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Seasonality and Adaptive Dynamics in Host-Parasite Systems in Wildlife

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- Ecology -

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General introduction

The second half of the 20th century showed a marked enhancement in hygiene practices, diagnostic methods, and drugs and vaccine development which permitted an extraordinary reduction in prevalence and mortality of several infectious diseases in developed countries. Nevertheless, infectious diseases remain the largest cause of death in the world.

In the last 30 years, next to the more traditional clinical and epidemiological approaches to the fight against disease, a new approach based on ecological principles has been introduced. It focuses on infectious disease occurrence from an ecological and evolutionary point of view, by taking into account the dynamics of host and pathogen interactions. In the ecological perspective, the disease occurrence patterns are products of basic biological processes (such as host interaction, migration, mutation) that may predict the spread and the course of the infection within and between populations. The main tools used to describe first-principle biological processes which generate time and space infection patterns are mathematical models. Through mathematical models it is possible to predict disease occurrence, but also to obtain a deeper understanding of the causative mechanisms underlying disease processes. Furthermore, mathematical models allow to test and perform disease control policies in a faster, cheaper, and a more ethically sustainable way than *in vivo* programs.

Historically, the first pioneering modelling applications concerned human diseases such as malaria (Ross, 1915) and measles (Kermack and McKendrick, 1927), but animal diseases have also become object of theoretical investigations (Anderson and May, 1979; May and Anderson, 1979). Diseases in domestic animals cause major economic impacts on the breeding sector, while diseases in wild animals may threaten endangered species survival. In addition, domestic and wild animal pathogens are responsible for several spillover infections to humans, as shown by recent cases of avian influenza, SARS and Ebola epidemics (called emerging infectious diseases). The ecology of the most part of emerging infectious diseases (EID) involves different host populations and it is characterized by infection transmission among wild, domestic and humans (Daszak et al., 2000). In order to represent complexity and differences among pathogen agents, theoretical ecologists have generated a theoretical taxonomy of pathogens that allows to split them into two groups: microparasite and macroparasite (Smith et al., 2005). Microparasites (e.g., virus, bacteria, protozoa, and prions) are usually described through compartmental models that characterize the hosts as a function of their infectious status (susceptible, infected, immune); while they omit to describe pathogen dynamics, because they may be always considered at equilibrium, since they are several orders of magnitude faster than the hosts (Kermack and McKendrick, 1927). Macroparasites (e.g., worms, ticks, and fleas) are described through

more complex models which take into account the number of parasites in the host and their distribution (Tallis and Donald, 1970; Crofton, 1971a,b).

In the present thesis I investigate the dynamics of microparasite diseases in wildlife. The aim of the work is to investigate host-pathogen relationships with specific interest in the effects of temporal, genetic, and social heterogeneities on infection dynamics. In particular, I will discuss the consequences of seasonal variations (temporal heterogeneity), different strain co-circulation (genetic heterogeneity), and age/stage structure (social heterogeneity) on epidemic course and disease control.

Historically, models for infectious diseases considered populations of host and pathogen to be well-mixed with homogeneous disease transmission among susceptible and infected individuals, and with homogeneous antigenic characteristic in pathogen population. In recent years, however, we have recognized that transmission may not be constant – varying with time, social structure, and/or age/stage-class – (Dietz, 1976; Castillo-Chavez, 1989; Lloyd-Smith et al., 2005) and the pathogenic strength of different pathogen strains neither – affecting transmission, virulence, and/or host immunity – (Koelle et al., 2006). While there are several theoretical and field evidences of heterogeneities in human infectious disease dynamics, not much information exists in the case of domestic animals (Matthews et al., 2006) and there is only anecdotal information in the case of wild animals (Heesterbeek and Roberts, 1995).

In this work I focused on the relationships between host-pathogen ecological dynamics and disease control. In particular, how both heterogeneities in host and pathogen populations affect control techniques effectiveness.

While the science of infectious diseases has made tremendous progress in the last several decades thanks, in part, to advances in molecular biology, immunology, medicine and mathematical modelling, the eradication of pathogens and parasites in wildlife relies very often only on two simple strategies, namely vaccination and culling, i.e., the removal of animals to push host population density below the threshold for disease invasion (Grenfell and Dobson, 1995). Quarantine and isolation through the construction of sanitary containments are rare options in the control of wildlife diseases and are applied primarily to domestic animals and farms such in the case of the foot-and-mouth epidemics in UK (Gilbert et al., 2005) and of avian flu epidemics in Asia (Ellis et al., 2004) often entailing huge economic losses.

Here, I focused on analyses of the culling effects on host and pathogen populations. The aim of the analyses is to show that the understanding of the ecological dynamics and parameters is unavoidable to provide effective control policies for disease eradication.

Ecological parameters are usually hard to estimate correctly in wild populations, but, in the case of infectious diseases, the rate of transmission of the pathogen agent is often the most complex process to evaluate. Of the many traits characterizing host species demography, body size is probably the most influential one, as many demographic parameters scale allometrically with host body size (Peters, 1983; Calder, 1984). Larger hosts are thus expected to have longer life expectancy, lower reproductive rate, slower dynamics and more sparse populations densities when compared to smaller host species. Such scaling laws (also called allometric laws) imply that ecological systems complexity can be reduced by considering processes according to their inherent scale. In this work I show how the allometric relationships, usually found for demographic parameters, may link host body size with the disease transmission rate and its basic reproduction number (i.e., the expected number of secondary cases produced by an infected host introduced into a susceptible population at its carrying capacity (Anderson and May, 1991)). Then, it is interesting to understand how the epidemiological dynamics vary as a function of the host body size. In other words, which epidemiological dynamics we might expect for small size hosts and which ones for large size hosts.

Seasonal variations in host birth rate, social aggregation, or resource availability are central features of the life of all temperate and many tropical habitats (Altizer et al., 2006). Usually, wildlife birth rates peak in the spring time, while intraspecific competition increases in the winter time, when the resources become scarce. Epidemiological parameters may also exhibit a seasonal trend; in particular, contact and transmission rates are inherently linked to animal mobility and social behaviour. Under the hypotheses of the allometric relationship between host size and demographic parameters, I analysed the effect of seasonal variation in different ecological and epidemiological parameters on disease dynamics.

Under the point of view of disease control, I analysed the effectiveness of depopulation policies in different ecological conditions. In particular, I focused on control effectiveness when strains with different virulence co-circulate in the host population and when disease transmission is a function of the age/stage class of the host individuals. In both cases, I found that (under certain conditions) culling policies may perform worse, in terms of disease control, than the do-nothing alternative. I also show in which conditions simple time-variant control policies can improve disease control in wildlife.

In the following chapters I propose some theoretical frameworks to investigate these heterogeneities in the context of wildlife diseases, with the aim to understand their effects on disease dynamics and to provide some suggestions on disease control. The thesis is organised as follows: in the next two chapters (2 and 3) I analyse the effects of seasonality (temporal heterogeneity) on epidemics in a wide

range of wildlife species. I illustrate these general points using rabies as a reference disease. I chose rabies because of its ability to spread, in principle, in every mammal population from mice to bears and because of the risks linked to exposure of humans to the bite of rabid animals. In chapter 2, I present and analyse a model able to describe rabies infections in several wild populations by using allometrical relationships to recast model parameters in different cases. In the third chapter I present the effects of seasonal variation in disease transmission and host birth rate on disease epidemics by highlighting the differences with the homogeneous case described in chapter 2. In the last three chapters, I discuss the effects of heterogeneities on disease control through culling (i.e., the selective removal of animal by hunting). In chapter 3, I present and analyse a model for describing the effects of culling on selection of pathogen strains with different virulence (genetic heterogeneity) and in chapter 4 I use this model to implement different classes of time-variant culling policies to minimize disease incidence. In the last chapter, I present and analyse a model for describing the effects of age/stage host population structure (social heterogeneity) on culling. I illustrate these general points using classical swine fever in wild boar as a reference disease. I chose classical swine fever because the etiologic agent responsible for the infection (classical swine fever virus) is an RNA virus characterised by mutation rates sufficiently high to generate genetic variability during the outbreaks. In addition, it caused serious economic losses in Europe from spillover infection to pig farms over the last twenty years.

The take-home message of all the studies shown in this thesis would be that both heterogeneities in host and pathogen populations dramatically affect disease dynamics in wildlife and their understanding is unavoidable in order to perform effective control policies apt to disease eradication.

GENERAL INTRODUCTION REFERENCES

Altizer S., Dobson A.P., Hosseini P., Hudson P., Pascual M., and Rohani P. 2006. Seasonality and the dynamics of infectious diseases, *Ecology Letters* **9**:467-484.

Anderson, R.M., and May, R.M. (1979) Population biology of infectious-diseases. 1, *Nature* **280**:361-367.

Anderson, R.M., and May, R.M. (1991) *Infectious Diseases in Humans: Dynamics and Control*. Oxford Science Publication, Oxford, UK.

Calder, W.A. (1984) *Size, function, and life history*, Dover Publications, Mineola, NY, USA.

Castillo-Chavez C, editor (1989) *Mathematical and Statistical Approaches to AIDS epidemiology*. New York.

Crofton, H.D., (1971a) A model of host–parasite relationships, *Parasitology* **63**:343–64.

Crofton, H.D., (1971b) A quantitative approach to parasitism, *Parasitology* **62**:179–93.

Daszak, P., Cunningham, A.A., and Hyatt, A.D. (2000) Emerging infectious diseases of wildlife-threats to biodiversity and human health, *Science* **287**:443-449.

Dietz, K. (1976) The incidence of infectious diseases under the influence of seasonal fluctuations, *Lecture Notes in Biomathematics* **11**:1-15.

Ellis T.M., Bousfield R.B., Bissett L.A., Dyrting K.C., Luk G.S.M., Tsim S.T., Surm-Ramirez K., Webster R.G., Guan Y. & Peiris J.S.M. (2004) Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002. *Avian Pathology*, **33**:492-505.

Gilbert M., Mitchell A., Bourn D., Mawdsley J., Cliton-Hadley R. and Wint W. (2005) Cattle movements and bovine tuberculosis in Great Britain, *Nature* **435**:491-496.

Grenfell B.T. and Dobson A.P. (1995) *Ecology of infectious diseases in Natural Populations*. Cambridge University Press, Cambridge.

Kermack, W.O., and McKendrick, A.G. (1927) Mathematical theory of epidemics, *Proceedings if the Royal Society B* **115**:700-721.

Koelle, K., Cobey, S., Grenfell, B., and Pasqual, M. (2006) Epochal evolution shapes and phylodynamics of interpandemic influenza A (H3N2) in humans, *Science* **314**: 1898-1903.

Heesterbeek JAP, Roberts MG (1995) Mathematical models for microparasite of wildlife. In: Grenfell BT, Dobson AP, editors. *Ecology of Infectious Diseases in Natural Populations*. Cambridge: Cambridge University Press. pp. 90-122.

Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM (2005) Superspreading and the effect of individual variation on disease emergence. *Nature* **438**:355-359.

Matthews L, Low JC, Gally DL, Pearce MC, Mellor DJ, et al. (2006) Heterogeneous shedding of *Escherichia coli* O157 in cattle and its implications for control. *Proceedings of the National Academy of Sciences of the United States of America* **103**:547-552.

May, R.M., and Anderson, R.M. (1979) Population biology of infectious-diseases. 2, *Nature* **280**:455-461.

Peters, R.H. (1983) *The Ecological Implications of Body Size*, Cambridge University Press, Cambridge, UK.

Ross, R. (1915) Some a priori pathometric equations, *British Medical Journal* **1**:546-547.

Smith, K.F., Dobson, A.P., McKenzie, E.F., Real, L.A., Smith, D.L., and Wilson, M.L. (2005) Ecological theory to enhance infectious disease control and public health policy, *Frontiers in Ecology and Environment* **3**(1):29-37.

Tallis, G.M., and Donald, R.L., (1970) Further models for the distribution on pasture of infective larvae of the strongyloid parasites of sheep, *Mathematical Biosciences* **7**:179–90.

2

Body-size scaling in an *SEI* model of wildlife diseases

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ABSTRACT

A number of wildlife pathogens are generalist and can affect different host species characterized by a wide range of body sizes. In this work I analyse the role of allometric scaling of host vital and epidemiological rates in a Susceptible-Exposed-Infected (SEI) model. My analysis shows that the transmission coefficient threshold for the disease to establish in the population scales allometrically (exponent=0.45) with host size as well as the threshold at which limit cycles occur. In contrast, the threshold of the basic reproduction number for sustained oscillations to occur is independent of the host size and is always greater than 5. In the case of rabies, I show that the oscillation periods predicted by the model match those observed in the field for a wide range of host sizes.

The population dynamics of the SEI model is also analysed in the case of pathogens affecting multiple coexisting hosts with different body sizes. My analyses show that the basic reproduction number for limit cycles to occur depends on the ratio between host sizes, that the oscillation period in a multihost community is set by the smaller species dynamics, and that intermediate interspecific disease transmission can stabilize the epidemic occurrence in wildlife communities.

1. INTRODUCTION

Pathogens are a ubiquitous, often neglected component of biodiversity which may have a tremendous impact on the population dynamics of their hosts and can play an important role in shaping the structure of ecological communities. Some pathogens, such as rabbit haemorrhagic disease virus, are species-specific, others, such as rabies or distemper viruses, are quite generalist and can affect many different host species. Of the many traits characterizing host species demography, body size is probably the most influential one, as many demographic parameters scale allometrically with host body size (Peters, 1983; Calder, 1984). Larger hosts are thus expected to have longer life expectancy, smaller reproductive rate, slower dynamics and more sparse populations densities when compared to smaller host species. Such scaling laws imply that ecological systems complexity can be reduced by considering processes according to their inherent scale. This approach has been used to describe food web structure (Cohen et al., 2003), home-range area (Jetz et al., 2005), and pathogens spread (De Leo and Dobson, 1996).

In the case of generalist pathogens, it is interesting to investigate how threshold conditions for the disease to invade and establish in a parasite-free host population change with different body size. Of course, many different ecological and epidemiological factors - ranging from immune response to interspecific competition, animal behaviour, feeding habits etc. - can regulate the ability of a pathogen to successfully establish in a host population. Some basic epidemiological parameters, such as the life expectancy of infected individuals and the time from inoculation to the first symptom, may exhibit a quite regular scaling pattern over a wide range of host species that may all be potentially infected by the same pathogen. For instance, in a recent study, J.M. Cable and B.J. Enquist (unpublished manuscript) have used epidemiological data on 16 host species affected by pseudorabies virus (PRV, *Herpesvirus suis*), 11 species by anthrax (*Bacillus anthracis*), and 21 species by rabies (*Lyssavirus sp.*) to show that interspecific variations in the host metabolic rate, which highly correlates to body size, strongly influence the timing of pathogenesis. As a consequence, epidemiological parameters such as the length of the latent period and the disease-induced mortality may also scale allometrically with host body size. Based on the evidence of allometric scaling available at the time, De Leo and Dobson (1996), without inferring relationships between transmission and size, had used a simple Susceptible-Infected (SI) model to show that transmission coefficients necessary to produce comparable values of R_0 in different species are themselves allometric functions of host body size. Here, I use a similar approach for an SEI (Susceptibles, Exposed, Infected) model of rabies that takes into account the empirical finding by J.M. Cable and B.J. Enquist (unpublished manuscript). I extend the pioneering model by Anderson

et al. (1981), who were first in proposing an SEI approach to study rabies in the wildlife, by explicitly accounting for the influence of body size. The dynamics of the SEI model can be more complex than the one predicted with a simpler SI (and SIR) model: in particular, if the latent period (the average time spent in the exposed class) is sufficiently long, the population dynamics of the infected host can be characterized by sustained oscillations (Swart, 1989; Pugliese, 1991). Epidemic cycles of this kind have already been observed in the field for many species infected by rabies, such as black-backed jackals (Courtin et al., 2000; Walton and Joly, 2003) and feral dogs (Bingham et al. 1999; Widdowson et al., 2002). See examples in Fig. 1.

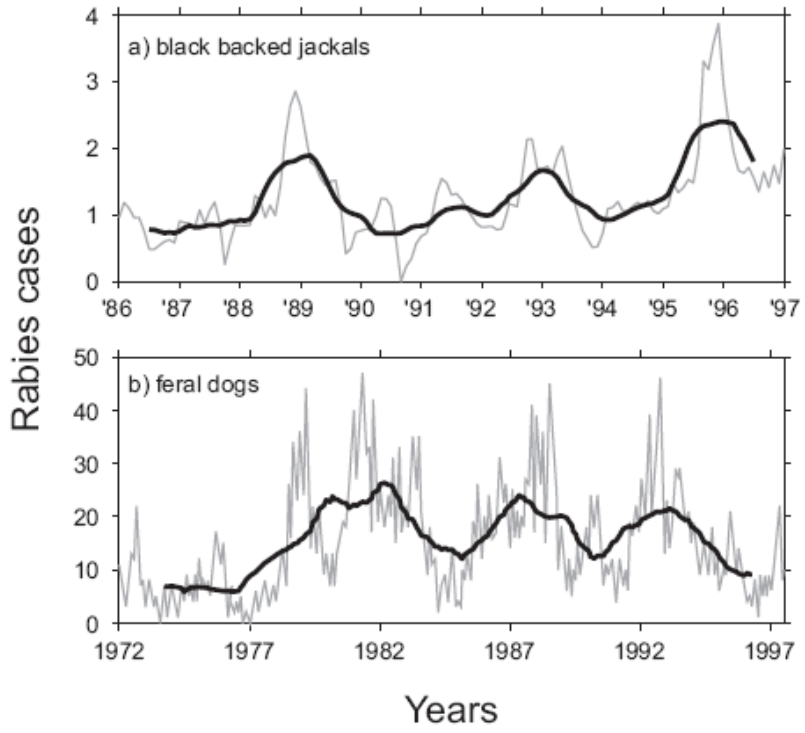

Fig. 1: Rabies confirmed cases (grey lines) with (a) moving 12-month centred mean (b) and 24-month centred mean (black lines) among black-backed jackals in central Namibia, 1986-1996 (a, data from Courtin et al., 2000) and feral dogs in Santa Cruz, Bolivia, 1972-1997 (b, data from Widdowson et al., 2002). Time series show sustained oscillations in the total number of infected in different host populations.

In the present chapter I explore how disease invasion and epidemic occurrence can depend on the host metabolic rates and body size. To address these issues, I first recast the basic Anderson et al.'s (1981) SEI model setting the birth and death rates and the carrying capacity of the host population as simple allometric functions of host body size. In accordance with the analysis of J.M. Cable and B.J. Enquist (unpublished manuscript) the latent period and the disease-induced mortality rate are

also assumed to scale allometrically with host body size. Threshold conditions are analysed under different assumptions on disease mortality and on the time spent in the exposed class by the hosts.

Recent work showed that single-host/single-pathogen relationships are not able to capture the epidemic dynamics in wildlife communities, because generalist pathogens may cause `apparent competition' between hosts (Hudson and Greenman, 1998) and cross-species transmission can modify pathogen evolution (Woolhouse et al., 2001). To account for this important point I extend a previous work by Dobson (2004) on a multiple-host SI model of wildlife disease and analyse the population dynamics of an SEI model in the case of inter-specific transmission among hosts with different body size. Inter-specific infections pose dramatic problems in conservation biology as shown by the case of Serengeti National Park where the lion population (*Panthera leo*) has been endangered by the canine distemper virus epidemic in feral dogs (*Canis lupus familiaris*) (Cleaveland et al., 2000), and Ethiopian wolves (*Canis simensis*) and African wild dogs (*Lycaon pictus*) have been threatened by rabies epidemics in feral dogs (Gascoyne et al., 1993; Sillero-Zubiri et al., 1997). Moreover, multihost models can be used to explain other epidemic dynamics, for example when host populations are not able to support infection endemically without reintroduction from outside species sources ('disease spillover' and 'apparent multihost' according to the classification of Fenton and Pedersen, 2005). In the case of rabies there are a lot of similar examples, such as grey wolf (*Canis lupus*) epidemics supported by foxes in North America (Brand et al., 1995) and side-striped jackal (*Canis adustus*) epidemics supported by dogs in Zimbabwe (Rhodes et al., 1998). Specifically, I want to identify the conditions under which a reservoir host species can drive other host species to extinction and analyse the population dynamics of multiple interacting hosts characterized by different body sizes.

The chapter is organized as follows: in the next section I present the basic structure of the allometric SEI model. In the third and fourth section, threshold conditions and model bifurcation diagrams are derived analytically and numerically with reference to the most important epidemiological parameters (latent period and disease mortality) and over a wide range of possible host body sizes. In the fifth section, I analyse the population dynamics of two host species characterized by different body size when a pathogen can affect both species with some degree of interspecific transmission. The results are finally summarized and discussed in the concluding section. Although specific numerical analyses have been developed by taking rabies as reference disease, the structure of the model analysed in the present work is quite general and can be considered valid for a range of lethal diseases of the wildlife. Therefore, the implications of my findings are quite broad.

2. THE ALLOMETRIC SEI MODEL

The epidemiology of a lethal disease within a homogeneous wildlife population has been traditionally modelled by partitioning the host population into three epidemiological classes - Susceptible (*S*), Exposed (*E*, i.e., infected but not yet infectious) and Infective (*I*) individuals - and by describing population dynamics of the three classes by means of ordinary differential equations. This simple deterministic approach was first developed in the seminal work of Anderson et al. (1981) to predict the impact of rabies in the European fox. I develop my analysis using the same model because, despite the simplicity of its formulation, it has been able to grasp the main features of observed epidemiological trends. In its original version, the SEI model assumes logistic growth of the host species in the absence of rabies, density-dependent transmission of the disease, and reproduction of disease-free animals only. Recovery and immunity is not included in the basic model. The ordinary differential equations that describe the dynamics of densities in the three population classes are:

$$\dot{S} = \nu S - (\mu + \gamma N)S - \beta SI \qquad (1a)$$

$$\dot{E} = \beta SI - (\sigma + \mu + \gamma N)E \qquad (1b)$$

$$\dot{I} = \sigma E - (\alpha + \mu + \gamma N)I \qquad (1c)$$

where $N = S + E + I$ is the total population density, ν and μ are the intrinsic birth and death rates, γ is the intraspecific competition coefficient (with $\gamma = r/K$, where $r = \nu - \mu$ is the intrinsic growth rate and K the carrying capacity), β is the transmission coefficient, σ is the rate at which an infected individual becomes infective ($1/\sigma$ being the mean latency period of rabies) and α the disease-induced mortality. By summing the right-hand sides of the Eq.s (1), one obtains the dynamics of *N*, namely:

$$\dot{N} = \nu S - (\mu + \gamma N)N - \alpha I \qquad (1d)$$

In order to account for a variety of mammalian host species, one can assume, as evidenced by Peters (1983), Silva and Downing (1995) and De Leo and Dobson (1996), that the basic vital rates scale allometrically with the host body size *w* as follows:

$$\nu = w^{-0.25} \quad (2a)$$

$$\mu = 0.4w^{-0.25} \quad (2b)$$

$$K = 16.2w^{-0.70} \quad (2c)$$

where w is expressed in kilograms, ν, μ and r in year^{-1} and K in individuals/km^2.

