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Impact of myxomatosis in relation to local persistence in wild rabbit populations: The role of waning immunity and the reproductive period

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Abstract

Many diseases are less severe when they are contracted in early life. For highly lethal diseases, such as myxomatosis in rabbits, getting infected early in life can represent the best chance for an individual to survive the disease. For myxomatosis, early infections are attenuated by maternal antibodies. This may lead to the immunisation of the host, preventing the subsequent development of the lethal form of the disease. But early infection of young individuals requires specific demographic and epidemiological contexts, such as a high transmission rate of the pathogen agent. To investigate other factors involved in the impact of such diseases, we have built a stochastic model of a rabbit metapopulation infected by myxomatosis. We show that the impact of the pathogen agent can be reduced by early infections only when the agent has a long local persistence time and/or when the host subpopulations are highly connected. The length of the reproductive period and the duration of acquired immunity are also important factors influencing the persistence of the pathogen and thus, the impact of the disease. Besides confirming the role of classical factors in the persistence of a pathogen agent, such as the size of the subpopulation or the degree of connectivity, our results highlight novel factors that can modulate the impact of diseases whose severity increase with age.

Keywords: Maternal immunity; Infectious diseases; Stochastic model; Metapopulation; Critical community size

1. Introduction

Sooner or later all parasites become extinct from their host population. How long this takes is a fundamental question of modern epidemiology. Many theoretical studies (Anderson and Britton, 2000; Nasell, 1995) have focussed on this question, giving rise to the concept of critical community size (CCS, Bartlett, 1956).

The CCS of a host population infected by a given parasite defines a point where the two time scales of extinction are very different between populations below or above the CCS. Above the CCS, the pathogen can maintain itself almost indefinitely and individuals are regularly exposed to the disease agent. Below the CCS, the agent will rapidly die out after its introduction. If reintroduction of the pathogen does not occur rapidly, the susceptible pool of the host population will be replaced, e.g. through births or waning immunity. The next reintroduction of the agent then results in a large epidemic since most individuals are susceptible.

As revealed by recent studies, this dichotomy in pathogen circulation may have important implications. Rapid extinction from a host population may have an evolutionary cost for the pathogen. In host populations made up of small and isolated subpopulations, persistent strains tend to replace invasive but non-persistent ones (Keeling, 2000). Another interesting example is the case of bubonic plague. The transmission of the bacteria *Yersinia pestis* to humans often occurs when the rat population is below the CCS (Keeling and Gilligan, 2000a, b). This is

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because large epidemics in rats generate a demographic crash in the host population causing fleas to transfer to an alternative host species, such as humans, transmitting the bacteria to them. These examples illustrate the fact that the CCS may significantly alter the entire relationship between the host and the parasite, whether the host population is above or below the CCS.

Recently, Fouchet et al. (2006) suspected a central role for pathogen persistence time in host–parasite interactions for which maternal antibodies can attenuate the disease. In such interactions, an early infection of the host is crucial since it permits active immunisation of the host without the cost of developing the normal and, typically, more severe form of the disease (Zinkernagel, 2001, 2003). Non-exposure at a young age could be detrimental because the young then becomes susceptible to developing the most severe form of the disease as soon as maternal protection has disappeared. Using a mathematical model, Fouchet et al. (2006) showed that the impact of such a disease ultimately decreases with its transmission rate and tends to be negligible for very high transmission rates. The model also revealed a lower impact of the disease for longer reproductive periods of the host and for waning (compared to lifelong) acquired immunity. The correlation found between the impact of the disease and factors that could influence the persistence of the parasite led Fouchet et al. (2006) to hypothesize that the impact of the disease could decrease with its persistence. The deterministic model employed in that study could not address this question.

In a more recent paper, Fouchet et al. (2007) have presented results that support this theory. They studied the impact of a disease potentially attenuated by maternal antibodies during the course of fragmentation of the host population. This study showed that the reduction in the average size of each host subpopulation, and thus of the local persistence time of the pathogen agent, initially led to an increase in the impact of the disease.

Here we chose the example of the rabbit (*Oryctolagus cuniculus*)–myxomatosis interaction to analyse the general case of infectious diseases that may have less impact on a population when young individuals can experience the infection during the time they are still protected by maternal immunity. We develop a stochastic model to understand how the impact of the disease is affected by extinction and reintroduction events. First, we quantify the extinction time by considering a simple homogeneous mixing model. This allows us to determine the key factors for virus persistence. Second, we connect a set of subpopulations with homogeneous mixing to form a metapopulation. To explore alternative possibilities to those tested by Fouchet et al. (2007), we analyse the case where persistence times are varied without altering the subpopulation size. We show that the suggestion intuited from the deterministic model provided by Fouchet et al. (2006), i.e. that waning immunity and the length of the reproductive period affects the impact of myxomatosis, was correct when a more relevant model was considered. We conclude that extinction and reintroduction events are crucial factors in the impact of the disease. This study allows us to isolate factors that can be important for disease management.

2. Material and methods

2.1. The rabbit–myxomatosis interaction

Rabbit populations are socially and spatially structured. Within a social group, conflicts occur between males for access to females, whereas females generally compete for access to reproductive sites. Fights between individuals of different social groups are less frequent, and are mainly due to defence of the group territory (Cowan, 1987). Dispersal of juveniles of less than four months of age is common. Males typically disperse more than females (Richardson et al., 2002).

In France, mean rabbit density varies between populations, ranging from less than 1 rabbit/ha to more than 20 rabbits/ha (Marchandeau et al., 2006). Rabbits are seasonal breeders, commencing around February and finishing between July and November, depending on food availability (Cooke, 1981, 1982; Myers and Poole, 1962; Poole, 1960; Wheeler and King, 1985; Wood, 1980). Mean annual mortality is approximately 50% (Cowan, 1987; Parer, 1977; Rogers et al., 1994).

Myxoma virus is a leporipoxvirus that induces myxomatosis in the European rabbit. When released in Australia (1950) and in Europe (1952) the virus spread extensively, causing significant damage to rabbit populations (Giban, 1956). During subsequent years the impact of the virus remained high, but was significantly lower than during the initial epidemics. Several factors may explain this decrease in virus impact. First, intermediate virulent strains, which are less virulent than the introduced strains, have selective advantage over these more virulent strains because more virulent strains have a smaller reproductive ratio (Dwyer et al., 1990; Fenner, 1983; Fenner and Fantini, 1999; Fenner and Ross, 1994). Second, rabbits have developed a genetic resistance against the virus (Sobey, 1969). Finally, rabbits that have survived myxomatosis become immune (Fenner and Ratcliffe, 1965; Saurat et al., 1980). Waning of acquired immunity has been observed in laboratory conditions (Saurat et al., 1980) and suspected in the field (Marchandeau and Boucraut-Baralon, 1999), but the capacity of adults to transmit the disease following re-infection is not yet established. Part of the immunity of the dam is transferred to offspring via maternal antibodies, which are protective for around one month (Fenner and Marshall, 1954; Kerr, 1997; Sobey and Conolly, 1975).

