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Persistence thresholds for phocine distemper virus infection in harbour seal *Phoca vitulina* metapopulations

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Summary

1. This paper explores the concept of the critical community size for persistence of infection in wildlife populations. We use as a case study the 1988 epidemic of phocine distemper virus in the North Sea population of harbour seals, *Phoca vitulina*.

2. We summarize the available data on this epidemic and use it to parameterize a stochastic compartmental model for an infection spreading through a spatial array of patches coupled by nearest-neighbour mixing, with replacement of susceptibles occurring as a discrete annual event.

3. A combination of analytical and simulation techniques is used to show that the high levels of transmission between different seal subpopulations, combined with the small annual birth cohort, act to make persistence of infection impossible in this harbour seal population at realistic population levels. The well known mechanisms by which metapopulation structures may act to promote persistence can be seen to have an effect only at weaker levels of spatial coupling, and higher levels of host recruitment, than those empirically observed.

Key-words: critical metapopulation distribution, mathematical modelling, morbillivirus, North Sea harbour seals, persistence.

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1. Introduction

In 1988, phocine distemper virus (PDV) killed a large fraction of the North Sea population of harbour seals, *Phoca vitulina* L. (Heide-Jørgenson *et al.* 1992a). Reviewing that mass mortality, Hall (1995) commented that 'if PDV behaves like other morbilliviruses it should have been eliminated from the North Sea, because the surviving population of susceptible animals is too small to allow the disease to persist or to permit the establishment of a new epidemic'. This concept of a threshold susceptible population has been a central one in ecological epidemiology since the work of Bartlett on measles 40 years ago (Bartlett 1956) and much theoretical work has been concerned to establish that persistence properties can be strongly dependent on mixing structure. In this paper we use the PDV example to study how the mixing that arises from a patchy host population affects persistence. A common theoretical approach to this problem is to interpret the host patches as habitat patches of a pathogen metapopulation (Hanski & Gilpin 1991). Under this assumption, we need to generalize Bartlett's critical community size, a scalar parameter, to a critical metapopulation distribution of population numbers across a particular metapopulation structure.

We ask which of the variables of this critical metapopulation distribution are central in determining persistence: for example, is it more important to know patch population sizes, the number of patches, the level of interpatch mixing or the total population size? Metapopulation theory has been used to estimate the minimum amount of suitable habitat – MASH (Hanski, Moilanen & Gyllenberg 1996) – necessary for a population to persist. On the other hand, conservation biologists have attempted to estimate the minimum size necessary for a population to have a particular probability of persisting for a certain length of time (the minimum viable population, MVP (Soulé 1987; Bjørge, Steen & Stenseth 1994)). The fact that the theoretical relationship between patch size and local extinction is well understood in an epidemiological setting has enabled us to investigate the way in which local and total population size interact in determining population persistence.

PDV did not persist in harbour seals in 1988: this paper asks whether this should have been surprising, or followed inevitably from the structure of the host population. It has been noted previously (Grenfell 1992; Tidd *et al*. 1993; Grenfell *et al*. 1994) that intermediate levels of coupling promote persistence in metapopulations: can the North Sea population be considered a metapopulation habitat for PDV and if so was coupling too low or too high for persistence? We also discuss a question of more general importance: under what conditions is it necessary to take account of the spatial structure of the population in order to reach this conclusion? We begin by reviewing the available data on harbour seals and PDV, before describing the mathematical model in detail and then presenting the results of the numerical simulations. Finally, we show how these results can be understood analytically and discuss the key features of the critical community size which emerge from this study.

1.1 HARBOUR SEAL POPULATION SIZES

Harbour, or common seals *Phoca vitulina* are found throughout much of the North Atlantic and North Pacific (Bonner 1989). Like all marine animals, reliable estimates of population size are difficult to make (Harwood *et al*. 1989). However, harbour seals often spend time ashore on 'haulouts', although the frequency with which they do so is variable and depends strongly on age, sex and time of year among other factors (Thompson 1989a,b). This behaviour enables population estimates to be based on land counts at the haulouts combined with estimates (of varying degrees of sophistication) of the proportion of time that animals spend in the water.

How many harbour seals are there in northern European waters? Estimates of seal herd sizes throughout Europe in 1989 are tabulated in Dietz, Heide-Jørgenson & Härkönen (1989); more recent data which also covers the Baltic and Barents seas has also been collected (Anonymous 1995). These estimates sum to about 50×10^3 animals, but such a sum needs to be treated with caution. When Thompson & Harwood (1990) used haulout counts combined with individual behaviour from telemetry studies, their estimate for the harbour seal population of Orkney was approximately three times higher than earlier, less sophisticated estimates (Vaughan 1975; McConnell 1985). They proposed that similar correction factors should be applied to other surveys in areas where haulouts were predominantly rocky, and suggested a pre-epidemic population estimate in Britain of $\approx 46 \times 10^3$, rather than the previous 21×10^3. As for world populations, Bigg (1981) estimated $400–600 \times 10^3$ harbour seals in the world, of which the East Atlantic subspecies *P. vitulina vitulina* made up $30–100 \times 10^3$ animals. Bonner (1989) claimed a world population of $300–400 \times 10^3$ and King (1983) stated 360×10^3. On the evidence of the Orkney study (Thompson & Harwood 1990), the stated ranges of uncertainty in these estimates are rather optimistic.

1.2 HARBOUR SEAL POPULATION STRUCTURE

Population structuring, and the mixing of different subpopulations, is as important as total population size in determining epidemic behaviour. Telemetry studies (Thompson & Miller 1990; Thompson *et al*. 1991) suggest that adult harbour seals have a high degree of site fidelity, but around 20% of pups have been observed to travel long distances (up to 500 km) in short periods of time (Thompson, Kovacs & McConnell 1994b). In the context of PDV epidemiology, 'mixing' corresponds not to mating but to contact close enough to transmit the morbillivirus. Although there is no empirical proof that this cannot happen in the water, we take it as axiomatic here that transmission only occurs between neighbouring animals at haulouts. The rapid spread of the virus in 1988 as shown in Fig. 1 demonstrates that there must be significant mixing between widely separated haulouts if this axiom is correct and if there was no further introduction of virus from elsewhere. Haulouts do, nevertheless, form a natural unit of population within which to consider an epidemic taking place. Such haulouts are typically aggregated into regions of greater or lesser definition: recent genetic analyses based on microsatellite polymorphisms (Goodman 1997) suggest six distinct population units: Ireland–Scotland, English east coast, Wadden Sea, Western Scandinavia, East Baltic and Iceland. This structuring into spatially distinct groups within each of which the epidemic fairly rapidly runs to completion (Heide-Jørgenson & Härkönen 1992) makes it natural to interpret haulouts and the regions they make up as units in a host metapopulation (Hanski 1991). Haulout sizes vary substantially and can be strongly dependent on local topography, but in the Wash haulout sizes are in the range of 15–500 (SMRU, unpublished data).

1.3 HARBOUR SEAL FERTILITY AND MORTALITY

Harbour seals have an annual pupping season from late May to early August with a peak in June (Thompson 1989b). Multiple births are rare, and most females do not ovulate until at least 3 years old. Once mature, 80–97% pup each year (Härkönen & Heide-Jørgenson 1990). This single annual birth per female provides one major constraint on the population growth rate.

Helander & Bignert (1992) found the number of pups born in the Swedish Baltic averaged 20–22% of the maximum number of seals counted in the area; Bigg (1969) observed 20% of a Canadian population to be cubs. Härkönen & Heide-Jørgenson (1990) used animals found dead in 1988 in the Kattegat-Skagerrak

area as a cross-sectional population to calculate fertility and mortality data. They recorded that 26% of those that could be aged were pups. Data from that study were used by Heide-Jørgenson, Härkönen & Åberg (1992b) to construct a Leslie matrix population model. In the asymptotic state of that model there are $\approx 0{\cdot}22$ female pups per female.