J.M. Cable and B.J. Enquist (unpublished manuscript) have also shown that the basic epidemiological parameters scale allometrically with the host body size in the same way as μ. Accordingly, I have assumed that the latent period ($1/\sigma$) and the infectious period ($1/\alpha$) - representing respectively the average time spent in the exposed and the infective class - are proportional to the mean life expectancy of the disease-free host ($1/\mu$) at low population density. More precisely, I assume that:

$$\sigma = n\mu = n0.4w^{-0.25} \quad (3a)$$

$$\alpha = m\mu = m0.4w^{-0.25} \quad (3b)$$

where n and m are always greater than one, because the times spent in exposed and infective classes are shorter than the mean life expectancy. For example, in the case of rabies in foxes, the host life expectancy is about 2 years, while the incubation period is one month and the life expectancy after infection is only a few days (about 5). Obviously, large values of the two parameters n and m correspond to pathogens with short latency period and high disease mortality rate, respectively. Integrating the relationships (2) and (3) into the original Anderson et al.'s (1981) system (1) produces a body-size-dependent model for rabies or diseases with similar characteristics. Contrary to σ and α, there is no evidence that the transmission coefficient β scales allometrically with host body size. Moreover, the transmission coefficient measurements are often difficult as it can be estimated only from extensive field data (Begon et al., 1999). For this reason, in the next section I will perform a sensitivity analysis of model (1) behaviours for a broad range of β values.

3. STABILITY ANALYSIS AND THRESHOLDS

Before exploring the influence of host body size w on the population dynamics of the host-pathogen relationship, it is important to briefly review the main features of model (1) which has been thoroughly analysed elsewhere (Swart, 1989). For convenience I consider model (1) in the variables N, E, I using Eq.s (1b), (1c), (1d) in which I set $S = N - E - I$. The model (1) has three equilibrium points: the trivial equilibrium $X_0 = (0,0,0)$, the disease-free equilibrium $X_1 = (K,0,0)$, and the enzootic equilibrium $X_2 = (N_{eq}, E_{eq}, I_{eq})$, where:

$$N_{eq} = (\nu\xi + \nu + \alpha)(\beta - \phi\nu)^{-1}$$

$$I_{eq} = (r - \gamma N_{eq})\beta^{-1}$$

$$E_{eq} = (\xi + \phi N_{eq})I_{eq}$$

with $\xi = (\alpha + \mu)/\sigma$ and $\phi = \gamma/\sigma$.

The equilibrium X_2 is biologically meaningful only when $N_{eq}, E_{eq}, I_{eq} \geq 0$.

By analysing the eigenvalues of the Jacobian matrix of model (1) it is possible to determine the stability of the three equilibria (see Swart, 1989 for details). The trivial equilibrium point X_0 represents the extinction of the host species and is always unstable when $\nu > \mu$. The disease-free equilibrium X_1, at which the host population is at its carrying capacity in absence of the disease, is stable if and only if

$$R_0 = \frac{\sigma\beta K}{(\sigma+\nu)(\alpha+\nu)} = 6.48\beta \frac{n}{(0.4n+1)} \frac{w^{-0.45}}{(0.4m+1)} < 1 \qquad (4)$$

where the parameter R_0 is the basic reproduction number of the disease, that is the expected number of secondary cases produced by an infected host introduced into a susceptible population at its carrying capacity (Anderson and May, 1991). Thus, the basic reproduction number scales allometrically with body size via the exponent -0.45 as in the SI model (De Leo and Dobson, 1996). Moreover, R_0 decreases with increasing disease mortality (which grows with m), while it increases and levels off with decreasing latent period (namely, with increasing n). In particular, R_0 tends to zero with decreasing ν, because no epidemic can establish with an infinite latency period, while R_0 increases with ν up to an asymptotic value which corresponds to a vanishing latency period (as in the SI model by De Leo and Dobson, 1996). It is easy to prove that the enzootic equilibrium X_2,

representing the case in which rabies persists endemically in the host population, becomes epidemiologically feasible (that is strictly positive) when X_1 loses its stability, i.e., as soon as R_0 exceeds unity. The manifold in the parameter space defined by equation $R_0 = 1$ is thus characterized by a transcritical bifurcation (Kuznetsov, 1995) in which the two equilibrium points X_1 and X_2 collide and exchange their stability. The condition for X_2 to be positive can also be expressed as

$$\beta > \beta_{TC} = \frac{(\sigma+\nu)(\alpha+\nu)}{\sigma K} = (0.4m+1)\frac{(0.4n+1)}{6.48n} w^{0.45} \qquad (5)$$

Therefore, I can state that the disease can persist in the host population if and only if the transmission coefficient of the disease β is above a minimum threshold value (called β_{TC}). The threshold for the transmission coefficient β_{TC}) scales allometrically with body size (exponent +0.45), increases linearly with μ and decreases with ν down to an asymptotic minimum value, which corresponds to a vanishing latency period.

It can be shown analytically that the enzootic equilibrium X_2 undergoes a supercritical Hopf bifurcation with the emergence of limit cycles when R_0 is sufficiently high, more precisely when

$$\beta > \beta_H = 0.037 \frac{w^{0.45}}{\Gamma_0(n,m)} \qquad (6)$$

where $\Gamma_0(n,m)$, function of n and m only, represents the smaller positive solution of equation number 6 in Swart (1989, pag. 201) when one replaces the model parameters with expressions (2) and (3) (see appendix for details). In simpler words, for $\beta < \beta_H$ the enzootic equilibrium X_2 is stable, while for $\beta > \beta_H$ there are stable sustained oscillations. From an epidemiological viewpoint, the reason for oscillations was explained by Anderson et al. (1981): rabies acts as a time-delayed density-dependent regulator of wildlife population growth, the time lag being determined by how long the host population density remains below a critical size. This will largely be influenced by host birth rates. The transmission coefficient along the Hopf bifurcation β_H) scales allometrically with exponent +0.45, just as the value β_{TC} did along the transcritical bifurcation.

A particularly interesting result is derived by looking at how the basic reproduction number R_0 changes along the Hopf bifurcation manifold. By substituting expression (6) for β_H into (4), it is easy to prove that the value of the basic reproduction number along the Hopf bifurcation manifold does not depend on the body size w of the host species but is a function of the epidemiological parameters n and m only. However, the period of the epizootic cycle corresponding to the Hopf

bifurcation does grow with the host body size *w*. In fact, along the Hopf bifurcation the oscillation period *T* (in years) of the densities in the three compartments of the host population is:

$$T = 2\pi / \rho \qquad (7)$$

where $\rho = \sqrt{\gamma N_{eq}(\alpha + \sigma + 2\mu + 2\gamma N_{eq})}$ is the modulus of the imaginary eigenvalues at the bifurcating enzootic equilibrium. By replacing Eq.s (2) and (3) into (7), it can be proved that *T* grows allometrically with body size with exponent +0.25.

Despite the simplicity of the mathematical formulation, the model is able to qualitatively grasp the dynamical behaviour of wildlife diseases observed in nature for which it is known that host species with larger body size exhibit a larger period of epizootic cycles. As illustrated in Fig. 2, the expected duration of the oscillation period derived by my model matches quite well that observed in the field for a number of different wildlife species affected by rabies (black dots). In Fig. 2 the solid line represents the minimum oscillation period of epidemics predicted by the SEI model (i.e., the period of cycles originating at the Hopf bifurcation), while the grey area shows feasible cycle periods for each host body size.

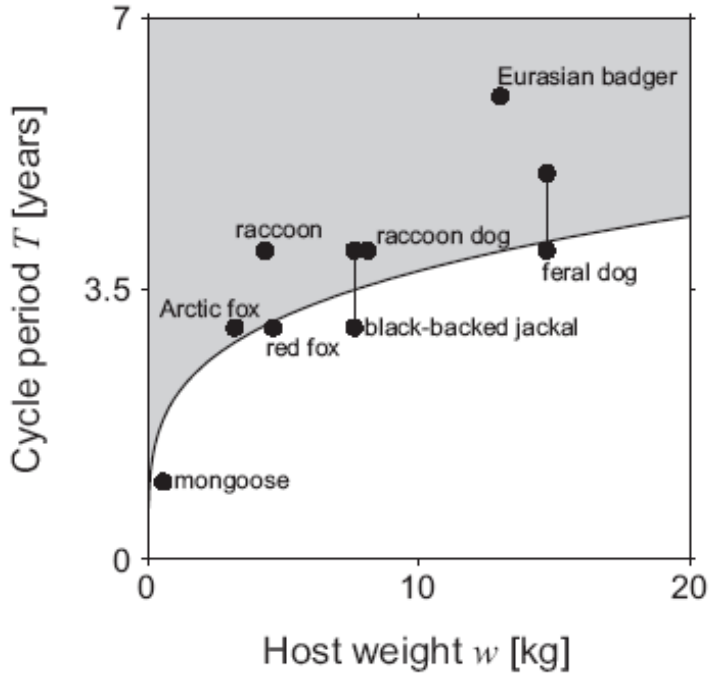

Fig. 2: The relationship between host body size and the period of sustained oscillations. The thick black line represents the period of cycles arising along the Hopf bifurcation, while the grey area represents feasible periods of sustained oscillations as predicted by the SEI model. The black points represent the minimum epizootic cycle period observed in the field for a range of mammal species affected by rabies. Thin lines connect points related to the same species. Data for: yellow mongoose (*Herpestes javanicus*), Arctic fox (*Alopex lagopus*), northern raccoon (*Procyon lotor*), red fox (*Vulpes vulpes*), black-backed jackal (*Canis mesomelas*), raccoon dog (*Nyctreutes procyonides*), Eurasia badger (*Meles meles*), and feral dog (*Canis familiaris*). See Supplementary Material for data details.

To sum up, the SEI model behaviour is completely determined by body size w, transmission coefficient β, latency rate n and disease mortality m. The complete bifurcation diagrams in the w-β, n-β, and m-β spaces are easily derived from Eq.s (5) and (6). These curves are shown in Fig. 3: in each of the three bifurcation diagrams a transcritical bifurcation curve (*tc*) separates a region *DF*, where the disease-free equilibrium is the only attractor of the model (1), from a region *EE*, where the model variables are attracted to the enzootic equilibrium. Through a supercritical Hopf bifurcation curve (*h*) the system enters the region *EC*: here the enzootic equilibrium is unstable and an attracting epizootic periodic solution appears, whose period increases with host body size w. Fig. 3a shows the bifurcation diagram in the w-β space. In the previous section I showed that the

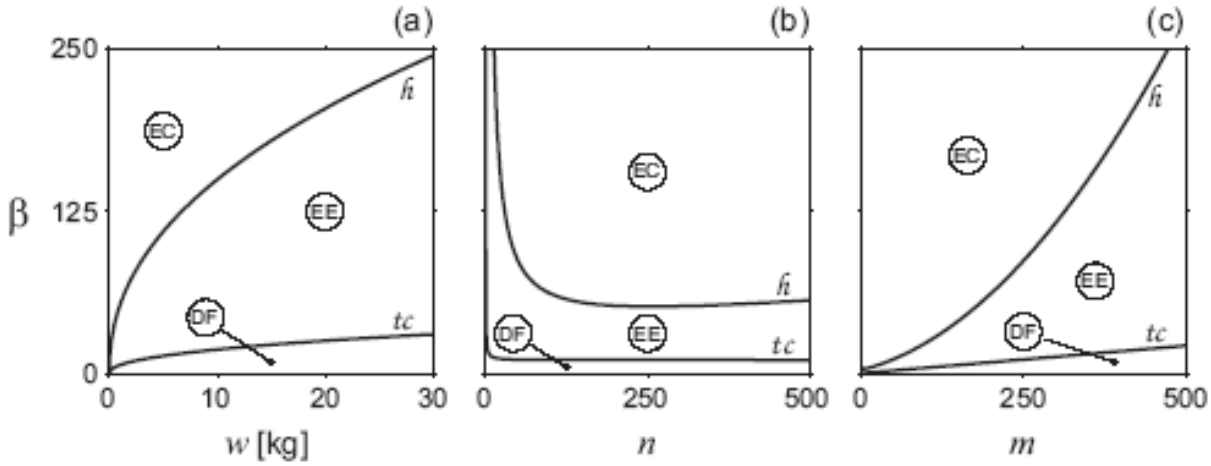

Fig. 3: Bifurcation diagrams of the SEI model in the w-β space (a), n-β space (b), and m-β space (c). In region *DF* (disease-free equilibrium) the virus becomes extinct. In region *EE* (enzootic equilibrium) the parasite survives in a constant host population. In region *EC* (epizootic cycle) the parasite survives in a fluctuating host population. The curve *tc* marks transcritical bifurcations and the curve *h* marks Hopf bifurcations. Other parameters set to: $m = 250$, in (a) and (b), $n = 50$, in (a) and (c), and $w = 3$ kg, in (b) and (c).

transmission coefficient (β) scales allometrically with host body size with exponent +0.45 along both the transcritical and the Hopf bifurcation curves (see Eq.s (5) and (6)). Fig. 3b, which shows the bifurcation diagram in the n-β space, demonstrates that the Hopf bifurcation curve exhibits a minimum when $n = m$, namely when the duration of the latency period equals the average time to death of a diseased individual. Fig. 3c shows the bifurcation diagram in the m-β space: the transcritical bifurcation curve is a linear function of m (see Eq. (5)); the Hopf bifurcation curve has a barely visible minimum for m equal to unity (i.e., natural mortality equals disease-induced mortality), but of course realistic values of m are much larger than one, as I explained above.

We showed that, along the Hopf bifurcation, R_0 is a function of the epidemiological parameters n and m only, not of host body size. How R_0 value changes along the Hopf bifurcation for different values of these parameters is reported in Fig. 4. It shows that limit cycles arise only for large values

of the basic reproduction number. On the other hand, even for high values of R_0, limit cycles occur only for intermediate n or m. In fact, if the latent period is very short, the SEI model tends to the SI model, while if it is too long, it tends to an SE model, neither of which can exhibit limit cycles (Gao et al., 1995; De Leo and Dobson, 1996). Interestingly enough, Fig. 4 shows that the Hopf bifurcations curves present a minimum R_0 when $n = m$, exactly as β_H does in Fig. 3b. This is true regardless of the specific value of n and m, as long as the duration of the latency period equals the expected time to death of a diseased individual. I can hypothesize a sort of resonance effect, in which similar average times spent in E and I classes favour the onset of oscillations. Moreover, the minimum value of R_0 for limit cycles to occur is about 5, regardless of host body size and specific values assigned to the allometric functions (2). In addition, I numerically analysed for fixed values of the basic reproduction number, the cycle period beyond the Hopf bifurcation (i.e., inside the regions EC of Fig. 3). It increases allometrically with host body size (with exponent +0.25) as along the Hopf bifurcation curve.

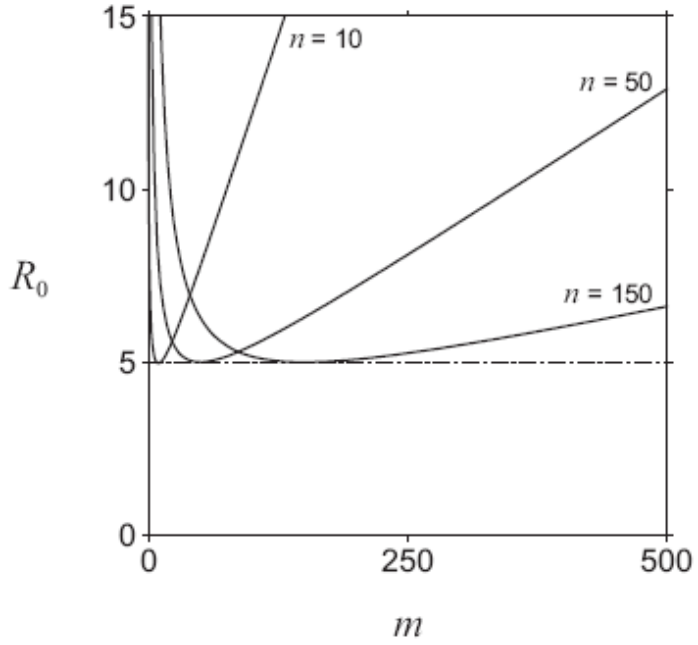

Fig. 4: Hopf bifurcation curves of the SEI model, computed by varying m and β (as in Fig. 3c), plotted in the m-R_0 space for different values of the relative latency rate n. Unspecified parameter values as in Fig. 3c.

4. THE MULTIPLE HOST SEI MODEL

As pathogens like rabies can affect and establish in a wide range of host species, there is a definite possibility that interspecific transmission may occur among hosts of different body sizes. In this section, I investigate the population dynamics of a multiple hosts infection by extending the analysis performed by Dobson (2004) for a multihost SI model to an SEI model of two host species with interspecific transmission, as described hereafter:

$$\dot{S}_i = \nu_i S_i - (\mu_i + \gamma_i N_i) S_i - S_i \sum_{j=1,2} \beta_{ij} I_j \qquad (8a)$$

$$\dot{E}_i = S_i \sum_{j=1,2} \beta_{ij} I_j - (\sigma_i + \mu_i + \gamma_i N_i) E_i \qquad (8b)$$

$$\dot{I}_i = \sigma_i E_i - (\alpha_i + \mu_i + \gamma_i N_i) I_i \qquad (8c)$$

where $i,j = 1,2$. As in paragraph 2, model parameters scale allometrically with the hosts' body size (Eq.s (2) and (3)). In addition, I assume that the disease has the same basic reproduction number in both populations. From now on, I assume that $w_1 < w_2$, without lack of generality. Then the intraspecific transmission coefficients β_{ii} (i.e., the transmission among individuals of the same species) can be obtained from Eq. (4) by using a unique value for R_0 and 2 different values for w. The interspecific transmission β_{ij} ($i \neq j$), which is the transmission among individuals of different species, is here assumed to be proportional to the mean of the intraspecific transmissions as in Dobson (2004), namely:

$$\beta_{ij} = e_{ij} c \left(\frac{\beta_{ii} + \beta_{jj}}{2} \right)$$

where $i,j = 1,2$ and c is the strength of interactions between species. I have assumed that between-species transmission is more difficult than within-species transmission, so that $0 \leq c \leq 1$. Dobson (2004) has thoroughly discussed the threshold conditions for disease invasion in a multihost SI model. Here, besides invasion thresholds, I analyse conditions for which the populations exhibit epizootic cycles and conditions for which a host population acts as a disease reservoir and drives the other host to extinction. In particular, my analysis shows that model behaviours do not depend on the absolute value of the two species body sizes, but only on their ratio. Results are reported in Fig. 5 which shows the bifurcation diagrams of model (8) as a function of the degree of interspecific transmission c and the intraspecific basic reproduction number R_0 (assumed equal for both species)

for different values of the ratio between the two species body sizes ($\delta w = w_2/w_1$). For this purpose I used a continuation method supported by the software LOCBIF (Khibnik et al., 1993) and CONTENT (Kuznetsov, 1998) which compute bifurcation curves starting from any bifurcation point by means of an adaptive prediction-correction continuation procedure with tangent prediction and Newton correction.

For low values of R_0, at each level of interspecific transmission there exists only the disease-free equilibrium, in which the two species coexist in the absence of disease. Dashed curve tc_1^e in Fig. 5 represents transcritical bifurcations (infection threshold) between the disease-free equilibrium and the enzootic one, where the two species coexist and the disease is present with a constant prevalence. Because of operating interspecific transmission, there exist no equilibria corresponding to the disease being present in one species, not in the other one. So, the curve tc_1^e does not depend on δw, the ratio between the hosts' body sizes. As shown by Dobson (2004), when transmission is density-dependent as in model (8), the presence of more species of susceptible hosts implies that the number of contacts between infected individuals and potentially susceptible hosts increases. In fact, Fig. 5 shows that, for large level of interspecific transmission c, disease may invade host populations also for values of intraspecific basic reproduction number R_0 smaller than 1.

Solid curves (h_i) in Fig. 5 represent Hopf bifurcations: increasing values of R_0 lead stable enzootic equilibria to instability and give rise to stable epizootic cycles. Bifurcations h_1 involve attractors in which the two host population coexist, while bifurcations h_2 (which exist only for large values of δw) involve attractors in which the larger species is extinct. As a consequence, the value of the basic reproduction number at which bifurcations h_2 occur is independent of the value of interspecific transmission c.

By increasing δw a diseased host species that would exhibit sustained oscillations when isolated ($c = 0$) can be characterized by a stable infectious equilibrium when coexisting with another species with sufficiently different body size if interspecific transmission is intermediate (see solid curves in Fig. 5). A further (more detailed) analysis shows that the cycle period along Hopf bifurcations (h_i) is always close to that of the smaller species when isolated; therefore it is the smaller host species that drives the population dynamics setting the period of oscillations.

Curves tc_2^e represent transcritical bifurcations of coexistence equilibria: increasing values of interspecific transmission c or reproduction number R_0 drive the coexistence equilibrium to instability and the species with smaller body size out-competes the other which goes extinct. Similarly, curves tc^c represent transcritical bifurcations of limit cycles: increasing values of c destabilise the epizootic cycle at which the two host species coexisted and the host species with

smaller body size out-competes the other and keeps exhibiting sustained oscillations, according to the specific value of R_0 (as in model (1)). It is interesting to notice that curves tc_2^e and tc^c appear in the bifurcation diagram only for sufficiently high values of δw (dark grey and black curves in Fig. 5, which correspond to $\delta w = 2$ and $\delta w = 10$, respectively). This implies that high differences in size among host species may increase the extinction risk of the species with larger body size. Further analyses, not reported here, show similar pattern of behaviours for multiple-host model (8) with more than two host species ($i,j = 1,...,n$ with $n > 2$).

As remarked by Dobson (2004) for the SI model, a sufficiently high degree of interspecific transmission c can invariably drive to extinction the species with slower dynamics. Here, I have similar results, because the species that becomes extinct for sufficiently large c is the one with larger body size; this is also true when epizootic cycles occur.

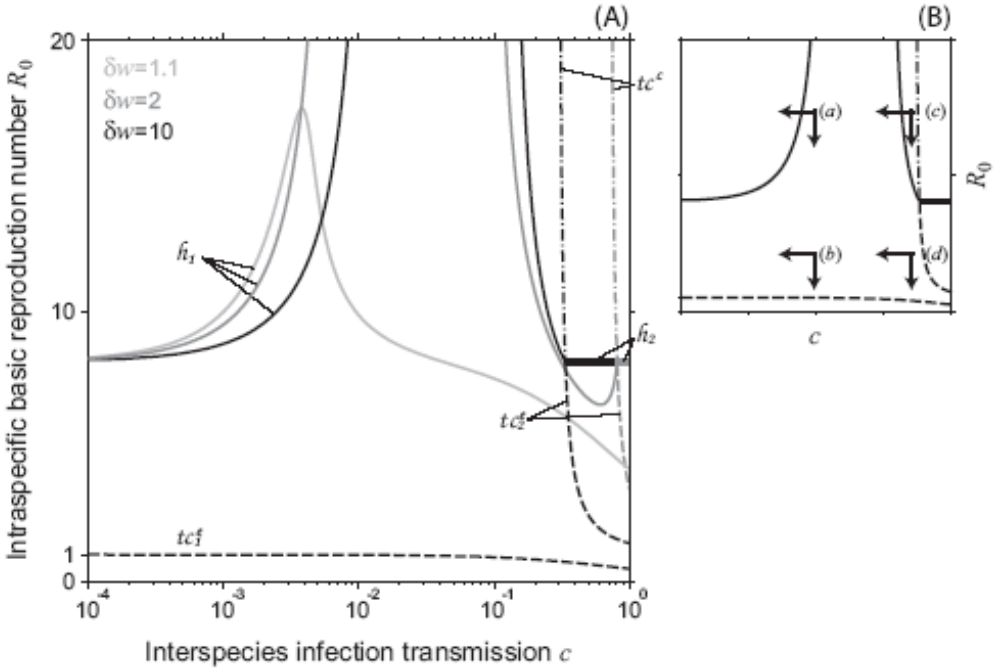

Fig. 5: Bifurcation diagram of the multiple host SEI model (8) in the c-R_0 space (plotted in semi-logarithmic scale). (A) Two host species with different body sizes ratio ($\delta w = w_2/w_1$): light grey curves ($\delta w = 1.1$), dark grey curves ($\delta w = 2$), and black curves ($\delta w = 10$). Thin solid lines (h_1), thick solid lines (h_2), dashed lines (tc_i^e), and dash-dotted lines (tc^c) represent Hopf bifurcations of coexisting equilibria, Hopf bifurcations of one species equilibria, transcritical bifurcations of equilibria, and transcritical bifurcations of cycles (see text for details).Other parameters as in Fig. 3.(B) Arrows describe the effect of different control strategies in the case of $\delta w = 10$ and four different situations corresponding to low/high basic reproduction number and low/high interspecies infection transmission. Dotted arrows correspond to reduction of c (blocking tactics), solid arrows to reduction of R_0 (target and reservoir control). See Discussion and conclusions paragraph for details.