The virus can be transmitted through three routes. Mechanical transmission by arthropod vectors, such as fleas and mosquitoes biting the host, is the most efficient (Fenner and Chapple, 1965). Mosquitoes are able to travel long distances and keep the virus active for long periods

(up to 220 days, Andrewes et al., 1956) but are not specific for rabbits. Fleas are specific for rabbits but keep the virus alive for a shorter period (maximum 100 days, Chapple and Lewis, 1965). While less efficient, direct transmission by contact between infected and non-infected rabbits is common (Aragao, 1927) and is the main transmission route when arthropods are absent (Chapuis et al., 1994). Finally, it has been suggested that the virus could remain infectious in soil (Joubert et al., 1974), but this hypothesis has not been explored fully.

3. Mathematical models

3.1. The homogeneous population model

The model we have developed extends the classical continuous time Markovian susceptible–infected–recovered (SIR) model. The flow diagram of the model is represented in Fig. 1. The rabbit population is divided into six compartments: maternally protected individuals (M), susceptible (S), severely infected (I), mildly infected (I_M), newly recovered (R_N) and formerly recovered (R_F); and one for infectious vectors (I_V). We call $N = M+S+I+I_M+R_N+R_F$ the size of the rabbit population. The model is stochastic and based on continuous Markov chains (Table 1).

We denote b as the host birth rate, which is constant within each month and variable between months. $\mu_0+\delta N$ is the size (N)-dependent mortality rate (modelled here by the logistic function), w and w_R are the rates at which immunity of maternally protected and fully protected individuals wanes, respectively, α is the additional mortality rate induced by the severe disease and σ and σ_M are the recovery rates of individuals infected by the severe and attenuated disease, respectively. Following recovery, an individual can remain infectious through the fleas it carries. We call V_I and V_M the number of vectors that are infected after the recovery of a severely or mildly infected individual, respectively. To simplify, we assume that vectors that have fed on severely and mildly infected individuals are identical. The only way by which severely and mildly infected individuals are differentiated in term of indirect transmission is through the number of vectors (V_I and V_M, respectively) that remain infectious after recovery or death. Infected vectors recover or die with a rate σ_V and become non-infectious (state not represented). Individuals protected by maternal antibodies (or alternatively previously recovered) get infected with a rate that is q (or q_R, respectively) times that of the susceptible individuals. Recently recovered individuals are fully protected. To model the transmission of the virus, we use the proportionate mixing model that is more appropriate for social species (Begon et al., 1999; de Jong et al., 1995). The strength of infection of the disease is then

$$\Lambda(t) = \frac{\beta I + \rho\beta I_M + \beta_V I_V}{N},$$

where β is the rate of transmission of the disease. We assume that mildly infected individuals are ρ times as

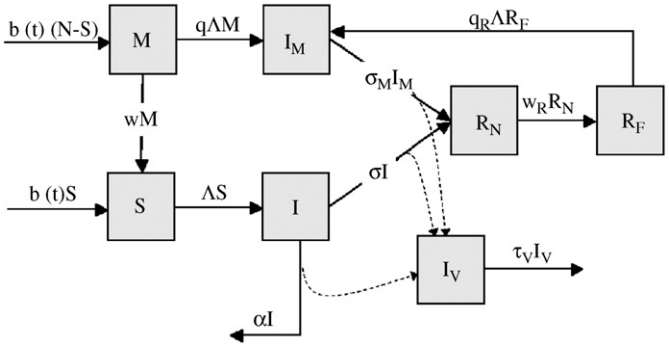

Fig. 1. Flow diagram between the seven compartments of the model: maternally protected individuals (M), susceptible (S), severely infected (I), mildly infected (I_M), newly recovered (R_N), formerly recovered (R_F) and infectious vectors (I_V). Death from causes other than myxomatosis may occur in the first six compartments (rabbit compartments) but has not been represented here to simplify the scheme. Death of severely or mildly infected rabbits also leads to an increase in I_V, i.e. the number of infectious fleas. Further details about the transition rates of the model are provided in the main text. Exact transition rates and effect of the transitions on the classes are given in Table 1. Biological meanings of the parameters are given in Table 2.

Table 1
Transition rates of the continuous time Markov chain

Transition	Transition rate
$(S, M, I, I_M, R_N, R_F, I_V) \to (S+1, M, I, I_M, R_N, R_F, I_V)$	$\tau_1 = b(t)S$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M+1, I, I_M, R_N, R_F, I_V)$	$\tau_2 = b(t)(N-S)$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S-1, M, I, I_M, R_N, R_F, I_V)$	$\tau_3 = (\mu_0+\delta N)S$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M-1, I, I_M, R_N, R_F, I_V)$	$\tau_4 = (\mu_0+\delta N)M$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I-1, I_M, R_N, R_F, I_V+V_I)$	$\tau_5 = (\mu_0+\delta N+\alpha)I$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M-1, R_N, R_F, I_V+V_M)$	$\tau_6 = (\mu_0+\delta N)I_M$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M, R_N-1, R_F, I_V)$	$\tau_7 = (\mu_0+\delta N)R_N$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M, R_N, R_F-1, I_V)$	$\tau_8 = (\mu_0+\delta N)R_F$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S-1, M, I+1, I_M, R_N, R_F, I_V)$	$\tau_9 = \Lambda(t)S$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M-1, I, I_M+1, R_N, R_F, I_V)$	$\tau_{10} = q\Lambda(t)M$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M+1, R_N, R_F-1, I_V)$	$\tau_{11} = q_R\Lambda(t)R_F$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S+1, M-1, I, I_M, R_N, R_F, I_V)$	$\tau_{12} = wM$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M, R_N-1, R_F+1, I_V)$	$\tau_{13} = w_R R_N$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I-1, I_M, R_N+1, R_F, I_V+V_I)$	$\tau_{14} = \sigma I$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M-1, R_N+1, R_F, I_V+V_M)$	$\tau_{15} = \sigma_M I_M$
$(S, M, I, I_M, R_N, R_F, I_V) \to (S, M, I, I_M, R_N, R_F, I_V-1)$	$\tau_{16} = \sigma_V I_V$

infectious as severely infected ones. We define β_V as the rate of transmission of the disease by infectious vectors. Since the transmission of the disease is mainly ensured by infected vectors even when the individual is already infected, we assume that there is a continuum of infectiousness of the individual during recovery or death induced by the virus, which is achieved by setting $\beta = \beta_V V_I$ and $\rho\beta = \beta_V V_M$.