Mortality, on the other hand, acts throughout the year. While seasonality in this factor is to be expected, there is no published quantitative analysis of this variation, which would in any case be obscured by seasonality in haulout behaviour. Accordingly, in this paper, we take mortality to act at a constant rate throughout the year. The simplest modelling assumption would be that this mortality rate is also independent of age and sex: there are three sources of data on this. Boulva & McLaren (1979) found that catch data from eastern Canada yielded an age profile consistent with an age-independent mortality rate of 0·188–0·193 year^{-1} in light hunting areas and 0·290 year^{-1} in a heavy hunting area. Bigg (1969) published a life table for a Canadian harbour seal population subject to hunting pressure. The log survivorships are approximately linear; fits to these data yields annual mortality rates for males of 0·29 year^{-1} and females of 0·15 year^{-1}, and a combined mortality rate of 0·20 year^{-1}. Analysis of these data with a Cox proportional hazard approach (S-Plus routine coxph) yields an excess mortality of males over females of only 11%, and significant only at the $P = 0{\cdot}06$ level, since the additional mortality is largely apparent at larger age-groups where sample size is small. The final source of data on age-related mortality comes from the cross-sectional study of Härkönen & Heide-Jørgenson (1990) on those animals dying in 1988 in the Kattegat-Skagerrak. This population appeared to have been growing uniformly in the years prior to 1988 and would be expected to have an age-structure in which cohort sizes decrease uniformly with age. However, the age-distribution of those animals that died was markedly bimodal, with a peak in both the first year class and the fifth year class, which suggests that animals under 5 were less susceptible to infection or mortality. For animals over 5 years, Härkönen & Heide-Jørgenson found that an age-independent annual mortality rate of 0·09 year^{-1} was consistent with the data for males but not with the female data, primarily because of the relatively large number of older females found dead. Nevertheless, these three studies together do suggest that an age-independent mortality rate in the absence of PDV is not an unreasonable modelling assumption, particularly if the relatively high first-year mortality is absorbed into the effective fertility rate. To compare this age-independent rate with the age-specific ones derived by Härkönen & Heide-Jørgenson, we need to consider the asymptotic age-distribution of their Leslie population model, which corresponds (data not shown) to a population in which 10·2% is removed annually by non-PDV mortality.

1.4 PHOCINE DISTEMPER VIRUS

Phocine distemper virus (PDV) is a morbillivirus, closely related to canine distemper virus (CDV) and one of a family of viruses including measles (Barrett *et al.* 1995). A few studies of the pathology of PDV in seals have been published (Visser *et al.* 1989; Harder *et al.* 1990, 1992) and it appears similar to that of CDV in seals (Visser *et al.* 1992), PDV in dogs (Osterhaus *et al.* 1988) and in other susceptible carnivores (Blixenkrone-Møller 1993 and references therein). In particular, it takes several days for infection to become patent and infectiousness to develop. Disease mortality is significant (Harder *et al.* 1992), although once recovered, animals appear immune for life (Harder *et al.* 1990). Heide-Jørgenson & Härkönen (1992) estimated the mean lengths of these latent and infectious periods as 3 and 12 days, respectively, largely based on the studies mentioned above. All the studies show recovery or mortality within 11–18 days, so a total mean generation time of 15 days is reasonable. The time at which animals become infectious is harder to estimate. One approach is to be guided by analogy with CDV where dogs develop fever before they shed virus, which would suggest a latency period of rather more than 3 days. Another approach is to detect the presence of virus in leukocytes. In two different experiments, viraemia was not found until day 7 in one set (Harder *et al.* 1990) but before day 5 in another set (Harder *et al.* 1992) in which the course of infection was less similar to the wildtype pathology. Accordingly, we take a latent period of ≈ 7 days and an infectious period of ≈ 6 days as our informed guess at these parameters. However, as Heide-Jørgenson & Härkönen point out, the relative lengths of these periods is not particularly important in estimating overall transmission during the period of infection (effectively, R_0, the number of secondary cases produced by an initial primary case) which is estimated from the data and so the daily transmission rate depends in a simple way on the estimate of the infectious period.

1.5 THE 1988 PDV EPIDEMIC

The epidemic of 1988 remains one of the best documented mass mortality events of wild sea mammals. Much of the raw data was summarized by Dietz *et al.* (1989) and reviewed by Heide-Jørgenson *et al.* (1992a); the spatial spread is illustrated in Harwood (1989) and Harwood (1990) and summarized in Fig. 1. The timings of these reports provide a basis for assessing the rate of spread of infection between haulouts and regions. Moreover, the detailed local reporting in some areas (Heide-Jørgenson & Härkönen 1992; Hall, Pomeroy & Harwood 1992; Thompson & Miller 1992) also enables assessment of the rate of spread within regions.

The initial source of the epidemic remains

unknown. The most plausible hypothesis is that it was related to an invasion of Norwegian waters by harp seals, *Phoca groenlandicus* Erxleben 1777, from populations in the Barents and Greenland Seas where PDV is believed to be endemic (Goodhart 1988; Stuen *et al*. 1994). In April 1988, unusually large numbers of aborted foetuses were found on the island of Anholt (Heide-Jørgenson & Härkönen 1988). From there, infection appears to have spread both eastward, to the southern Baltic and then the Swedish and Norwegian coasts, and westward to the Wadden Sea, and then the Wash, Scotland and the Irish Sea (Fig. 1). Estimates of the total mortality from this epidemic rely on reporting of dead animals washed up at accessible sites. Dietz *et al*. (1989) summed all of these reports to produce a mortality estimate of 18×10^3 animals, corresponding to a case mortality rate of 36% if we assume that every animal became infected and accept the estimate of 50×10^3 in Anonymous (1995) for the pre-epidemic population size.

Mortality rates appeared to vary around the North Sea (Heide-Jørgenson *et al*. 1992a). On the east coast of Scotland, 10–20% of the population were estimated to have died (Thompson & Miller 1992), while mortalities in the eastern North Sea may have reached 60%. It remains unclear (Thompson & Miller 1992) whether this reflected decreased transmission or decreased susceptibility to disease. Only 52% (35/68) of the Moray Firth animals were reported as seropositive (Thompson *et al*. 1992) while 95% of females in the Kattegat were believed infected based on the abortion rate (Heide-Jørgenson *et al*. 1992a); de Koeijer, Diekmann & Reijnders (1997) point out that in populations with the mass-action mixing defined below, lower case mortality rates can themselves lead to lower population prevalences of infection.

1.6 PDV IN OTHER SEAL SPECIES

PDV is believed to be endemic in some other seal species (Stuen *et al*. 1994). In the North Sea the only commonly found seals are the harbour seal and the grey seal *Halichoerus grypus* Fabricius 1791. The latter is also thought to have been free of infection prior to 1988 on the basis of serological evidence (Harwood *et al*. 1989). At least 185 grey seals were found dead during the 1988 epidemic with similar pathological symptoms to those in harbour seals, so the infection appears to have been present in the grey seal population. Serological evidence is that it was present at comparable prevalences to that in the harbour seal population (Harwood *et al*. 1989), suggesting that PDV mortality was a great deal lower in grey seals. This lower mortality, together with the fact that most populations of grey seals are in remote areas, means that there are a great deal less data on the spread of the epidemic within this species. We assume in this paper that there is no significant cross-species transmission and restrict ourselves below to populations of harbour seals only.