5. DISCUSSION AND CONCLUSIONS

In this chapter I have presented a class of simple SEI models in which basic vital rates and epidemiological parameters are set via allometric scaling with host body size in order to describe the spread of a lethal disease in a wide range of wildlife host species.

My analysis shows that the minimum basic reproduction number R_0 necessary to sustain epizootic cycles does not depend upon host body size or allometric formulation of model parameters, but is a function of the relative duration of the latent period and the relative mean time to death of infected individuals with respect to the mean life expectancy of a disease-free host. The SEI model predicts that epizootic cycles cannot arise if the basic reproduction number is smaller than 5 regardless of host body size. This suggests the need of a sort of minimum activation energy (represented by the strength of R_0) for oscillation to arise, that is a structural property of the SEI model and not of the parameters chosen. On the other hand, field observations of rabid populations in the wild show that epizootic cycles may actually occur also for R_0 as low as 1.5-2.5 (Coleman and Dye, 1996; Kitala et al., 2002). As a consequence, it is possible that other factors, such as spatial dynamics or age structure or social hierarchy, and, most important, seasonal forcing, may actually play an important role in generating the observed patterns. The interplay between body size scaling of ecological and epidemiological parameters and these heterogeneity factors will be the subject of further investigations. Nevertheless, the relationship between host body size and the expected period of oscillations, as predicted by my SEI model, matches very well the field observations for a range of mammalian host species infected by rabies. Thus, my model might be used to roughly extrapolate the period of epizootic cycles in species for which data are not available.

Furthermore, simple extensions of the model are particularly suitable to describe infections in wildlife communities and networks consisting of animals with a spectrum of body sizes, in order to describe spillover, multiple-host, and multiple-pathogen dynamics. In the present chapter I have analysed multiple host interactions in the simple case of one pathogen infecting different host species. In the literature, several works analysed parasite establishment (Holt et al., 2003; Dobson, 2004), host extinction risk (de Castro et al., 2005; Fenton and Pedersen, 2005), and parasite evolution (Woolhouse et al., 2001; Gandon, 2004) in multihost communities, but little attention was paid to non-equilibrium behaviours. Here, I have put the stress on the epidemic events occurrence, deriving conditions for which epizootic cycles arise and underlining their features. I have found that, contrary to single-host models, the value of the basic reproduction number for sustained oscillation to occur strongly depends on the sizes of the two hosts (in particular on their ratio). Epidemic dynamics tends to stabilize for intermediate value of interspecific transmission c if

species affected by the disease have different body sizes (see Fig. 5). Since c represents the level of coupling between population species, this result is in agreement with findings in metapopulation models of disease, in which intermediate level of host dispersal favours stability and synchrony of infections (Keeling and Rohani, 2002). Moreover, when two coexisting host populations exhibit limit cycles, the period of oscillation near the Hopf bifurcation is mainly driven by the smaller species. In addition, for sufficiently high values of interspecific transmission and species size ratio, the host species with faster population dynamics (smaller body size) can drive the slower one (larger body size) to extinction. In practice, the smaller species acts as a disease reservoir. In fact, I have found that the extinction conditions of the larger species depend primarily on the transmission from the smaller host to the larger one (i.e., parameter β_{21} in model (8)). Therefore, policies for preventing the threatened host extinction should also devote efforts to avoiding reservoir-target transmission in addition to traditional measures such as vaccination of the endangered species.

There are other implications of my results for disease control in wildlife communities. Haydon et al. (2002) identified three different control strategies in multihost systems: *target control* and *reservoir control*, which are aimed at controlling infection within each populations (in model (8) the target is the larger size species and the reservoir is the smaller size one) and *blocking tactics*, to prevent transmission between species. These control strategies correspond to reducing R_0 and c in model (8), respectively. The benefits of these different approaches vary according to the difference in size of infected host species and to transmission conditions.

For host-pathogen systems with low interspecific transmission c, blocking tactics will be ineffectual, while control of within-species transmission proves to be effective under the same starting conditions. Indeed, in cases of high basic reproduction number (e.g., see point (*a*) in Fig. 5B in the case of large δw values), blocking tactics will drive the system toward large oscillations thus increasing the likelihood of host stochastic extinction `during transient depression of population' (sensu de Castro and Bolker, 2005), while target and reservoir controls tend to damp epizootic oscillations. In cases of low R_0 (see point (*b*) in Fig. 5B), control of within-species transmission is also more effective, driving the system toward the disease-free threshold.

On the contrary, for hosts-pathogen systems with high levels of c (points (*c*) and (*d*) in Fig. 5B), blocking tactics are effective because they move the target species away from extinction. Moreover, when R_0 is high (point (*c*) in Fig. 5B), they also reduce oscillation in the hosts' populations. In cases of low R_0 (point (*d*) in Fig. 5B), control of within-species transmission is also effective, driving the system toward the disease-free threshold. In the light of these considerations, it turns out that an adequate estimation of transmission levels (within and between populations) is crucial to implementing effective control policies of rabies and similar diseases in wildlife systems.

The main features of the dynamics of the basic SEI body-size-dependent host-pathogen system are quite robust with respect to other variations in the model structure. In fact, further analysis not reported here demonstrates that results do not change substantially if I introduce spatial structure (patchy environment). Apparently, the introduction of more realistic details in the model does not significantly modify the relationship between the body size of the host and the characteristic transmission rate that allows for multi-years periodicity to occur. I suspect that allometry holds for a wide class of variations of the basic SEI models.

There are a large number of other diseases in which the host can develop temporary or permanent immunity. The introduction of an immunity class strongly changes the epidemic dynamics. Such model was analysed by Coyne et al. (1989). They showed that even for small values of the immunity, the Hopf bifurcation that arises for increasing transmission rates in the SEI model disappears.

Recently, several works stressed the crucial role of social, spatial (Cross et al., 2005), and age/stage (Bolzoni et al., 2007) heterogeneity to understand transmission pattern of wildlife disease. In this context, the explicit introduction in the model of the host social organization will be an interesting development. For example, Brashares et al. (2000) show that group size in African antilope (family Bovidae) is allometrically related to species body size. This suggests that the within-group disease transmission in these species can be described as an allometric function of the body size as well.

Even though the relationships I found between host body size, transmission rate and resulting dynamics should not be interpreted as universal laws, they can provide useful hints on the kind of population dynamics in host-pathogen systems that is most likely to occur over a broad range of host body sizes. Information on the expected population dynamics can be used to design field campaigns to gather further data for the estimation of the basic epidemiological parameters. It is also useful to guide control and eradication policies, when action must be taken rapidly and information on host species is scanty, as it usually occurs in the case of many endangered populations.

CHAPTER 2 APPENDIX

Hopf bifurcation condition for model (1) found by Swart (1989, Eq.6 pag. 201) is a 4^{th} degree equation in the variable $\gamma\beta^{-1}$:

$$
\begin{aligned}
&(\gamma\beta^{-1})^4 \nu\alpha(Q+r\nu)^2 - (\gamma\beta^{-1})^3[Q\{\nu(-\nu^2\alpha - \nu^2\sigma + 7\alpha\nu\sigma + \nu\alpha^2 + \nu\sigma^2 + \dots \\
&+ \nu\mu\alpha + \nu\mu\sigma + 7\alpha^2\sigma + 7\alpha\sigma^2 - 2\alpha\sigma\mu) + 7\alpha^2\sigma^2\} + 4\sigma\alpha r^2\nu^2] + \dots \\
&- (\gamma\beta^{-1})^2\sigma[Q\{4\alpha^2\nu + 4\sigma^2\nu + 2\mu^2\nu + 4\alpha\sigma\nu + 5\alpha\mu\nu + 2\nu^2\alpha + 2\nu^2\sigma + \dots \\
&- \nu^2\mu + 6\alpha^2\sigma + 6\alpha\sigma^2 + 13\alpha\sigma\mu\} - 6\alpha r^2\sigma\nu] + \dots \\
&- (\gamma\beta^{-1})\sigma^2[Q\{\alpha^2 + \sigma^2 + 3\alpha\sigma + 6\alpha\mu + 6\sigma\mu + 2\nu\mu + 3\mu^2 - \alpha\nu + \sigma\nu\} + \dots \\
&+ 4\alpha\sigma r^2] + \sigma^3 r[\mu(\alpha+\sigma+\mu) + \alpha\sigma] = 0
\end{aligned}
\qquad (A1)
$$

where $Q = \nu(\alpha + \sigma + \mu) + \alpha\sigma$.

By replacing allometric expressions (2) and (3) into Eq. (A1), I obtain the following relationship:

$$
[(\gamma\beta^{-1})^4\Gamma^4(n,m) + (\gamma\beta^{-1})^3\Gamma^3(n,m) + (\gamma\beta^{-1})^2\Gamma^2(n,m) + (\gamma\beta^{-1})\Gamma^1(n,m) + \Gamma^0(n,m)]w^{-3/2} = 0 \qquad (A2)
$$

where the Γ^i's (i = 1,…,5) are suitable functions of n and m only. As shown by Swart (1989), Eq. (A2) has two positive solutions, say $\Gamma_0(n,m)$ and $\Gamma_1(n,m)$, but only with the first (the smaller one) the inequality (5) – i.e., the existence of a positive endemic equilibrium – is satisfied. Hence, relationship (6) – i.e., $\beta = \gamma/\Gamma_0(n,m) = 0.037\ w\text{^}\{0.45\}/\ \Gamma_0(n,m)$ – guarantees the existence of two purely imaginary eigenvalues of the characteristic equation of model (1). Moreover, Swart (1989) has already proved that this solution satisfies the Hopf bifurcation transversality conditions. Then, relationship (6) represents Hopf condition for model (1).

CHAPTER 2 REFERENCES

Anderson, R.M., Jackson, H.C., May, R.M. and Smith, A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-771.

Anderson, R.M., and May, R.M. (1991) *Infectious Diseases in Humans: Dynamics and Control*. Oxford Science Publication, Oxford, UK.

Begon, M., Hazel, S.M., Baxby, D., Bown, K., Cavanagh, R., Chantrey, J., Jones, T., and Bennett, M. (1999) Transmission dynamics of zoonotic pathogen within and between wildlife host species, *Proceedings of the Royal Society B* **266**:1939-1945.

Bingham, J., Foggin, C.M., Wanderler, A.I., and Hill, F.W.G. (1999) The epidemiology of rabies in Zimbabwe. 1. Rabies in dogs (*Canis familiaris*), *Onderstepoort Journal of Veterinary Research* **66** (1):1-10.

Bolzoni, L., Real, L., and De Leo, G. (2007) Transmission heterogeneity and control strategies for infectious disease emergence, *PLoS ONE* **2**(8):e747.

Bolzoni, L., Dobson, A.P., Gatto, M., and De Leo G.A. (under review) The allometric scaling and seasonality in the epidemics of wildlife diseases, *American Naturalist*

Brand, C.J., Pybus, M.J., Ballard, W.B., and Peterson, R.O. (1995) Infectious and parasitic diseases of the gray wolf and their potential effects on wolf populations in North America, in *Ecology and Conservation of Wolves in a Changing World* (L. Carbyn, ed.), pp. 419– 514. Canadian Circumpolar Institute, Edmonton, Canada.

Brashares, J.S., Garland, T., and Arcese, P. (2000) Phylogenetic analysis of coadaptation in behavior, diet, and body size in the African antelope, *Behavioural Ecology* **11**:452–463.

Calder, W.A. (1984) *Size, function, and life history*, Dover Publications, Mineola, NY, USA.

Cleaveland, S., Appel, M.G.J., Chalmers, W.S.K., Chillingworth, C., Kaare, M., and Dye, C. (2000) Serological and demographic evidence for domestic dogs as a source of canine distemper virus infection for Serengeti wildlife, *Veterinary Microbiology* **72**(3-4):217-227.

Cohen, J.E., Jonsson, T., and Carpenter, S.R. (2003) Ecological community description using the food webs, species abundance, and body size, *Proceedings of the Royal Society B* **100**:1781-1786.

Coleman, P.G., and Dye, C., (1996) Immunization coverage required to prevent outbreaks of dog rabies, *Vaccine* **14** (3):185-186.

Courtine, F., Carpenter, T.E., Paskin, R.D., and Chomel, B.B. (2000) Temporal patterns of domestic and wildlife rabies in central Namibia stock-ranching area, 1986-1996, *Preventive Veterinary Medicine* **43**:13-28.

Coyne, M.J., Smith, G. and McAllister, F.E. (1989) Mathematical model for the population biology of rabies in raccoons in the mid-Atlantic states, *American Journal of Veterinary Research* **50**:2148-2154.

Cross, P.C., Lloyd-Smith, J.O., Johnson, P.L.F., and Getz, W.M. (2005) Duelling timescales of host movement and disease recovery determine invasion of disease in structured populations, *Ecology Letters* **8**:587-595.

de Castro, F., and Bolker, B. (2005) Mechanisms of disease-induced extinction, *Ecology Letters* **8**:117-126.

De Leo, G.A. and Dobson, A.P. (1996) Allometry and simple epidemic models for microparasites, *Nature* **379**:720-722.

Dobson, A. (2004) Population dynamics of pathogens with multiple host species, *American Naturalist* **164** (5):S64-S78.

Fenton, A., and Pedersen, A.B. (2005) Community epidemiology framework for classifying disease threats, *Emerging Infectious Diseases* **11**:1815-1821.

Gandon, S. (2004) Evolution of multihost parasites, *Evolution* **58**:455-469.

Gao, L.Q., Mena-Lorca, J., and Hethcote, H.W. (1995) Four SEI endemic models with periodicity and separatrices, *Mathematical Biosciences* **128**:157-184.

Gascoyne, S.C., King, A.A., Laurenson, M.K., Borner, M., Schildger, B., and Barrat, J. (1993) Aspects of rabies infection and control in the conservation of the African wild dog (*Lycaon pictus*) in the Serengeti region, Tanzania, *Onderstepoort Journal of Veterinary Research* **60**:415-420.

Haydon, D.T., Cleaveland, S., Taylor, L.H., and Laurenson, M.K. (2002) Identifying reservoirs of infection: A conceptual and practical challenge, *Emergong Infectious Diseases* **8**:1468-1473.

Holt, R.D., Dobson, A.P., Begon, M., Bowers, R.G., and Schauber, E.M. (2003) Parasite establishment in host communities, *Ecology Letters* **6**:837-842.

Hudson, P., and Greenman, J. (1998) Competition mediated by parasites: biological and theoretical progress, *Trends in Ecology and Evolution* **13**:387-390.

Jetz, W., Carbone, C., Fulford, J., and Brown, J.H. (2005) The scaling of animal use space, *Science* **306**:266-268.

Keeling, M.J., and Rohani, P. (2002) Estimating spatial coupling in epidemiological systems: a mechanistic approach, *Ecology Letters* **5**:20-29.

Khibnik, A.I., Kuznetsov, Y.A., Levitin, V.V., and Nikolaev, E.V. (1993) Continuation techniques and interactive software for bifurcation analysis of ODEs and iterated maps, *Physica D* **62**:360-371.

Kitala, P.M., McDermott, J.J., Coleman. P.G., and Dye, C. (2002) Comparison of vaccination strategies for control of dog rabies in Machakos District, Kenya, *Epidemiology and Infection* **129** (1):215-222.

Kuznetsov Y.A., (1995) *Elements of Applied Bifurcation Theory*, Springer-Verlag, New York, USA.

Kuznetsov, Y.A., (1998) CONTENT – *integrated environment for analysis of dynamical systems*. Tutorial. Ecole Normal Superieure de Lyon. Rapport de Recherche UPMA-98-224.

Peters, R.H. (1983) *The Ecological Implications of Body Size*, Cambridge University Press, Cambridge, UK.

Pugliese, A. (1991) An SEI epidemic model with varying population size, in *Differential Equation Models in Biology, Epidemiology and Ecology* (Lect. Notes Biomath. 92) Busenberg, S., and Martelli, M., Eds., Springer-Verlag, New York, pp. 121-138.

Rhodes, C.J., Atkinson, R.P.D., Anderson, R.M., and Macdonald, D.W. (1998) Rabies in Zimbabwe: reservoir dogs and the implications for disease control, *Philosophical Transaction of the Royal Society B* **353**:999-1010.

Sillero-Zubiri, C., Macdonald, D., and the IUCN/SSC Canid Specialist Group (1997) *The Ethiopian wolf – Status Survey and Conservation Action Plan*, IUCN, Giand, Switzerland.

Silva, M. and Downing, J.A. (1995) The allometric scaling of density and body mass: a nonlinear relationship for terrestrial mammals, *American Naturalist* **145**:707-727.

Swart, J.H. (1989) Hopf bifurcation and stable limit cycle behavior in the spread of infectious diseases, with special application to fox rabies, *Mathematical Biosciences* **95**:199-207.

Walton, L.R., and Joly, D.O. (2003) Canis mesomelas, *Mammalian Species* **715**:1-9.

Widdowson, M.-A., Morales, G.J., Chavez, S., and McGrane, J. (2002) Epidemiology of urban canine rabies, Santa Cruz, Bolivia, 1972-1997, *Epidemiology and Infection* **8**:458-461.

Woolhouse, M.E.J., Taylor, L.H. and Haydon, D.T. (2001) Population biology of multihost pathogens, *Science* **292**:1109-1112.

CHAPTER 2 SUPPLEMENTARY MATERIAL

Table S1: Figure 1 data details

Common name	Scientific name	Mass [kg]	Period [yr]
Yellow mongoose	*Herpestes javanicus*	0.55 (1)	1 (2)
Arctic fox	*Alopex lagopus*	3.19 (1)	3 (3)
Northern raccoon	*Procyon lotor*	4.3 (4)	4 (4)
Red fox	*Vulpes vulpes*	4.6 (1)	3 (3)
Black-backed jackal	*Canis mesomelas*	7.7 (5)	3 (6)
Black-backed jackal	*Canis mesomelas*	7.7 (5)	4 (7)
Raccoon dog	*Nyctereutes procyonides*	8.0 (8)	4 (9)
Eurasian badger	*Meles meles*	13.0 (1)	6 (10)
Feral dog	*Canis familiaris*	14.7 (11)	4 (12)
Feral dog	*Canis familiaris*	14.7 (11)	5 (13)

Tab. S1: Table S1 summarizes basic information and bibliographic references about data used for Fig. 1 in main text. Column 1 and 2: common and scientific name of host species; Column 3: weight of host species (in kg) and related reference (in brackets); Column 4: minimum epizootic cycle period observed in populations infected by rabies (in years) and related reference (in brackets).

TABLE S1 REFERENCES

[1] C. Carbone, J. Gittleman (2002) A common rule for the scaling of carnivore density, *Science* **295**:2273–2276.

[2] C. Everard, G. Baer, A. James (1974) Epidemiology of mongoose rabies in grenada, *Journal of Wildlife Diseases* **10**:190–196.

[3] R. Anderson, H. Jackson, R. May, A. Smith (1981) Population dynamics of rabies in Europe, *Nature* **289**:765–771.

[4] J. Childs, A. Curns, M. Dey, L. Real, L. Feinstein, O. Bjørnstad, J. Krebs (2003) Predicting the local dynamics of epizootic rabies among rac-coons in the United States, *Proceedings of the National Academy of Sciences of the United States of America* **100**:1781–1786.

[5] C. Carbone, G. Cowlishaw, N. Isaac, J. Rowcliffe (2005) How far do animals go? Determinants of day range in mammals, *American Naturalist* **165**:290–297.

[6] F. Courtin, T. Carpenter, R. Paskin, B. Chomel (2000) Temporal patterns of domestic and wildlife rabies in central Namibia stock-ranching area, 1986-1996, *Preventive Veterinary Medicine* **43**:13–28.

[7] L. Walton, D. Joly (2003) Canis mesomelas, *Mammalian Species* **715**:1–9.

[8] A. Atanasov (2005) Allometric ralationship between the length of pregnancy and body weight in mammals, *Bulgarian Journal of Veterinary Medicine* **8**:13–22.

[9] C.-H. Kim, C.-G. Lee, H.-C. Yoon, H.-M. Nam, C.-K. Park, J.-C. Lee, M.-I. Kang, S.-H. Wee (2006) Rabies, an emerging disease in Korea, *Journal of Veterinay Medicine Series B* **53**:111–115.

[10] G. Smith (2002) The role of the Badger (Meles meles) in rabies epizootiology and the implications for Great Britain, *Mammal Review* **32**:12–25.

[11] J. Butler, J. du Toit, J. Bingham (2004) Free-ranging domestic dogs (*Canis familiaris*) as predators and prey in rural Zimbabwe: threats of competition and disease to large wild carnivores, *Biological Conservation* **115**:369–378.

[12] J. Bingham, C. Foggin, A. Wanderler, F. Hill (1999) The epidemiology of rabies in Zimbabwe. 1. Rabies in dogs (*Canis familiaris*), *Onderstepoort Journal of Veterinary Research* **66**:1–10.

[13] M.-A. Widdowson, G. Morales, S. Chavez, J. McGrane (2002) Epidemiology of urban canine rabies, Santa Cruz, Bolivia, 1972-1997, *Epidemiology and Infection* **8**:458–461.

3

Allometric scaling and seasonality in the epidemics of wildlife diseases

Submitted Chapter: Luca Bolzoni, Andrew P. Dobson, Marino Gatto and Giulio A. De Leo, Allometric scaling and seasonality in the epidemics of wildlife diseases, American Naturalist, submitted.

ABSTRACT

I present an SEI (Susceptibles-Exposed-Infectives) model to analyse the effects of seasonality on epidemics, mainly of rabies, in a wide range of wildlife species. Model parameters have been cast as simple allometric functions of host body size. Bifurcation diagrams have been derived for different levels of seasonality in the transmission rate and for different values of the pathogen basic reproduction number R_0 over a broad range of body sizes. While the unforced SEI model exhibits long-term epizootic cycles only for large values of R_0, the seasonal model exhibits multi-year periodicity for small values of R_0. The oscillation period predicted by the seasonal model is consistent with those observed in the field for different host species. These conclusions are not affected by alternative assumptions for the shape of seasonality nor for the parameters that exhibit seasonal variations. However, the introduction of host immunity (which occurs for rabies in some species and is typical of many other wildlife diseases) significantly modifies the epidemic dynamics; multi-year cycles now require a large level of seasonal forcing. My analysis suggests that the explicit inclusion of seasonality in model of wildlife disease may be crucial to correctly describe the epidemics of pathogens of wildlife that inhabit strongly seasonal environments.

