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Modelling hantavirus in fluctuating populations of bank voles: the role of indirect transmission on virus persistence

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Summary

1. Using field data published in the literature, we investigated pathogen dynamics and conditions of persistence in a mathematical model of the bank vole (*Clethrionomys glareolus*)–Puumala hantavirus system. The host population is assumed to have a 3-year periodic cycle. The duration of very low host density is critical for virus transmission and survival.
2. Field epidemiological data strongly suggested a transmission of the hantavirus by the contaminated environment. We thus studied whether this 'indirect' transmission affected the virus persistence in the host population.
3. The model assumptions were derived from the following conditions found in the literature: (1) there is no additional mortality nor fecundity loss due to the virus in infected hosts, thus the cyclic demographical pattern is not due to the virus; (2) no remission has been observed, thus we did not consider the existence of recovered individuals; (3) adult females are territorial and juveniles disperse to find a new territory and reach sexual maturity. A fragmented landscape was assumed to occur: individuals can live in favourable or unfavourable patches.
4. The model was a compartmental model; the population was structured into susceptible or infectious individuals. We considered two age classes, juveniles and adults, and two sites (populations) connected by juvenile dispersal.
5. Model dynamics accurately predicted the cyclic trend in disease prevalence as observed in epidemiological studies. They also showed that indirect transmission significantly increased the probability for the virus to persist during the low-density period of the host population. More precisely, even a low survival rate of the virus outside the host was sufficient to decrease extinction risk of the infection by stochastic events.
6. Elasticity analysis showed a high robustness of the model to changes in the parameters of indirect transmission but a high sensitivity to changes in adult density.

Key-words: compartmental epidemiological model, contamination by the ground, host–virus system dynamics, multi-annual cycles.

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Introduction

The long-term spread and persistence of viral diseases are generally believed to depend essentially on the number and type of contacts between hosts and thus the number of transmission opportunities (Swinton 1998). Most host–parasite systems that have been studied are characterized by continuous, uninterrupted interactions between individuals over time. Recently, attention has focused on spatial heterogeneity of disease transmission (Grenfell & Harwood 1997) but little consideration has been given to the influence of cyclic host population growth on virus persistence, except about the susceptible part of a constant population (Grenfell & Bolker 1994). In the most extreme cases, the susceptible host population may disappear entirely (Berthier *et al*. 2000 in a feral cat (*Felis catus*) population). Several small mammal populations are subject to regular, often abrupt, seasonal or yearly population size variability.

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The success of viruses facing such disturbance depends on their ability to avoid extinction in the host population.

Within the Bunyaviridae family, the hantavirus genus provides a good example of interaction between viruses and fluctuating host populations. Hantaviruses fall into the emerging or re-emerging disease category since the first human infection was detected in France in 1982 and the first epidemic spread of American hantavirus pulmonary syndrome (HPS) occurred in 1993 (Schmaljohn & Hjelle 1997). In Eurasia, these hantaviruses are responsible for haemorrhagic fever with renal syndrome (HFRS), a zoonotic disease of varying severity (see McCaughey & Hart 2000 for a recent review). In Western Europe, the aetiological agent of HFRS is the Puumala virus. The main hosts of hantaviruses are rodents or insectivores, but each strain of virus is specific to a host species (Monroe *et al*. 1999). The bank vole is the host of the Puumala virus strain and vector of the mildest form of HFRS, nephropathia epidemica (NE).

In this paper, we wished to examine the dynamics of hantavirus in a bank vole population that fluctuates seasonally and also yearly with a 3-year period in some parts of its distribution area (Hansson, Jedrzejewska & Jedrzejewski 2000; Yoccoz, Hansson & Ims 2000; Heyman *et al*. 2001). Although bank vole populations may reach very low densities in the Ardennes area of Belgium (as low as one individual per hectare during several months: Escutenaire *et al*. 2000; unpublished data), the Puumala hantavirus (PUU) is endemic.

Two strategies whereby a virus could persist in rodent populations during low-density periods have been discussed previously (Begon *et al*. 1999; Abbot, Ksiazek & Mills 1999). The first strategy relates to the chronic feature of the infection: infection of a long-lived class of individuals provides a reservoir of infected hosts which sustains the virus during the period of low host density. Such a persistence mode is possible because there is no associated host mortality and the virus is shed chronically by infected rodents (Verhagen *et al*. 1986; Bernshtein *et al*. 1999). An example is the American hantavirus 'Sin Nombre' that infects dominant individuals, the most long-lived class, of deer mice *Peromyscus maniculatus* (Abbot *et al*. 1999). Infection occurs via a bite from an infected individual and a correlation between wounds and seropositivity to Sin Nombre has been found (Abbot *et al*. 1999). Such a correlation has never been reported in the bank vole because aggressive encounters are much less frequent than in deer mice (Mironov 1990). The environment of bank voles in Eastern France is much less heterogeneous than in the Western American desert and dominance status does not result in markedly different survival rates among social classes. This chronic strategy cannot explain the long-term persistence of the Puumala virus in the fluctuating bank vole population.

The second strategy is to survive in stable, or at least asynchronous, populations of a reservoir host living in sympatry with the primary host (Begon *et al*. 1999). Such a dual host tropism allows the virus to persist for extended periods of time. Bank voles could then become infected from these reservoir hosts when bank vole density increases (Mills *et al*. 1999; Escutenaire *et al*. 2000). Such host switches have been documented in the evolutionary history of rodent–hantavirus systems (Vapalahti *et al*. 1997, 1999; Scharninghausen *et al*. 1999) while a viral adaptation to different species has been observed over a short time scale (Monroe *et al*. 1999). The wood mouse *Apodemus sylvaticus* has been recently detected PUU antibody-positive by ELISA (Escutenaire *et al*. 2000) but this technique presents a lack of virus strain specificity (Heyman *et al*. 1999). However, positive wood mice were found only during the peak of vole density (Escutenaire *et al*. 2000). Thus this appears to be a spillover situation rather than a secondary reservoir situation.

A third strategy for persistence during low-density periods consists of viral survival outside its host and has been overlooked until now. Human contamination by hantaviruses occurs mainly through inhalation of dust contaminated by rodent secretas (Ahlm *et al*. 1997; Chaturvedi *et al*. 2000; Ijaz, Suchmann & Hjelle 2000). Also, the presence of infected bank voles in low-density phases is related to humid environments (Verhagen *et al*. 1986; Ahlm *et al*. 1997). Thus the focal high prevalence of PUU in bank voles (Heyman *et al*. 2001) could be explained by survival of the virus in the soil litter, depending on microclimatic or chemical parameters. This suggests that the virus remains active outside the host. Viral survival in the damp ground could permit transmission of the virus to a susceptible bank vole without the physical presence of the infectious rodent. Some viruses are known to have adopted such a strategy, e.g. the parvovirus infection in the domestic cat *F. catus* (Berthier *et al*. 2000).