We use the standard Monte Carlo approach to simulate the process. Since independent Poisson processes describe the different possible transitions, the total rate at which events occur is given by the sum of rates $\tau = \sum_{i=1}^{16} \tau_i$ describing these different transitions. So the lag time until the occurrence of the next event is exponential with mean τ^{-1} (Cow and Miller, 1965). To perform a single step of the simulation, two random numbers are generated: the first, generated from the exponential distribution of rate τ, determines the time until the occurrence of the next event; and the second one determines the event that will occur, each event having a probability $p_i = \tau_i/\tau$.

Parameter values have been estimated in order to represent what is known about rabbit biology (Table 2). Except for four parameters, simulations of the Markovian process were run using fixed parameter values, the four exceptions being: δ that is inversely proportional to the mean size of the disease-free rabbit population, the length of the reproductive period (short or long, with long reproductive periods corresponding to additional litters in autumn and more births during the year), the duration of acquired immunity (lifelong or waning) and the number of infected vectors arising from the recovery of an infected individual. These first two parameters vary between populations and thus, cannot be fixed. Despite evidence that a recovered rabbit may become re-infected (Marchandeau and Boucraut-Baralon, 1999; Saurat et al., 1980), it is unknown whether a re-infected rabbit may transmit the disease to other rabbits. Here, we assume that a rabbit never dies from re-infection. So if it cannot transmit the virus after re-infection, from an epidemiological point of view, it appears as if it cannot be re-infected. For the size of the host population we tested a continuous range of values, whereas for the length of the reproductive period and the duration of acquired immunity we tested only two possibilities: a short and a long reproductive period and a six-month or lifelong immunity (see Table 2).

Table 2
Parameters' value (time unit is the month)

Parameter	Symbol	Value
Initial mortality rate	μ_0	0.001
Relationship between the density dependent mortality rates according to the reproductive period		$\delta_S = 0.5542\delta_L$
Rate of waning of maternal immunity	w	1
Rate of waning of acquired immunity	w_R	If immunity wanes: 1/6 Else: 0
Additional mortality rate due to myxomatosis	α	0.6
Rabbit recovery rate from the severe disease	σ	0.4
Rabbit recovery rate from the attenuated disease	σ_M	1
Vector recovery rate	σ_V	0.66
Transmission rate	β	100
Relative susceptibility of maternally protected rabbits	q	1
Relative susceptibility of partly protected rabbits	q_R	1
Relative transmission rate of mildly infected rabbits	ρ	1
Reintroduction rate	ε	1/12

To maintain the continuum in virus transmission during recovery or death induced by the virus, we chose $\rho = 1$ and $V_I = V_M$. We analysed different models for the vectors: (i) in the realistic model, several vectors are released after rabbit recovery. We chose $V_I = 10$ in agreement with observations for fleas (Mead-Briggs and Vaughan, 1975); (ii) in the simplified model, $V_I = 1$. This model, although less realistic, presents the interesting property of seriously decreasing the simulation time; and (iii) the vector absence model, where $V_I = 0$ (the equations $\beta = \beta_V V_I$ and $\rho\beta = \beta_V V_M$ are no longer fulfilled). Vector characteristics are based on the biology of fleas, the main vector of myxomatosis in France. We chose $\sigma_V = 0.66\,\text{month}^{-1}$, so that after 100 days a small proportion of fleas remain infectious (Chapple and Lewis, 1965).

Demographic parameters are chosen as follows. The birth rate varies between months (Fig. 2). Results obtained from the disease-free model (i.e. all individuals are susceptible and the virus is never introduced) reveal that the mean annual mortality rate depends on the birth rate. The birth rate is scaled so that births compensate for the annual mortality of the population (around 50%, slightly higher for long reproductive period models and slightly lower for short reproductive period models). Rabbits are known for their invasive capacity; so we chose a low initial death rate μ_0. In the absence of myxomatosis, the population reaches a pseudo-cyclic state where its mean size $\overline{N}$ is inversely proportional to δ ($\overline{N} \approx 0.0568\delta^{-1}$ for a short reproductive period and $\overline{N} \approx 0.1025\delta^{-1}$ for a long one). To compare populations with different reproductive periods, we always chose different values of δ that resulted in the same mean disease-free population size. If we call δ_S and δ_L the values of δ associated with short and long reproductive periods, respectively, we will always have the relationship $\delta_S = 0.5542\delta_L$.

Concerning the epidemiological parameters, theoretical studies have shown that the selected strain of myxomatosis should have a case mortality of around 60% (Dwyer et al., 1990; Levin and Pimentel, 1981), corresponding to an infectious period of around one month. We assume that mild diseases last as long as severe ones ($\sigma_M = \sigma + \alpha$). As the transmission rate of myxomatosis strongly depends on the presence of vectors, it can vary significantly between rabbit populations. Field studies (Marchandeau and

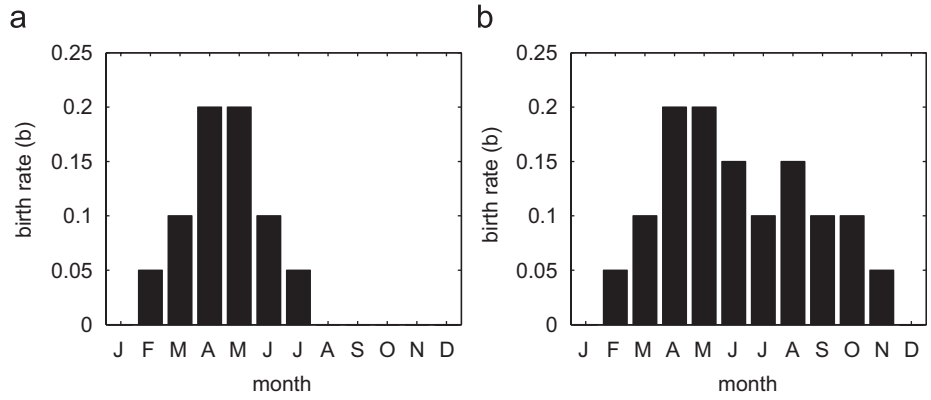

Fig. 2. Monthly birth rates of rabbits according to the length of the reproductive period: (a) short or (b) long.

Boucraut-Baralon, 1999) have shown that in some populations almost all rabbits are seropositive over long periods, suggesting that the local transmission rate of myxomatosis can be very high. This is a necessary condition for rapid infection of the juveniles in infected subpopulations, which is the case we investigate here. The effect of low and intermediate local transmission rates of myxomatosis has been treated in a deterministic version of the model elsewhere (Fouchet et al., 2006). This situation is not of interest here because it does not allow rapid infection of young rabbits. Parameters related to the attenuated route of transmission of the disease (i.e. ρ, q and q_R) are chosen arbitrarily since their real values are unknown. Fouchet et al. (2006) revealed only a quantitative impact of these parameters. The impact of the main factors (i.e. the transmission rate of the virus, the length of the reproductive period and the waning of acquired immunity) remained true for different values of the parameters associated with the attenuated transmission route of the disease (i.e. ρ, q and q_R).

