the average of the coordinates of those traps. Then, we calculated the "capture distances", i.e. the distance from the rodent's reference location to each trap in which it was captured. We aggregated capture distances from all rodents into one of six categorical groups: i) 8-23m; ii) 23-38m; iii) 38-68m; iv) 68-150m; v) 150-450m; vi) >450m. This choice mirrored the spatial discretization of trap positions, and corresponds to captures occurring at a distance from the reference location of about i) 1 trap, ii) 2 traps, iii) 3 to 4 traps, iv) more than 4 traps but within the same grid, v) captures occurring in an adjacent grid, and vi) captures in non-adjacent grids.

Based on a preliminary analysis of capture distances (see Supplementary Material), we assumed that all animals have the same home range, which remains constant over time. We defined the following functional form for the home range (Eq. 1), representing the probability of the rodent to be found at a distance d from its reference location:

$$\frac{1}{d} \quad (1)$$

where α and β regulate the decay of probability with distance and K is a normalization constant.

Home range parameters α and β were estimated by minimizing the squared error between $f(d)$ and the empirical frequency distribution of capture distances.

Spatial structure in infections

To evaluate spatial transmission effects in the epidemiological dynamics, we considered the number of infected mice captured each year across the four grids (Table 1). In the null hypothesis that transmission is homogeneous over space, infected mice should be equally distributed across the grids; we tested this hypothesis using a multinomial test with four categories (corresponding to the four capture grids) and 25% probability for all categories.

Population model

We developed an agent-based model to represent the vital dynamics (i.e. births and deaths) of the mouse population inhabiting the site of data collection during the upsurge of positivity in 2010-2013 (Rizzoli et al. 2015). The modeled site comprises a rectangular territory of 221x1320 meters, enclosing the five data collection grids (Figure 1). The simulated population is initialized with a number of rodents based on the empirically observed average population density in the study site and outbreak years (about 6 rodents/ha). The average mortality rate of rodents was measured at about 0.25 / month from CMR data using the Jolly-Seber model (Jolly 1965; Seber 1965), corresponding to an average lifespan of 120 days (see Supplementary material). Survival rates were found to decrease during months of peak population density, consistently over multiple years, possibly due to increased predation from other species, competition for food, increased fighting during mating or decreased survival of juveniles. We did not explicitly model these phenomena, but instead took the simplifying assumption that mortality of rodents in the model occur at a density-dependent Poisson rate. Furthermore, a number of newborns are added each day to the population, according to a time-varying Poisson rate that grows during spring and falls to zero in autumn and

winter. Mortality and natality parameters were set to values that minimized the error between the observed and modeled population densities, as detailed in the Supplementary Material. Rodents at initialization and newborns were assigned to a reference location chosen uniformly over the space, as suggested by the empirical distribution of the reference locations of captured mice.

Hantavirus transmission dynamics

Hantavirus transmission dynamics were simulated over the study area for the period 2010-2013.

Specifically, the probability π_j of a susceptible rodent j to be infected over time step Δt (set to 1 day) is given by Eq. 2:

$$(2)$$

where λ_j is a density-dependent force of infection. The latter is defined by Eq. 3:

$$(3)$$

where β is the transmission rate, N is the current number of rodents in the simulated population, I_k if the k -th rodent is infected and 0 otherwise, r_{jk} is the distance between the reference location of the susceptible individual j and that of the k -th rodent, and $f(r_{jk})$ is the probability of finding the susceptible rodent at distance r_{jk} from its reference location. The dependence of the force of infection on distance via the estimated home range encodes the role of animal movements in the epizootic dynamics. Based on recent experimental observations, we assumed an SI transmission model, corresponding to lifelong hantaviral shedding by infected rodents at a constant rate (Voutilainen 2015).