Here, we investigate the importance of this potential indirect mode of transmission in virus persistence in fluctuating bank vole populations using a mathematical modelling approach. We begin by reviewing the available data on bank voles and hantaviruses, in order to identify the important epidemiological, biological and clinical features of the infection epidemic. Then, we describe the structure of the mathematical models, including and excluding indirect transmission. Next, we present results of numerical simulations. Finally, we discuss our findings in relation to the key features of virus persistence, concentrating especially on data required to test the predictions of the model.

Hantavirus–bank vole system

BANK VOLE POPULATION STRUCTURE AND DYNAMICS

Bank voles are characterized by a short life expectancy of several months (Gliwicz 1983; Yoccoz & Mesnager 1998) and seasonally and multi-annually fluctuating

populations: numbers increase during one reproductive season, stay high until the following summer, then rapidly decrease during winter to very low densities for 1–2 years (Hansson *et al*. 2000). In Fennoscandia, density varied by a factor of 10–100 within a cycle of 3–4 years (Haukisalmi & Henttonen 1990). During a 3-year study (1996–99, Escutenaire *et al*. 2000; Heyman *et al*. 2001) in the Ardennes, population density varied from one to 70 individuals per hectare. These large and rapid changes are made possible both by the large reproductive output of bank voles and by the fact that up to three to four generations can follow each other in a given summer.

Litter size and length of reproductive season vary among years, but the observed variation does not appear to be important for population dynamics (Bujalska 1988; Verhagen, Leirs & Verheyen 2000). The number of births is related to the number of breeding females, which changes with respect to phase and density: at peak phase and high densities, bank voles mature later and at a lower rate than at increasing and low densities (from 1% to 100% according to density, Bujalska 1988, 1990; Prévot-Julliard *et al*. 1999). In addition to recruitment rate, pregnancy rate is much lower when densities are high than when densities are low (Tkadlec & Zejda 1998; Verhagen *et al*. 2000). Bank voles are generalist consumers and habitat quality correlates with density of shelters and plant cover (which form the protective layer against predators), rather than with a specific source of food. Vole density may differ substantially within the same area of forest depending on the abundance and spatial distribution of shelters. Because breeding females are territorial the number of suitable places for sexually active females is limited by the distribution of the understorey, which significantly affects habitat quality (Mazurkiewicz 1994). Delay in sexual maturation is thought to be due to social constraints (Bujalska 1988, 1990; Prévot-Julliard *et al*. 1999; Verhagen *et al*. 2000) linked to female territoriality (Bondrup-Nielsen 1985; Bujalska 1988, 1990; Gliwicz 1993; Kapusta & Marchlewska-Koj 1998) and resource availability (Prévot-Julliard *et al*. 1999; Verhagen *et al*. 2000). Juveniles of both sexes disperse in order to find a territory where they can reproduce (Bondrup-Nielsen 1985; Gliwicz & Ims 2000). Sexual maturation is associated with dispersal occurrence and is often acquired soon after settlement in a new territory (Ishibashi, Saitoh & Kawata 1998 for *Clethrionomys rufocanus*). In habitats rich in terms of shelter and food, territories are smaller and more juveniles settle in their natal patch than in poor habitats: at a given density, pressure to departure is lower in optimal sites in comparison to suboptimal sites (Ishibashi *et al*. 1998).

HANTAVIRUS-ASSOCIATED INFECTION EPIDEMIC

Once infected, individuals do not recover from the disease (Schmaljohn & Hjelle 1997) but the virus does not affect survival and fecundity (Yanagihara, Amyx & Gadjusek 1985; Bernshtein *et al*. 1999, for a study in natural populations). No gender effects in prevalence have been documented in the bank vole (Verhagen *et al*. 1986; Escutenaire *et al*. 2000) except for one-study (Bernshtein *et al*. 1999). The delay between time of infection and time of excretion in this chronic infection is short compared to rodent life expectancy. Only one study has reported a vertical transmission of Seoul and Hantaan serotypes between mother and offspring in *Rattus norvegicus* and *A. agrarius* (Song 1999; see McCaughey & Hart 2000 and Hart & Bennett 1999 for recent reviews on hantaviruses). We will therefore assume neither exposed class or vertical transmission.

Juveniles and adults differ in their probability to contract infection (adults are found infected more often than juveniles: Verhagen *et al*. 1986; Calisher *et al*. 1999). Maturing individuals change their behaviour dramatically for a short time period. During the juvenile stage they stay within their mother's territory; they have few opportunities to be exposed to the virus. During dispersion, they cross several adult vole territories and explore a greater area than at any other stage of their life. They are probably very cautious with regard to scent marks to detect empty territories. When they look for a territory, their probability of being exposed to the virus is likely to increase. Those juvenile dispersers should have great importance in virus dispersion, even if they constitute a minority of the infected population.

When density increases, the utilized area (the percentage of traps visited in the capture plot) increases; and so does the intensity of space use (the number of bank voles captured per specific trap) (Mazurkiewicz 1994), which implies an increasing number of overlapping territories. Landscape features, resource abundance, rodent community structure and behaviour of infected hosts have been proposed as factors influencing the patchy distribution of hantavirus infection (Glass *et al*. 1998; Abbot *et al*. 1999; Boone *et al*. 2000). The first two factors influence the spatial behaviour of bank voles (Bondrup-Nielsen 1985), while the last two factors result from this spatial behaviour.

Because transmission is considered widely to be airborne between rodents, this corresponds to mass action transmission rather than to proportionate mixing (Mena-Lorca & Hethcote 1992). We thus hypothesize that the number of contacts increases linearly with host population density.

Mathematical model of the bank vole–hantavirus system

BANK VOLE POPULATION DYNAMICS

The cyclicity of host populations at seasonal and multi-annual scales is the most striking feature of

bank vole dynamics. This cyclicity does not result from infection by hantaviruses. Many hypotheses have been discussed to explain the cyclicity of vole densities, e.g. predation and variation of food levels (Jedrzejewska & Jedrzejewski 1998), without any definitive consensus (Hansson *et al*. 2000; Yoccoz *et al*. 2001). In our first model, we generated a realistic demographic cycle using a small number of parameters: seasonal variation of birth rate and carrying capacities and density dependence of sexual maturation and juvenile dispersal. Our model included two age classes (juveniles and adults) in each patch. The sexes were not differentiated here as prevalence is widely the same in both of them.

We assumed that the reproductive season lasted 6 months per year (Verhagen *et al*. 2000) and that fecundity rates decreased with adult density. We assumed that only juveniles dispersed to acquire sexual maturity. Dispersal is associated with a survival cost and intensity of dispersal is assumed to be dependent on adult density (Bondrup-Nielsen 1985; Gliwicz 1993; Gliwicz & Ims 2000). We considered a population distributed over two sites, differing in quality (optimal and suboptimal) and connected by juvenile dispersal. Overall carrying capacity and recruitment of breeding individuals were regulated by a site-specific density-dependent term. We assumed that carrying capacity would fluctuate as seed and fruit production vary over a 3-year period (Ostfeld & Keesing 2000). These changes in carrying capacity appeared crucial for modelling the fluctuating vole dynamics (Hansen, Stenseth & Henttonen 1999 in a study of *C. rufocanus*). Seasonal variation of density dependence (Yoccoz *et al*. 2001) was not considered explicitly but occurs through the assumption of a density-dependent maturation process. For example, only 50% of juveniles matured in their natal habitat as soon as physiologically possible, i.e. at 1 month (Bujalska 1990), when adult density reached 25 rodents $\times$ ha^{-1}; whereas the other 50% of juveniles dispersed and acquired sexual maturity in the other (suboptimal) site. The proportion of maturation in the natal patch decreased with density.