1.7 PERSISTENCE OF PDV IN HARBOUR SEAL POPULATIONS

Evidence for the continuing transmission of PDV in harbour seals after 1988 remains equivocal. Seropositive samples were reported from Dutch seals born after 1988 (Visser *et al*. 1993) but none from Germany (Harder *et al*. 1993), the Wash (Hughes *et al*. 1992) and the Moray Firth (Thompson *et al*. 1996). This may reflect differences in transmission between areas, or may be accounted for by differences in protocol and interpretation. There are no reports of continued excess mortality at any of these sites, so we assume below that transmission did not continue beyond early 1989, or that if it did so, it was of a strain of virus of reduced virulence.

2. Mathematical formulation

We now set up a mathematical model sufficient to reproduce the salient features of the 1988 epidemic using the biological knowledge described above. The key features of the model are represented in a typical simulation output in Fig. 2: it consists of discrete stochastic epidemics in a linear sequence of patches, each weakly coupled to its nearest neighbours.

2.1 MODEL STRUCTURE

The population is divided into a number of different patches corresponding to seal populations at particular haulouts, with N_i representing the population size for haulout i. Within each patch there is a standard *SEIR* model, for the numbers susceptible S_i, infected but not infectious E_i, infectious I_i, and recovered R_i.

A deterministic representation of this model would be as follows:

$$\dot{S}_i = -\lambda_i S_i - \mu S_i \qquad \text{eqn 1}$$

$$\dot{E}_i = \lambda_i S_i - (\mu + \sigma)E_i \qquad \text{eqn 2}$$

$$\dot{I}_i = \sigma E_i - (\mu + \alpha + \gamma)I_i \qquad \text{eqn 3}$$

$$\dot{R}_i = \gamma I_i - \mu R_i \qquad \text{eqn 4}$$

together with an annual birth input. Non-PDV mortality is represented as an age-independent per-capita rate μ while infected animals leave the latent stage at a rate σ to become infectious. While infectious they suffer an additional mortality rate α or cease to be infectious at a rate γ (so that the fraction of animals who die of the infection is $m = \alpha/(\alpha + \gamma)$). Once recovered, individuals remain immune for life. The simulations use a stochastic version of the above model in which each per-capita transition rate is interpreted as a hazard for transition occurring between discrete population compartments, so that the tran-

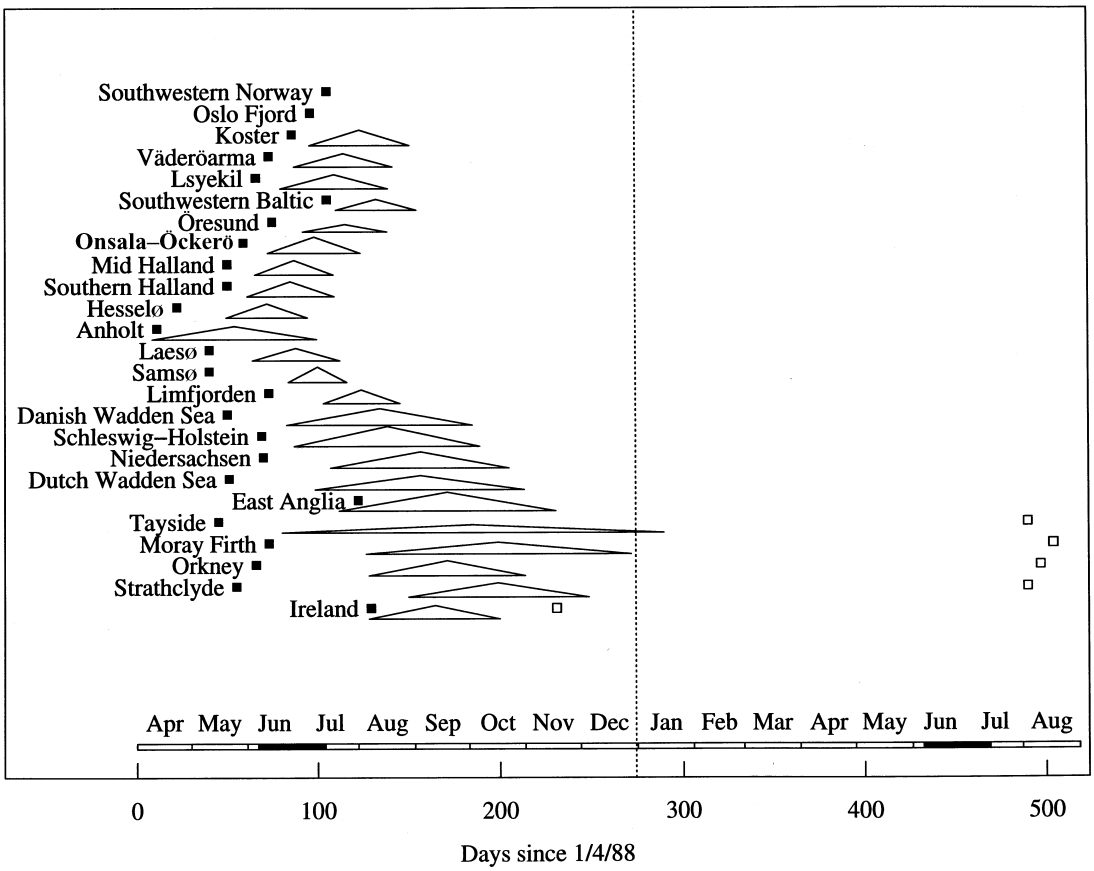

Fig. 1. Timing of recorded mortality from the 1988 PDV epidemic. Closed box: first recorded case in each location. Triangle: centred on peak reporting time, with width equal to length of period in which mid 90% of cases recorded and height proportional to logarithm of total number of cases. Open box marks last recorded case in those location where known (in other locations cases are those up to December 1988). Shaded period of month bar is approximate pupping season. Data from Dietz *et al.* (1989) and Harwood & Hall (unpublished data, SMRU). The vertical ordering of sites is based partially on that in Dietz *et al.* (1989), and otherwise on geographical proximity.

sition $S_i \to S_i - 1$ occurs in the interval $(t, t + \delta t)$ with probability $(\mu + \lambda_i)\ S_i \delta t$. Using a fixed δt of 0·001 years, the number of transition events of each type is calculated by treating it as the outcome of a sequence of independent binomial trials of all possible transitions, or an approximating Normal or Poisson variate when appropriate (Evans, Hastings & Peacock 1993; Ripley 1987).

The only element of this local dynamics which depends on the rest of the system outside the patch is the force of infection λ, which contains information on the mixing structure of the system: there is assumed to be no movement of seals between patches. There is no age-structure in this model.

Births are assumed to occur once a year in a simple density-dependent manner. Each patch is assigned a carrying capacity K, and the number of births in a patch of size N is taken to be the minimum of $K–N$ and rN where r is the maximum fecundity rate.