For each set of parameters, we performed 1000 iterations using the software Matlab. Initially, we chose $S = \bar{N}$, $I = 1$ and $M = I_M = R_N = R_F = I_V = 0$, thus representing the introduction of one severely infected individual in a fully susceptible population.

3.2. The metapopulation model

The metapopulation is composed of a set of n subpopulations. Each subpopulation works independently like the homogenous population previously described, except for the transmission rate of the disease, which is given by

$$\Lambda^i(t) = \frac{\beta I^i + \rho\beta I^i_M + \beta_V I^i_V}{N^i} + \theta \sum_{j \neq i} \frac{\beta I^j + \rho\beta I^j_M + \beta_V I^j_V}{N^j},$$

where θ is defined by the fact that $\beta\theta$ is the contact rate between two individuals belonging to different subpopulations. The values i and j represent indices of subpopulations. X^i is equivalent to X in the homogeneous models, but applied to the ith subpopulation. Migration of individuals between subpopulations is not considered here.

To prevent the global extinction of myxomatosis, one severely infected rabbit is introduced through migration from an external population (not represented in this model) with a rate ε/n in each subpopulation. ε then represents the rate at which the severely infected individual is re-introduced in the entire metapopulation. As in the homogeneous mixing model, in the initial state all subpopulations are made up of $\bar{N}$ (the mean disease-free subpopulation size $\bar{N}$ is the same as if the subpopulation was isolated) susceptible individuals except in one subpopulation where one infected rabbit is introduced.

4. Results

4.1. Persistence pattern of myxomatosis in a homogeneous population

4.1.1. Effect of the reproductive period and waning immunity

First we consider a model without vector transmission.

The length of the reproductive period and the duration of immunity are critical determining factors for the persistence of the virus (Fig. 3). If we assume lifelong immunity, only births give rise to non-immune rabbits. When the reproductive period is short, most young are infected during the first epidemic (results not shown) and the virus has to survive until the next breeding period with almost no disease-susceptible rabbit in the population. Persistence of the virus is therefore low. When the reproductive period is long, newborn rabbits are present for most of the year, providing greater opportunities for the virus to persist.

If we hypothesise that immunity acquired after recovery wanes with time, re-infections can occur following loss of immunity. When the reproductive period is short, the persistence of the virus between two breeding periods may be ensured by re-infections. When the reproductive period is longer, re-infections also allow the virus to persist longer in the population.

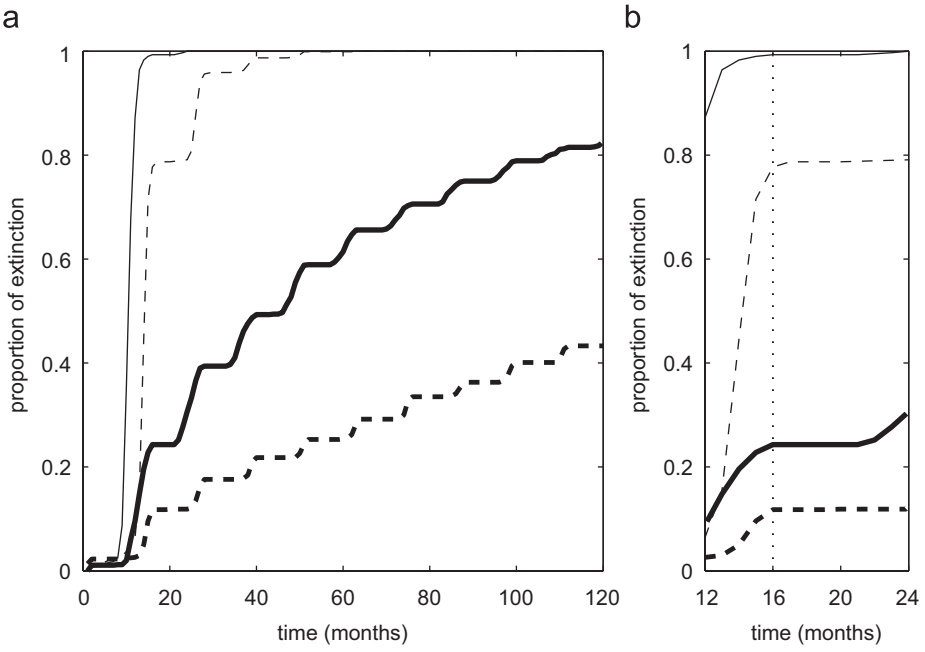

Fig. 3. Evolution of the proportion of 1000 simulations in which the virus is extinct after a given time ($\delta_L = 0.001$ corresponding to a mean disease-free subpopulation size of approximately 100 rabbits). Solid lines = short reproductive period; dashed lines = long reproductive period. Bold lines = waning immunity; thin lines = lifelong immunity. (a) Over the first 10 years of the simulations and (b) between $t = 12$ and 24 months. (b) is, in fact, an enlargement of part of (a) and represents the extinction pattern over a one-year period. The straight line $t = 16$ months is also represented and illustrates the beginning of the non-extinction period.

The seasonality of the extinction pattern is interesting. Fig. 3b shows that for all reproductive periods and durations of immunity, it is very unlikely that the virus will go extinct between April and August. Indeed, during this period there is a preponderance of young rabbits. Therefore, the critical period for myxomatosis persistence is between September and March. As a result we can define cycles for myxomatosis: if the virus is still present at the beginning of April, it will spread easily in newborns and persist for at least six months. After this, its persistence can be compromised. Later, we estimate the impact of myxomatosis in its endemic state during a given year. In order to eliminate situations where myxomatosis rapidly becomes extinct, we start the one-year study period in April when, if the virus is present, it will certainly spread intensively before extinction.

One has to remember that these considerations only apply to isolated populations where the virus persists. This is not always the case in the field and the first cases of myxomatosis may, in fact, occur later in the year if it requires reintroduction from external populations (as we will see below).

The time before extinction of the virus increases with the population size (Fig. 4), consistently with previous work on the CCS (Bartlett, 1956). The effects of the reproductive period and of the duration of acquired immunity remain true whatever the population size, but are more important for a larger population size.