1. INTRODUCTION

Seasonal forcing can have a dramatic impact on the dynamics of ecological and epidemiological non-linear systems (Olsen et al., 1988; Hanski et al., 1993, Keeling et al., 2001) and thus realistic models should account for the influence of seasonally varying exogenous factors that affect disease dynamics (Altizer et al., 2006; Olsen and Schaffer, 1990; Greenman et al., 2004; Koelle et al., 2005b). Seasonal variations in host birth rate, social aggregation, or resource availability are central features of the life of all temperate and many tropical habitats (Altizer et al., 2006, Aron and Schwartz, 1984). Usually, wildlife birth rates peak in the spring time (e.g. see Bingham and Purchase, 2002), while intraspecific competition increases in the winter time, when the resources become scarce. Epidemiological parameters may also exhibit a seasonal trend; in particular, the contact and transmission rates are inherently linked to animal mobility and social behaviour. For example, the transmission of rabies among African black-backed jackals (*Canis mesomelas*) is facilitated by the dry season, when they increase their home range due to the scarcity of water (McKenzie, 1993). Among European red foxes (*Vulpes vulpes*), the transmission coefficient of rabies increases with their mobility during the mating season, and decreases when parents become more sedentary while raising the offspring (Pastoret and Brochier, 1999).

The effect of seasonality on host-parasite dynamics has received increasingly larger attention in the past twenty years, especially in human diseases (Hethcote and York, 1984; Bolker and Grenfell, 1993; Grenfell et al., 1995; Kamo and Sasaki, 2002; Greenman et al., 2004). Several studies have shown that seasonality in the transmission rate can enormously complicate the population dynamics of host–parasite interaction and produce a sequence of bifurcations corresponding to cycles with multiyear periods or even chaos for high levels of seasonal variation (Schwartz and Smith, 1983; Aron and Schwartz, 1984; Schwartz, 1985; Keeling and Grenfell, 1997; Keeling et al., 2001; Rohani et al., 2002; Greenman et al., 2004). This has recently led to new sets of questions regarding the adaptive dynamics of pathogens in a seasonal environment (Koelle et al., 2005a; Kamo and Sasaki, 2005) and the maintenance of pathogen diversity (McKenzie et al., 2001).

The importance of seasonality in population ecology has been recognized long ago (Nisbet and Gurney, 1982), but the role played by seasonal fluctuations in wildlife diseases have attracted somehow less attention than in human diseases, probably because of the general lack of long historical records of disease in wildlife. As notable exceptions I can cite Ruxton (1996) who analysed an SEIR (Susceptible, Exposed but not infectious yet, Infective and Recovered) model of bovine tuberculosis in a badger host

population capable of Malthusian growth and showed that seasonality in model parameters is unable to sustain epidemic cycles; and Briggs and Godfray (1996) who studied the interaction between an insect and its pathogen in a seasonal environment when host dynamics is characterized by discrete generations.

On the other hand, the population dynamics of a free-living host is generally affected by intraspecific competition for resources or space. The interaction between the effect of seasonality and those due to density-dependent processes deserves particular attention. However, a systematic analysis of a seasonally forced SEI model of a self-regulating wildlife host has not been presented yet, although Ireland et al. (2004) have recently analysed the complex dynamics of a seasonally forced SIR model of a self regulating population. Nevertheless the SIR framework does not account for the time delay between the onset of infection and the actual infectivity of the host. This delay is particularly important to understand the dynamics of disease in the wildlife, as pointed out by Anderson et al. (1981) in their seminal SEI model of rabies. In fact, if the latent period (the average time spent in the infected-but-not-infectious class) is sufficiently long, the population dynamics of the non-seasonal host can be characterized by sustained oscillations (Swart, 1989; Pugliese, 1991). The interplay between the intrinsic tendency to oscillate of these non-linear epidemiological systems with seasonal fluctuations of host fertility or transmission rate can elicit complex dynamical patterns (Keeling et al., 2001). This was anticipated by Kuznetsov and Piccardi (1994) who derived the general bifurcation diagram of a seasonally forced SEIR model of human diseases in a constant population.

The aim of this chapter is to thoroughly investigate the dynamics of seasonally forced SEI(R) of lethal diseases in the wildlife. I use an SEI model of rabies as a reference example since rabies is one of the most significant zoonoses worldwide and can affect a wide range of different host species. Rabies dynamics can be well described by SEI models: it has considerable latent period (usually longer than the infectious one) and assures low survival probability to the full-blown infected (absence of recovery class). On the other hand, in some species (as raccoon and skunks), individuals exposed to rabies can develop natural immunity without develop full-blown disease (i.e., without become infected). Each year, about 30,000-50,000 people die from rabies in the developing world and hundreds of millions of dollars are spent on rabies control in the developed countries, mainly for animal vaccination and postexposure prophylaxis. Rabies is quite generalist and can infect hosts ranging from a few grams (mice) to several hundreds of kg (bears). Moreover, the main key features of its dynamics can be captured in a quite general mathematical framework that applies to other infectious diseases. As a

consequence, the rabies SEI model provides important general insights into the dynamical properties for a wider range of zoonoses.

I perform the epidemiological analysis by casting host demographic rates as allometric functions of host body size. In fact, larger hosts are expected to have longer life expectancy, smaller reproductive rate, slower dynamics and more sparse population densities when compared to smaller host species (Peters, 1983). Moreover, Bolzoni et al. (2007) have shown that oscillations arising in the autonomous (i.e., non-seasonal) SEI model of a rabid host scale allometrically with its body size; in particular this work shows that hosts with larger body size exhibit longer periods of oscillation. As fluctuations in the fertility and/or mortality of the host, as well as in the transmission rate typically have a one-year period, the interplay of seasonal forcing with the intrinsic oscillation frequency due to host-pathogen interaction may be different for hosts with different body size. Specifically, here I want to assess whether the introduction of seasonality can explain the observed patterns of multi-year periodicity in rabies epidemics. Also, I extend the present analysis to diseases other than rabies by investigating the dynamics of a diseased host that is able to develop some level of immune response. Although this is possible unlikely for rabies (except in bats), it does often occur in other viral disease of wildlife such as rinderpest, distemper, brucellosis, and hog cholera.

This chapter is organized as follows: in the next section I introduce the non-seasonal, allometrically-scaled SEI epidemic model originally developed by Anderson et al. (1981) and thoroughly described by Bolzoni et al. (2007). Then, I investigate the effect of different levels of seasonality in the transmission coefficient on the population dynamics of the infected host for species characterized by a wide range of body sizes. To verify the robustness of the results, I derive the bifurcation diagrams when host birth rate (instead of transmission coefficient) exhibits seasonal fluctuations and investigate the effect of different shapes of seasonal forcing functions. The model is then modified so as to include an immune class and the population dynamics are again analysed under this new assumption.

2. THE BASIC SEI MODEL

The first SEI model of rabies was derived in the seminal paper by Anderson et al. (1981) to describe the spread of this infectious disease in European foxes and assess the efficacy of culling and vaccination for disease control and eradication. Some years later Coyne et al. (1989) presented a modified version of the epidemiological model so as to account also for the development of acquired immunity in raccoons. In this chapter I will mainly use the original version of the Anderson et al. (1981) model which does not include an immune class, namely:

$$\dot{S} = \nu S - (\mu + \gamma N)S - \beta SI \qquad (1a)$$

$$\dot{E} = \beta SI - (\sigma + \mu + \gamma N)E \qquad (1b)$$

$$\dot{I} = \sigma E - (\alpha + \mu + \gamma N)I \qquad (1c)$$

Here S, E, and I are the densities of susceptible, infected but not infectious, and infective individuals in the population, respectively; N is the total population density, i.e. $N = S + E + I$; ν, μ, γ are the ecological parameters: intrinsic birth and death rates, and intraspecific competition coefficient, respectively; β, σ, and α are the epidemiological parameters: transmission coefficient, latency rate ($1/\sigma$ being the mean latency period), and disease-induced mortality, respectively. I refer to existing literature for a comprehensive stability analysis of the unforced SEI model (Swart, 1989; Pugliese, 1991; Gao et al., 1995).

To account for a wide range of host species, according to Silva and Downing (1995) and J.M. Cable and B.J. Enquist (unpublished manuscript) and following De Leo and Dobson (1996), I have cast the demographic and epidemiological parameters of the model as simple allometric functions of mean host body size w:

$$\nu = 1.0 w^{-0.25} \qquad (2a)$$

$$\mu = 0.4 w^{-0.25} \qquad (2b)$$

$$K = \frac{\nu - \mu}{\gamma} = 16.2 w^{-0.70} \qquad (2c)$$

$$\sigma = 20 w^{-0.25} \qquad (2d)$$

$$\alpha = 100 w^{-0.25} \qquad (2e)$$

where body size w is in [kg], carrying capacity K in [#individuals km^{-2}], and the rates in [yr^{-1}]. Even though this model is quite simple, it is able to capture the main features of the population dynamics of

rabies. A detailed analysis of the dynamics of the non-seasonal allometric SEI model of a lethal disease has been presented in Bolzoni et al. (2007). Their work shows that the threshold values of the transmission coefficient β_{th} for the disease to establish in the population scales allometrically with host body size as well as the threshold values β_H ($>\beta_{th}$) for limit cycles to occur; both exhibit the same power scaling, namely they increase with body size as $w^{0.45}$. In contrast, the threshold value of the basic reproduction number $R_0 = \sigma\beta K/(\sigma+\nu)(\alpha+\nu)$ for sustained oscillations to occur is independent of the host size.

In order to analyse the effect of seasonality on the basic SEI model, I assume that the transmission rate can be expressed as a sinusoidal function of time *t* (Dietz, 1976):

$$\beta(t) = \beta_0\left(1+\varepsilon\sin(2\pi t)\right) \qquad (3)$$

where β_0 is the mean transmission coefficient (or baseline of transmission) and $0 \le \varepsilon \le 1$ is the degree of seasonality (or strength of the seasonal forcing). The periodically forced model is thus obtained by substituting Eq. (3) into model (1) with the allometric relationships (2).The model behaviour has been analysed through bifurcation analysis using numerical continuation methods implemented in the specialized software LOCBIF (Khibnik et al., 1993) and CONTENT (Kuznetsov, 1998). The dynamical features of the seasonal model are illustrated in the following section.

3. RESULTS

Since empirical estimates of transmission coefficient in wildlife diseases are hard to be found (see e.g., Begon et al., 1999), it is essential to understand how behaviours of the SEI model changes under a wide range of values assigned to parameters ε and β_0 that fully describe disease transmission in a seasonal environment. Fig. 1 shows the bifurcation diagram of the periodically forced SEI model in the ε–β_0 space for a host with body mass of 1 kg. I only show bifurcation curves corresponding to attractors, as this simplifies the interpretation of the diagram.

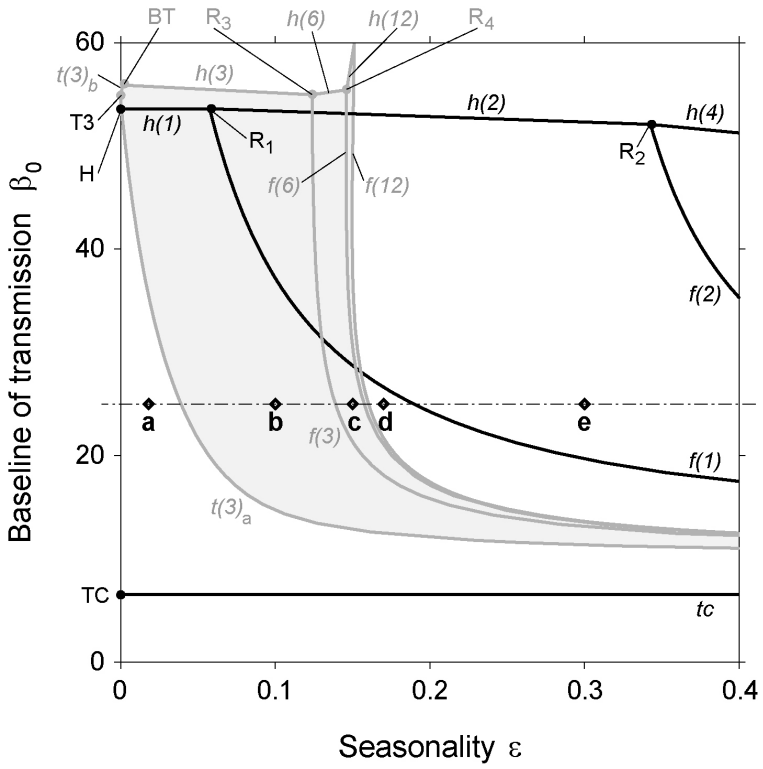

Fig. 1: Bifurcation diagram of the seasonally forced SEI model in the ε (seasonality)– β_0 (transmission coefficient) parameter space. The black bifurcation curves mark the appearance of cycles from the attractors of the unforced SEI model. The light grey bifurcation curves involve attractors that appear due to the frequency locking associated with period-three cycles. The parameter values of the model have been allometrically scaled for a host with body size w = 1 kg. Point TC is the starting point of the transcritical bifurcation curve (*tc*); H is the Hopf bifurcation point in the unforced model; BT represents a Bogdanov-Takens point and R_i (with i = 1,2,3,4) represent strong resonance 1:2 points; $h(i)$ represent the Neimark-Sacker bifurcation curves where cycles of period i arise; $f(i)$ represent flip (period doubling) bifurcation curves where cycles of period i arise; the point T3 on the β_0 axis identifies the value of the transmission coefficient that corresponds to a three-year epizootic cycle and is the root of two tangent bifurcation curves, $t(3)_a$ and $t(3)_b$, which delimit the grey region of the parameter space called Arnol'd tongue. The population dynamics corresponding to the points a-e of the parameter space along the dash-dotted line are illustrated in Fig. 2.

Along the vertical axis ($\varepsilon = 0$) it is possible to identify, for increasing values of the baseline of transmission β_0, the simple bifurcation sequence of the non-seasonal model. For $\beta_0 <$ TC (that is, the transcritical bifurcation point characterized by $R_0 = 1$, the threshold for pathogen establishment), rabies is not able to invade the host population and the system settles to its natural 'carrying capacity' (a disease-free equilibrium). For TC $< \beta_0 <$ H, the pathogen is able to invade its host population that eventually reaches a stable enzootic equilibrium; for $\beta_0 >$ H (the Hopf bifurcation point) the system exhibits stable epizootic cycles: the period of oscillation is greater than two years and increases for increasing value of the transmission coefficient. The introduction of seasonality ($\varepsilon > 0$) does not affect the disease-free equilibrium while it remarkably changes the model behaviour for $\beta_0 >$ TC. Quite obviously, a small degree of seasonality transforms the enzootic equilibrium of the non-seasonal, unforced model into an epizootic cycle of one-year period (see Fig. 2a), and the epizootic cycles of the unforced model (when $\beta_0 >$ H) into quasi-periodic solutions. However stronger seasonal fluctuations of the transmission coefficient $\beta(t)$ can give rise to more complex dynamic behaviours that are mainly rooted into point T3 on the β_0 axis.

Hereafter I report only major epidemiological results linked to the bifurcation analysis of model (1) and refer to Appendix A in Supplementary Material for a detailed description of Fig. 1. T3 is not a bifurcation point in the non-seasonal model ($\varepsilon = 0$): it is the value of the transmission coefficient corresponding to an epizootic cycle of three-years period. According to the classical bifurcation theory of periodically forced models (Kuznetsov, 1995), T3 is the root of a pair of so called "tangent bifurcation" curves ($t(3)_a$ and $t(3)_b$ in Fig.1) that identify a region in the parameter space ε–β_0 called Arnol'd tongue (the grey area of Fig. 1). Within this region the population dynamics can resonate with the seasonal forcing function – a phenomenon called frequency locking – and give rise to a period-three cycle. As a consequence, within the Arnol'd tongue, two attractors coexist: the first one corresponds to the small, period-one cycle generated by the seasonal forcing function for $\beta_0 <$ H (such as that represented in Fig. 2a). The second attractor, that arises through frequency locking, is characterized by an outbreak that occurs every three years, followed by a two-year phase of endemism (see Fig. 2b corresponding to point *b* in Fig. 1). For increasing levels of seasonality ε, on the boundary $f(3)$ of Fig. 1 the stable period-three cycle undergoes a so called "flip bifurcation" and is transformed into a stable period-six cycle (see Fig. 2c), a phenomenon called period-doubling. A further increases of the level of seasonality ε produces a cascade of period-doubling bifurcations ($f(6)$, $f(12)$, …, $f(\infty)$) that occurs close by $f(3)$. Along the $f(\infty)$ curve a chaotic attractor appears, but numerical simulations from several initial

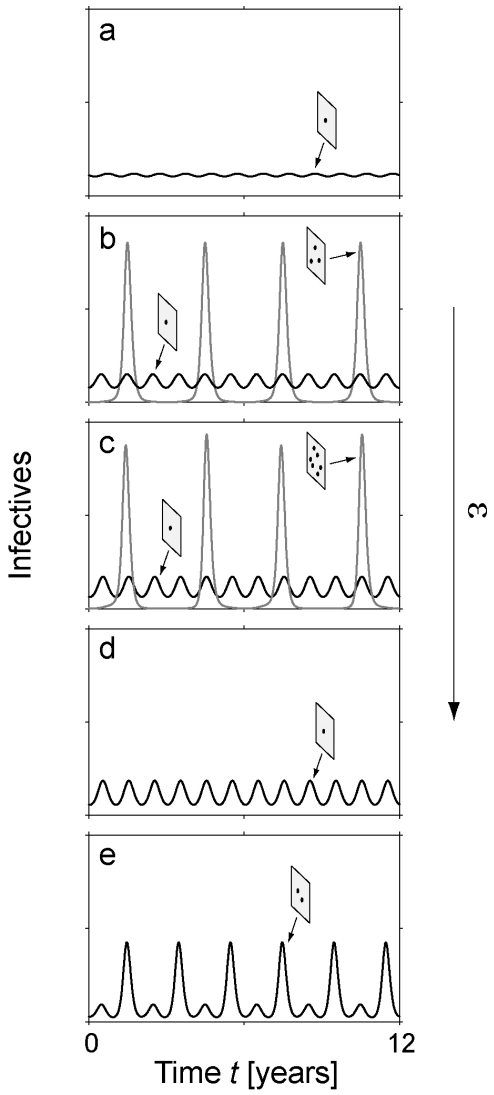

Fig. 2: The prevalence of infective hosts $I(t)$ in the attractors of the periodically forced SEI model for increasing values of seasonality ε along the dash-dotted line of Fig. 1. Fig.s *a-e* are obtained by setting the parameter values as those at points a, b, c, d, e of figure 1. The grey rectangles are the corresponding Poincaré section of the attractors: the number of dots represents the period of the cycles. In Fig.s *b* and *c* there are two coexisting attractors (black and grey curves).

conditions have shown that its basin of attraction is too small to have any ecological and epidemiological significance. As a consequence, population dynamics will basically converge back toward the stable one-year cycle that occurs also for smaller ε (Fig. 2d, corresponding to point d in Fig. 1).

On the other hand, an increase of the baseline of transmission β_0 brings the cycles to instability through Neimark-Sacker bifurcations $h(3)$ corresponding to the appearance of quasi-periodic solutions.

According to the bifurcation theory for seasonally-forced models, along the vertical axis there exist infinite points T4,T5,… of frequency locking corresponding to cycles of period 4,5,..., in which bifurcation curves similar to those originated in point T3 are rooted. I have omitted these curves in Fig. 1 because of their little ecological significance. In fact, in general, periodic solutions with large oscillation period have very small basins of attraction (Schwartz, 1985), and therefore the state of the system in the presence of environmental noise is very likely to converge towards attractors with smaller oscillation period (Greenman et al., 2004), specifically the small, smooth, period-one cycle or the period-three cycle characterized by a pronounced outbreak that coexist in the grey area rooted in T3. Further technical comments on Fig. 1 are reported in Appendix A.

Fig. 3 provides a synoptic view of the dynamic behaviour outlined in Fig. 1 for host species characterized by three different body sizes: 1, 5, and 10 kg, respectively. To facilitate the comparative analysis, I have rescaled the vertical axis as a function of the average basic reproduction number as R_0 is proportional to the mean transmission coefficient β_0.

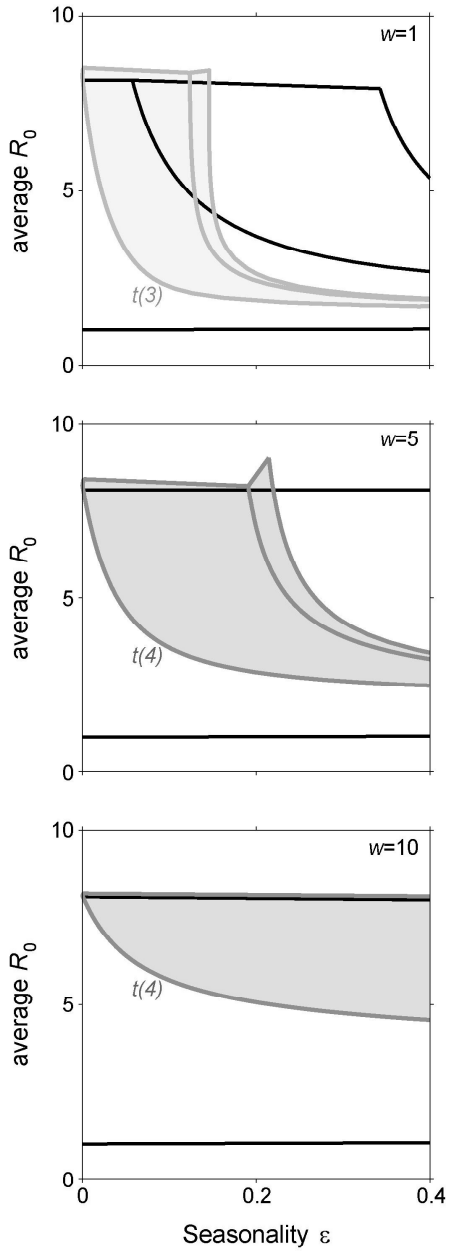

Fig. 3: The effects of increasing host body size w [kg] on the bifurcation diagram of the seasonal SEI model in the ε–R_0 space. Fig. 3a is for w = 1 (e.g., mustelids), Fig. 3b is for w = 5 (e.g., foxes), and Fig. 3c is for w = 10 (e.g., jackals). For the meaning of the curves shown in figure 3a see figure 1. In figures 3b and 3c, the black curves correspond to *tc* and *h(1)* bifurcations; the dark grey curves are the bifurcation curves involving a period-four cycle that appears through frequency locking; Dark grey areas represent the parameter regions in which four-years epizootic cycles appeared by frequency locking and attractors with one-year return time of epidemics coexist.