2.2 FORCE OF INFECTION AND NEAREST NEIGHBOUR MIXING

In this section we define a function for the force of infection and present evidence for the relative magnitudes of transmission within and between patches. The resourceful work of Heide-Jørgenson & Härkönen (1992) on the course of infection within haul-outs allowed an initial estimate of the mode and intensity of transmission. This can be described in terms of the basic reproductive number R_0 of the infection: the number of secondary cases produced by an initial primary case. They showed that in populations of size (N) varying from 80 to 1500, R_0 was approximately constant. In a terminology introduced by de Jong, Diekmann & Heesterbeck (1995), Diekmann *et al.* (1996a) and de Koeijer *et al.* (1997) pointed out that this is more consistent with 'mass action' mixing than 'pseudo mass action mixing'. (In the notation defined above, 'mass action' corresponds to a force of infection of the form $\lambda = \beta I/N$ and pseudo mass action to $\lambda = \beta I$.) Heide-Jørgenson & Härkönen (1992) gave estimates for a quantity they called $\hat{p}N$, which can be multiplied by the infectious period to derive estimates for $R_0(N)$. These, each weighted by an estimated standard error of $R_0(N)/\sqrt{N}$ (Becker 1995), can be used in a linear regression of R_0 against N to reject the pseudo mass action hypothesis $R_0(N) \propto N$ but not to reject the mass action hypothesis $R_0(N) = \text{const}$. (Best weighted linear fit: $\log_{10}R_0 = 0{\cdot}690–0{\cdot}091 \log_{10}N$, SE

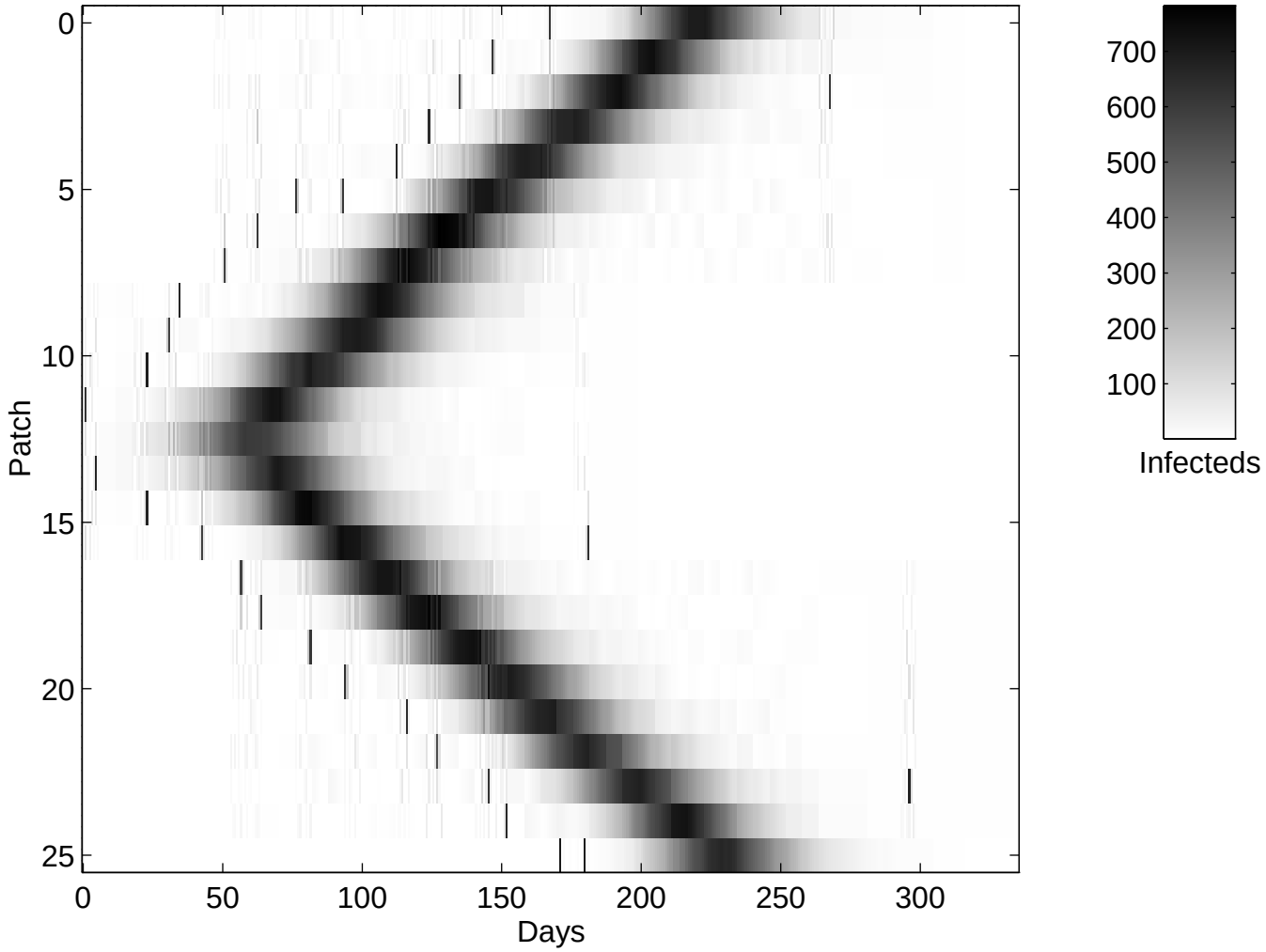

Fig. 2. Typical model simulation with parameter values as in Table 1 and $m = 0{\cdot}2$ and $\rho = 0{\cdot}1$, with 50 000 animals distributed among 25 patches, showing number infected ($E_i + I_i$) in each patch i after initial infection on day 0 in patch 12. Vertical bars indicate new infections occurring in a patch with no current infections.

of slope 0·0676 and the slope is not significantly different from zero, $P = 0{\cdot}27$).

The force of infection for an individual in haulout i is made up as follows:

$$\lambda_i = \beta\left[(1-\rho)\frac{I_i}{N_i} + \rho\frac{\Sigma_{j=i-1,i,i+1}I_j}{\Sigma_{j=i-1,i,i+1}N_j}\right] \qquad \text{eqn 5}$$

so that ρ reflects the relative frequency of between-haulout mixing while β is a contact rate. Patches at the edge of the array only mix with their immediate internal neighbours: the boundary conditions are zero rather than periodic. This is a representation of a nearest-neighbour mixing process, which describes 1988 data well and allows some analytical progress (Swinton 1998). While the discussion of within-patch mixing above gives us some confidence in the first term in eqn 5, the second is inevitably more speculative: it is consistent with a picture in which all of the seals in the neighbourhood are in a common 'mixing pool'. An alternative assumption, where contacts with one patch do not make contacts with another patch less likely, might be of the form $\Sigma_j(I_j/N_j)$; we fix here on the first for definiteness.

We expect that between-patch mixing is small compared to within-patch mixing. In the limit $\rho = 0$, the model is reduced to a single patch with a standard *SEIR* model. It is straightforward to observe that small infections in the deterministic model will only increase if $R_0 > 1$ where $R_0 = \beta/(\gamma + \alpha + \mu) \times \sigma/(\sigma + \mu)$. Since nondisease mortality is negligible during the brief infectious period (so $\mu \ll \sigma$) in this paper we define

$$R_0 = \frac{\beta}{\gamma + \alpha + \mu}. \qquad \text{eqn 6}$$

By applying stochastic threshold theorems (Bailey 1975; Svensson 1995), we expect there to be a threshold at $R_0 = 1$ in the corresponding stochastic model separating the cases where a major epidemic is likely or unlikely. It is possible to extend this analysis to the

multiple patch case in both deterministic (Dieckmann, Heesterbeck & Metz 1990) and stochastic settings (Ball, Mollison & Scalia-Tomba 1997) but the definition in eqn 6 remains the relevant one when the initial infection is confined to a single one of a set of weakly coupled patches. We use R_0 merely as a convenient dimensionless measure of transmissibility, in that we use the estimates above as a means to estimate β.