Estimation of model parameters

Each simulation is initialized with a fully susceptible population, in which a single infectious individual (index animal) is introduced at day t_0 , between January 1st, 2009 and June 1st, 2010 (i.e. before the first observation of an infectious rodent in 2010). We do not consider further immigration events of infectious rodents after t_0 . Posterior distributions for the free model parameters (t_0 and

the transmission rate β) were estimated by exploring the binomial likelihood associated to capture data of seropositive individuals with a Monte Carlo Markov Chain (MCMC) approach (see Supplementary Material). Model predictions were obtained by running 100 stochastic model realizations for each of 100 combinations of parameter values sampled from the estimated posterior distributions. We computed the probability of stochastic fadeout over time, the expected prevalence at equilibrium, and the average number of secondary infections R_e caused by each infected rodent during the first simulated year. Given the low hantavirus prevalence throughout 2010 (about 5%) (Rizzoli et al. 2015), R_e can be considered a reasonable approximation of the basic reproductive number R_0 (Anderson & May 1991). Finally, we tested the sensitivity of model predictions with respect to assumptions on home range and population density (see Supplementary Material).

Results

Rodent home range

A total of 2,734 individual *A. flavicollis*, were live-captured and individually tagged over the 14 years of data collection. Figure 2 shows that the estimated home range ($a = 21.65$ m, $b = 1.93$) compares well with the empirical distribution of capture distances. The average territorial radius of rodents can be estimated as the average capture distance, which was found to be 22.9 m (95% CI: 21.5-24.3m).

The disaggregation of capture distances by year shows peaks in the average territorial radius in 2003, 2006 and 2010-2011 (Figure 3). Considering all years of observation, a statistically significant negative correlation was found between rodent density and average territorial radius in the same year (Spearman's $\rho = -0.58$, $p=0.042$). The average territorial radius considering only years 2010-2013 was 24.0 m, not significantly different from the average over all other years (t-test p-value: 0.62); this finding justifies the use of a home range estimated using movements from the whole observation period.

Hantavirus transmission dynamics

The observed seasonality of the population density resulted in a temporary growth of the force of infection and viral prevalence throughout spring and summer of each year. When population density declines in autumn and winter, due to the end of the mating season combined with natural mortality, the number of seropositive rodents also falls. The empirical observations of seroprevalence in the considered population are well reproduced by the model, as observed numbers of seropositive rodents are within model-estimated distributions, and in most cases close to the model-estimated mean (Figure 4). The increase in the amplitude of observed seroprevalence oscillations over the four simulation years (2010-2013) is interpreted by the model as increasing viral spread (i.e. the invasion phase of the infection).

The model estimates the initial introduction of the infected index animal generating the observed outbreak to have occurred at some point between February 2009 and March 2010, with a peak probability narrowly centered on June 2009 (Table 2 and Supplementary Material). The transmission parameter β (Table 2), multiplied by the home range probability distribution function, defines a distance-dependent transmission probability (displayed in the Supplementary Material). The estimated value of β implies that an infectious rodent could transmit the virus each day to about 4.6% (95% CI: 3.6 – 5.5%) of susceptible rodents living within its territorial radius (22.9m). This estimate of the transmission parameter translates into an average number of secondary infections per infected mouse, R_e , of about 4.5 (95% CI: 0.65-15.8) (Figure 5A), well above the epidemic threshold of 1. Thus, the estimated value of R_e is compatible with the observation of an outbreak, and its large variability is mainly due to the population density oscillations that induce a high stochasticity in the transmission process. The probability of an epidemic fadeout of a hantavirus outbreak started by a single infected host introduced in a completely susceptible rodent population is 58% by the end of 2009 and 80% by the end of 2010 (Figure 5B). In other words, the model