First, we present the demographic model without the disease

Population dynamics on site 1 (optimal):

$$\begin{cases} \dfrac{dJ_1}{dt} = b \times A_1 - [m_j + kj \times (J_1 + A_1)] \times J_1 - \dfrac{\tau \times J_1}{(1 + \gamma_1 \times A_1)} \\ \dfrac{dA_1}{dt} = \dfrac{\tau \times J_1}{(1 + \gamma_1 \times A_1) \times (1 + \delta_1 \times A_1)} + \dfrac{\tau \times s_{21} \times \delta_2 \times A_2}{(1 + \gamma_2 \times A_2) \times (1 + \delta_2 \times A_2)} \times J_2 - [m_a + ka_1 \times (J_1 + A_1)] \times A_1 \end{cases}$$

Population dynamics on site 2 (suboptimal):

$$\begin{cases} \dfrac{dJ_2}{dt} = b \times A_2 - [m_j + kj \times (J_2 + A_2)] \times J_2 - \dfrac{\tau \times J_2}{(1 + \gamma_2 \times A_2)} \\ \dfrac{dA_2}{dt} = \dfrac{\tau \times J_2}{(1 + \gamma_2 \times A_2) \times (1 + \delta_2 \times A_2)} + \dfrac{\tau \times s_{12} \times \delta_1 \times A_1}{(1 + \gamma_1 \times A_1) \times (1 + \delta_1 \times A_1)} \times J_1 - [m_a + ka_2 \times (J_2 + A_2)] \times A_2 \end{cases}$$

where:
J_i and A_i = juvenile and adult densities on site i;
m_j, m_a = juvenile and adult natural mortality, respectively;
$b(t)$ = number of juveniles produced per adult breeding female per year;
$kj(t)$, $ka_1(t)$, $ka_2(t)$ = induced density-dependent effect and seasonal variation on mortality rates for juvenile and adult classes (see below for the relationships with the carrying capacities in the periodic case);
τ = reciprocal of the length of juvenile stage;
γ_1, γ_2 = density-dependent effect on the maturation rate of juveniles, e.g. for $A_1 = 1/\gamma_1$, 50% of juvenile females mature in patch 1 (Mazurkiewicz 1994; Ishibashi *et al*. 1998; Prévot-Julliard *et al*. 1999);
δ_1, δ_2 = induced adult density dependence on the juvenile dispersal rate (Ishibashi *et al*. 1998), e.g. for $A_1 = 1/\delta_1$, 50% of juveniles moved from patch 1 to patch 2. Site quality was inversely related to γ and δ as demonstrated by Ylönen (1990); and s_{12}, s_{21} = survival rate of dispersing juveniles between the two patches, e.g. predation or starvation.

EPIDEMIOLOGICAL MODEL

The host population was divided into two categories: susceptible, S, and infected, I. We collapsed the exposed stage, because it is very short (several days, McCaughey & Hart 2000) and assumed direct transmission from the infectious class to the susceptible one. Dynamics of each patch was modelled by a standard SI model. Birth and death rates were not affected by infection (Yanagihara *et al*. 1985). For the sake of simplicity, we assumed that juveniles did not become infected during dispersal: susceptible juveniles left their natal site and established in a new site as susceptible adults.

We chose a classical mass-action term βSI as the incidence function. Begon *et al*. (1998) showed that mass-action gives a good description of the dynamics of the bank vole–cowpox system. We then integrated disease dynamics with direct transmission into the previous model. Lastly, we incorporated ground contamination and decontamination by the virus (see Fig. 1).

Population dynamics on site 1 (optimal):

$$\begin{cases}
\frac{dSj_1}{dt} = b \times (Sa_1 + Ia_1) - [m_j + kj \times (Sj_1 + Ia_1 + Sa_1 + Ia_1)] \times Sj_1 - \frac{\tau \times Sj_1}{(1 + \gamma_1 \times (Sa_1 + Ia_1))} - \beta \times (Ij_1 + Ia_1) \times Sj_1 - \varepsilon \times G_1 \times Sj_1 \\
\frac{dIj_1}{dt} = \beta \times (Ij_1 + Ia_1) \times Sj_1 + \varepsilon \times G_1 \times Sj_1 - [m_j + kj \times (Sj_1 + Ia_1 + Sa_1 + Ia_1)] \times Ij_1 - \frac{\tau \times Ij_1}{(1 + \gamma_1 \times (Sa_1 + Ia_1))} \\
\frac{dSa_1}{dt} = \frac{\tau \times Sj_1}{(1+\gamma_1 \times (Sa_1 + Ia_1)) \times (1 + \delta_1 \times (Sa_1 + Ia_1))} + \frac{\tau \times Sj_2 \times s_{21} \times \delta_2 \times (Sa_2 + Ia_2)}{(1+\gamma_2 \times (Sa_2 + Ia_2)) \times (1 + \delta_2 \times (Sa_2 + Ia_2))} - [m_a + ka_1 \times (Sj_1 + Ia_1 + Sa_1 + Ia_1)] \times Sa_1 - \beta \times (Ij_1 + Ia_1) \times Sa_1 - \varepsilon \times G_1 \times Sa_1 \\
\frac{dIa_1}{dt} = \frac{\tau \times Ij_1}{(1+\gamma_1 \times (Sa_1 + Ia_1)) \times (1 + \delta_1 \times (Sa_1 + Ia_1))} + \frac{\tau \times Ij_2 \times s_{21} \times \delta_2 \times (Sa_2 + Ia_2)}{(1+\gamma_2 \times (Sa_2 + Ia_2)) \times (1 + \delta_2 \times (Sa_2 + Ia_2))} - [m_a + ka_1 \times (Sj_1 + Ia_1 + Sa_1 + Ia_1)] \times Ia_1 + \beta \times (Ij_1 + Ia_1) \times Sa_1 + \varepsilon \times G_1 \times Sa_1
\end{cases}$$