Can estimates of β and R_0 drawn from seal populations of 70–1500 be extrapolated to ever larger populations in our search for a population size that allows persistence? The answer clearly depends on how the host population responds to increases in population size: in particular how density changes as population size changes and the relationship between density and transmission, but also the likelihood of a population already spatially structured splitting off new subpopulations as it grows. There is some theoretical justification for maintaining a mass-action transmission with constant β, based on mechanistic assumptions about the contact process (Heesterbeek & Metz 1993). de Jong *et al.* (1995) examined the empirical evidence in the literature and found four comparisons between theory and data of which none falsified the mass-action assumption and three out of four falsified the pseudo-mass action. Those four comparisons did not include the PDV epidemic data, which, as we have seen also provides evidence for mass action and against pseudo mass action. Theoretical techniques for distinguishing between these processes in data, and for locating mixing processes as a point on a continuum rather than as a choice between two alternatives, are in their infancy though, and in particular it is important to recognize that rejecting pseudo mass action as a relevant scaling is not the same as validating mass action. Nevertheless, since both the directly relevant empirical data and the theoretical arguments point in the same direction we choose transmission functions of the mass action form. A direct consequence of this is that the basic reproductive rate R_0 can be independent of the population size N in the sense that we can plausibly take the transmission coefficient β in eqn 6 as independent of N.

2.3 ESTIMATION OF COUPLING STRENGTH

As well as estimating within-haulout mixing, the observed 1988 data can be used to give us rough estimates of the between-haulout mixing by treating the locations named in Fig. 1 as individual patches. We can estimate the between patch mixing ρ either by comparing the simulation output with the observations in Fig. 1 or by using the theoretical result (Swinton 1998) that T_T, the expected time for a transit to occur between two patches is independent of N for N large and is approximately related to the between patch mixing ρ by $\rho = (1/2R_0)\,e^{-(R_0-1)T_T/G}$ where G is the generation time of infection (the sum of the infectious and latent periods). Figure 3 shows the number of days between each new recorded outbreak from the 1988 epidemic. Most of the patches are separated by differences of less than 10 days, and inserting $T_T = 10$ days into this formula combined with the parameter estimates below yields an estimate of $\rho = 0{\cdot}05$. This figure should be viewed with caution, because it is derived by assuming not only that N is large but also that infection spreads through the continuous time mechanism described by the deterministic differential equations, which is likely to be a bad description of events within the first one or two generation periods of infection when numbers of infectives are small. Nevertheless, it is of interest that it is of the same order of magnitude as the value $\rho \approx 0{\cdot}1$ which arises by attempting to mimic the observations (Fig. 1) with the numerical simulations (Fig. 2) by eye. Thus, we use baseline interpatch mixing of the order of 10% of that within a patch. Base parameters used are summarized for convenience in Table 1; departures from this parameter set are described for individual runs.

3. Extinction times for models without replacement

The twin assumptions of a discrete annual birth rate and nearest-neighbour mixing allow us to make a substantial amount of analytical progress with the model system. It is obvious that an infection that fades out before the end of one year cannot persist in the population no matter how high the birth rate. Accordingly, we begin by studying the properties of the time to (inevitable) extinction in systems with no replacement of susceptibles. We shall see subsequently that these properties will have a strong bearing on persistence times for models with replacement.

The problem of determining the distribution of extinction times for the standard epidemic model in a single patch was first solved by Barbour (1975) for large N in a model with no latent class. Conditional on a major epidemic occurring, and under the approximation $f = 0$ corresponding to almost all individuals eventually becoming infected, his Theorem 2 implies that for a generation time of G, the expected extinction time T_E is given by

$$\frac{T_E}{G} \to \frac{R_0}{R_0 - 1}\log N \qquad \text{eqn 7}$$

at large N. More recent results of Svensson (1995) extend this analysis to include the effect of a latent period.

How should this expression be modified for multiple patches? Figure 4 shows the results of a simulation for parameter values relevant to PDV (save that, for clarity, the interpatch coupling is 100-fold weaker than that estimated above). The single patch runs show the approximately linear growth of T_E with

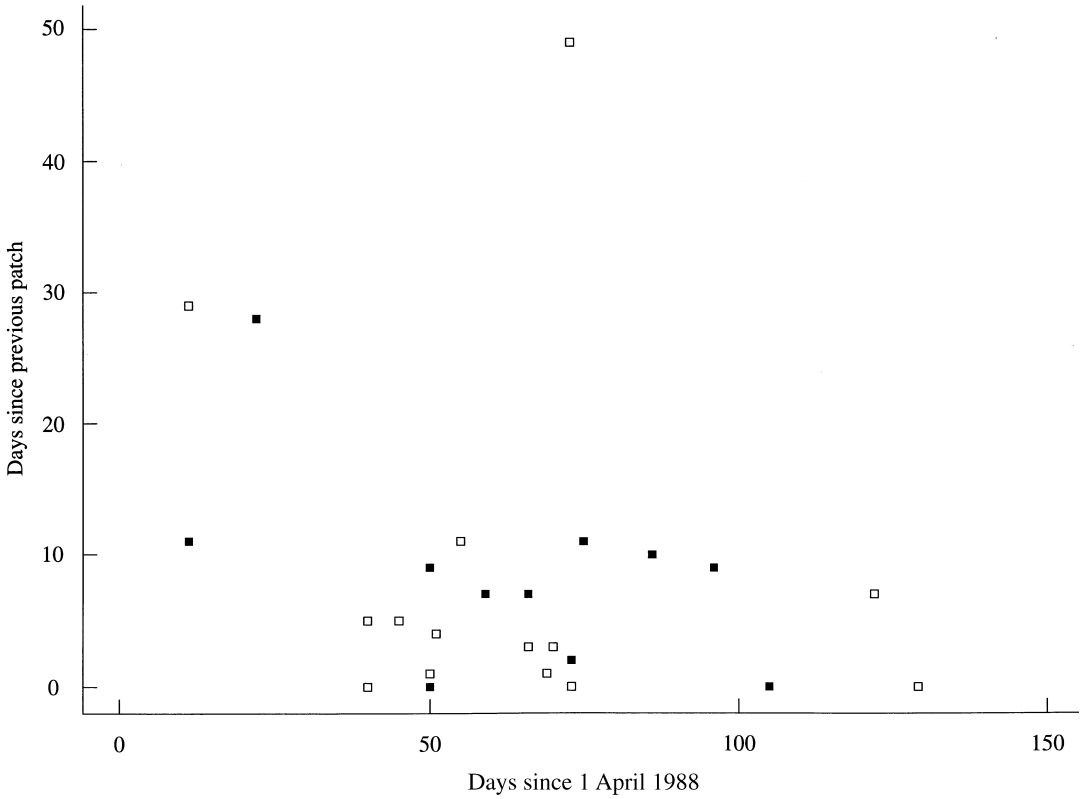

Fig. 3. Differences between successive new outbreaks on the east (open squares; mean 7·8 days) and west (closed squares; mean 8·4 days) wings of the 1988 epidemic (i.e. sites above and below Anholt in Fig. 1).

Table 1. Basic and derived parameters

Estimated parameter	Symbol	Typical value	Discussion
Death rate	μ	0·1–0·2 year^{-1}	Section 1.3
Latent period	L	0·02 years ($\approx$7 days)	Section 1.4
Infectious period	D	0·02 years ($\approx$7 days)	Section 1.4
Case mortality	m	0·1–0·6 per infected animal	Section 1.4
Basic reproductive ratio	R_0	2·8	Section 2.2
Replacement birth rate	r	0·2 year^{-1}	Section 1.3
Inter-patch mixing	ρ	0·05–0·1	Section 2.3
Derived parameter	**Symbol**	**Derived value**	**Discussion**
Loss of latency	σ	$\sigma = 1/L$	Section 2.1
Recovery rate	γ	$\gamma = (1 - m)/D$	Section 2.1
Mortality rate	α	$\alpha = m/D$	Section 2.1
Generation time	G	$G = D + L$	Section 2.1
Transmission rate	β	$\beta = R_0/D$	Section 2.2

log N as predicted. For multipatch runs, the situation is more complicated. For small N, it is unlikely that infection from the initial patch spreads successfully into the second patch, and so the extinction time is independent of the number of patches n. For large N (here, bigger than around 10^5), the transit time to the next patch is approximately constant, and so the total time to extinction is the time to spread through one patch plus this transit time multiplied by the number of transits. That the transit time is independent of N can be seen by considering the time taken to transit between two patches, the first of size N_1 in which the epidemic is established, and the second of size N_2 in which it is not. The force of infection for an individual in the second patch is assumed to scale like $1/N_1$, so the risk that any member of the second patch becomes infected scales like N_2/N_1. If the relative patch sizes remain the same as $N = N_1 + N_2$ increases, this risk remains independent of N. This argument is described in greater detail elsewhere (Swinton 1998), where an explicit expression is derived for the transit time and the threshold patch size for transits to occur. The biological reason for the existence of a threshold patch size lies in the mass action assumption that individuals