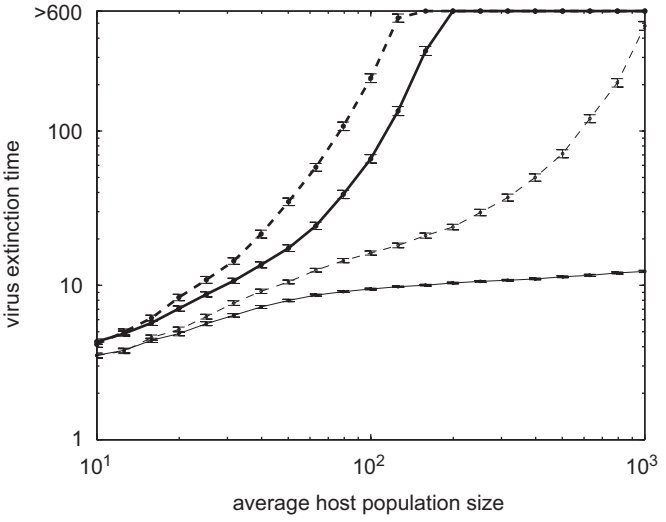

Fig. 4. Mean extinction time (in months) of myxomatosis with 95% CI (confidence interval) calculated over 1000 simulations, according to the size of the host population. Solid lines = short reproductive period; dashed lines = long reproductive period. Bold lines = waning immunity; thin lines = lifelong immunity.

4.1.2. Impact of the choice of the model for vector transmission

Everything that has been said in the previous section remains qualitatively true, whatever the model for vector transmission (Fig. 5). The extinction time of myxomatosis increases with the rabbit population size and with the

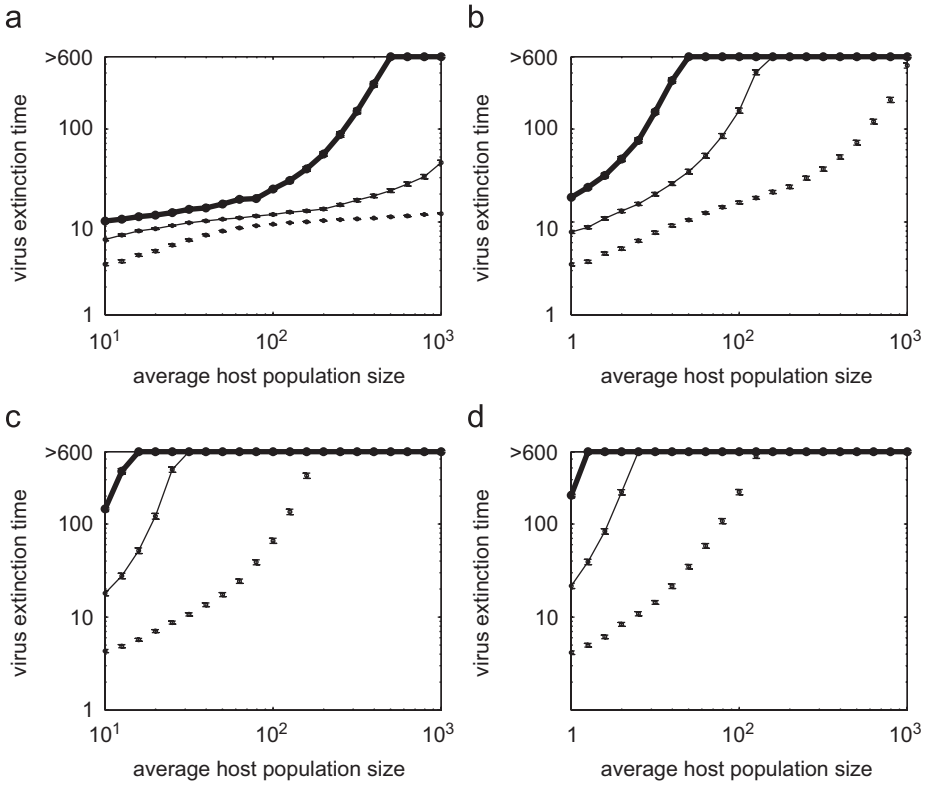

Fig. 5. Effect of vectors on the mean extinction time (in months) of myxomatosis (with 95% CI) for a short (a and c) or a long (b and d) reproductive period and where immunity is lifelong (a and b) or waning (c and d). No line = no vector; thin lines = 1 vector released; bold lines = 10 vectors released.

length of the reproductive period, and decreases with the duration of acquired immunity.

We find an important quantitative impact of the flea model on the extinction time of myxomatosis (see Fig. 5). Unsurprisingly, the model without fleas always predicts a shorter extinction time. Vectors represent a reservoir for the virus that facilitates its persistence in the absence of susceptible hosts. Such a role has already been suggested for fleas, permitting the persistence of the virus through the winter in France (Gilot et al., 1979).

The number of fleas released after recovery or death of infected individuals also had an important quantitative impact on the extinction time of myxomatosis (see Fig. 5). This can be explained by the fact that when one infected vector bears the burden of infection, the mean time before its loss of infectiousness is an exponential law of rate $\sigma_V{}^{-1}$. Conversely, when V_I infected vectors bear the burden of infection, the mean time before the death of the last infected vector is the maximum of V_I exponential laws of the same rate $\sigma_V{}^{-1}$ and, on average, increases with V_I. When the number of released vectors is greater than one, rabbits remain indirectly infectious for a longer period. Even if only one flea is infectious at the end of the period, it is sufficient to allow the virus persist until subsequent births or loss of immunity. Extinction time then increases with the number of released fleas.

Fig. 5 shows the large spectrum of values for the CCS of rabbits facing myxomatosis. For example, the minimum rabbit population size above which myxomatosis persists for more than 10 years ranges from less than 10 rabbits for a long reproductive period, waning immunity and a model with 10 fleas to more than 1000 rabbits for a short reproductive period, no waning immunity and a model without fleas (see Fig. 5).

4.1.3. Impact of myxomatosis in a metapopulation

Here, we study the impact of myxomatosis in a metapopulation according to the extinction time of myxomatosis within subpopulations. To simplify, we compare four situations that differ only in the length of the reproductive period of the rabbits and the duration of acquired immunity. Other parameters remain constant. We also chose a model without a vector. We set $\delta_L = 0.001$, corresponding to a mean population size of approximately 100 rabbits. With these parameters, the extinction time of myxomatosis in subpopulations is 9.51 months for a short reproductive period with lifelong immunity (95% CI: [9.40; 9.63]), 15.75 months for a long reproductive period with lifelong immunity (95% CI: [15.29; 16.21]), 65.68 months for a short reproductive period with waning immunity (95% CI: [61.42; 69.94]) and 220.68 months for a long reproductive period with waning immunity (95% CI: [207.23; 234.13]). The large range of extinction times for these four scenarios permits us to analyse the impact of myxomatosis according to its local extinction time.

To ensure that the different impacts of myxomatosis between the four situations is due to differences in virus persistence, we first analyse the impact of myxomatosis in these populations when they are isolated (homogeneous model) and while the virus persists. In such situations extinctions and reintroductions have no effect, simply because they never occur. As an indicator of the impact of myxomatosis, we chose the mean ratio of the number of rabbits that have died from the disease during a given time period by the total number of individuals that have lived during the same period. This mean ratio is only calculated for simulations in which the virus is present at the beginning of the period. We define several time periods, all of them starting at the beginning of the 4th month (April) and lasting exactly one year. Starting in April allows us to consider only the simulations where the virus has a significant level of circulation during the considered period. We also assume that the virus is introduced at $t = 4$ months instead of $t = 0$.