Population dynamics on site 2 (suboptimal):

$$\begin{cases}
\frac{dSj_2}{dt} = b \times (Sa_2 + Ia_2) - [m_j + kj \times (Sj_2 + Ia_2 + Sa_2 + Ia_2)] \times Sj_2 - \frac{\tau \times Sj_2}{(1 + \gamma_2 \times (Sa_2 + Ia_2))} - \beta \times (Ij_2 + Ia_2) \times Sj_2 - \varepsilon \times G_2 \times Sj_2 \\
\frac{dIj_2}{dt} = \beta \times (Ij_2 + Ia_2) \times Sj_2 + \varepsilon \times G_2 \times Sj_2 - [m_j + kj \times (Sj_2 + Ia_2 + Sa_2 + Ia_2)] \times Ij_2 - \frac{\tau \times Ij_2}{(1 + \gamma_2 \times (Sa_2 + Ia_2))} \\
\frac{dSa_2}{dt} = \frac{\tau \times Sj_2}{(1+\gamma_2 \times (Sa_2 + Ia_2)) \times (1 + \delta_2 \times (Sa_2 + Ia_2))} + \frac{\tau \times Sj_1 \times s_{12} \times \delta_1 \times (Sa_1 + Ia_1)}{(1+\gamma_1 \times (Sa_1 + Ia_1)) \times (1 + \delta_1 \times (Sa_1 + Ia_1))} - [m_a + ka_2 \times (Sj_2 + Ia_2 + Sa_2 + Ia_2)] \times Sa_2 - \beta \times (Ij_2 + Ia_2) \times Sa_2 - \varepsilon \times G_2 \times Sa_2 \\
\frac{dIa_2}{dt} = \frac{\tau \times Ij_2}{(1+\gamma_2 \times (Sa_2 + Ia_2)) \times (1 + \delta_2 \times (Sa_2 + Ia_2))} + \frac{\tau \times Ij_1 \times s_{12} \times \delta_1 \times (Sa_1 + Ia_1)}{(1+\gamma_1 \times (Sa_1 + Ia_1)) \times (1 + \delta_1 \times (Sa_1 + Ia_1))} - [m_a + ka_2 \times (Sj_2 + Ia_2 + Sa_2 + Ia_2)] \times Ia_2 + \beta \times (Ij_2 + Ia_2) \times Sa_2 + \varepsilon \times G_2 \times Sa_2
\end{cases}$$

where:
Sj_i, Sa_i, Ij_i, Ia_i = susceptible and infected densities for juveniles and adults, respectively; and β = mass action incidence contact rate.

The modelling approach of site contamination/decontamination dynamics was similar to the one used in Berthier *et al*. (2000):

$$\frac{dG_i}{dt} = \varphi \times (Ij_i + Ia_i) \times (1 - G_i) - d \times G_i \quad i = 1, 2$$

where
G_i = contaminated proportion of patches i;
ε = indirect rodent contamination rate (ground to rodents);
φ = ground contamination rate (rodents to ground); and
d = ground decontamination rate.

ELASTICITY ANALYSIS

The distinguishing characteristic of our model is the combination of the interaction between the hantavirus and bank voles with realistic host population cyclic dynamics, at the cost of analytical tractability. Moreover, some demographic and epidemiological parameters were largely unknown. We thus conducted elasticity analyses of the model with indirect transmission by a series of numerical simulations to determine the set of parameters that had most influence on disease dynamics. Elasticity (De Kroon *et al*. 1986) was derived from the model by calculating $e_a = \left(\frac{a}{\lambda}\right) \times \left(\frac{d\lambda}{da}\right)$ where a denotes the parameter in question and $\left(\frac{d\lambda}{da}\right)$ is the sensitivity of λ to changes in a. The relative effect of each parameter to changes in prevalence, population density and contaminated ground proportion, the model outputs which best described disease dynamics, were thus estimated through elasticity analysis. We derived elasticity, calculated numerically, by varying the parameter by $\pm 10\%$.

Models and simulations were performed with MATLAB (The MathWorks Inc.).

SIMULATIONS

Parameter values were defined on a yearly scale. The maximum prevalence was estimated as the ratio between the maximum density of infected rodents and the maximum density reached by the population at the peak year. A short time gap existed between those two events because of the delay between the maximum rate of infectious contacts and the peak number of infected rodents. Our estimate was more meaningful than the instantaneous prevalence, which could be very high immediately following the rapid decline during the resulting low densities.

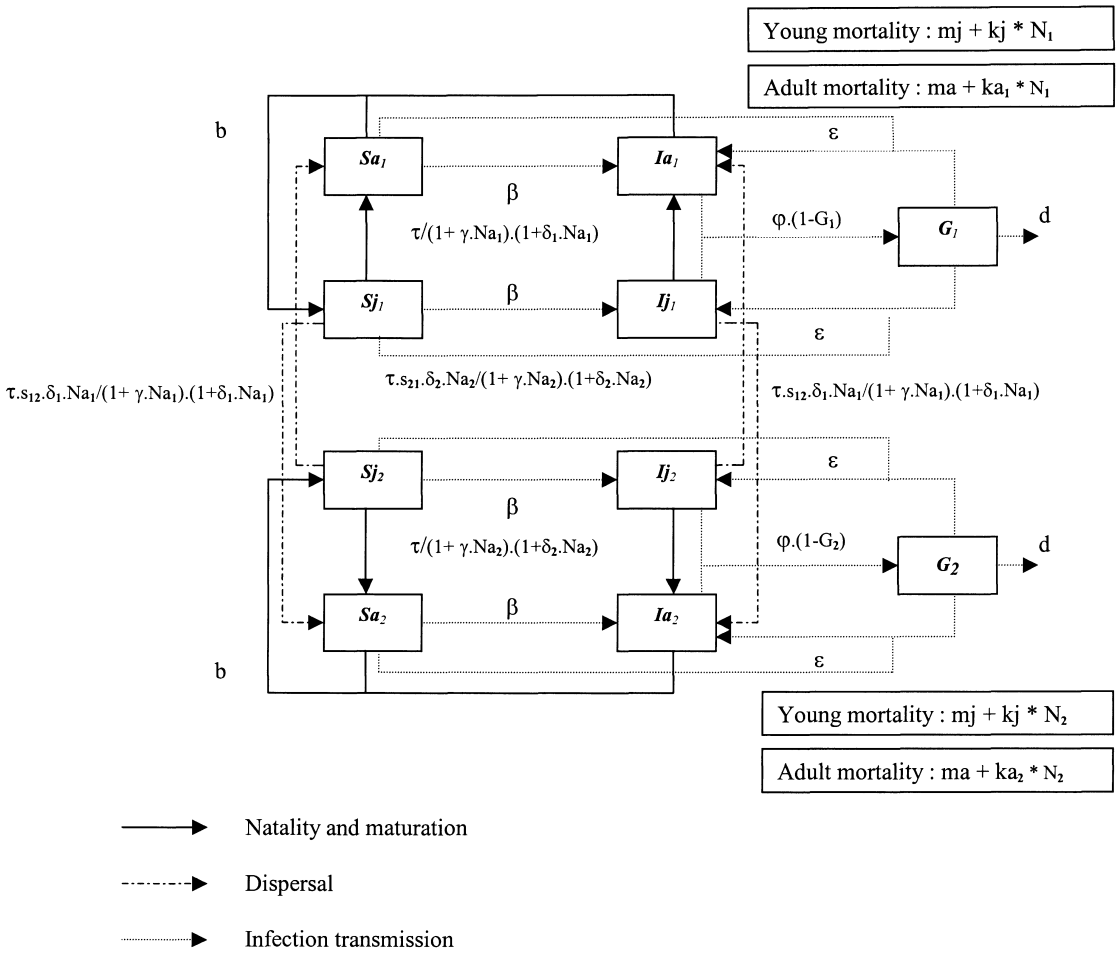

Fig. 1. Schema of the bank vole–hantavirus mathematical model (see text for description of parameters).