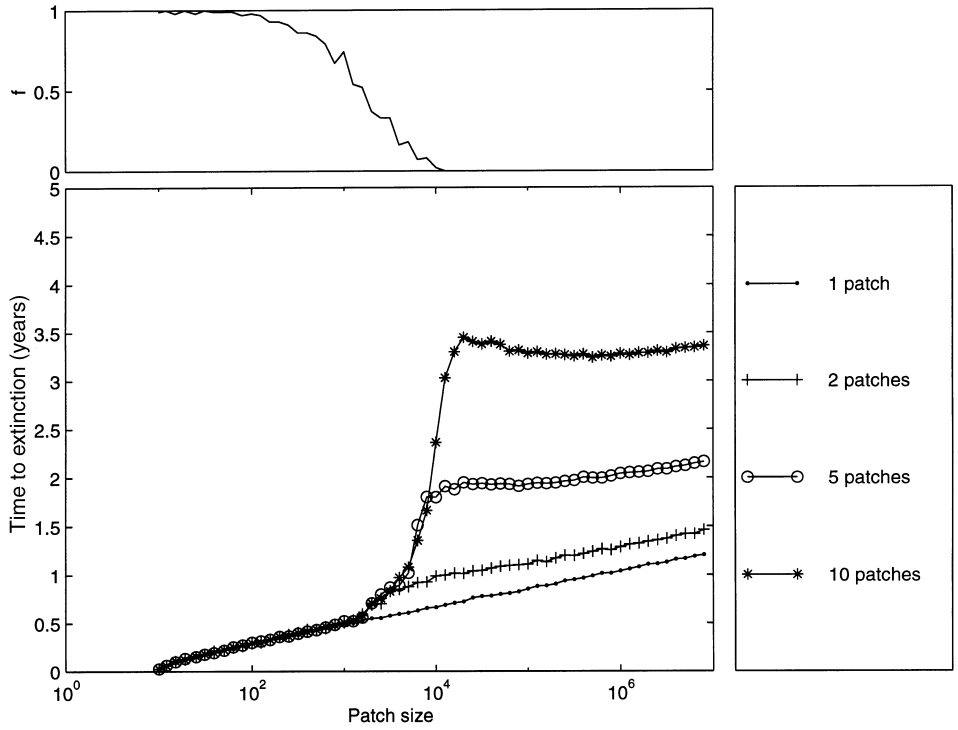

Fig. 4. Lower panel: extinction times without births as a function of patch size for a model with 1, 2, 5 or 10 patches. Median of 100 simulations at each population size. Parameters $\sigma = 25\ \text{year}^{-1}$, $\gamma = 50\ \text{year}^{-1}$, $\alpha = 50\ \text{year}^{-1}$, $\beta = 280\ \text{year}^{-1}$, $\rho = 0{\cdot}001$. Top panel: fraction, f, of the time that infection goes extinct in first patch before spreading to second patch in the two-patch model.

make only a fixed number of infectious contacts, independent of population size. Thus, individual risk does not scale with population size, but the risk of a one-off population event such as a transit does, since it compounds the individual risk for each member of the population.

The nonmonotonicity of the extinction time curves is a product of the phase transition near N_c between the two regimes of large and small N. As N decreases but remains above the critical N_c, transits take longer and longer to occur (and are thus less likely to occur at all). Thus, the total time stretches by this transit time (scaled by the number of patches) although its variance increases. As N decreases down through N_c, the transit time can increase no more, but the per-patch extinction rate increases, so that the median time to extinction of the whole system decreases. Finally, for $N < N_c$, transits do not occur at all.

4. Persistence thresholds for models with replacement

We now come to the central question of the paper: how do persistence thresholds, in the presence of replacement, depend on population size? We distinguish two forms of persistence: the most important is long-term persistence (LP) which we define here to mean that, with probability greater than 50%, infection will persist in the population for at least 100 years. In order to study the properties of LP, it is useful to introduce a much weaker definition of persistence: annual persistence (AP) which means that infection will, with probability greater than 50%, persist in the population for longer than 1 year. Since births only occur annually and we assume that the introduction of infection is immediately after the first birth season, AP is clearly independent of the demographic parameters governing recruitment, and critical parameters for AP can be calculated from the arguments of the previous section or read off a graph like Fig. 4. AP is obviously a minimum requirement for LP and provides a guide to the necessary requirements for LP. Suppose that the critical patch size for AP in a single patch is N_y. At the end of a year, the number of new susceptibles entering the population is rN. A crude estimate for the critical community size for LP could then be $N = N_y/r$, so that the infection takes at least 1 year to get through the newborn susceptibles and the cycle can repeat itself. This can only be a crude estimate because of two conflicting corrections corresponding to the two components making up the persistence time in a multipatch model. The first component, the time it takes to spread within a patch, is increased because the basic reproductive ratio is decreased by a factor of r: the diluting effect of the presence of about $(1-r)N$ immunes. The second component, the time it takes to spread to all the patches, is decreased for a rather different reason. In general, the birth season will happen when epidemics are still raging, at various levels, in a number of patches, so that the assumption of a single introduction of infection in one patch, used to find N_y, does not hold. Thus,

the number of patches available to transit to and start new infections in is reduced. Thus, we would expect to find a larger gap between the critical patch size for AP and LP in a multipatch than in a single patch model. Nevertheless, when about 20% of the population are replaced each year, we do find that at the population size when persistence occurs, the corresponding model without births has an extinction time in the 1–4 year range.

4.1 CRITICAL POPULATION SIZE FOR PDV

Figure 5 shows how the time to extinction varies as a function of patch size for the base estimates we took for PDV. The key implication of this figure is that the critical community size for this model population (at least 10^8) is several orders of magnitude greater than the known North Sea population (up to 10^5) or even world population (up to 10^6) of harbour seals, and that persistence of infection for more than a year or so would have been extremely unlikely. These simulations suggest that the persistence time of infection with about 25 patches of 2000 animals each is about a year (compare Fig. 1). The possible determinants of this critical community size can be organized under three headings: demographic parameters controlling the birth of susceptibles; epidemic parameters controlling the spread within patches; and spatial parameters controlling the spatial structuring of the epidemic, which we now consider in turn.

4.2 SENSITIVITY TO DEMOGRAPHY

In the 1988 epidemic, infection was circulating for at least 9 months and perhaps longer; it might be argued that the infection came close to achieving persistence since had it lasted for one or two generations more it could have spread to a whole new birth cohort. Figure 5 suggests that this was not so because the size of the new birth cohort was too small: slightly larger population sizes that tip the persistence time over 1 year still do not persist.

A deterministic model of infection in a single patch of the form $I = \beta SI/N - \gamma I$ suggests that infection can only persist endemically if the fraction susceptible at the beginning of the year (just after the birth cohort) satisfies $R_0 S/N > 1$. For $R_0 = 2{\cdot}8$ that requires a birth cohort to make up a fraction greater than about $1/2{\cdot}8 = 35\%$ of the population. At a maximum replacement rate of just 20%, this suggests that infection can never persist in a single patch, no matter how large the population size, so that there is no critical community size in this case. When there are multiple patches, infection needs to be avoided in each patch for several years to allow the susceptible fraction time to recover; in the meantime it must be maintained elsewhere in the system.