The bifurcation diagrams show that hosts with small body size (and large birth and death rate according to the allometric relationships) may exhibit population dynamic trajectories more complex than those of hosts with large body size (and small birth and death rate). As shown in Fig.s 3b and 3c, the cascade of flip bifurcations involving period-one cycles is not present anymore for host of 5 and 10 kg. Furthermore, the first frequency locking point on the vertical axis corresponds to cycles of period four (dark grey curves). As a consequence, hosts with larger body size are likely to exhibit larger epizootic oscillations than host with smaller body size, which means a longer inter-epidemic phase and a higher peaks of infection during the epidemics. Finally, hosts with larger body size can exhibit long-term epizootic cycles only for values of the basic reproduction number R_0 larger than that of host with small body size. Accordingly, for R_0 values ranging between 2 and 3, only small species can exhibit multi-year periodicity, while larger species do not.

Numerical simulations of seasonal SEI model dynamics, starting from different initial conditions, show that, in parameter regions in which multiple attractors coexist (the grey areas in Fig. 1 and 3), the attractor with the lowest frequency locking period (3 years for hosts of 1 kg, 4 years for hosts of 5 and 10 kg) has the largest basin of attraction. In the case of point 'b' of Fig. 1 for a host of 1 kg, simulations starting from initial conditions chosen randomly in the range $0.75K<S_0<K$ and $0<I_0<0.01K$ show that the period-three cycle basin of attraction is about twice as large as the period-one cycle one (in 62% of cases trajectories converge toward

period-three cycle, 25% converging to period-one and 13% converging to epizootic cycles with period larger than the 3 years, see also Figure A1 in Supplementary Material). As a consequence, numerical simulations confirm the theoretical prediction that dynamical regime corresponding to the smallest frequency locking are the most likely to occur in wildlife host populations.

Fig. 4 shows the smallest frequency locking period as a function of the mean host body size (broken dark, grey, horizontal line) it also illustrates the oscillation period observed for some mammal species that are known to be important reservoirs for rabies. Log-log regression shows significant positive correlation between observed period of epizootic cycles and host body size (slope = 0.49, 95% CI: 0.28-0.58, $R^2 = 0.85$, $n = 10$); Reduced Major Axis regression was used to calculate the slope because there is an equal probability of measurement error for both variables; the confidence intervals (CI) were estimated by bootstrapping (1000 iterations). The grey area of Fig. 4 corresponds to feasible cyclic solutions with period of oscillation larger than the minimum one arising through frequency locking (e.g. 3 years for host ranging between 1 and 6 kg and 4 years host between 6 and 18 kg). As shown in Fig. 4, the oscillation period predicted by my seasonally-forced SEI model matches the observed one quite well. Only in the case of black-blacked jackal the period of oscillation predicted by the model parameterised according to the expected vital rates in Eqs. (2) for a 7 kg animal is larger than the one observed by Courtin et al. (2000) (4 years instead of 3); yet, further analyses show that if carrying capacity is only slightly larger than that predicted by Eq. (2c), the model will generate cycles of the observed length.

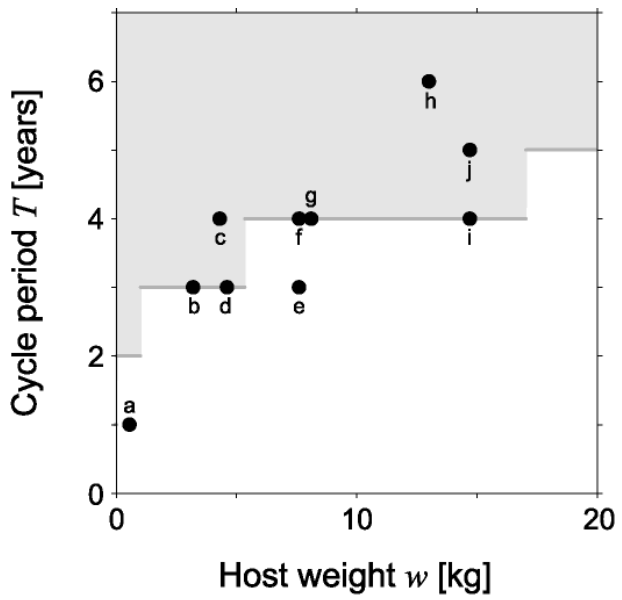

Fig. 4: Comparison of minimum oscillation periods predicted by seasonal SEI model against existing data for rabies. Broken dark grey line represents the smallest period of frequency locking as a function of the host body size w (in kg). The black points represent the minimum epizootic cycle estimated for some mammal species: a) mongoose; b) Arctic fox; c) northern raccoon; d) red fox; e) and f) black-backed jackal; g) raccoon dog; h) Eurasian badger; i) and j) feral dog (see Table A1 for data details). Grey area is the region in the plane predicted by seasonal SEI model, in which epizootic cycle can occur. The parameters σ and α are fixed to $24w^{-0.25}$ and $100w^{-0.25}$, respectively.

I have not been able to find information about epizootic cycles in populations infected by rabies with body size larger than 15 kg; although this is in perfect agreement with the prediction of my model which predicts that hosts with larger body size will only exhibit epizootic oscillations for

very large values (and possibly non-realistic) of the basic reproduction number R_0.

3.1. Seasonality in host birth rate and in other parameters

Seasonality may obviously affect demographic or epidemiological parameters other than the transmission rate. The host fertility rate, for instance, usually exhibits quite regular fluctuations in both temperate and tropical areas in correspondence of the succession of dry and rainy or hot and cold seasons. I have thus analysed the dynamical properties of the model assuming that host birth rate is a sinusoidal function of time, namely (and as also described in White et al. (1996) and Ireland et al. (2004)),:

$$\nu = \nu_0 w^{-0.25}\left(1+\varepsilon\sin(2\pi t)\right) \qquad (4)$$

where $\nu_0\ w^{-0.25}$ is the average value of the intrinsic birth rate and ε again reflects the magnitude of seasonal variations, as in Eq. (3). As shown in Fig. 5, the bifurcation diagram of the modified model derived under the assumption of seasonal birth rate, plotted in the ε-ν_0 space, is similar to that of the SEI model with seasonally transmission rate depicted in Fig. 1. The curves' meaning in Fig. 5 is the same as in Fig. 1. It is to be remarked that even in the case of a seasonal birth rate, more complex behaviours, namely multi-year periodicity for low R_0 and ε, are possible only for hosts with smaller body size.

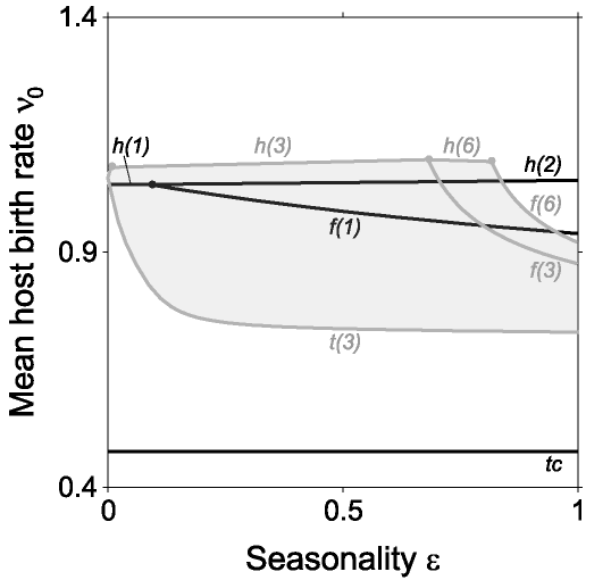

Fig. 5: Bifurcation diagram for model (1) under the assumption of a seasonally fluctuating birth rate of the host. I use uses the same conventions of Fig. 1 plotting regions of dynamic behaviour in the ε-ν_0 space. The black bifurcation curves originate from the Hopf bifurcation point of the unforced SEI model. The light grey bifurcation curves involve attractors that appear via the first frequency locking (period-three years cycle). The curves' meaning is the same as in Fig. 1. The mean transmission coefficient β_0 has been fixed to 50.

As the reproductive season might be remarkably short (as pointed out in Roberts and Kao, 1998), I have also derived the bifurcation diagram of the model using a pulse-like function for the host birth rate:

$$\nu = \nu_0 w^{-0.25} \left(\frac{(1+\varepsilon \sin(2\pi t))^2}{\left(1+\frac{\varepsilon^2}{2}\right)} \right) \qquad (5)$$

where $\nu_0 \, w^{-0.25}$ is again the average value of the intrinsic birth rate and the term in the brackets is the seasonal forcing function (whose average value is equal to unity for each ε). It turns out that even in this case, the qualitative behaviour of the modified seasonal SEI model is not topologically different from the one with a sinusoidal transmission rate.

As observed by Altizer et al. (2006), the actual dynamics depends upon which parameters are assumed to be seasonal and the shape and level of seasonality. Yet, further analyses not reported here show that the qualitative behaviour of the seasonal SEI model does not depend upon which demographic or epidemiological parameters actually characterize the seasonal fluctuations, a phenomenon that was observed in other seasonally forced population models (Gragnani and Rinaldi, 1995). The results I have derived here are thus quite robust with respect to alternative hypotheses on the type of seasonality.

3.2. The effect of the host immune response

Most host species do not produce an effective immune response to the rabies virus, so the infection leads inexorably to the death of the infected individual. However, for a few wildlife species (such as raccoons and skunks) rabies may occasionally not be fatal (Coyne et al., 1989). More commonly, there are a large number of other diseases in which the host can develop temporary or permanent immunity. In this section I explore the consequences of naturally acquired immunity of the host for the epidemic dynamics of the seasonally forced model. I have incorporated a new class R into model (1) for individuals becoming immune as a result of infection. In the case of rabies the exposed individuals become immune without developing full-blown infection – i.e., without moving into class I – as shown by Coyne et al. (1989). Hence the epidemic model can be rewritten in the following manner:

$$\dot{S} = \nu(S+R) - (\mu + \gamma N)S - \beta(t)SI \qquad (6a)$$

$$\dot{E} = \beta(t)SI - (\sigma + \mu + \gamma N)E \qquad (6b)$$

$$\dot{I} = (1-\rho)\sigma E - (\alpha + \mu + \gamma N)I \qquad (6c)$$

$$\dot{R} = \rho\sigma E - (\mu + \gamma N)R \qquad (6d)$$

where the *S*, *E*, and *I* classes have the same meaning as in model (1), as well as parameters ν, μ, γ, σ, α, and $\beta(t)$. The parameter ρ represents the mean fraction of infected individuals that develop a permanent immune response to the pathogen; *R* thus represents the density of hosts that have developed an immune response. I have assumed that immune individuals are fully reproductive. *N* is the total population density, namely $N = S + E + I + R$. Obviously, when the probability of developing immunity tends to zero ($\rho \to 0$), we come back to the classical SEI model (1). A similar non-seasonal version of model (6) was analysed by Coyne et al. (1989) and Childs et al. (2000). They showed that even for small values of the immunity ρ, the Hopf bifurcation that arises for increasing transmission rates in the SEI model disappears for realistic values of the basic reproduction number R_0, and thus no limit cycles can occur in the non-seasonal SEIR model. The consequence is that no cyclic solution can arise through frequency locking and, thus, multi-year periodicity only appears in response to high levels of seasonal forcing; it does not occur anymore for low level of seasonality (see grey region in Fig. 6) regardless of host body size.

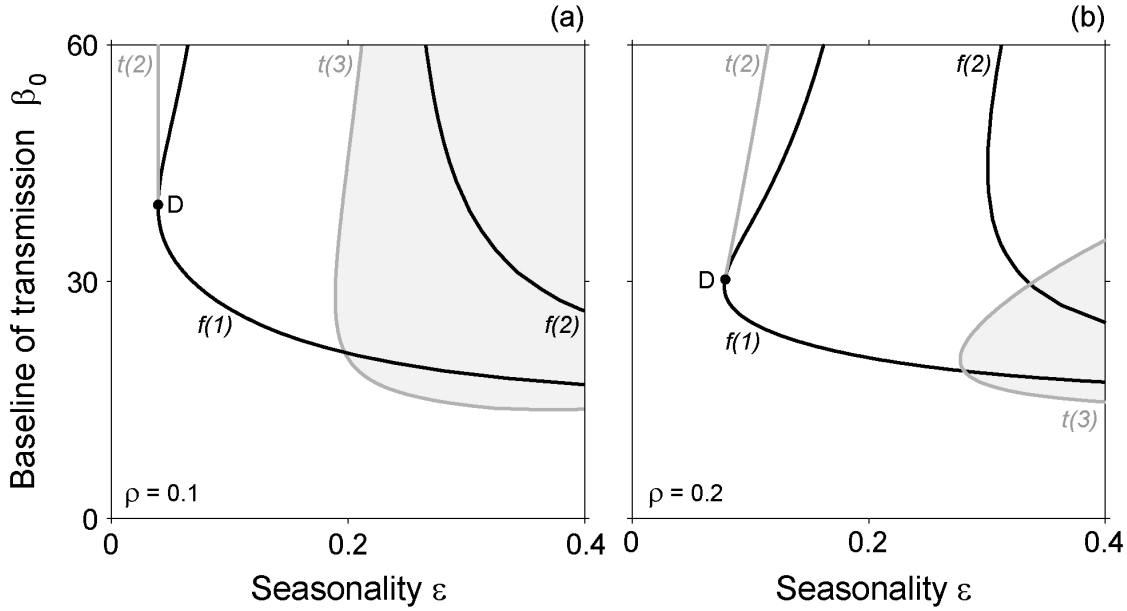

Fig. 6: Bifurcation diagram in the ε-β_0 space for the model (6) with the coefficient of transmission periodically forced with function (3), calculated for two different values of natural immunity (ρ = 0.1 and ρ = 0.2). The black curves mark the appearance of cycles from the bifurcation of attractors of the unforced model. The light grey curves involve attractors that appear due to tangent bifurcations associated with period three cycles. See the main text for the meaning of the points and curves shown in the figure. Grey area represents the parameter region in which three-years epizootic cycles and attractors with annual peak of epidemics (one- and two-years cycles) coexist. Other parameter values of the model are fixed as in Fig. 1.

I refer to Appendix B in Supplementary Material for a detailed description of the bifurcation diagram depicted in Fig. 6.

Results obtained with model (6) are independent to the assumption, true for rabies, that exposed individuals skip full-blown infection stage before become immune. In fact, I found analogous results to those in Fig. 6 with a Susceptible-Exposed-Infected-Recovered model in which exposed individuals become infected before develop immunity.

Moreover, it is interesting to note that results similar to those showed for the SEIR model with host density-dependence were obtained by Kuznetsov and Piccardi (1994) for models describing childhood diseases and by Casagrandi et al. (2006) for model describing influenza epidemics in constant human populations, where host immunity was included. The same results apply as in model (6) when seasonality is included in host birth rate, the presence of an immune class buffers the system against more complex dynamics. These results are in accordance with those obtained by Ireland et al. (2004) for a SIR model with host density dependence.

4. DISCUSSION

In this chapter I have analysed the importance of seasonality in lethal diseases of self regulating wildlife populations. Through allometric scaling of demographic and epidemiological parameters I have examined the dynamics of the epidemiological system over a wide range of host body sizes. My analysis shows that, while the unforced SEI model exhibits long-term epizootic cycles only for large values of the reproduction number R_0 (Bolzoni et al., 2007), the seasonally forced model can exhibit multi-year periodicity for much smaller values (< 5) of R_0. Furthermore, bifurcation analysis shows that hosts with small mean body size may exhibit complex dynamics even at small levels of seasonal forcing (ε). The resonance (frequency locking) is the key mechanism that determines the onset of multi-year periodic cycles for low transmission coefficients, and the larger the host the longer the oscillation period. The typical period predicted by my SEI model for different species of hosts infected with rabies is in accordance with field observations (see Fig. 4 and Table A1). This correspondence can be used to predict the frequency of outbreaks for diseases established in new populations by knowing only the host body size.

My analysis shows that the explicit consideration of the latency period, namely the period between the onset of infection and the time when the infected animal becomes infective, may dramatically change the population dynamics of the infectious disease with respect to what predicted by SI-like models of a self-regulating host population (Ireland et al. 2004). In fact, multi-year periodicity can occur even for very low levels of seasonality in the case of a seasonally forced SEI model, while this is not possible in the simpler SI-like models. Moreover, in the seasonally forced SEI model, high levels of seasonality coupled with high values of the basic reproduction number R_0 can potential produce chaotic dynamics that arise through bifurcations involving quasi-periodic orbits for increasing values of the basic reproduction number or through a cascade of period-doubling bifurcations for increasing values of seasonality. However, the basins of attraction of the chaotic attractors that arise from frequency locking are quite small and, even for intermediate or high level of seasonality, the system basically tends to display yearly peaks of infectives (see Fig. 2d and 2e).

These conclusions are quite robust with respect to alternative assumptions on how seasonality is introduced in the model. The same qualitative structure of the bifurcation diagram is retained when seasonality is included in demographic or epidemiological parameters other than transmission rate, even when more than one parameter has seasonal oscillation, and when significant phase differences

between the periods of oscillations of the seasonally forced parameters are included. The same holds true for different shapes of the seasonal forcing function.

In contrast, in an SEIR model no multi-year periodicity will occur at low levels of seasonality when a small fraction of infected hosts is able to develop a successful immune response without becoming infective. By setting the parameters as in (2), the SEIR model cannot show long-term cycles arising from frequency locking for values of immunity (ρ) greater than 0.036 (independently of the host size w and the average transmission coefficient β_0). The crucial role of the class R in the model behaviour suggests that a correct estimate of the degree of immunity in the host population is necessary to understand the disease dynamics and to implement successful control policies. Moreover, class R can also mimic the immunity induced in host population by the oral vaccination. Then, the introduction of vaccination policies (with the effect to increase the value of ρ) can drive host population dynamics from a long period epizootic behaviour with high epidemic peaks (frequency locking oscillations) to a short period one for the same level of seasonality.

A number of other processes have not been accounted for in the present study - such as spatial dynamics, ,multiple-strain interactions and stochastic fade out of the disease during the endemic phase - these might be relevant in determining the observed detailed patterns of behaviour in specific rabies outbreaks (Mollison, 1991; Mollison and Levin, 1995; Rohani et al., 2002; Real et al., 2005). Nevertheless, the allometric scaling approach adopted here provides key insights into the broad patterns of behaviour likely to be observed in a large class of hosts species exposed to lethal pathogens and living in seasonal environments. In fact, as already outlined by Grenfell et al. (1995) and Keeling et al. (2001) for human disease, the explicit introduction of seasonality into models of host-parasite interaction in the wildlife is a crucial element of realism. Without this key ingredient, it would be impossible to reproduce and explain the multi-year cycles observed for low values of the basic reproduction number R_0.

CHAPTER 3 REFERENCES

Altizer S., Dobson A.P., Hosseini P., Hudson P., Pascual M., and Rohani P. (2006) Seasonality and the dynamics of infectious diseases, *Ecology Letters* **9**:467-484.

Anderson, R.M., Jackson, H.C., May, R.M., and Smith, A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-71.

Aron, J.L., and Schwartz, I.B. (1984) Seasonality and period-doubling bifurcations in an epidemic model, *Journal of Theoretical Biology* **110**:665-679.

Begon, M., Hazel, S.M., Baxby, D., Bown, K., Cavanagh, R., Chantrey, J., Jones, T., and Bennett, M. (1999) Transmission dynamics of a zoonotic pathogen within and between wildlife host species, *Proceedings of the Royal Society B* **266**:1939-1945.

Bingham, J., and Purchase, G.K. (2002) Reproduction in the jackals *Canis adustus* Sundevall, 1846, and *Canis Mesomelas* Schreber, 1778 (Carnivora: Canidae), in Zimbabwe, *African Zoology* **37**:21-26.

Bolker, B.M., and Grenfell, B.T. (1993) Chaos and biological complexity in measles dynamics, *Proceedings of the Royal Society B* **251**:75-81.

Bolzoni, L., De Leo, G.A., Gatto, M., and Dobson, A.P. (2006) Body-size scaling in an SEI model of wildlife disease, *Theoretical Population Biology*, accepted.

Briggs, C.J., and Godfray H.C.J. (1996) The dynamics of insect-pathogen interactions in seasonal environments, *Theoretical Population Biology* **50**:149-177.

Casagrandi, R., Bolzoni, L., Levin, S.A., and Andreasen, V. (2006) The SIRC model and influenza A, *Mathematical Biosciences* **200**:152-169.

Childs, J.E., Curns, A.T., Dey, M.E., Real, L.A., Feinstein, L., Bjørnstad, O.N., and Krebs, J.W. (2000) Predicting the local dynamics of epizootic rabies among raccoons in the United States, *Proceedings of the National Academy of Sciences USA* **97**:13666-13671.

Coyne, M.J., Smith, G., and McAllister, F.E. (1989) Mathematical model for the population biology of rabies in raccoons in the mid-Atlantic states, *American Journal of Veterinary Research* **50**:2148-2154.

De Leo, G.A., and Dobson, A.P. (1996) Allometry and simple epidemic models for microparasites, *Nature* **379**:720-22.

De Leo G., Dobson, A., and Goodman, A. (2002) Wildlife Perspectives on the Evolution of Virulence. Pages 26–38 *in* U. Dieckmann, J.A.J. Metz, M.W. Sabelis, and K. Sigmund, ed. *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management*. Cambridge University Press, Cambridge.

Dietz, K. (1976) The incidence of infectious diseases under the influence of seasonal fluctuations, *Lecture Notes in Biomathematics* **11**:1-15.

Gao, L.Q., Mena-Lorca, J., and Hethcote, H.W. (1995) Four SEI endemic models with periodicity and separatrices, *Mathematical Biosciences* **128**:157-184.

Gragnani, A., and Rinaldi, S. (1995) A universal bifurcation diagram for seasonally perturbed predator-prey models, *Bulletin of Mathematical Biology* **57**:701-712.

Greenman, J., Kamo, M., and Boots, M. (2004) External forcing of ecological and epidemiological systems: a resonance approach, *Physica D* **190**:136-151.

Grenfell, B.T., Bolker, B.M., and Kleczkowski, A. (1995) Seasonality and extinction in chaotic metapopulations, *Proceedings of the Royal Society B* **259**:97–103.

Hanski, I., Turchin, P., Korpimäki, E., and Henttonen, H. (1993) Population oscillations of boreal rodents: regulation by mustelid predators leads to chaos, *Nature* **364**:232-235.

Hethcote, H.W., and York, J.A. (1984) *Gonorrhea Transmission Dynamics and Control*. Springer-Verlag, Berlin.

Ireland, J.M., Norman, R.A., and Greenman, J.V. (2004) The effect of seasonal host birth rates on population dynamics: the importance of resonance*, Journal of Theoretical Biology* **231**:229-238.

Kamo, M., and Sasaki, A. (2002) The effect of cross-immunity and seasonal forcing in multi-strain epidemic model, *Physica D* **165**:228-241.

Kamo, M., and Sasaki, A. (2005) Evolution toward multi-year periodicity in epidemics, *Ecology Letters* **8**:378-385.

Keeling, M.J., and Grenfell, B.T. (1997) Disease extinction and community size: modeling the persistence of measles, *Science* **275**:65-67.

Keeling, M.J., Rohani, P., and Grenfell, B.T. (2001) Seasonally forced dynamics explored as switching between attractors, *Physica D* **148**:335-347.

Kermack, W.O., and McKendrick, A.G. (1927) Mathematical theory of epidemics, *Proceedings of the Royal Society B* **115**:700-721.

Khibnik, A.I., Kuznetsov, Yu.A., Levitin, V.V., and Nikolaev, E.V. (1993) Continuation techniques and interactive software for bifurcation analysis of ODEs and iterated maps, *Physica D* **62**:360-71.