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predicts that, under the same conditions that originated the observed outbreak, transmission could spontaneously fade out within 2 years from the initial introduction in four out of five cases. This finding may explain the intermittent detection of hantavirus in the previous years and why presence of the virus in the area did not give rise to a sizeable outbreak: repeated introductions of index animals have likely resulted in epidemic stochastic fadeouts. According to model predictions, the probability of observing sustained transmission until the end of 2013 was only 12% (since 88% of simulations underwent stochastic fadeout by that time). The model additionally predicts that, of all simulations that remained endemic after 2013, about two fifths will go extinct within 2025, corresponding to a 4.7% yearly probability of endemic stochastic fadeout (see Supplementary Material for this calculation). This constant probability of extinction is explained by the model in terms of transmission bottlenecks in winter: every year, seasonal oscillations in the rodent population density dramatically reduce the number of infectious rodents, as well as the number and spatial proximity of susceptible individuals able to take up the infection, thereby increasing the chance of breaking the transmission chain. On top of seasonal oscillations in the relative prevalence, the model estimates a general increasing trend in seroprevalence in the period 2010-2013, which is predicted to stabilize, on average, after 2014 (Figure 6). In the absence of stochastic fadeout, the expected yearly prevalence at equilibrium is about 24% (3-57%).

The explicit inclusion of distance-dependence in transmission allowed the model to reproduce the spatial structure of infection data. In particular, we found that the distribution of observed infections over the four grids was significantly different from an equiprobable multinomial in 2013 (p -value <0.05 , Table 1); the statistical test did not reach significance in previous years because of the small sample size, but p -values tended to be low (Table 1). When implementing the same test on simulated infections in the spatial transmission model, the multinomial test was significant about half of the times (see Supplementary Material) and only 17% of simulations in the spatial model resulted in a p -value above 0.35 (the maximum obtained with our data, Table 1).

For comparison, a model with homogeneous mixing can reproduce the observed longitudinal seroprevalence with equal accuracy as the spatial model; however, infections would be equiprobably distributed across the four grids, thereby failing to capture the observed spatial pattern in data (see Supplementary Material).

Discussion

We investigated the role of stochastic effects associated to population dynamics and territorial behavior on the epidemiological dynamics of a zoonotic pathogen, using data from an outbreak of Dobrava-Belgrade hantavirus in a population of *A. flavicollis* (Rizzoli et al. 2015). Using an agent-based transmission model accounting for population density oscillations and rodent home ranges, we reproduced the observed outbreak under the assumption that a single infectious rodent was introduced in a completely naïve population at some point in 2009. The model was able to capture the observed intra-year and inter-year variations in the number of seropositive mice. The estimated number of secondary infections per infected rodent (as a proxy for the basic reproduction number) was far above the epidemic threshold; however, a high variability across simulations was found, due to oscillations in population size. This variability resulted in a high probability of epidemic stochastic fadeouts after the introduction of the first index case (Anderson & May 1991), providing a plausible and parsimonious interpretation for the intermittent, low prevalence of DOBV observed in previous years (2001-2008). Since the prevalence in the first 8 years of monitoring was too low to be compatible with sustained transmission, we propose that repeated introductions of the virus resulted in sporadic transmission events but eventually ended with stochastic fadeout of the transmission chains. The source of repeated introductions is likely the migration of infected mice from neighboring areas. For example, DOBV was detected in 2007 and 2008 in other live-capture grids deployed for parallel surveillance projects, situated a few hundred meters to the north of the study area. Although these grids are ecologically separated from the study area by environmental obstacles (a forest service road and open fields), exchange of rodents between these additional grids

and the study area was recorded. Estimating the rate of immigration of infected animals is extremely difficult, as it depends on the rate of immigrating rodents from neighboring areas and on the unknown relative prevalence of infection in their sites of origin. The analysis of time series of captures of infected rodents in 2000-2008 (Rizzoli et al. 2015) suggests that infectious mice have immigrated in the study area on average every 2 to 4 years. However, over this period of time, a transmission chain initiated by a previously immigrated index animal has a high chance of becoming extinct; conversely, if an outbreak has commenced, the overall prevalence will have likely stabilized to a value that will be barely affected by the second immigrated infectious rodent.

Our model predicts that stochastic effects play an important role in disease dynamics even after the infection has established, by allowing a constant probability of endemic stochastic fadeouts due to transmission bottlenecks during winters, when both population density and infection prevalence reach their lowest levels. The 4.7% yearly probability of stochastic fadeout suggested by our transmission model is likely to be an underestimate, considering that observed population density troughs tend to be deeper than model-simulated ones (see Supplementary Material). In the absence of stochastic fadeouts, the average prevalence at equilibrium is predicted to oscillate between a minimum of about 10% in winter and a maximum of 39% in summer, resulting in an increased potential risk of spillover to humans with respect to 2013.