Thus, for small R_0, weak coupling, or a small annual birth rate, the critical community size is determined largely by the spatial structure of the population: there have to be enough patches to enable a long sequence of successive colonizations of other patches between any two major epidemics in one patch. For larger R_0, strong coupling, or a larger birth rate, it is the timing of susceptible recruitment that is essential, and this is more sensitive to the demographic assumptions.

The effect of birth rate can be seen in Fig. 6, which compares the results of Fig. 5 with simulations that raise the birth rate parameter r to 0·3 and a yet more

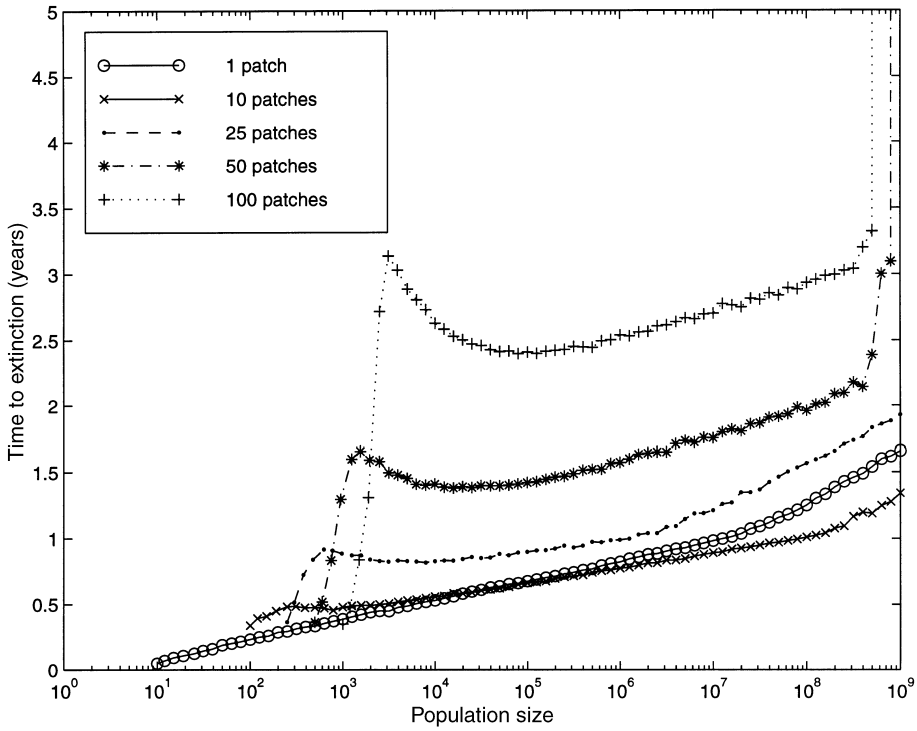

Fig. 5. Median extinction times of 100 simulations at each population size using base parameter values in Table 1, for nearest neighbour mixing with the initial case of infection introduced in the central patch.

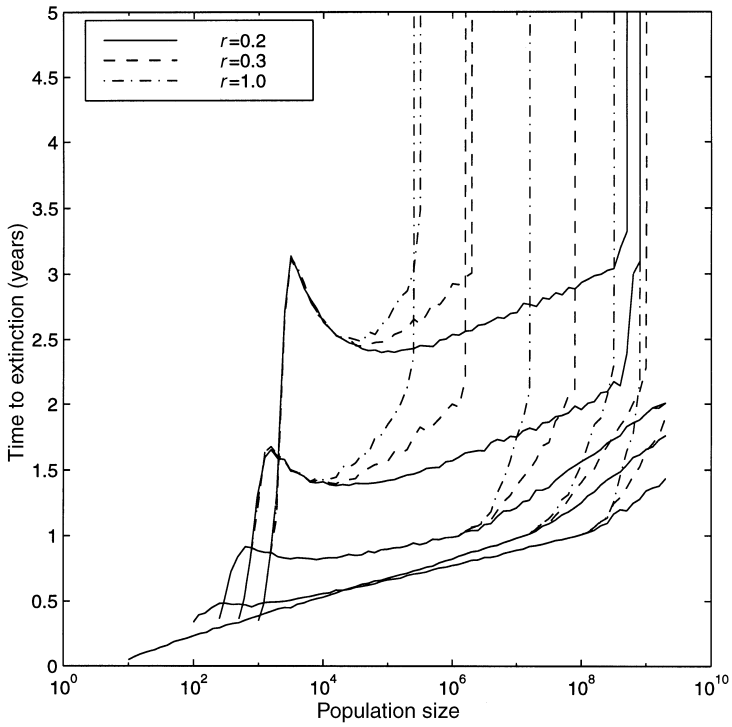

Fig. 6. Demography and persistence. As Fig. 5, with 1, 10, 25, 50, 100 patches as before (now unlabelled) but also showing the median extinction times for the higher birth rate cases $r = 0{\cdot}3$ and $r = 1{\cdot}0$. Once persistence times are longer than a year, the higher birth rate allows infection to persist a little longer in each patch and reduces the patch size at which the transition to persistence occurs.

extreme set in which it is assumed that $r = 1$, so that all animals which die in the course of the year are replaced at the pupping season. The primary effect of increasing r is to decrease the critical community size: the mechanism by which this occurs can be seen only to be effective once the patch sizes are large enough to ensure patch to patch transmission. Even at the unrealistically high birth rate $r = 1$, however, the critical community size remains large.

This discussion has so far ignored the impact of infection-induced mortality. Infections with a high degree of lethality in a population maintained at a given size will have a higher replacement rate of susceptibles and thus might generally be expected to find it easier to persist: this effect can be shown to exist at large r but is not significant at realistic r at which the density-dependent susceptible recruitment rate is already saturated. A reduction in population size will also promote transmission under the mass-action assumption but the effect of this will be small at these parameter values (Diekmann, de Koeijer & Metz 1996b).

4.3 SENSITIVITY TO EPIDEMIOLOGY

The previous section argued that for a higher R_0, critical sizes for annual persistence (AP) would be more closely related to those for long-term persistence (LP). This is supported by Fig. 7: although the extinction times below 1 year are briefer than in Fig. 5, as predicted by eqn 7, once there are enough patches to tip the extinction time over 1 year there is a more rapid transition to persistence. R_0 is only a summary parameter of the epidemiological dynamics and we also carried out a number of simulations using the parameter values of (Heide-Jørgenson & Härkönen 1992) with a similar R_0 but a shorter latent period: the results did not differ in substance from those presented below.