Koelle, K., Pascual, M., and Yunus, M (2005a) Pathogen adaptation to seasonal forcing and climate change, *Proceedings of the Royal Society B* **272**:971-977.

Koelle, K. Rodò, X., Pascual, M., Yunus, Md., and Mostafa G. (2005b) Refractory periods and climate forcing in cholera dynamics, *Nature* **436**:696-700.

Kuznetsov, Yu.A. (1995) *Elements of Applied Bifurcation Theory*. Springer-Verlag, New York.

Kuznetsov, Yu.A. (1998) CONTENT - Integrated environment for analysis of dynamical systems. Ecole Normale Superieure de Lyon, Rapport de Recherche UPMA-98-224.

Kuznetsov, Y.A., and Piccardi, C. (1994) Bifurcation analysis of periodic SEIR and SIR epidemic models, *Journal of Mathematical Biology* **32**:109-21.

McKenzie, A.A. (1993) Biology of the black-backed jackal with reference of rabies, *Onderstepoort Journal of Veterinary Research* **60**:367-371.

McKenzie, F.E., Killen G.F., Beier J.C., and Bossert W.H. (2001) Seasonality, parasite diversity, and local extinctions in *plasmodium falciparum* malaria, *Ecology* **82**:2673-2681.

Mollison, D. (1991) Dependence of epidemic and population processes on basic parameters, *Mathematical Biosciences* **107**:255-287.

Mollison, D., and Levin, S. (1995) Spatial dynamics of parasitism. Pages 384-398 *in* A. Dobson and B. Grenfell, ed. *Ecology of Infectious Diseases in Natural Populations*. Cambridge University Press, Cambridge.

Nisbet, R., and Gurney, W. (1982) *Modelling Fluctuating Populations*. John Wiley & Sons, New York.

Olsen, L.F., Truty, G.L., and Schaffer, W.M. (1988) Oscillations and chaos in epidemics: a nonlinear dynamic study of six childhood diseases in Copenhagen, Denmark, *Theoretical Population Biology* **33**:344-370.

Olsen, L.F., and W.M. Schaffer (1990) Chaos vs. noisy periodicity: Alternative hypotheses for childhood epidemics, *Science* **249**:499-504.

Pastoret, P.P., and Brochier, B. (1999) Epidemiology and control of fox rabies in Europe, *Vaccine* **17**:1750-1754.

Peters, R.H. (1983) *The ecological implications of body size: Cambridge studies in ecology*. Cambridge University Press, Cambridge.

Pugliese, A. (1991) An SEI epidemic model with varying population size. Pages 121-138. *in* S. Busenberg, and M. Martelli, ed. *Differential Equation Models in Biology, Epidemiology and Ecology* (Lecture Notes Biomathematics 92). Springer-Verlag, New York.

Real, L.A., Russell, C., Waller, L., Smith, D., and Childs, J. (2005) Spatial Dynamics and Molecular Ecology of North American Rabies, *Journal of Heredity* **96**:1-8.

Roberts, M.G., and Kao, R.R. (1998) The dynamics of an infectious disease in a population with birth pulses, *Mathematical Biosciences* **149**:23–36.

Rohani, P., Keeling, M.J., and Grenfell, B.T. (2002) The interplay between determinism and stochasticity in childhood diseases, *American Naturalist* **159**:469–481.

Ruxton, G.D. (1996) The effects of stochasticity and seasonality on model dynamics: Bovine tuberculosis in badgers, *Journal of Animal Ecology* **65**:495-500.

Schwartz, I.B. (1985) Multiple stable recurrent outbreaks and predictability in seasonally forced nonlinear epidemic models, *Journal of Mathematical Biology* **21**:347-361

Schwartz, I.B., and Smith, L.H. (1983) Infinite subharmonic bifurcation in a SEIR epidemic model, *Journal of Mathematical Biology* **18**:233-253.

Silva, M., and Downing, J.A. (1995) The allometric scaling of density and body mass: a nonlinear relationship for terrestrial mammals, *American Naturalist* **145**:707-727.

Swart, J.H. (1989) Hopf bifurcation and stable limit cycle behaviour in the spread of infectious diseases, with special application to fox rabies, *Mathematical Biosciences* **95**:199-207.

White, K.A.J., Grenfell, B.T., Hendry, R.J., Lejeune, O., and Murray, J.D. (1996) Effect of seasonal host reproduction on host-macroparasite, *Mathematical Biosciences* **137**:79–99.

CHAPTER 3 SUPPLEMENTARY MATERIAL

The following supplementary material is available for this chapter:

Appendix A *Description of the full bifurcation diagram generated by the SEI model (1)*

Appendix B *Description of the full bifurcation diagram generated by the SEIR model (6)*

Table A1 *Data details in Fig. 4*

Figure A1 *Basin of attraction of attractors: point 'b' in Fig. 1*

APPENDIX A:

Description of the full bifurcation diagram generated by the SEI model (1)

As shown in Fig. 1, TC is the starting point of a transcritical bifurcation curve (*tc*) for $\varepsilon > 0$: when crossing the curve *tc* for decreasing values of β_0, stable period-one epizootic cycles become unstable and the pathogen declines to extinction. This bifurcation represents the disease invasion threshold (i.e., the condition necessary for parasite to invade and establish in the host population) corresponding to $R_0 = 1$ in the non-seasonal model (Kermack and McKendrick, 1927). Then point H is the starting point of the Neimark-Sacker bifurcation curve *h*(*1*). By crossing the curve *h*(*1*) for increasing values of mean transmission coefficient (β_0), the stable period-one cycle becomes unstable, and a quasi-periodic attractor appears (see Kuznetsov, 1995, for details). The bifurcation curve *h*(*1*) ends in the codimension-two point of strong resonance 1:2 (R_1), that is a point where two different bifurcation conditions are satisfied. In fact, two other bifurcation curves start from R_1: the flip bifurcation *f*(*1*) and the Neimark-Sacker bifurcation *h*(*2*). The *f*(*1*) bifurcation involves a stable, period-one, cycle. For increasing levels of seasonal forcing (ε), the period-one cycle becomes unstable and a stable period two cycle appears (see Fig. 2e). The *h*(*2*) bifurcation involves the stable period-two cycle that appeared from the *f*(*1*) bifurcation: when crossing this curve for increasing value of transmission (β_0) the period-two cycle becomes unstable and a quasi-periodic attractor appears. The Neimark-Sacker bifurcation curve *h*(*2*) ends in another codimension-two point of strong resonance 1:2 (R_2). Here, two other bifurcation curves arise: a flip *f*(*2*) and a Neimark-Sacker *h*(*4*) bifurcation curve, respectively. These curves have properties similar to the *f*(*1*) and *h*(*2*) curves, but they involve cycles with double period.

APPENDIX B:

Description of the full bifurcation diagram generated by the SEIR model (6)

For $R_0 > 1$, the only attractor of model (6) for small values of seasonality is a period-one cycle that can undergo a period doubling (*flip*) bifurcation when crossing the boundary *f*(*1*) in Fig. 6. The bifurcation curve *f*(*1*) is supercritical for values of the mean transmission coefficient β_0 smaller than that corresponding to point D, which is a codimension-2 degenerate flip bifurcation point (which is also the root of the tangent bifurcation curve *t*(*2*)), and subcritical elsewhere. By crossing the supercritical branch of the bifurcation *f*(*1*) for increasing values of seasonality the stable period-one cycle becomes unstable and a stable period-two cycle appears. When crossing the subcritical branch for increasing values of seasonality, the stable period-one cycle and the unstable period-two cycle, which originated from the tangent bifurcation *t(2*), collide and give rise to an unstable period-one cycle; hence, the only attractor is the stable period-two cycle that also originated from the tangent bifurcation *t*(*2*). For greater values of ε the period-two cycle undergoes a flip bifurcation along the curve *f*(*2*), and a stable period-four cycle appears. By crossing the tangent bifurcation *t*(*3*) for increasing values of seasonality, a stable period-three cycle occurs (along with an unstable one): this cycle coexists with the stable period-one cycle below *f*(*1*), with the stable period-two cycle between *f*(*1*) and *f*(*2*) and with the stable period-four cycle above *f*(*2*).

Due to the lack of stable sustained cycles in the unforced SEIR model, frequency locking is not possible in the seasonal forced version of the SEIR model. As a consequence, epizootic cycles with period longer than three years (grey area in Fig. 6) are possible only for high values of seasonal variation (ε). Fig. 6 shows that the parametric region in the ε–β_0 space, for which pluriennial epizootic cycles can occur, decreases in size for increasing values of immunity (ρ). This is due to the fact that the Neimark-Sacker bifurcations *h*(.) depicted in Fig. 1 disappear even for small values of immunity; hence, at low seasonality levels, there exist no quasi-periodic attractors in models that incorporate immunity, even for high values of disease transmission rate.

Table A1:

Tag	Common name	Scientific name	Mass (kg)	Period (y)
a	Mongoose	*Herpestes javanicus*	0.55 [1]	1 [6]
b	Arctic fox	*Alopex lagopus*	3.19 [1]	3 [7]
c	Northern raccoon	*Procyon lotor*	4.3 [2]	4 [2]
d	Red fox	*Vulpes vulpes*	4.6 [1]	3 [7]
e	Black-backed jackal	*Canis mesomelas*	7.7 [3]	3 [8]
f	Black-backed jackal	*Canis mesomelas*	7.7 [3]	4 [9]
g	Raccoon dog	*Nyctereutes procyonides*	8.0 [4]	4 [10]
h	Eurasian badger	*Meles meles*	13.0 [1]	6 [11]
i	Feral dog	*Canis familiaris*	14.7 [5]	4 [12]
j	Feral dog	*Canis familiaris*	14.7 [5]	5 [13]

Table A1: Table A1 summarizes details about data using in Fig. 4 in main text. Column 1: alphabetical labels assigned in Fig. 4 to rabies host species; Columns 2 and 3: common and scientific name of host species; Column 4: weight of host species (in kg) and related reference (in square brackets); Column 5: minimum epizootic cycle period observed in populations infected by rabies (in years) and related reference (in square brackets).

References in Table A1

[1] Carbone, C., and Gittleman, J. (2002) A common rule for the scaling of carnivore density, *Science* **295**:2273-2276.

[2] Childs, J.E., Curns, A.T., Dey, M.E., Real, L.A., Feinstein, L., Bjornstad, O.N., and Krebs, J.W. (2000) Predicting the local dynamics of epizootic rabies among raccoons in the United States, *Proceedings of the National Academy of Sciences* USA **97**:13666-13671.

[3] Carbone, C., Cowlishaw, G., Isaac, N.J.B., and Rowcliffe, J.M. (2005) How far do animals go? Determinants of day range in mammals, *American Naturalist* **165**:290-297.

[4] Atanasov, A.T. (2005) Allometric relationship between the length of pregnancy and body weight in mammals, *Bulgarian Journal of Veterinary Medicine* **8**:13-22.

[5] Butler, J.R.A., du Toit, J.T., and Bingham, J. (2004) Free-ranging domestic dogs (Canis familiaris) as predators and prey in rural Zimbabwe: threats of competition and disease to large wild carnivores, *Biological Conservation* **115**:369-378.

[6] Everard, C.O.R., Baer, G.M., and James, A. (1974) Epidemiology of mongoose rabies in Grenada, *Journal of Wildlife Diseases* **10**:190-196.

[7] Anderson, R.M., Jackson, H.C., May, R.M., and Smith, A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-71.

[8] Courtin, F., Carpenter, T.E., Paskin, R.D., and Chomel, B.B. (2000) Temporal patterns of domestic and wildlife rabies in central Namibia stock-ranching area, 1986-1996, *Preventive Veterinary Medicine* **43**:13-28.

[9] Walton, L.R., and Joly, D.O. (2003) Canis mesomelas, *Mammal Species* **715**:1-9.

[10] Kim, C.-H., Lee, C.-G., Yoon, H.C., Nam, H.-M., Park, C.-K., Lee, J.-C., Kang, M.-I., and Wee, S.-H. (2006) Rabies, an emerging disease in Korea, *Journal of Veterinary Medicine B* **53**:111-115.

[11] Smith, G.C. (2002) The role of the Badger (*Meles meles*) in rabies epizootiology and the implications for Great Britain, *Mammal Review* **32**:12-25.

[12] Bingham, J., Foggin, C.M., Wanderler, A.I., and Hill, F.W.G. (1999) The epidemiology of rabies in Zimbabwe. 1. Rabies in dogs (Canis familiaris), *Onderstepoort Journal of Veterinary Research* **66**:1-10.

[13] Widdowson, M.-A., Morales, G.J., Chavez, S., and McGrane, J. (2002) Epidemiology of urban canine rabies, Santa Cruz, Bolivia, 1972-1997, *Epidemiology and Infection* **8**:458-461.

Figure A1:

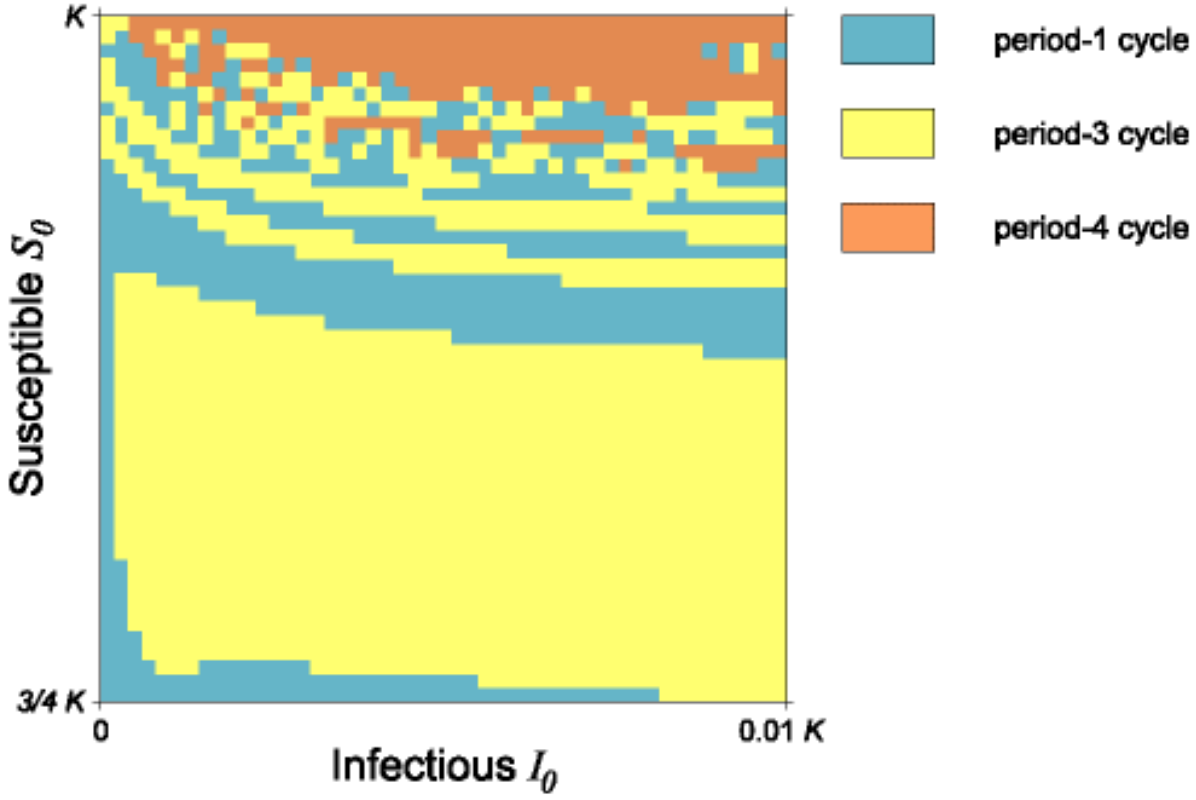

Fig. A1: Basin of attraction of three stable cycles coexisting in model (1) for parameter settings as in point 'b' of Fig. 1. Initial states in the blue, yellow, and red sets indicate convergence to a period-1, -3 and -4 respectively. Convergence to periodic attractors has been simulated for 2500 initial conditions: with susceptibles (S_0) varying from $0.75K$ and K, infectious (I_0) varying from 0 and $0.01K$, and exposed (E_0) equal to 0.

4

Effects of culling on virulence evolution: The case of classical swine fever

ABSTRACT

Eradication of the classical swine fever in wild boar population is usually attempted by host depopulation. The wild boar threshold density for infection extinction is very low, and is rarely reached by increasing hunting or culling. When the depopulation effort does not reach the threshold of extinction, a possible perturbation on the virus virulence evolution might occur. Empirically, the decrease of contact rate between infectious and susceptible animals will favour the less virulent strain. A SI(R) model coupled with two virus strains of different virulence was used in order to evaluate the impact of host population management in the dynamics of virulence evolution. Surprisingly, when a reduced depopulation effort is applied the whole prevalence increases, because the decrease of the most virulent strain abundance is overcompensated by the increase of the less virulent one. The latter spreads due to the relatively low host density resulting in an higher prevalence. Furthermore, acquired disease immunity may dramatically affect strain selection with distinct scenarios possible depending on depopulation pressure, which increases uncertainty on control effectiveness. If so, depopulation in the wild should be accurately planned and performed exclusively when the host threshold density can be reached in a reasonable way.

1. INTRODUCTION

Host-pathogen are among the most complex interspecific interactions. The pathogenic agent depends completely on its host for resources and transmission to other susceptible hosts. On the other hand, presence of pathogens cause a general reduction in host fitness through a decrease in survival and fertility, and alteration of anti-predatory behaviours. As a consequence, the relationship may affect both host and pathogen evolution. Generally speaking, in the case of genetically different pathogen strains co-circulating in genetically distinct host population, the most frequent host genotype suffers the large pathogen burden, because infection easily spreads in high density populations. If dominant host genotype density drops due to the decrease in fitness by parasitism, another host genotype will become dominant. But, by increasing in density, its vulnerability to the disease will also raise. This implies cyclical behaviours in host-pathogen dynamics, which have a firm theoretical interpretation in literature (Anderson and May, 1991), while field observations are quite rare. The main reason is the asymmetry in generation times between host and pathogen, that differ in several order of magnitude. Only pathogen genetic changes are clearly detectable in the short time. Rabbit myxomatosis in Australia represents the best known case of evolution in pathogen virulence, where highly virulent strains were supplanted by better transmittable but less virulent strains (Fenner and Ratcliff, 1965; Fenner, 1994). Recent findings highlight virulence evolution in several viral and bacterial diseases: the human HIV, where virulence is evolving toward lower values (Arien et al., 2007), and the pathogenic *Escherichia coli*, where virulence is evolving toward higher values (Reid et al., 2000).

The problem of virulence evolution is relevant not only from the theoretical point of view (Read, 1995), but also for its large implications in human health (Wilson et al., 1994). Several emerging diseases (e.g., Lyme disease, Hantavirus, Ebola) were already circulating in restricted areas in wild animal populations (Gibbons, 1993; Leroy et al., 2005) and – afterwards evolutionary pressure linked to climate change and land use – they emerged as zoonotic threats for humans and other species (Schrag and Wiener, 1995; Daszak et al., 2000). Data from the World Health Organization (www.who.org) and Center for Disease Control and Prevention (www.cdc.gov) have shown that infectious diseases are the main cause of mortality in developing countries because of social, cultural, and environmental aspects such as: demographic growth, poverty, malnutrition, increase in mobility, and changes in land use (Wilson et al., 1994). Virulence evolution implies disease control problems in developed country also, as indicated by cases of virulence control in hospitals. Theoretical models and field observations have shown that extensive use of vaccines and antibiotics may cause, in specific conditions, the selection of strains resistant to common control therapies (Björkman and Phillips-Howard, 1990; Anderson and May, 1991; Smith et al., 2005). Furthermore,

several theoretical works showed that infection control through vaccination may affect the evolution of disease induced mortality in different ways (Gandon et al., 2001; Iannelli et al., 2005).

Recently, disease spread between wild and domestic animals has become a significant health problem due to their economic and veterinary consequences and risks for human health (Longini et al., 2005). The classical swine fever (CSF) is a highly infectious disease of domestic and wild pigs. Whereas the incidence of CSF in Western Europe is decreasing (despite outbreaks in Germany in 2006), the disease is still endemic in many regions, such as South-East Asia, Eastern Europe, and Central and Southern America (Edwards et al., 2000). CSF in Europe is a notifiable disease, according to Council Directive 82/894/EEC. A case notification in intensive livestock farm implies the compulsory slaughter of the whole herd, by causing considerable economic losses (Horst et al., 1997; De Vos et al., 2005).

Wild boar (*Sus scrofa*) are considered the main reservoir for the classical swine fever permitting the disease transmission to domestic animals (Aubert et al., 1994). Then, a great deal of effort has been focused on the eradication of the disease in wildlife. Historically, control and eradication of classical swine fever in wild boar have been performed through selective removal of animal by hunting (used term hereafter: culling). Theoretical models showed that diseases may be eradicated from wild host population by reducing host density below a fixed threshold (called *critical community size*) and, consequently, reducing the contact rate between infected and susceptible animals (Anderson et al., 1981). Culling is not exempt of criticism (Szent-Iványky, 1984; Laddomada, 2000). Guberti et al. (1998) observed that culling may change wild boar population structure in favour of younger and more-susceptible individuals since hunters usually prefer to shoot older, less-susceptible individuals. Moreover, the original population density may be quickly re-established as a result of the high fertility of wild boar. As a consequence, the threshold level is never reached and the disease cannot be completely eradicated (Laddomada, 2000). Finally, hunting parties may push wild boar from their natural home range. This could lead to an increase in contact rate despite a reduction in population density (Guberti, 1991; Sodeikat and Pohlmeyer, 2002). Practically, culling might not lead to the eradication of the infection in the wild, but the opposite: by reducing host density, disease endemisation could be favoured. Furthermore, host density drop may favour selection of less virulent strain in wild boar, but equally dangerous in domestic pig. Less virulent strains may persist in more sparse population posing a more dangerous threat to pig farm.

The aim of this chapter is to evaluate if, and under which condition, depopulation by culling could select for lower virulent strains able to persist in more sparse host populations. I used the compartment model approach by performing a SI(R) (Susceptible-Infected-Recovered) model (Kermack and McKendrick, 1927) with two different infectious individual classes and taking into

account the competition effects between strains of different virulence. I also discussed the effect of host immunity on strain selection. I chose CSF as a reference disease because the etiologic agent responsible for the infection (classical swine fever virus) is an RNA virus with a mutation rate sufficiently high to generate genetic variability during the outbreaks (Stadejek et al., 1997; Greiser Wilke et al., 1998; Hofmann and Bossy, 1998; Vilcek and Belak, 1998).

2. THE MODEL

In this section, I introduce a two-strain epidemic model for a wildlife host population. I build the epidemic model through different level of complexity (Scott and Smith, 1994) by starting with the description of the disease-free host dynamics and, subsequently, by introducing the one- and two-strain disease dynamics.