The transmission dynamics of the considered outbreak can be reproduced by a non-spatial, homogenous transmission model (see Supplementary Material), with similar accuracy and qualitative conclusions. However, we showed that the inclusion of the territorial behavior of rodents was needed to reproduce the spatial heterogeneity of infection data.

Longitudinal capture data collected over 14 years allowed us to derive some useful results on the territorial behavior of rodents, which we discuss briefly. We estimated the rodents' average territorial radius about 23m, a value that compares well with the 14m (95%CI 5-24m) found for

Slovenian conspecifics subject to territorial competition with *Apodemus agrarius* (Vukicevic-Radic et al. 2006). Animal movement may be influenced by a number of factors, including habitat quality, population density, sex, age and season (Erlinge et al. 1990; Hubbs & Boonstra 1998; Getz et al. 2005; Steinmann et al. 2005; Moorhouse & Macdonald 2008). We found that rodents from years of lower average population density had significantly larger territories (territorial radius up to 34m) than rodents in high population density years (as low as 17m). This finding is consistent with previous results (Ostfeld & Canham 1995; Mazurkiewicz & Rajska-Jurgiel 1998; Priotto, Steinmann & Polop 2002), which show that home range size increases when population density is lower. We also found slightly larger territorial radii for males than females, but no seasonal variation (Supplementary Material); there was insufficient information on rodent age to assess possible temporal adjustments of the territorial radius over a rodent's lifetime.

The main limitations of this study derive from gaps of knowledge on hantavirus transmission and that of DOBV in particular. More specifically, the model assumed lifelong transmission (SI model) based on recent findings showing lifelong shedding of the Puumala hantavirus in saliva, urine and faeces of its rodent host, the bank vole (*Myodes glareolus*) (Voutilainen et al. 2015). However, the natural history of infection may be different for different genotypes (e.g. DOBV) and hosts (e.g. the yellow-necked mice). The only data available on DOBV in *A. flavicollis* seems to suggest an overall reduction of the viral load in several tissues after one month from initial infection. However, these data were based on only five individuals, and results are even less clear when considering only measures from body fluids and tissue relevant for transmission, i.e. blood and bladder/urine (Korva et al. 2009).

A key model assumption is the density-dependent force of infection. Previous mathematical models describing the dynamics of rodent-hantavirus interactions (Sauvage et al. 2003; Sauvage et al. 2007) used density-dependence to model transmission occurring by environmental spreading of the virus,

and frequency-dependence to represent direct contact during mating and fighting, Both density- and frequency-dependent components of the force of infection were found to be necessary to reproduce Puumala virus transmission dynamics (Sauvage et al. 2003; Sauvage et al. 2007). In our case, however, the longitudinal seroprevalence and the spatial structure of DOBV infections were reproduced without the need of a frequency-dependent component of transmission. Our modeling choice was dictated mainly by the inability of our experimental setting to provide information on direct encounters among mice. In contrast, capture data allowed us to model the rodent home range, and consequently their potential for both spatial environmental dissemination of the virus through their excreta and for encountering neighboring rodents via animal movement. However, it is not possible to discriminate the relative contribution of the two routes from the available data.