Parameter values used in our models

Demographic parameters

$b = |20*\sin(2*pi*(t - 0{\cdot}15))| + 20*\sin(2*pi*(t - 0{\cdot}15))$, which is periodic with a period of 1 year, and is zero over 6 months (October–March). This birth function allows for a 6-month-long breeding season and implies five litters of five offspring per female per breeding season (Innès & Millar 1994). There was no density dependence incorporated because Verhagen *et al.* (2000) reported only a weak relation between litter size and density;

$m_j = 6$; $m_a = 2$ for a 6-month turn-over of the adult population;

$t = 12$: rate at which juveniles become adults;

(Bujalska 1990); and γ_1, $\gamma_2 = 0{\cdot}04$: density dependence damping on sexual maturation.

The density-dependent effect and seasonal variation on mortality rates for juvenile and adult classes are given by: $k_j(t) = (10 - m_j)/K_j(t)$; $ka_i(t) = (10 - m_a)/Ka_i(t)$ i = [1,2], where 10 is about the average annual value of the birth rate (per reproductive individual).

Three-year periodic carrying capacities

$K_j = 3*(10 + (\cos(2*\pi*(t))/3)^2 - 9{\cdot}5*(\sin(2*\pi*(t)/3)))$;

$Ka_1 = 6*(10 + (\cos(2*\pi*(t + 0{\cdot}35))/3)^2 - 8*(\sin(2*\pi*(t + 0{\cdot}35)/3)))$; and

$Ka_2 = 4*(10 + (\cos(2*\pi*(t + 0{\cdot}35))/3)^2 - 8*(\sin(2*\pi*(t + 0{\cdot}35)/3)))$.

Thus, patch 1 was the optimal patch and patch 2 was the suboptimal one.

Also:

$\delta_{12} = 0{\cdot}1$; $\delta_{21} = 0{\cdot}2$: density dependence damping on dispersal; and $s_{12} = 0{\cdot}95$; $s_{21} = 0{\cdot}85$: juveniles leaving the suboptimal patch have a lower survival rate during dispersal.

Infection parameters

The direct transmission contact rate, β, is unknown in bank vole populations. It was calibrated using Begon *et al.*'s (1998) estimate in the bank vole–cowpox system. Because the latter takes into account the number of contacts and the probability of cowpox transmission during the contact, we modified their estimate as follows: a direct contact rate of 0·38 is the lower limit that makes the number of infected voles below 0·4 in both sites for more than 15 months. Those features correspond to the minimum values that allow for persistence of the virus in the following limit conditions: for each cycle a newly infected vole having the maximal observed survival and the maximal home range maintains the infection during the silent phase until the 0·4 infectious × ha^{-1} threshold is reached again.

Indirect transmission parameters

$\varepsilon = 9$: the incidence contact rate of indirect transmission; we took a conservative indirect contact rate assuming that on average all the area is visited once every 6 weeks.

$\varphi = 0{\cdot}3$: the proportion of territory contaminated by secretions of one infectious individual per year; Rozenfeld, Le Boulengé & Rasmont (1987) showed a strategic choice of scent marks deposit in male bank voles on their territory borders, their feeding points area and even the rival own burrows. These marked areas are the more probably explored by other bank voles;

and $d = 52$: the reciprocal of the virus survival outside the host, e.g. in the ground. Very little is known about hantavirus survival outside the host. Here we assumed survival to last 1 week.

Simulation results were examined after trajectories had reached a stable periodic state. The two cycles shown are those between 21 and 27 years after the start of the simulation. As a set of initial conditions, we considered a population composed of 10 susceptible overwintered adults $\times$ ha^{-1} and one additional infectious adult on the optimal patch.

Results

POPULATION DYNAMICS IN THE DISEASE-FREE CASE

Figure 2 shows the pattern of bank vole demography over a 3-year multi-annual cycle without hantavirus infection. At the beginning of a cycle, density increased to 16 rodents $\times$ ha^{-1} on the optimal patch and 12·5 rodents $\times$ ha^{-1} on the suboptimal patch; after the reproductive season, winter density dropped to 1·6 rodents $\times$ ha^{-1} and 1·1 rodents $\times$ ha^{-1}, respectively, the lowest densities of the cycle. In the second year, densities reached 39 rodents $\times$ ha^{-1} and 31·5 rodents $\times$ ha^{-1} and then peaked at 61·5 rodents $\times$ ha^{-1} and 50·5 rodents $\times$ ha^{-1} in the third year on the optimal and suboptimal patches, respectively, before the final crash of the cycle. Then a new 3-year cycle commenced. At the most favourable periods of the year, i.e. summer, densities were up to 22–28% higher in the optimal than in the suboptimal patch. Juveniles were present during 6 months each year, corresponding to the reproductive season (April–September). This 3-year pattern fits well with field observations of bank voles (Prévot-Julliard *et al*. 1999; Escutenaire *et al*. 2000).

HOST–PARASITE DYNAMICS WITHOUT INDIRECT TRANSMISSION

During the first breeding season of the cycle, the hantavirus seemed to disappear until the beginning of the peak year (Fig. 3). Then the number of infected rodents increased rapidly up to 6·4 rodents $\times$ ha^{-1} on the optimal site and to 2·9 rodents $\times$ ha^{-1} on the suboptimal site before decreasing again. The prevalence in adults (23·9% in the optimal site and 13·8% in the suboptimal one) is higher than in juveniles (6·4% in the optimal site and 2·5% in the suboptimal one) and the overall