The discrimination of non-disease persistent simulations reduces the number of simulations for which the impact of myxomatosis is calculated and consequently, decreases the accuracy of the results. To counteract this we ran more simulations for the situations where the time before extinction is shorter (100,000 for a short reproductive period with lifelong immunity, 10,000 for a long reproductive with lifelong immunity and 1000 for waning immunity, whatever the length of the reproductive period).

As found previously (Fouchet et al., 2006), the impact of myxomatosis is highest during the period immediately following its introduction (Fig. 6). This is simply because when the virus is introduced, no rabbit is immune and hence all infections are severe. In the following year, the impact of myxomatosis is largely reduced and there is little year-to-year variation in disease impact (see Fig. 6). In this quasi-steady state, the impact of the disease does not decrease with its persistence. The scenario of lowest persistence does not correspond to the maximum impact of the virus (see Fig. 6). In fact, the impact of myxomatosis is little affected by its persistence time. Since the greatest impact of myxomatosis occurs immediately after its introduction, reintroductions of myxomatosis (whether they occur sooner or later) after its extinction should be important to estimate the true impact of the virus.

One of the main differences between homogeneous mixing and metapopulation models is the seasonal occurrence of myxomatosis. In the homogeneous mixing model myxomatosis is never lost (because we remove the extinction cases from the results). At the beginning of the reproductive period there is a large amount of (partly) susceptible rabbits (juveniles) and the virus is present. An epidemic can occur (here between April and August, Fig. 7a). In a metapopulation, the seasonal occurrence of myxomatosis depends on the degree of connectivity between subpopulations. In poorly connected metapopulations, the virus persists only in some populations every year and it takes several months for the virus to spread to the entire metapopulation. The epidemic of myxomatosis is delayed (here between July and December, Fig. 7b). Most juveniles are infected after the vanishment of their maternal antibodies and develop the severe form of the disease when infected. There is an important correlation between the month of occurrence of myxomatosis and its impact. With increasing connectivity between subpopulations, epidemics occur sooner and so are less severe (Fig. 7c, note that for $\theta < 2 \times 10^{-5}$ epidemic peaks always occur in September).

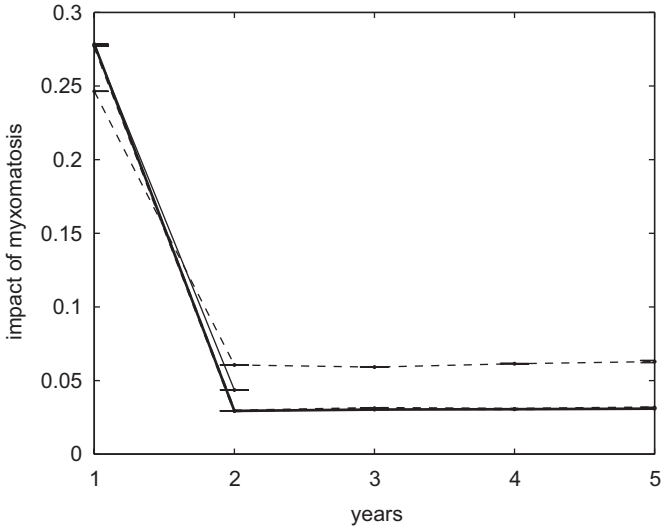

Fig. 6. Mean impact of myxomatosis (with 95% CI) during the kth period of time (i.e. the kth year) in a homogeneous population with 100 rabbits ($\delta_L = 0.001$). This impact is defined as the number of rabbits that died from myxomatosis (i.e. dead while in the I compartment) between times $t = 12k-8$ and $12k+4$, divided by the total number of rabbits living during the same period. The latter quantity is the sum of the number of rabbits present at the beginning of the period plus the number of rabbits born during that period. Solid thin lines = short reproductive period with lifelong immunity (100,000 simulations); dashed thin lines = long reproductive period with lifelong immunity (10,000 simulations); solid bold lines = short reproductive period with waning immunity (1000 simulations) and dashed bold lines = long reproductive period with waning immunity (1000 simulations).

We obtain consistent results when we look at the global impact of myxomatosis (Fig. 8). In poorly connected subpopulations, epidemics are severe but do not occur every year. The time interval between two epidemics is so large that the global impact of the virus is always very low. As the connectivity between subpopulations increases, the frequency of the epidemics also increases and thus, the impact of myxomatosis increases. When the connectivity between subpopulations is high enough epidemics occur almost every year. At this stage the impact of the disease mainly depends on the seasonal occurrence of the disease and thus decreases with the connectivity between subpopulations (θ). At the extreme, for $\theta = 1$, the impact of myxomatosis is almost null because the metapopulation is equivalent to a homogeneous one with 10,000 rabbits and a transmission rate of 10,000 (result not shown). In such a population, the results of the stochastic model mirror those