On top of intra-annual oscillations in population density due to the vital dynamics of yellow-necked mice, inter-annual changes in the average yearly density were observed during the whole period of observation of our rodent population. These fluctuations are probably related to changes in abundance of food resources, such as mast years where a super abundance of seed occurs, which in turn can depend heavily on climatic variables (Piovesan & Adams 2001; Övergaard, Gemmel & Karlsson 2007). Additional explanations for inter-annual population changes may also be found in predator dynamics (Jędrzejewski & Jędrzejewska 1993) as well as in the epidemiology of other infections/parasites affecting the fecundity or survival of yellow-necked mice. The complex interactions among all these factors make inter-year variations in population density very hard to predict. During 2010-2013, the population density remained relatively stable; therefore, our parameter estimation should not have been affected significantly by these considerations. To assess the possible outcome of population changes, a sensitivity analysis of model predictions was performed using the same posterior distribution for parameters and different scenarios for population densities and rodent home range (Supplementary Material). Higher densities and broader home ranges both increase the equilibrium prevalence and reduce the probability of

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stochastic fadeouts. Since population density and the breadth of the home range were inversely correlated, we also tested the impact of a high population density scenario combined with a narrow home range and vice versa. In this case, we observed that population density exerts a dominating force on model predictions. In the case of a mast year with population density and rodent home range close to those observed in 2007 (worst case scenario for hantavirus transmission), we expect the prevalence to rise towards an oscillating equilibrium around 57%, with no chance of endemic fadeouts. On the other hand, if the population density should fall to levels as low as that of 2003, an endemic fade out would be highly likely within a few years, even accounting for the increased territorial radius of rodents.

In summary, multiple factors are responsible for the presence, persistence and spread of hantavirus in rodent populations. In a previous study (Rizzoli et al. 2015), we pointed out the importance of the mean annual precipitation and maximum temperature, together with higher individual body mass as possible drivers of increased hantavirus prevalence. Here, we inferred that the ecological characteristics of the considered population (animal home range and oscillations in population size) induce a high stochasticity in transmission dynamics that can bring the infection to extinction. Predictions on the actual course of the outbreak are highly uncertain and suggest continued surveillance on the rodent population is necessary. Nonetheless, accounting for stochastic effects provided a robust interpretation of pre-outbreak dynamics, identified variations in rodent home range and population density as crucial factors for sustaining transmission, and allowed us to gauge the probability and severity of potential future scenarios.

Author contributions

GG, PP, SM, VT and SP conceived of the study; VT collected the data; GG and VT analyzed the data; GG performed model simulations; GG, PP, SM, VT, SP, HH and AR contributed to interpret the results; GG, PP, SM, VT, SP, HH and AR drafted the manuscript.

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The authors declare no conflict of interest.

Data accessibility

The datasets supporting this article have been uploaded as part of the supplementary material.

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Grid	2010	2011	2012	2013
A	0	2	3	1
C	2	5	7	1
E	0	0	2	7
F	2	3	3	1
p-value	0.34	0.16	0.35	0.02

Figures and Tables

Table 1. Distribution of infected mice by capture grid and year and p-values from equiprobable multinomial tests.

Parameter	Meaning	Unit	Mean	95% CI
t_0	Date of introduction of index animal	date	August 13 th 2009	March 21 st 2009 - February 17 th 2010
β	Transmission parameter	days ⁻¹	$9.42 \cdot 10^{-2}$	$(7.41 - 11.3) \cdot 10^{-2}$

Table 2. Parameter estimates from the posterior distributions.

Figure 1. Study site map in Cavedine, Italy with location of five capture grids (A, C, SG, E and F), and a corresponding model abstraction.

Figure 2. Empirical frequency distribution of rodents' capture distances from the reference location and corresponding probability estimates using the home range.

Figure 3: Average territorial radius and 95%CI (black points and lines, respectively) vs. estimated rodent density (yellow line) over time.

Figure 4. Observed numbers of rodents testing seropositive for DOBV at each capture session (blue circles) and corresponding posterior distributions (mean, 50%CI and 95%CI; yellow) estimated by the model.

Figure 5. A) Histogram of the estimated number of secondary infections generated by the index case during the first year of infection; B) Cumulative probability of stochastic fadeouts, based on the analysis of 10,000 stochastic simulations with parameters sampled from their posterior distributions and starting from a single infectious host.

Figure 6. Model estimates on the relative prevalence of DOBV in the study site for 15 years of simulation. Solid line: average prevalence; dark shaded areas: predictions between the first and third quartiles; light shaded areas: 95% CI.