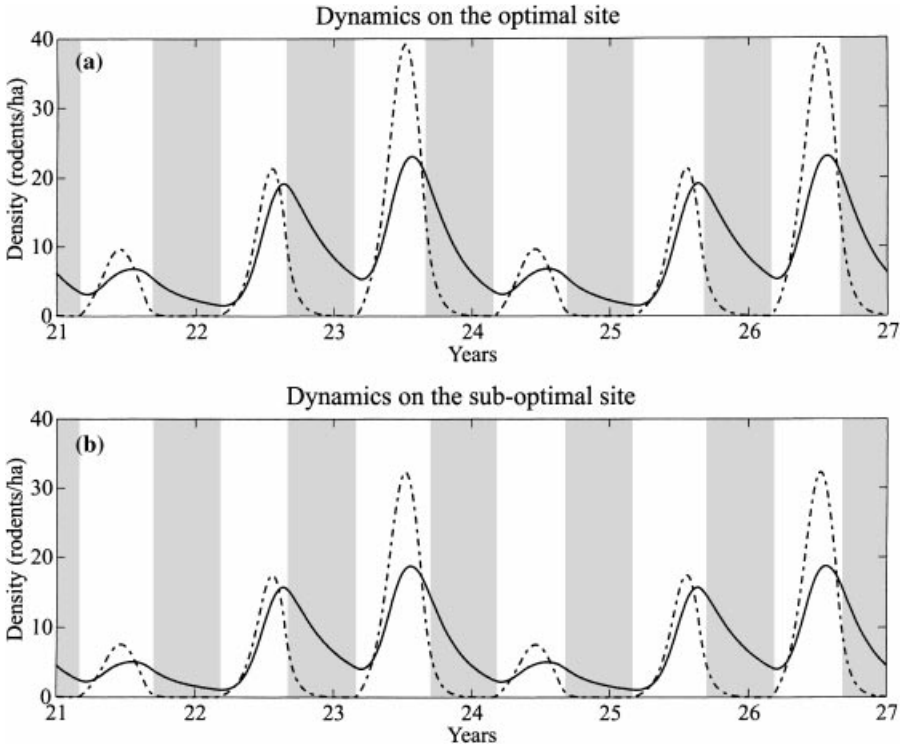

Fig. 2. Global rodent dynamics modelled on the two sites (a and b) without hantavirus infection for two cycles. The evolution of juvenile density on the two sites is represented by dotted lines and the adult density by solid lines. The succession of the breeding and non-breeding seasons ('summer' and 'winter' seasons) is represented by white or tinted areas, respectively).

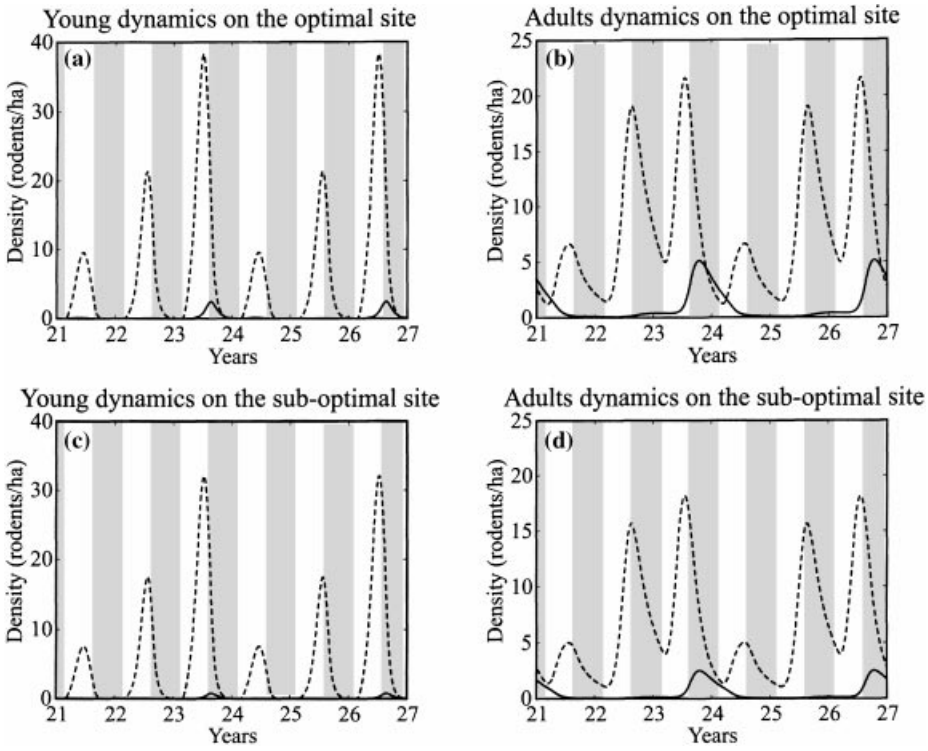

Fig. 3. Dynamics of four different population classes of rodents (adults or juveniles, infected with hantavirus (solid lines) or not (dotted lines)) modelled on the two sites (a, b and c, d) for two cycles without indirect transmission. The modelled cycles are stable and repeated indefinitely after the first 20 years of infection spread. Breeding and non-breeding seasons are represented in white and tinted areas, respectively.

calculated prevalence peaked at 10·4% in the optimal patch during the peak year, and at 5·7% in the suboptimal one. These prevalence levels were not consistent with the peak prevalence of 67% reported in the study by Escutenaire *et al*. (2000). A 67% prevalence numerically requires an ecologically unacceptable direct contact rate, i.e. 0·7, which means that each rodent must come in close contact (i.e. close enough to allow virus transmission) with more than 80 susceptible conspecific hosts during its lifetime ($\beta.N(t).m$ with $N(t)$ = 60). Bank voles typically show a pattern of temporal avoidance (Mironov 1990), even during years of peak density. This contradiction reinforces the hypothesis of an alternate route of transmission.

HOST–PARASITE DYNAMICS WITH INDIRECT TRANSMISSION

The proportion of contaminated area also cycled with the same pattern as that of adult infected voles (Figs 3 and 4). The contaminated proportions fluctuated within an interval ranging from 0·06% to 9% in the optimal patch and from 0·02% to 5% in the suboptimal patch. These proportions never fell to zero, which means that the ground can play the role of reservoir for the virus.

The intensity of the epidemic was higher in the model with indirect transmission (Fig. 5) than that with direct transmission (Fig. 3). Indirect transmission clearly altered the course of the epidemic in the host population. During the peak year, prevalence reached 28·5% on the optimal site and 19% on the suboptimal site with indirect transmission. As previously, the prevalence in adults (60·6% in the optimal site and 41·7% in the suboptimal one) is higher than in juveniles (21·5% in the optimal site and 10·3% in the suboptimal one). The virus did not persist if we set disperser survival to zero (results not shown). The period when the virus was almost absent was short: 15 months with less than one infectious rodent × ha^{-1} for the two sites with indirect transmission vs. 25 months with only direct transmission.

ELASTICITY ANALYSIS

As is expected for the abundance of species with a low adult survival and a short generation time (e.g. Yoccoz *et al*. 1998), the elasticity of reproductive rates (fecundity and sexual maturation) was larger than the elasticity of adult mortality rate (Fig. 6). For prevalence, the parameters associated with the density of breeding adults (direct contact rate, fecundity and adult mortality rates) had the highest impact. This last feature was expected as the prevalence, and hence the infected numbers, differ greatly between the two sites (see above). The proportion of area contaminated by Puumala was affected mainly by the direct contact rate and the demography of juveniles. The parameters describing the indirect transmission had a low elasticity. Only the results for the optimal site are presented, as the elasticity analysis is similar for the suboptimal site.