2.1. Host dynamics without disease

Lets $S(t)$ the susceptible host density in the population. In the absence of infective agent, the population dynamics may be described as follows:

$$\dot{S} = G(S)S \qquad (1)$$

where $\dot{S}$ is the rate of change of S with respect to time; $G(S)$, the growth rate, a monotonically decreasing function of S, with $G(0) > 0$ and $G(K) = 0$ (where K is the carrying capacity of the host). As a consequence, equation (1) has two different equilibria (corresponding to $\dot{S} = 0$) for $S = 0$ and $S = K$. These results are true for a large range of $G(S)$ functions; however, without losing generality, I assume that host population grows with logistic dynamics as follows (Verhulst, 1838):

$$G(S) = r\left(1 - \frac{S}{K}\right) \qquad (2)$$

where r [time^{-1}] is the intrinsic growth rate (i.e., the growth rate at low population density).

2.2. One-strain epidemic model

Looking from an epidemiological point of view, in the case of a single infective agent (e.g., strain 1), the host community can be subdivided at any time (t) into two compartments with respect to the circulating strain: susceptible individuals $S(t)$ (i.e., those which do not already experience the infection) and infected individuals $I_1(t)$ (i.e., those who are infected by the strain 1). The host-parasite dynamics may be described as follows:

$$\dot{S} = G(S)S - \beta_1 S I_1 \qquad (3a)$$

$$\dot{I}_1 = \beta_1 S I_1 - (\alpha_1 + \mu) I_1 \qquad (3b)$$

Following conventional lines (Kermack and McKendrick, 1927), I assume that the rate at which hosts acquire infection is proportional to the number of encounters between susceptible and infected individuals: $\beta_1 S I_1$; where β_1 [time^{-1} #infected host^{-1}] represents the transmission coefficient, with

β_1^{-1} proportional to the average time interval between host contacts; μ [time^{-1}] represents the natural mortality rate of a disease-free host, and its inverse (μ^{-1}) can be easily calibrated as the average lifetime of the host species. Finally, α_1 [time^{-1}] represents the increasing in mortality rate due to the infection (usually called disease-induced mortality or virulence). Therefore, $(\alpha_1 + \mu)^{-1}$ represents the average lifetime of a host infected by the strain 1. It is possible to prove that the strain 1 infective agent can spread in the population if and only if:

$$R_0 = \frac{\beta_1 K}{\alpha_1 + \mu} > 1 \qquad (4)$$

where R_0 is the basic reproduction number, i.e., the average number of secondary infections by a primary infection in a totally susceptible population at its carrying capacity K (Anderson and May, 1979). Alternatively, I can state that the disease can persist in the host population if and only if the carrying capacity of the host population is set above a fixed threshold,

$$K > K_{T1} = \frac{\alpha_1 + \mu}{\beta_1} \qquad (5)$$

that is, the strain 1 infective agent can spread in the population if and only if the host density (K) is larger than the threshold level K_{T1} (which can be termed *critical community size* (Bartlett, 1957)). This means that, under the threshold level described in (5), the host population is too sparse and there are too few contacts among individuals to sustain the infection. Equation (5) shows that, for the value of the transmission coefficient (β_1), the lower the disease-induced mortality (α_1), the more difficult it is to achieve the disease eradication. As a consequence, it is more difficult to eradicate a low virulent strain than a high virulent one. Indeed, a low virulent strain can persist in more sparse population since larger life expectancy for infected hosts allows more possibility for contacts between individuals.

If $R_0 > 1$, after a transient period, susceptible and infected hosts reach a stable equilibrium:

$$S^* = \frac{\alpha_1 + \mu}{\beta_1} = K_{T1} \qquad (6a)$$

$$I_1^* = \frac{G(S^*)}{\beta_1} \qquad (6b)$$

equations in (6) are usually defined as endemic equilibrium.

2.3. Disease control through culling for one circulating strain

By using the threshold criteria defined above, I introduce the analysis of the disease control policy effectiveness based on culling, i.e. the selective removal of animals from the population. The core issue of culling strategy is to push host population density below the threshold for disease invasion through the removal of a sufficient number of specimens (Grenfell and Dobson, 1995).

Lets c the culling rate, which represents the eradication effort. This formulation assumes that the animals culled each year are a constant fraction of the population, rather than a fixed quota. Then, model (3) with the add of disease control through culling takes the form:

$$\dot{S} = G(S)S - (\beta_1 S I_1 + cS) \qquad (7a)$$

$$\dot{I}_1 = \beta_1 S I_1 - (\alpha_1 + \mu + c) I_1 \qquad (7b)$$

I assume that all classes are subject to culling. If the assessment of the clinical state of animals on the field was possible, it would implement more selective forms of culling. In practice, this is not possible in wild populations and the culling equally affects all the epidemiological classes.

For sufficiently large culling rate values, the disease cannot persist in the population. The most precautionary policy implies the totally prevention of the disease spread. It is possible to prove that for a sufficiently large effort, the number of infected always decreases. Mathematically:

$$c > c^* = (\alpha_1 + \mu)(R_0 - 1) \qquad (8)$$

where R_0 is defined as in (4).

If host population growth follows logistic dynamics (2), the threshold value of culling rate for disease eradication will be:

$$c > c_e = \frac{r}{r + \beta_1 K}(\alpha_1 + \mu)(R_0 - 1) = \frac{r}{r + \beta_1 K} c^* \qquad (9)$$

Equation (9) shows that c_e is always smaller than c^*. It follows that, by applying culling efforts between values c_e and c^* ($c^* > c > c_e$), the infection initially spreads in the population and producing an epidemic peak will subsequently not be able to persist and becomes extinct.

2.4. One-host and two-strain epidemic model with culling

If two infective agents co-circulate in the population, the host-pathogen system can be described with a three compartmental model with a susceptible class $S(t)$, i.e. healthy individuals that can be infected by both strains, and two infected classes $I_1(t)$ and $I_2(t)$, i.e. individuals infected by strain 1 (with low virulence) and strain 2 (with high virulence), respectively. Thus the model takes the form:

$$\dot{S} = G(S)S - (\beta_1 SI_1 + \beta_2 SI_2 + cS) \quad (10a)$$

$$\dot{I}_1 = \beta_1 SI_1 - (\alpha_1 + \mu + c)I_1 - \beta_{12} I_1 I_2 \quad (10b)$$

$$\dot{I}_2 = \beta_2 SI_2 - (\alpha_2 + \mu + c)I_2 + \beta_{12} I_1 I_2 \quad (10c)$$

where $G(S)$, μ and c are as indicated in (3); α_1 and α_2 are respectively the strain 1 and strain 2 disease-induced mortality rates (with $\alpha_2 >> \alpha_1$); β_1 (β_2) is the strain 1 (strain 2) transmission coefficient from strain 1 (strain 2) infected to susceptible individual; β_{12} is the super-infection transmission coefficient denoting the rate of transmission from $I_2(t)$ to $I_1(t)$. Hosts can leave the susceptible compartment (S) for three reasons: *i*) to die independently from infection, *ii*) to contact strain 1 infected and moving in class I_1, *iii*) to contact strain 2 infected and moving in class I_2. I assume that individuals infected by the strain 1 (I_1) which come into contact with individuals infected by the second strain (I_2) become re-infected with the strain 2. This process is referred to as *super-infection*. The biological assumption justifying super-infection processes is that more virulent pathogens reproduce themselves faster within the host than the less virulent ones. Then, when an individual already harbouring the strain 1 is infected by the strain 2, it is assumed that the more virulent strain will out-compete the less virulent strain within the infected host (Nowak and May, 1994). The super-infection process as in (10b,c) describes the limit case of within-host competition between strains, without taking into account cases of coinfection (i.e., the contemporary infection from different pathogens in the same host), where both strains coexist in the host. Preliminary analyses showed that model behaviours (presented in the next sections) do not qualitatively change introducing coinfection processes in (10). Therefore, in order to minimize model complexity, I present results related to the model without coinfection.

2.5. Further assumptions

In this section I specify some hypotheses on model (10) parameters. First, strain 2 virulence is larger than strain 1; this difference is translated mathematically through inequality:

$$\alpha_2 >> \alpha_1 \quad (11)$$

Therefore, strain 2 disease-induced mortality is larger than strain 1; with individuals in class I_2 exhibiting a shorter life expectancy than individuals in class I_1.

Second, transmission coefficient values do not need strict assumptions: in epidemic modelling it is usually assumed that β_2 is equal or larger than β_1, since larger virulence implies faster replication rate inside the host and therefore larger transmission probability (Nowak and May, 1994). Be that as

it may, I assumed that the strain 1 basic reproduction number (R_{01}) is larger than that of the strain 2 (R_{02}), that is:

$$R_{01} = \frac{\beta_1 K}{\alpha_1 + \mu} > \frac{\beta_2 K}{\alpha_2 + \mu} = R_{02} > 1 \qquad (12)$$

This implies that, by considering the two strain infections separately, the eradication threshold for the strain 1 (K_{T1}) is lower than the strain 2 threshold (K_{T2}). In other words, strain 1 eradication is more difficult than the eradication of the strain 2.

In the next section I analyse model (10) behaviours as a function of the super-infection transmission coefficient (β_{12}) and of the culling effort (c). I present the analysis in two different step. First, I discuss the conditions for the two strains coexistence and exclusion in the absence of control. Second, I use the case of classical swine fever in wild boar to analyse the effects of the control through culling on strain competition.

3. RESULTS: Coexistence or competitive exclusion?

In the absence of control, I may distinguish two sub-cases. In the absence ($\beta_{12} = 0$) and in the presence of super-infection ($\beta_{12} > 0$). In the first case it is possible to prove that the strain with faster reproduction (i.e., larger basic reproduction number R_0) spreads in the population out-competing that with a slower rate. For model (10), since $R_{01} > R_{02}$, the less virulent strain (strain 1) out-competes the more virulent one (strain 2), that becomes extinct in the population. In other words, strain 1 has a competitive advantage compared to strain 2 because of its ability to persist in populations with lower density ($K_{T1} < K_{T2}$). Individuals infected by strain 1 have higher life expectancy than strain 2 infected. They circulate in the population for more time infecting on average more susceptible individuals. In the absence of super-infection, the competition selects strains with low virulence, because high virulent strains kill their host too fast to be competitive.

In the second sub-case, presence of super-infection ($\beta_{12} > 0$), the model (10) behaviour depends upon the value of super-infection transmission (β_{12}). I define:

$$\Delta K_T = K_{T2} - K_{T1}$$

Since infected densities defined as in (6) are:

$$I_1^* = \frac{G(K_{T1})}{\beta_1} \quad \text{e} \quad I_2^* = \frac{G(K_{T2})}{\beta_2}$$

It is possible to distinguish three different competition outcomes as a function of the super-infection transmission coefficient (β_{12}): if

$$0 < \beta_{12} < \frac{\beta_2 \Delta K_T}{I_1^*} \qquad (13a)$$

the strain 1 out-competes strain 2; if

$$\frac{\beta_2 \Delta K_T}{I_1^*} < \beta_{12} < \frac{\beta_1 \Delta K_T}{I_2^*} \qquad (13b)$$

both strains coexist in the population; if

$$\beta_{12} > \frac{\beta_1 \Delta K_T}{I_2^*} \qquad (13c)$$

the strain 2 out-competes strain 1.

Therefore, two strains with different virulence may coexist in the population if and only if: *i*) super-infection mechanisms play out; *ii*) the super-infection transmission is sufficiently large (see (13)). Furthermore, it is possible to proof that larger carrying capacities (K) favour strain coexistence. As a consequence, high host densities favour the persistence of large virulent strains, unable to persist at low population densities.

3.1. The case of classical swine fever

In this section I analyse how disease control policies through culling affect the competition processes between strains. I use the classical swine fever in a wild boar population located in North-Eastern Sardinia (Italy) as a reference disease (Guberti et al., 1996; Guberti et al., 1998). Parameter values used in the numerical simulations as shown in Table 1. The disease-free wild boar population density is 600 individuals in an area of 220 km^2, that corresponds to 2.73 individuals/km^2. The intrinsic birth rate at low density is 0.7 [years^{-1}]. The mortality rate for disease-free individuals is 0.2 [years^{-1}] which corresponds to a life expectancy of 5 years. Regarding the epidemiological parameters, I assumed the life expectancy for host infected by strain 1 is 70 days, then α_1 = 1/70 [days^{-1}] = 5 [years^{-1}]; and the life expectancy for host infected by strain 2 is 24 days, then α_2 = 1/24 [days^{-1}] = 15 [years^{-1}]. I set the transmission coefficients in Table 1 to obtain basic reproduction numbers consistent with Guberti et al. (1998) results, that is R_{01} = 4.6 and R_{02} = 2.37.

Unfortunately, direct or indirect estimates of super-infection transmission are not available for the classical swine fever. To show a possible counter-intuitive deleterious effect of culling I analysed

model (10) in the case of large β_{12} values (as in 13c). I assume β_{12} is equal to 0.84, which implies that the more virulent strain (strain 2) out-competes the less virulent one in the absence of culling.
I computed the asymptotic behaviours of model (10) variables as a function of the culling effort c (which corresponds to the annual population fraction harvested). The model behaviours were analysed through bifurcation analysis using numerical continuation methods implemented in the specialized software LOCBIF (Khibnik et al., 1993) and CONTENT (Kuznetsov, 1998).

Parameter	**Symbol**	**Value**	**Measure unit**
Intrinsic growth rate	r	0.7	year^{-1}
Natural mortality rate	μ	0.2	year^{-1}
Carrying capacity	K	600	#individuals/220 km^2
low virulent strain disease-induced mortality	α_1	5	year^{-1}
high virulent strain disease-induced mortality	α_2	15	year^{-1}
low virulent strain transmission rate	β_1	0.04	#strain 1 infected/ Year^{-1}
high virulent strain transmission rate	β_2	0.06	#strain 2 infected/ Year^{-1}
super-infection transmission rate	β_{12}	0.84	#strain 2 infected/ Year^{-1}

Tab. 1: Parameters values as estimated by Guberti et al. (1996) and Guberti et al. (1998) for classical swine fever in wild boar in Sardinia (Italy).

In Fig. 1 I show the disease prevalence in the host population as a function of the fraction of the animals removed annually. When only strain 2 circulates in the population, the disease prevalence at the equilibrium in the absence of culling is about 2.6%. Increasing culling effort, prevalence decreases monotonically until the disease eradication, which is obtained by culling more than 32% of the population annually; then the critical community size is 1.15 individuals/km^2 (see light gray dashed curve in Fig. 1). When only strain 1 circulates in the population, the disease prevalence at the equilibrium in the absence of culling is higher than case of larger virulence, about 9.5%. The complete disease eradication needs larger culling effort (about 41% of individuals removed annually) and the critical community size is 0.59 individuals/km^2, which is 50% lower than the previous case (see dark gray dashed curve in Fig. 1). When both strains circulate at the same time in the host population, model (10) shows more complex behaviours, as described in Fig. 1. In the absence of culling effort the more virulent strain (strain 2) out-competes the less virulent one and establishes itself in the population (see dark grey solid curve in Fig. 1). Increasing culling effort, strain 2 prevalence decreases as seen in the single strain case until the fraction of individuals

removed reaches c. 5% of the total population. Above this threshold the decrease of host density due to culling favours the less virulent strain persistence and the two strains coexist in the population (grey region in Fig. 1). In the grey region, the strain 1 prevalence increases with the culling effort, while strain 2 prevalence drops faster than in the single strain scenario. When the fraction of removed individuals exceeds 17-18% the less virulent strain (strain 1) out-competes the more virulent one and establishes itself in the population. Further increases in culling effort cause decrease in strain 1 prevalence until complete disease eradication at 42% of removed individuals.

I notice that, for intermediate value of culling, the total disease prevalence in the population increases with the effort (see thin black curve in Fig. 1), as opposed to the single strain cases.

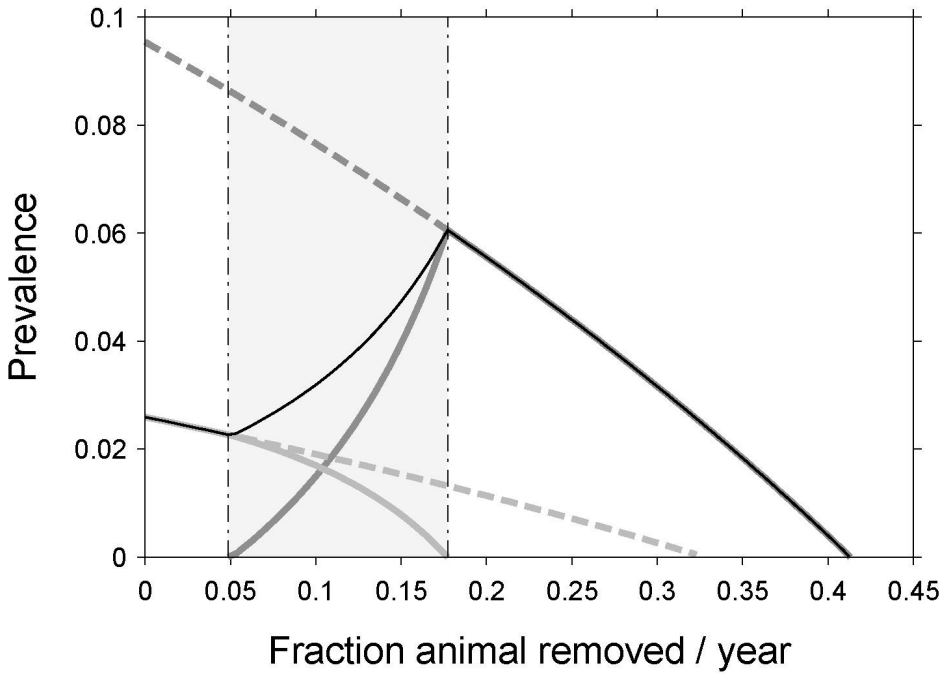

Fig. 1: Prevalence of the less virulent strain I_1 (dark grey curve), more virulent strain I_2 (light grey curve), and total prevalence (black thin curve) at the equilibrium point of model (10) as function of the fraction animal removed annually. Solid lines represent the equilibria in the two-strains model, while dashed lines represent the equilibria in the one-strain model. Parameter values as in Tab. 1.

The increase of prevalence as a function of culling effort may have a dramatic effect in management policies. Indeed, the contemporary presence of super-infection mechanisms and culling policies may modify the result of the strain competition affecting the total prevalence of the disease. As shown in Fig. 1, removing efforts powerful enough for the eradication of the strain 2 from the population (about 30% of individual removed) favour condition to the strain 1 spread and persistence, with the consequence of an increase of disease prevalence. Then, this policy not only proves to be ineffective (because can not eradicate the disease), but also counter-productive for disease control.

3.2. The effect of immunity

In previous paragraphs I analysed the outcomes of strain competition due to culling control by using the most simple SI multi-strain model to highlight the key mechanisms promoting strain selection. In this paragraph I discuss the consequences on strain selection of host acquired immunity. I introduce a new compartment in model (10) to describe individuals who recover after the infection (*R* class). Then, the strain competition model with immunity takes the form:

$$\dot{S} = G(S)S - (\beta_1 SI_1 + \beta_2 SI_2 + cS) \quad (14a)$$

$$\dot{I}_1 = \beta_1 SI_1 - (\alpha_1 + \mu + \delta + c)I_1 - \beta_{12} I_1 I_2 \quad (14b)$$

$$\dot{I}_2 = \beta_2 SI_2 - (\alpha_2 + \mu + \delta + c)I_2 + \beta_{12} I_1 I_2 \quad (14c)$$

$$\dot{R} = \delta I_1 + \delta I_2 - (\mu + c)R \quad (14c)$$

where δ [time^{-1}] is the recovery rate of the infected individuals under the assumption that both strains have the same recovery rate.

I summarize the results obtained by model (14) in Fig. 2 by showing the bifurcation diagram of model (14) in the space of fraction animal removed annually and recovery rate parameters. In the absence of culling (vertical axis) the more virulent strain (I_2) persists for any values of recovery rate lower than δ_4 (i.e., $R_0 > 1$), while the less virulent one (I_1) persists only for intermediate values of recovery rate ($\delta_2 < \delta < \delta_3$), unable to exclude the other strain by the competition. Along the horizontal axis ($\delta = 0$) it is possible to identify the bifurcation sequence of the without-immunity model (10): more virulent strain persistence for low culling efforts (I_2 region), strain coexistence for intermediate culling efforts (Coex region), less virulent strain persistence for high culling efforts (I_1 region), and disease extinction (Disease-free region) for culling effort larger than c_e (see (9)). Increasing the recovery rate it is possible to obtain complete disease extinction for lower value of culling effort, and Fig. 2 shows that the extinction threshold is a linear function of δ (black curve). On the contrary, strain competition in grey regions (where disease persists) shows more complex behaviours as a function of the recovery rate. For low values of δ ($< \delta_1$), both strain exclusion and strain coexistence are feasible for different level of culling, as in the case of absence of immunity. For $\delta_1 < \delta < \delta_2$, the more virulent strain (I_2) cannot out-compete the less virulent strain for any level of culling; then, strain coexistence and less virulent strain persistence (I_1) are the only two feasible competition outputs. For $\delta_2 < \delta < \delta_3$, both strain exclusion and strain coexistence are feasible, while for $\delta_3 < \delta < \delta_4$ only the more virulent strain can persist in the population.

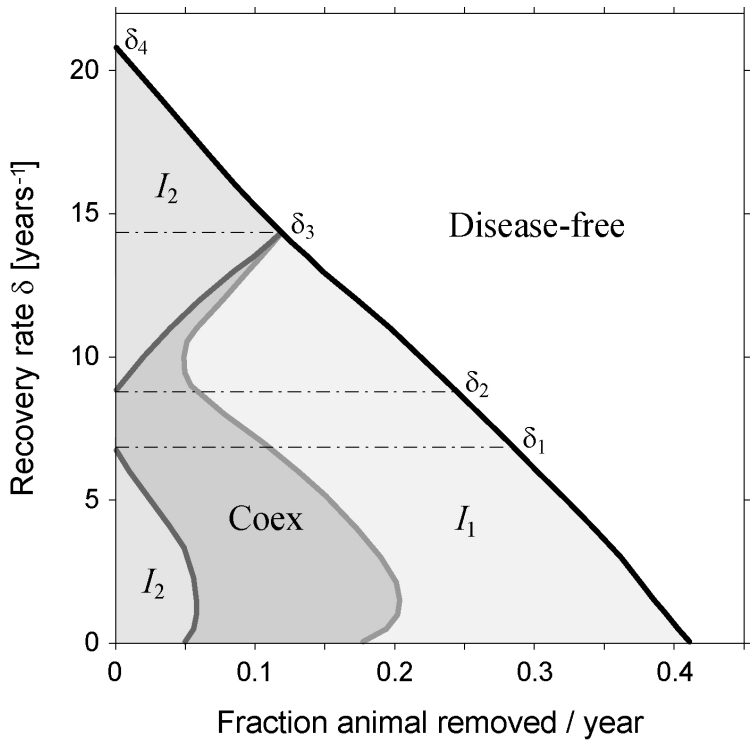

Fig. 2: Bifurcation diagram of the SIR model (14) in the parameter space of fraction animal removed annually and recovery rate. In parameter region 'Disease-free' infection can not persists in the population; in region I_1 (I_2) only the less (more) virulent strain persists; in region 'Coex' both strain coexist. See the main text for further details. Other parameter values as in Tab. 1.

As shown by model (14) analysis, disease immunity may affect strain selection. Furthermore, change in recovery rate does not have univocal effects on strain competition, favouring alternatively low and high virulence strain persistence, in terms of initial recovery rate value and culling pressure.