4.4 SPATIAL STRUCTURING AND PERSISTENCE

Figure 6 also reveals some of the effect of spatial substructure. As a single population is subdivided into 10 subpatches, the extinction time decreases at large N: this is because the time taken to spread through each individual patch decreases. As the degree of subdivision increases, this effect is outweighed by the number of transits the infection must take between each patch. Figure 8 shows how this effect depends on the strength of interpatch coupling times. For extinction times, this is in agreement with the theory on patches without replacement (Swinton 1998) that when the intensity of interpatch coupling ρ is reduced, the expected transit time from patch to patch at large N is predicted to increase like $\log 1/\rho$, while the critical patch size at which transits occur at all is predicted to scale like $1/\rho$. Although this produces very long transient infections lasting up to a decade, it has little effect on persistence: as coupling becomes weaker and weaker, it is the ability of the infection to persist within a single patch which determines global persistence and

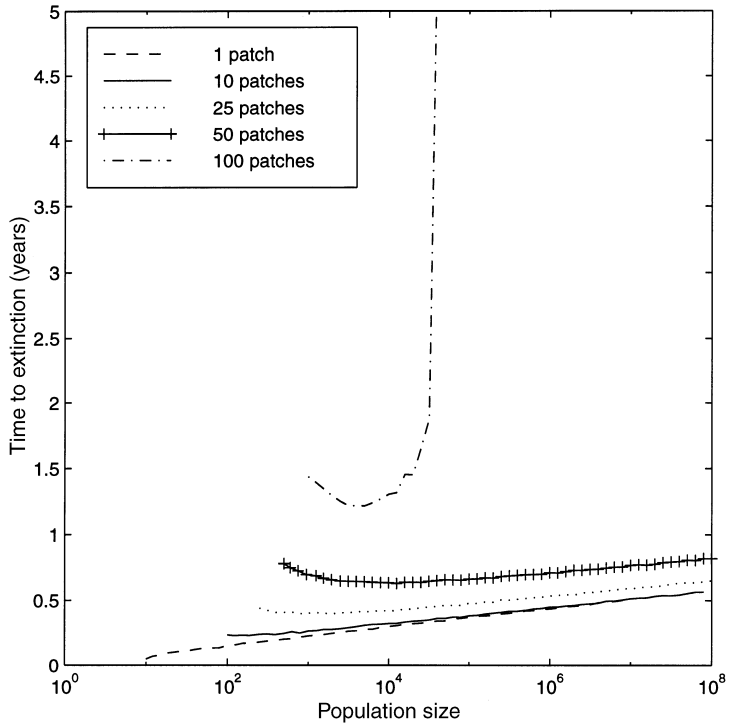

Fig. 7. Epidemiology and persistence: sensitivity to raising R_0. Parameter values as Fig. 5 but with $\beta = 500$ year^{-1} so that $R_0 = 10$. The higher R_0 speeds the epidemic within individual patches, so the slopes of the curves before persistence are flatter than in Fig. 5, but also makes it easier for the infection to persist in postepidemic patches, so that the transition to persistence occurs at lower patch sizes once there are enough patches.

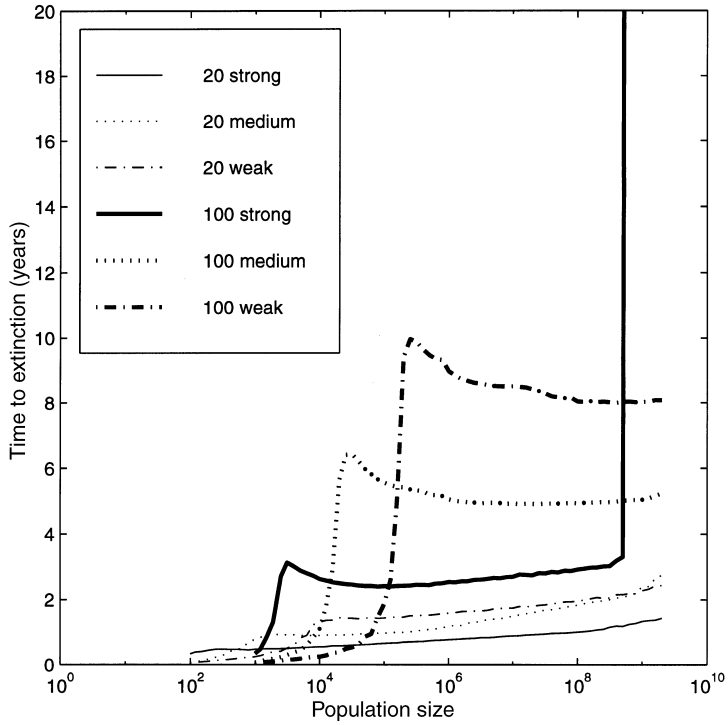

Fig. 8. Reduced interpatch coupling changes extinction times but not persistence sizes. Critical population sizes for persistence as in Fig. 6 with either 20 or 100 patches, and interpatch coupling $\rho = 0{\cdot}1$ (strong), $\rho = 0{\cdot}01$ (medium), $\rho = 0{\cdot}001$ (weak).

that, as we have seen, requires very large population sizes.

5. Conclusion

The most important questions about the critical community size for PDV in harbour seals in the North Sea are whether such a threshold population size exists at all and, if so, whether it is larger or smaller than the current population size. The results of the natural experiment of 1988 tell us that it, if it exists, is probably larger. In this paper we have gone further and found that at the best point estimates, the critical community size is so large (10^8 animals, several orders of mag-

nitude greater than the known world population size) that it can only be considered to exist in the unlikely belief that observed seal population biology and corresponding model assumptions can be meaningfully extrapolated to these huge extremes.

More meaningful than a particular number, though, is the confirmation that the level of the threshold is rather more sensitive to the demographic factors controlling the supply of susceptibles than epidemic ones. This arises because the epidemic is one which is capable of reaching the majority of susceptibles in each birth cohort. We have also demonstrated that for this example the very existence of the critical community size at reasonable levels depends on the assumption of spatial substructuring: without this, infection spreads too rapidly through the limited size birth cohort.

A necessary caveat to this discussion is the recent observation (Keeling & Grenfell 1997) that modifying the assumption of exponentially distributed incubation times can markedly alter predicted critical community sizes for measles. The specific setting of that work includes seasonal forcing and age-structure in analysing endemic persistence at the bottom of seasonal troughs, while we are concerned primarily with persistence through the first trough after invasion of a wholly susceptible population, but further work is clearly necessary along these lines. A further issue likely to be of importance in persistence is the nature of between-patch coupling discussed briefly in Section 2.2: emerging methods for quantifying regional dispersal, at least at a reproductive level, may be very useful here (Goodman 1995).

We have seen that the structural determinants of peristence differ markedly in different areas of parameter space. If between-patch coupling is fairly weak, the number of patches is of crucial importance for prolonging the infection until the next birth period, but not for the ability of the infection to exploit the new supply of susceptibles. If coupling is stronger, it is the size of each patch which controls persistence. The rapid spread of 1988 is evidence that coupling was strong in the North Sea, and so the infection inevitably died out because individual patches with populations of a thousand animals or so could not sustain the infection.

PDV infection has been detected in other harbour seal populations: one-third of Canadian harbour seals tested between 1972 and 1988 had morbillivirus antibodies (Henderson *et al*. 1992), and an increase in strandings of western Atlantic harbour seals in 1991–92 has been attributed to PDV (Duignan *et al*. 1995). Commenting on that event, Duignan and colleagues wrote that 'infection may be maintained in the smaller harbour seal population through casual contact with grey seals' (Duignan *et al*. 1995). Harp seals, which have a world population in excess of 5×10^6, have also been implicated in transferring infection to harbour seals. Hall (1995) has suggested that cross-species transmission provides a mechanism which would weakly couple a reservoir of infection in harp seals to the harbour seal population. The approach outlined in this paper is particularly appropriate for evaluating this mechanism. A particularly interesting feature of observed PDV dynamics is the contrast between the rapid and intense North Sea epidemic and a less dramatic, 'smouldering', infection in the western Atlantic: one possible if speculative explanation for this is that the western epidemic is taking place in a host metapopulation equally strongly coupled but where events in neighbouring patches have become less closely correlated than in the eastern epidemic. The 'rescue effect' of metapopulation theory (Brown & Kodric-Brown 1977) suggests that even at high levels of coupling, it should be easier for an infection to persist in a decorrelated spatial structure than where there is an initial, highly localized invasion (Earn, Rotani & Grenfell 1997). There is clearly a need for a better theoretical analysis of the implications of this correlation structure for the persistence of infection, and a closer epidemiological examination of the nature of between species transmission of morbilliviruses.

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