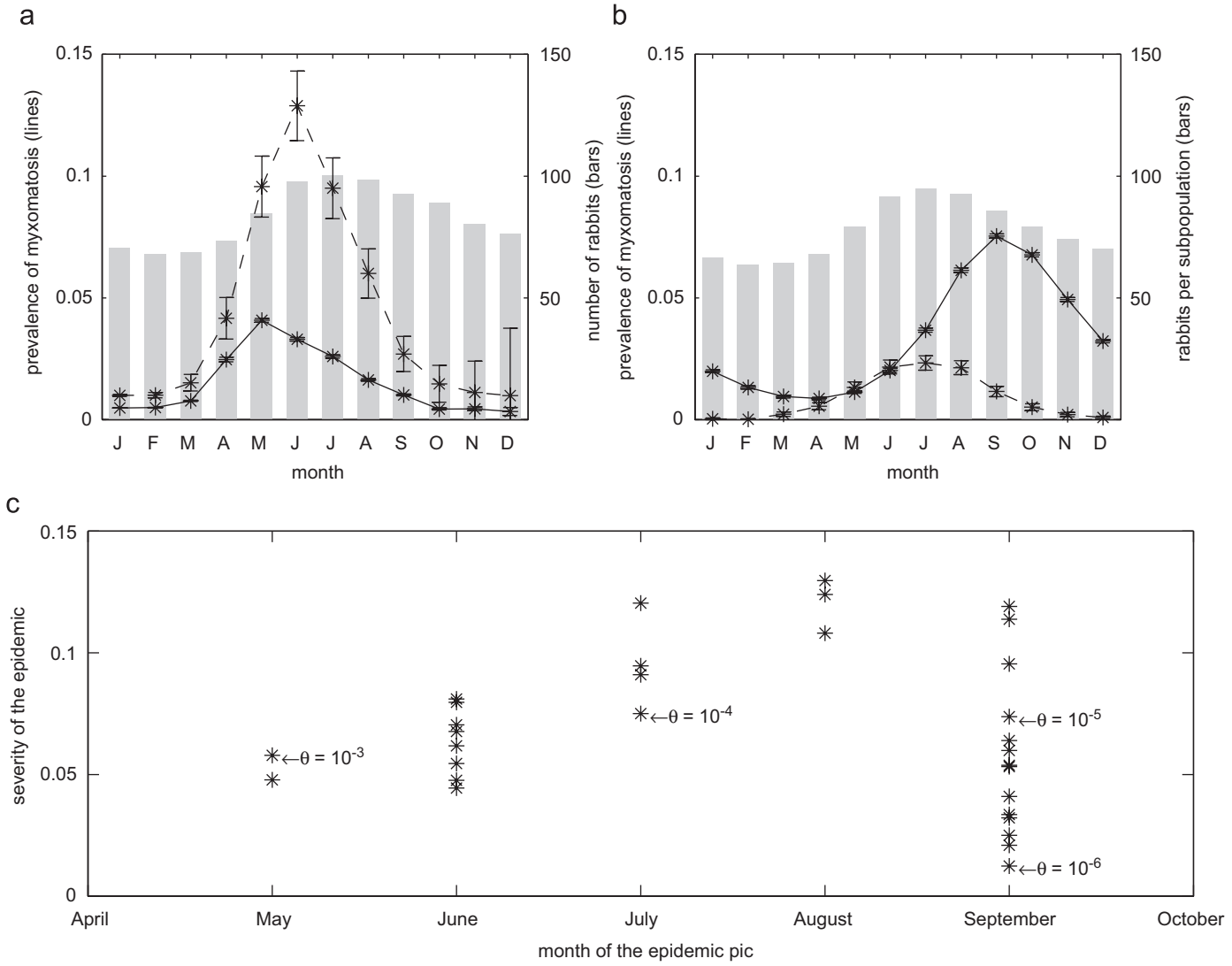

Fig. 7. Relation between the seasonal prevalence of myxomatosis and its impact. (a–b) mean prevalence of severe (solid lines) and mild (dashed lines) myxomatosis with 95% CI (left axis) and mean number of rabbits per subpopulation (bars, right axis); (a) for the homogeneous mixing model (only one subpopulation, the mean number of rabbits per subpopulation is then the mean number of rabbits in the entire population). Results are averaged over the cases of non-extinction of the 12 last months of a 24 months simulation (after that the virus goes extinct in most replicates, see e.g. Fig. 6) (10,000 simulations); (b) for a metapopulation made up of 100 subpopulations having a level of connectivity $\theta = 10^{-5}$. Results are averaged over the 20 last years of a 30 years simulation (100 simulations). (c) Relation between the epidemic month (defined as the month during which the prevalence is maximal) and the severity of the epidemic (defined as the mean prevalence of severe myxomatosis during the epidemic month) (100 simulations). Simulations have been performed for 31 different values of θ geometrically distributed between 10^{-6} and 10^{-3}. In all subplots the subpopulation carrying capacity is 100 rabbits, the reproductive period is short and immunity is lifelong.

of the deterministic one, which predicts an almost zero impact of myxomatosis (Fouchet et al., 2006).

Now we find an important effect of disease persistence on the impact of myxomatosis (see Fig. 8), especially for intermediate levels of connectivity between subpopulations. Due to the high local transmission rate, the presence of the virus permits early infection of juveniles who develop attenuated disease followed by active immunisation. As long as the virus persists within subpopulations, juveniles do not suffer from severe myxomatosis (see Fig. 6). If the virus goes extinct and is not reintroduced quickly, the young lose their maternal protection and become susceptible to the severe form of the disease. When the virus is reintroduced to the subpopulation, most individuals develop the severe form of the disease, inducing a high death rate.

When comparing the contrasting impact of myxomatosis between the different scenarios, it appears clear that these differences cannot be explained by the slight disparities obtained from the homogeneous mixing model (see Fig. 6). In the homogeneous mixing models, for each year the difference in the impact of myxomatosis between situations is never greater than 0.03. This cannot explain the huge differences observed in Fig. 8. The only way to explain these differences is to consider extinctions and reintroduction events.

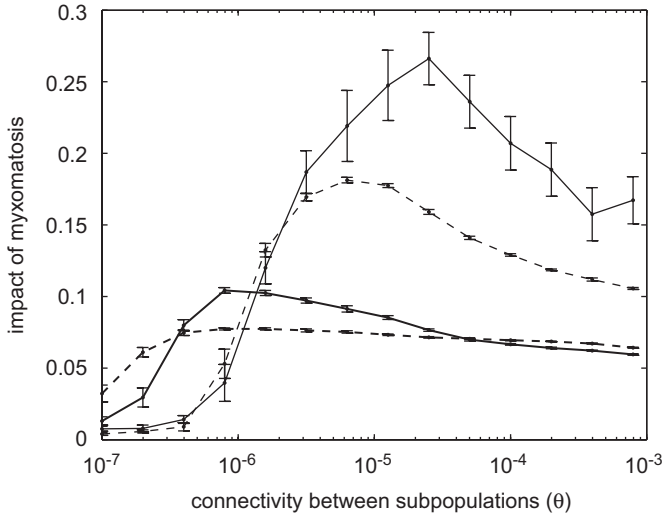

Fig. 8. Impact of myxomatosis (with 95% CI) in a metapopulation during the kth period of time (i.e. the kth year, $\delta_L = 0.001$ corresponding to a mean disease-free subpopulation size of approximately 100 rabbits) according to the contact rate between subpopulations (θ). The impact of the disease is represented by the average number of individuals dying over the final 20 years of a 30-year simulation, divided by the total number of individuals that have lived during that same period (i.e., the number of individuals present at the beginning of the period plus all the births that have occurred during that period). Solid lines—short reproductive period; dashed lines—long reproductive period. Bold lines—waning immunity; thin lines—lifelong immunity. Number of subpopulations is 100 and the number of simulations is 10.

5. Discussion

5.1. Impact of a disease potentially attenuated by maternal antibodies

Asymptomatic and mild infections are becoming increasingly studied in mathematical modelling (Codeco and Luz, 2001; Fouchet et al., 2006, 2007; Glass and Grenfell, 2003, 2004; Gomes et al., 2004; Mossong and Muller, 2003). Here, using the example of the rabbit–myxomatosis interaction, we show that attenuated infections can have important consequences for the host population. Provided that the local transmission rate is significant, an intense circulation of the myxoma virus can be beneficial for the population since the young are exposed to the virus while they still carry maternal antibodies, leading to only rare viral-induced mortality. The local persistence time of the virus plays a central role in the attenuation of disease severity because the prolonged absence of the virus prevents the young from activating their immune system before protection from maternal antibodies wanes. However, high connectivity between subpopulations can offset poor local persistence by permitting frequent reintroductions of the virus.