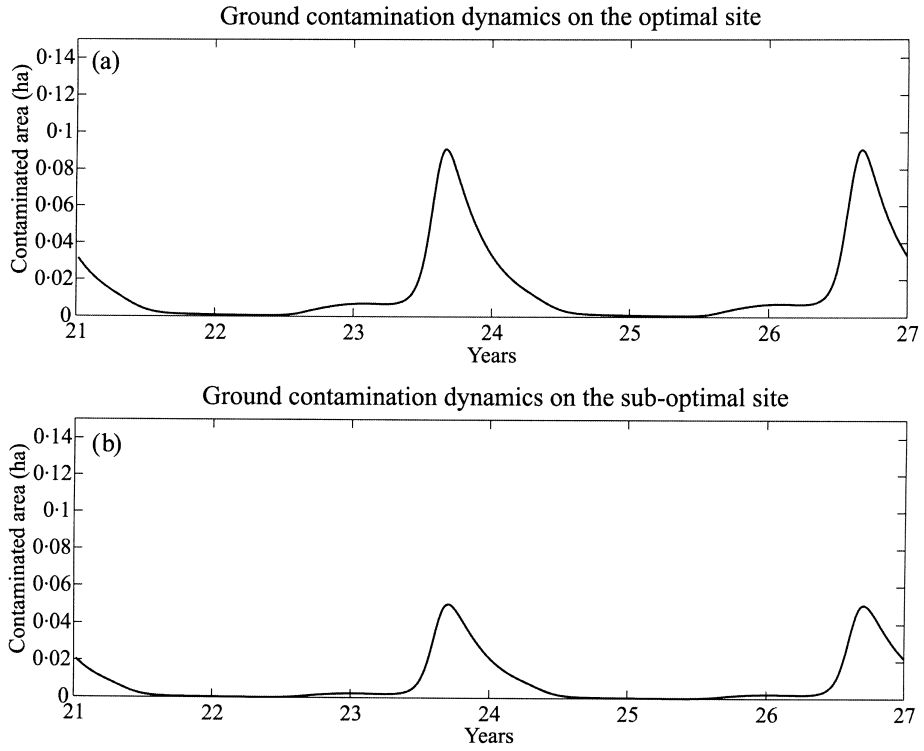

Fig. 4. Area of PUU-infected ground on the two bank vole sites (a and b) over two rodent population cycles.

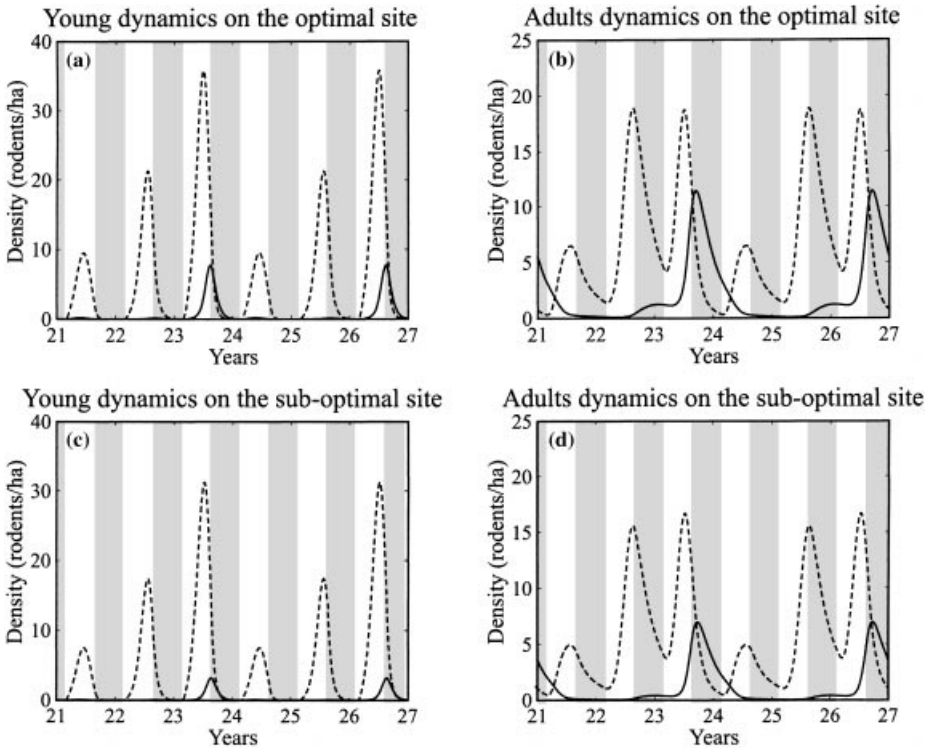

Fig. 5. Dynamics of four different population classes of rodents (adults or juveniles, infected with hantavirus (solid lines) or not (dotted lines) modelled on the two sites (a, b and c, d) for two cycles in the presence of indirect transmission. Breeding and non-breeding seasons are represented in white and tinted areas, respectively.

Discussion

Escutenaire *et al.* (2000) have described bank vole–Puumala dynamics in Belgium near the French border. The pattern was closed to our own observations in France (unpublished data), but revealed a slightly higher seroprevalence. In autumn 1996, the prevalence recorded was 20·1% and decreased to 14·3% in spring 1997. In autumn 1997, the prevalence was 6·6% and it remained about 6·5% in 1998 despite the vole density

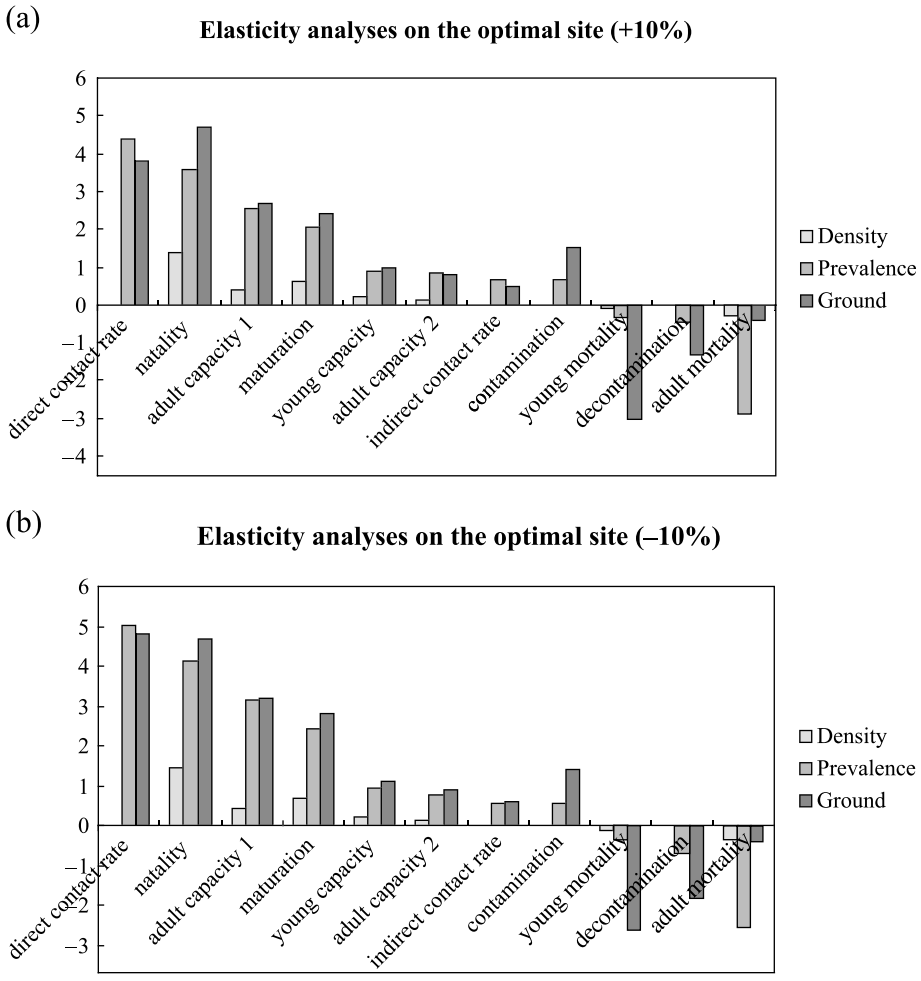

Fig. 6. Elasticity values (optimal site) for 11 parameters of the complete bank vole–hantavirus model with indirect transmission, using a variation of ±10% (a, +10%; b, –10%) according to the elasticity analysis (see text). We present the impact on maximum population density reached during the peak year, on estimated maximum prevalence for each site and on the contaminated proportion of the litter area. The higher the absolute value of the elasticity, the more sensitive the model to the corresponding parameter.

increase. The seroprevalence increased greatly and rapidly in 1999 to reach a mean of 47·7% in the capture plots (for a range from 10% to 67% for the four plots studied). The main features of this pattern are caught well by the model: 2 years of low seroprevalence and a rapid increase the peak year of the 3-year host demographic cycle. Moreover, adults are infected more often than juveniles, as expected due to the accumulation of cases with age. Escutenaire *et al.* (2000) reported periods of virus non-detection in each of their four plots studied: one season for two of them, 1 year for one and 15 months in the last plot.

The originality of the bank vole–hantavirus system over other well-studied cyclic systems such as the fox-rabies (Suppo *et al.* 2000) or human–measles system (Grenfell & Bolker 1994) lies in the fact that fluctuations in the susceptible host population are not caused by the virus. Mathematical modelling of the hantavirus–bank vole system, taking into account indirect transmission, captures accurately many features of observed epidemic dynamics. We found that the risk of extinction of the hantavirus was decreased when indirect transmission was incorporated. Indirect transmission leads to a high prevalence at high host density, which was not obtained with biologically realistic parameters of direct transmission. Indirect transmission also decreased the length of time the virus was almost absent and thus the probability of infection extinction by stochastic events. All these observations support the indirect transmission hypothesis.

By survival outside the host, we consider survival in the forest litter environment and not in the air. Hantavirus is excreted preferentially in urine and bank voles are territorial during the breeding season. A territory is delimited by the owner through urine deposit. Each urine release mixes with soil water that spreads the virus over a small volume of litter. Conditions are optimal for conservation of the virus virulence: it remains in a hydrosolution and is protected from sunlight and heat by forest cover and soil litter (e.g. Edwards 2000 for the swine fever virus). The contaminated surfaces constitute areas where new infections of voles can occur without the physical presence of infectious rodents. Because territorial mammals mark the borders of their territory daily (Rozenfeld *et al.* 1987), a high proportion of this border area can be permanently

infectious, even if the survival of the virus is only few days. Scent marks are attractive to territorial mammals, increasing the probability for a foraging rodent to explore the marked area at the border of its territory compared to other interior areas. This mechanism could greatly enhance the spread of infection, despite the temporal avoidance behaviour of voles. Infection could occur through direct investigation of scent marks of an infectious neighbour or through removal of contaminated dust from the pelage that was acquired while foraging in a contaminated area. Thus, even if an infectious vole dies, the next owner of the territory could be infected several days after disappearance of the infectious vole.

The elasticity analysis indicated that the demographic parameters that control the supply of susceptible hosts (sexual maturation, adult mortality and adult capacity), and to a lesser extent the direct contact rate, are the most important parameters driving the system. Note that elasticities do not necessarily reflect the actual impact of a parameter in a population since some parameters may be more variable than others, and therefore the assumption of the same relative change in the various parameters made for calculating elasticities may not be valid in practice. A precise measure of these parameters in field studies is thus required. Simulations suggested that indirect transmission acts as a reservoir which supplies the host population with a few infected individuals but in sufficient numbers to permit the virus to spread rapidly to the whole population through direct transmission.

Infection acquisition from contaminated ground to healthy individuals could be a much more general strategy used by viruses to persist than recognized until now. Ground transmission could explain the high, unexpected number of new infections in a study of bank voles by Begon *et al.* (1999). In this study of interspecific transmission of cowpox, there were more newly infected bank voles than expected through direct transmission either from infectious conspecifics or infectious wood mice. The unknown source of infection could be due to ground contamination. In addition, the indirect transmission hypothesis could explain the pattern of infection from northern European countries to France. First, it is compatible with Verhagen *et al.*'s (1986) observation of different prevalences associated with different environmental humidities. The humidity factor could explain the persistence of the virus in a given area. Secondly, differences in climatic conditions and in bank vole demography among western European areas could result in differences in survival of the virus in the ground, and can modulate the importance of direct and indirect transmission for virus persistence. Several studies have reported the coexistence of different genotypes of the same hantavirus in a same area, even in the Puumala hantavirus strain (Escutenaire *et al.* 2001), and genetic reassortment among those viruses (see Henderson *et al.* 1995; Rowe *et al.* 1995; Rodriguez *et al.* 1998, for the Sin Nombre virus case). A further important issue in persistence is the survival rate of the virus according to soil conditions (e.g. pH and humidity because hantaviruses are susceptible to acid and dry conditions) and the proportion of the territory contaminated by the infectious owner.

The relative importance of direct and indirect transmission in the spread of hantavirus infection will need further investigation according to the physical and chemical properties of the soil. There are currently insufficient data to definitely reject the autonomous or the secondary reservoir hypothesis. Contradictory data exist concerning the secondary host species: hantavirus phylogeny analysis shows a strong coevolution between a virus and its main hosts (Schmaljohn & Hjelle 1997; Monroe *et al.* 1999) but cases exist where two host species are infected or have been infected by the same virus (Vapalahti *et al.* 1997, 1999; Scharninghausen *et al.* 1999). There is clearly a need for a better theoretical analysis of these different features of the bank vole–hantavirus system and their implication for the persistence of infection. Moreover, the social structure of bank voles and the dynamics of excretion of the virus in the saliva and in the urine change with the time of year. In particular, males have larger territories during the breeding season and are less aggressive than females (Ishibashi *et al.* 1998; Kapusta & Marchiewska-Koj 1998) and survival differs between sexes by season (Verhagen *et al.* 2000). Males could then have a greater influence on infection propagation than suspected until now (Bernshtein *et al.* 1999). The presence of clusters of bank voles during winter (De Jonge 1983; Karlsson & Ås 1987; Bujalska 1990) may increase social contact between voles, in shared burrows, during the period of high virus secretion in saliva (Verhagen *et al.* 1986). A final comment about social features and spread of infection is the differential pattern of urine marks deposited by dominant and subordinate male voles (Rozenfeld *et al.* 1987). Thus, individual behaviour can be crucial to understanding the persistence of the Puumala virus, especially at low density. Such features must be incorporated in future individual-based models to analyse their respective impact in virus propagation and persistence.

The main result is that transmission by the contaminated ground may matter and should therefore be properly assessed in the field.

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