There is an important correlation between the impact of the virus and its seasonal occurrence. Early epidemics (i.e. in spring) of myxomatosis will have a low impact whereas late ones (in fall) will have a strong impact. The model can also help to understand the seasonal incidence of myxomatosis. In the field, the epidemic peak of mayxomatosis occurs in autumn (Boag, 1988; Ross and Tittensor, 1986). A smaller peak can be observed in spring (Joubert et al., 1973; Ross and Tittensor, 1986; Ross et al., 1989). In the model, epidemic peaks of myxomatosis occur in September as soon as the connectivity between subpopulations is below a given threshold. In addition, the severity of the epidemic depends on the month when it occurs. The fact that most cases of myxomatosis are observed in autumn could be because earlier epidemics are less severe and thus harder to detect.

Spring epidemics are typical of metapopulations where the subpopulations are highly connected and/or can keep the virus over long periods (see Fig. 7a). It is not surprising to observe them in the field. Their presence can be accentuated by several factors such as a larger investment of resources in reproduction during spring (Alitzer et al., 2006; Nelson and Demas, 1996), which leads to a lower investment in the immune response. It is interesting to note that the model is consistent with observations despite the absence of seasonality in the vector transmission rate, an argument often raised to explain the seasonal incidence of myxomatosis (Chekchack et al., 2000; Shepherd and Edmonds, 1978; Sobey and Conolly, 1971). In fact, the two scenarios are not exclusive. In particular, the low abundance of fleas during summer may delay the epidemics of myxomatosis and accentuate its impact.

These results are consistent with those found by Fouchet et al. (2007) in a different context. Here, the effect of duration of disease persistence is studied without varying the host subpopulation size. Parameters influencing the persistence time could also have modified the impact of the disease in terms of the absence of extinction/reintroduction events. But results obtained in isolated homogeneously mixed populations show that this is only partly true. Only by allowing extinction/reintroduction events through linking subpopulations into a metapopulation model can the observed differences in the impact of myxomatosis according to its persistence time be explained. This demonstrates the crucial role of local persistence time in the impact of diseases potentially attenuated in early life.

Estimating the effect of waning immunity is vital because it shows how much it can affect the spread and impact of the pathogen agent. In the worst-case scenario tested here, it could increase by more than three-fold the impact of myxomatosis. Determining the duration of immunity induced by a disease or a vaccine is vital to understand the impact and circulation of such a disease. It is often a complicated task in the field, as illustrated here. After initial infection by the myxoma virus, a rabbit has a low probability of dying from re-infection. Nevertheless, re-infection may be possible. In host populations, where the contact rate is high and where the virus persists for several years, most re-infections are attenuated and so are hard to detect. Rabbits carry protective antibodies during their entire life and their immunity thus appears to be lifelong.

5.2. Extinction pattern of myxomatosis

The results presented here highlight the importance of determining the extinction pattern of a parasite whose infection can be attenuated by maternal antibodies or any other protective mechanism. Rabbit populations can be divided into three categories according to their size. In small populations, the myxoma virus generates an epidemic and then disappears. When populations are of medium size, the virus can be endemic for several years but finally disappears. In large ones, the virus is endemic and almost never becomes extinct. These results are consistent with the concept of CCS (Bartlett, 1956) as described, for example, for measles (Keeling and Grenfell, 1997, 2002) and phocine distemper virus (Swinton et al., 1998). Previous studies revealed that the persistence of a parasite in a host population depends upon several parameters such as the distribution of the infectious period (Anderson and Britton, 2000; Keeling and Grenfell, 1997; Lloyd, 2001a, b), the host spatial structure (Bolker and Grenfell, 1995; Park et al., 2002), the birth rate (Swinton et al., 1998), the basic reproductive rate (Anderson and Britton, 2000; Swinton et al., 1998) or seasonality (Grenfell et al., 1995).

In the rabbit–myxomatosis interaction, the CCS can be very low due to the high reproductive rate of rabbits (between 12 and 50 young per female per year, Fenner and Fantini, 1999) and the relatively long period of virus excretion by infected vectors (Andrewes et al., 1956; Chapple and Lewis, 1965). Here, we studied the impact of the reproductive period, the waning of acquired immunity and the model for vector transmission on the extinction time. When the reproductive period is long, newborn, and thus susceptible rabbits, are present throughout the year, which is favourable for virus persistence.

For the same reason, waning of acquired immunity lengthens the time before extinction of myxomatosis. Here, the duration of acquired immunity was revealed to be even more important than the length of the reproductive period. For example, let us consider a population with a short reproductive period where all subpopulations are made up of 10 rabbits and with a realistic model of 10 fleas/rabbit. Depending on whether or not acquired immunity wanes with time, the mean time before extinction of myxomatosis can range from less than one year (the virus has a high probability of fading out after the first epidemic) to more than 10 years (the virus has a very high probability of persisting from one year to the next).

The choice of the model for vector transmission was found to have a significant impact on the extinction time of myxomatosis. If only one flea is released after the recovery or death of an infected rabbit, the individual remains infectious for a period that follows an exponential law. When several fleas are released, the loss of indirect infectiousness is more regular and the individual remains indirectly infectious for a longer period. These results can be compared with work on the impact of the distribution of the infectious period on the extinction time of parasites (Anderson and Britton, 2000; Keeling and Grenfell, 1997; Lloyd, 2001a, b). These studies, including this one, highlight the need to model more realistic laws for transition times in epidemiology.

5.3. Stochastic vs deterministic approaches

One objective of this paper was to test the suggestion arising from the study by Fouchet et al. (2006) that waning immunity and the length of the reproductive period are two important factors for the impact of myxomatosis. In the deterministic model, the effects of the length of the reproductive period and of the duration of acquired immunity on the impact of myxomatosis were modelled based on unrealistic predictions. The deterministic model could not predict a finite extinction time of the parasite. Due to a lack of susceptible individuals, the number of infected animals fell to very low values (e.g. 10^{-6}) after each epidemic. The large number of susceptible rabbits generated by births then caused the number of infected individuals to increase following the approximate and simplified equation $\mathrm{d}I/\mathrm{d}t = \beta SI/N$. At the beginning of the population increase, S is a constant, so the number of infected individuals grows exponentially at a rate lower than β. If $\beta = 100$ and if initially the number of infected individuals is 10^{-6}, it takes at least three months for the number of infected individuals to reach 1. During these three months, young rabbits lose their maternal protection and become susceptible to the severe form of the disease. This delay, which is purely mathematical, has a strong impact on the system. The model we have built here is, in this sense, far more realistic and allows us to confirm our suspicions that arose from the determinist model. A model can be a source of intuition, however, misleading initially, and motivating further investigations to confirm those intuitions.

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