4. DISCUSSION AND CONCLUSIONS

The results here presented suggest that depopulation through culling may theoretically favour the selection of less virulent strains in wildlife diseases. This implies a decrease in the critical community size threshold for disease extinction (K_T) and, consequently, an increase in the culling effort for disease eradication. Furthermore, culling policies providing intermediate level of animal removal may produce an increase in the total prevalence of the disease in a population, with opposite results than expected. Thus, culling effort for complete disease eradication may be unfeasible due to large implementation costs or because of the risk for host population persistence.

The results obtained with model (10) suggest that disease control through host removal may affect virulence selection only in the presence of super-infection. Therefore, in the case of classical swine fever, it will be necessary to verify through laboratory and field tests if during the epidemic: *i*) genetically and antigenically different strains coexist, as shown by Stadejeck et al. (1997) for epidemics in Estonia, Poland, Hungary, and Slovakia in the 1990s and Hoffmann and Bossy (1998) for 1993 epidemic in Switzerland; *ii*) host immunological response varies in different strains, suggesting different virulence, as shown by Kosmidou et al. (1998). Then, if both conditions are satisfied, it is possible that, by manipulating host density through culling, less virulent strains will be selected with management consequences as highlighted above. Similarly, Iannelli et al. (2005) showed that control of human disease through vaccination may lead to the establishment of less virulent strains in the presence of super-infection.

In the presence of co-infection or super-infection optimal policies do not exist *a priori*. As suggested by model (10) analysis, if large levels of culling are not possible, disease control may cause larger infection than the do-nothing policy. The analysis of model (10) transients shows large oscillations in the number of infected, thus large epidemic peaks alternate with long inter-epidemic periods characterized by very low level of infection. Therefore, it is possible that, during the inter-epidemic periods, infection might be extinct due to environmental noise (stochastic fade-out, see de Castro and Bolker, 2005). Preliminary results obtained through the stochastic version of model (10) confirm this expectation. On the contrary, an insufficient depopulation does not provide disease eradication, and may cause dumping in epidemic oscillation favouring disease endemisation. I analysed the effects of host acquired immunity on strain selection. My investigations showed that disease immunity may dramatically affect strain selection and that variation in recovery rate does not have univocal effects on strain competition. Then, combining control policies of culling and animal treatment or vaccination (that increase host resistance) may cause the selection of unpredictable values of disease virulence.

CHAPTER 4 REFERENCES

Anderson R.M., Jackson H.C., May R.M. and Smith A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-771

Anderson R.M. and May R.M. (1979) Population biology of infectious diseases: Part I, *Nature* **280**:361-367

Anderson R.M. and May R.M. (1991) *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford.

Arien K.K., Vanham G. and Arts E.J. (2007) Is HIV-1 evolving to a less virulent form in humans?, *Nature Reviews Microbiology* **5**:141-151

Aubert M., Picard M., Fouquet E., Conde J., Cruciere C., Ferry R., Albina E., Barrat J. and Vedeau F. (1994) Classical swine fever in wild boar, *Annales de Medicine Veterinaire* **138**:239-247

Bartlett M.S. (1957) Measles periodicity and community size, *Journal of the Royal Statistical Society A* **120**:48-70

Björkman A. and Phillips-Howard P.A. (1990) The epidemiology of drug resistance malaria, *Transactions of the Royal Society of Tropical Medicine and Hygiene* **84**:177-180

Daszak P., Cunningham A.A. and Hyatt A.D. (2000) Emerging infectious diseases of wildlife - threats to biodiversity and human health, *Science* **287**:443-449

de Castro F. and Bolker B. (2005) Mechanisms of disease induced extinction, *Ecology Letters* **8**:117-126

De Vos C.J., Saatkamp H.W. and Huirne R.B.M. (2005) Cost-effectiveness of measures to prevent classical swinw fever introduction into The Netherlands, *Preventive Veterinary Medicine* **70**:235-256

Edwards S., Fukusho A., Lefèvre P.-C., Lipowski A., Pejsak Z., Roehe P. and Wastergaard J. (2000) Classical swinw fever: the global situation, *Veterinary Microbiology* **73**:103-119

Fenner F. (1994) Myxomatosis. In: *Parasitic and Infectious Diseases: Epidemiology and Ecology* (eds. Scott ME and Smith G), pp. 337-346. Academic Press, London

Fenner F. and Ratcliff F.N. (1965) *Myxomatosis*. Cambridge University Press, Cambridge.

Gandon S., Mackinnon M.J., Nee S. and Read A.F. (2001) Imperfect vaccines and the evolution of pathogen virulence, *Nature* **414**:751-756

Gibbons A. (1993) Where are "new" diseases born? *Science* **261**:6

Greiser Wilke I., Depner K., Fritzemeier J., Haas L. and Moenning V. (1998) Application of a computer program for genetic typing of classical swine fever virus isolates from Germany, *Journal of Virology* **75**:141-150

Grenfell B.T. and Dobson A.P. (1995) *Ecology of Infectious Diseases in Natural Populations*. Cambridge University Press, Cambridge.

Guberti V. (1991) Fauna e patologie a denuncia obbligatoria: il caso della peste Suina Classica nel cinghiale in Toscana. *Supplemento alle Ricerche di Biologia e della Selvaggina*, XIX, 393-403

Guberti V., Cossu P., Bozzi F., Cabras P., Ruiu A., Pirino A., Mereu G., Bassu M. and Firinu A. (1996) Aspetti demografici della popolazione di cinghiale nella provincia di Nuoro: effetti del modello di gestione. In: *I Convegno programmi di ricerca finalizzati degli Istituti Zooprofilattici Sperimentali* (ed. concressi I), p. 87

Guberti V., Rutili D., Ferrari G., Patta C. and Oggiano A. (1998) Estimate of the threshold abundance for the persistence of the classical swine fever in the wild boar population of eastern Sardinia, Italy. In: *Measure to control classical swine fever in European Wild Boar*, pp. 54-61. European Union, Perugia, Italy

Hofmann M. and Bossy S. (1998) Molecular epidemiological analysis of classical swine fever virus isolates from the 1993 disease outbreaks in Switzerland, *Schweizer Archiv fur Tierheilkunde* **140**:365-370

Horst H.S., Huirne R.B.M. and Dijkhuizen A.A. (1997) Risks and economic consequences of introducing classical swine fever into the Netherlands by feeding swill to swine, *Revue Scientifique et Technique de l'Office International des Epizooties* **16**:207-214

Iannelli M., Martcheva M. and Li X.-Z. (2005) Strain replacement in an epidemic model with super-infection and perfect vaccination, *Mathematical Biosciences* **195**:23-46

Kermack W.O. and McKendrick A.G. (1927) A contribution to the mathematical theory of epidemics, *Proceedings of the Royal Society of London B* **115**:700-721

Khibnik A.I., Kuznetsov Y.A., Levitin V.V. and Nikolaev E.V. (1993) Continuation techniques and interactive software for bifurcation analysis of ODEs and iterated maps, *Physica D* **62**:360-371

Kosmidou A., Buttner R. and Meyers G. (1998) Isolation and characterization of cytopathogenic classical swine fever virus (CSFV), *Archives of Virology* **143**:1295-1309

Kuznetsov Y.A. (1998) CONTENT - Integrated environment for analysis of dynamical systems. In. Ecole Normale Superieure de Lyon

Laddomada A. (2000) Incidence and control of CSF in wild boar in Europe, *Veterinary Microbiology* **73**:121-130

Leroy E.M., Kumulungui B., Porrut X., Rouquet P., Hassanin A., Yaba P., Délicat A., Paweska J.T., Gonzalez J.-P. and Swanepoel R. (2005) Fruit bats as reserovoirs of Ebola virus, *Nature* **438**:575-576

Longini I.M., Nizam A., Xu S., Ungchusak K., Hanshaoworakul W., Cummings D.A.T. and Halloran M.E. (2005) Containing pandemic influenza at the source, *Science* **309**:1083-1087

Nowak M.A. and May R.M. (1994) Superinfection and the evolution of parasite virulence, *Proceedings of the Royal Society of London B* **255**:81-89

Read A.P. (1995) Genetics and Evolution of Infectious Diseases in Natural Populations Group Report. In: *Ecology of Infectious Diseases in Natural Populations* (eds. Grenfell BT and Dobson AP), pp. 450-477. Cambridge University Press, Cambridge

Reid S.D., Herbelin C.J., Bumbaugh A.C., Selander R.K. and Whittam T.S. (2000) Parallel evolution of virulence in pathogenic *Escherichia coli*, *Nature* **406**:64-67

Schrag S.J. and Wiener P. (1995) Emerging infectious disease: What are the relative roles of ecology and evolution? *Trends in Ecology and Evolution* **10**:319-324

Scott M.E. and Smith G. (1994) *Parasitic and Infectious Diseases: Epidemiology and Ecology*, Academic Press, New York.

Smith D.L., Levin S.A. and Laxminarayan R. (2005) Strategic interactions in multi-institutional epidemics of antibiotic resistance, *Proceedings of the National Academy of Sciences of United States of America* **102**:3153-3158

Sodeikat G. and Pohlmeyer K. (2002) Temporary home range modifications of wild boar family groups (*Sus scrofa L.*) caused by drive hunts in Lower Saxony (Germany), *Zeitschrift fur Jagdwissenschaft* **48**:161-166

Stadejek T., Vilcek S., Lowings J.P., Ballagi-Pordany A., Paton D.J. and Belak S. (1997) Genetic heterogeneity of classical swine fever virus in Central Europe, *Virus Research* **52**:195-204

Szent-Iványky T. (1984) La peste porcine classique: nouvelles méthodes de prophylaxie et d'éradication, *Revue Scientifique et Technique de l'Office International des Epizooties*, **3**:487-505

Verhulst P.F. (1838) Notice sur la loi que la population suit dans son accroissement, *Correspondence Mathématique et Physique* **10**:103-121

Vilcek S. and Belak S. (1998) Classical swine fever virus: Discrimination between vaccine strains and European field viruses by restriction endonuclease cleavage of PCR amplicons, *Acta Veterinaria Scandinavica* **39**:395-400

Wilson M.E., Levins R. and Spielman A. (1994) *Diseases in Evolution: Global Changes and Emergence of Infectious Diseases*, New York Academy of Science, New York.

5

A cost analysis of alternative culling strategies for the eradication of classical swine fever in wildlife

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ABSTRACT

In the epidemiological literature, the eradication of a wildlife disease through culling is usually described in terms of a constant hunting rate to simulate the selective removal of animals from the population. By using simple SI (Susceptible-Infected) models it is easy to prove that if the hunting rate is high enough the population eventually drops below a critical threshold level under which the pathogen is deemed to be extinct. However, hunting costs as well as the monetary benefits of disease control are almost systematically neglected. Moreover, the hunting rate is usually assumed to be constant over time, while in reality, health authorities can implement more flexible culling policies. In this chapter I examine a class of more realistic time-variant culling strategies in a cost-benefit framework. Culling strategies differ in the way decisions are made about when and how much to cull. That is, whether hunting occurs when disease prevalence, host population density or the number of carcasses exceeds (or is below) a given threshold. For each culling strategy, the optimal value of the control parameters and the hunting rate are those that minimize the sum of the culling costs and the sanitary costs associated with infection over a specific period of time. Classical swine fever (CSF) in wild boar populations has been taken as a reference example because of its potential economic impact on industrialized and developing countries.

I show that the optimal time-flexible culling strategy is invariably more efficient than the best traditional strategy in which the hunting rate is held constant through time. I also show that the type of hunting strategy that is selected as optimal depends on the shape of the cost functions.

1 INTRODUCTION

Classical swine fever (CSF) is a highly infectious disease; outbreaks of it are responsible for severe losses in pig farming worldwide. While the incidence of CSF in Western Europe is decreasing, the disease is still endemic in many regions, such as South-East Asia, Eastern Europe, and Central and South America (Edwards et al., 2000). There is still debate on the relative efficacy of different strategies to control and prevent disease outbreaks. In the European Union, Mexico and Brazil, the preventive vaccination of susceptible animals on pig farms is prohibited. Measures for the control and eradication of CSF in domestic pigs usually include the pre-emptive slaughtering of an entire herd when an infected pig is detected and the establishment of protection and surveillance zones around pig-farms to prevent animal translocation outside the potentially contaminated area (Wilpshaar et al., 2002). The economic impact of these measures on the pig industry can be dramatic in industrialized countries (e.g., 11 million animals have been slaughtered in the Netherlands in 1997-98; 2 million in Germany, and more than 2 million in Spain, Belgium and Italy combined during the same period) and in developing ones (e.g., 414,000 animals have been slaughtered in Cuba from 1993 to 1997). As a consequence, pig farmers have asked for effective and comprehensive strategies to prevent disease outbreaks, rather than controlling them once they have occurred. In many countries, but especially in Russia and her former Eastern Block allies, the wild boar (*Sus scrofa*) is implicated as a reservoir of classical swine fever and as supporting disease transmission to domestic animals (Aubert et al., 1994). For this reason, a great deal of effort has been focused on the eradication of the disease in wildlife. The main disease control measure in wild boar relies on culling, that is the selective removal of animals by hunting, to draw population densities below the critical threshold for the eradication of the disease. In animal epidemiology, it is well known that when transmission is density-dependent – as in CSF – a suitable reduction in the contact rate between infected and susceptible animals forces the disease to fade out (Anderson et al., 1981). Vaccination policies have also been tested (e.g., see Kaden et al., 1997), and have been to slow the spatial diffusion of the virus, but have proved to be ineffective in achieving disease eradication. One potential reason is that younger animals are both more susceptible to CSF, since they have not yet developed an immune response, and are a difficult target for vaccination in the wild, because vaccine-bearing baits are usually picked up by older, more experienced (and less-susceptible) individuals. In practice, this prevents the vaccination of the younger, more susceptible age classes, and limits the effectiveness of vaccination.

Since population size, demographic vital rates, epidemiological parameters and rates of movement are hard to estimate through fieldwork, the disease dynamics may remain poorly understood (Artois et al., 2001). For all these reasons, the control of the disease in wildlife is definitely more

challenging than in the case of pig farms. Unfortunately, while the epidemiological aspects of infectious disease eradication in wildlife (Artois et al., 2001; Matthews et al., 2003; Karsten et al., 2005a,b) and the economic effectiveness of implemented agricultural policies (De Vos et al., 2005) have been the subject of some investigation, the economic costs and benefits associated with different eradication strategies in wildlife have scarcely been analysed.

The purpose of the present chapter is the evaluation of the effectiveness of a number of alternative culling policies on the basis of the costs associated with wild boar culling and with the transmission risk from wild boar to domestic pigs. More specifically, the aim is to assess whether and how time-variable culling policies can be more efficient than the best constant-culling policy.

The problem is approached within a conceptual framework in which the goal is to minimize the total costs by finding the best trade-off between culling cost and sanitary cost of CSF. While in principle the problem could be solved through optimal control techniques in order to derive unconstrained, very flexible, and detailed culling strategies, in practice, only simple policies based on a few control parameters can be implemented. The wildlife agencies that implement culling strategies are faced with logistical limitations and constrained by government regulations that prevent them from applying complex, adaptive eradication policies. Especially (but not exclusively) in developing countries disease control activities are further constrained by limited funding. As a consequence, I have analysed a broad range of culling policies defined by only a few control parameters and a number of variables observable in the field, such as wild boar density and the disease prevalence in the population. In this sense, I concentrated the investigation to a sub-optimal class of culling policies applied to a SI epidemic model developed by De Leo and Guberti (2003) to simulate the dynamics of CSF in wildlife. I illustrate the mathematical formulation of the cost functions associated with a CSF policy that only needs simple and easily retrievable or measurable data or information for implementation.

The chapter is organized as follows: after a brief description of the epidemic model of a wild boar population with culling activities, I analyse the performance of different time-variant culling policies selected from a fixed class of policies. Finally, I present the results of a sensitivity analysis and discuss the main results obtained with the model.

2 EPIDEMIOLOGICAL MODEL

In order to simulate the costs and monetary benefits of different culling strategies, the epidemiology of CSF has been simulated using a modified version of the model developed by De Leo and Guberti (2003). The model assumes a self-regulating wild boar population with a density-dependent birth rate: i.e., I describe a population, $N(t)$, with logistic growth in the absence of disease with intrinsic growth rate r and carrying capacity K (Verhulst, 1838).

$$\dot{N} = rN\left(1 - \frac{N}{K}\right) \qquad (1)$$

When the model includes epidemic dynamics, the wild boar population, $N(t)$, can be generally divided into different compartments: a susceptible class $S(t)$ – i.e., healthy individuals that can be infected by the disease – and an infected class $I(t)$ – i.e., sick individuals that can infect other individuals. Following conventional lines (Kermack and McKendrick, 1927), I assume that the rate at which wild boar acquire CSF is proportional to the number of encounters between susceptible and infected wild boar: βSI; where β is the transmission coefficient, with $1/\beta$ being proportional to the average time interval between wild boar contacts.

The causative disease agent, the CSF virus (CSFV), has a high degree of genetic variability and different strains of CSFV can co-circulate in a single host population (Stadejek et al., 1997; Pan et al., 2005). Usually, these strains are characterized by different epidemiological parameters, such as the degree of virulence and transmission, and they compete with each other to become established in the host population (Gennip et al., 2004; Kaden et al., 2004b). In this chapter, I describe the simplest competition model between strains: a two-strain epidemic model in which one strain can infect individuals already infected by the other (called a super-infection mechanism). Both of the two CSFV strains can infect susceptible individuals: the low virulent strain (strain 1) is characterized by a low disease-induced mortality rate, α_1, and the more virulent strain (strain 2) is characterized by a high disease-induced mortality rate, α_2. Accordingly, the wild boar population, $N(t)$, in model (1) is divided into three compartments: density of susceptible individuals, $S(t)$, density of individuals infected with strain 1, $I_1(t)$, and density of individuals infected with strain 2, $I_2(t)$. For a susceptible wild boar, the per-capita probability of getting a type-1 infection is proportional to the density of type-1 infected individuals, $I_1(t)$, through the transmission rate β_1; while, the probability of getting a type-2 infection is proportional to, $I_2(t)$, and β_2 transmission. β_{12} is the super-infection coefficient denoting the rate of transmission from $I_2(t)$ to $I_1(t)$. When an individual already harbouring the type-1 strain is infected by the type-2 strain, it is assumed that the more virulent strain out-competes the less virulent one within the infected host (Nowak and May, 1994).

The final model is given by:

$$\dot{S} = rS\left(1-\frac{N}{K}\right) - \beta_1 f(u) S I_1 - \beta_2 f(u) S I_2 - uS \qquad (2a)$$

$$\dot{I}_1 = \beta_1 f(u) S I_1 - (\alpha_1 + \mu + u) I_1 - \beta_{12} f(u) I_1 I_2 \qquad (2b)$$

$$\dot{I}_2 = \beta_2 f(u) S I_2 - (\alpha_2 + \mu + u) I_2 + \beta_{12} f(u) I_1 I_2 \qquad (2c)$$

where μ is the natural mortality rate, u the culling effort, N is the total population size ($N = S + I_1 + I_2$) and $f(u) = 1 + a\frac{u^2}{b+u^2}$, a function accounting for the increase in animal contact rate that occurs

Parameter	Symbol	Value	Measure unit
Intrinsic growth rate	r	0.5	year^{-1}
Natural mortality rate	μ	0.2	year^{-1}
Carrying capacity	K	600	#individuals/220 km^2
low virulent strain disease-induced mortality	α_1	5	year^{-1}
high virulent strain disease-induced mortality	α_2	15	year^{-1}
low virulent strain transmission rate	β_1	0.04	#strain 1 infected/ Year^{-1}
high virulent strain transmission rate	β_2	0.06	#strain 2 infected/ Year^{-1}
super-infection transmission rate	β_{12}	0.86	#strain 2 infected/ Year^{-1}

Tab. 1: Parameters values as estimated by Guberti et al. (1996) and Guberti et al. (1998).

during hunting when wild boar are driven from their natural home range (Sodeikat and Pohlmeyer, 2002). Function $f(u)$ mimics the type III functional response of a predator, where a is the maximum increase in transmission and b is the half-saturation constant (Hassell et al., 1977). In describing the home range increase due to hunting, I chose an S-shaped functional response (as type III) rather than the classical type II functional response because, at low hunting levels, wild boar groups may not leave their home range, while they leave it permanently if the hunting level is high (Maillard and Fournier, 1995) thus increasing the contact rate between infected and susceptible individuals. Demographic and epidemiological parameters, reported in Tab. 1, have been estimated by De Leo and Guberti (2003) with reference to the wild boar population of Sardinia (Italy) where CSF is endemic (Guberti et al., 1996; Guberti et al., 1998).

It follows that, when isolated, the culling rate for the eradication of the more virulent strain, calculated through model (2), is about $c = 0.28$ year^{-1} (that is, culling 28% of the host population in a year), while, for the eradication of the less virulent strain, c is about 0.38 year^{-1} (see Fig. 1 where I show the prevalence of the two different strains at the model equilibria as a function of the culling effort). As a consequence, it is more difficult to eradicate the less virulent strain than the more virulent one, since the less virulent strain can persist in a less dense population. The population density is a key control parameter when the two strains compete for the same host. De Leo and Guberti (2003) showed that if the population carrying capacity is sufficiently high and there is no hunting mortality, the more virulent strain out-competes the less virulent one and establishes itself in the host population (see strain 2 region in Fig. 1); yet, the small reduction in the population density caused by culling allows the less virulent strain to coexist with the more virulent one (see coexistence region in Fig. 1). By further increasing the culling effort, it is possible to eradicate the more virulent strain from the population without eradicating the less virulent strain, since the threshold density for eradication of the less virulent strain is substantially lower (see strain 1 region in Fig. 1). As a consequence, the culling effort required to completely eradicate the disease from the population (i.e., both strains) can be substantially larger than the culling effort estimated by assuming that only the more virulent strain is established in the infected population. Therefore, if the culling effort is not large enough for the complete eradication of the disease from the population, the effects of culling may be worse than the "do-nothing" alternative, as shown in Fig. 1. In fact, disease prevalence (as well as the number of infected individuals) under moderate culling can be larger than in the case of no-culling. On the other hand, very high culling efforts can be too expensive to be achieved.

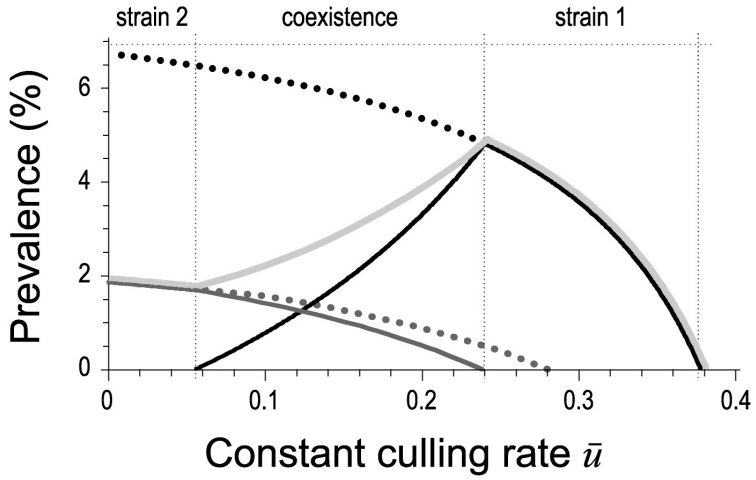

Fig. 1: Prevalence of the less virulent strain I_1 (black curve), more virulent strain I_2 (dark grey curve), and total prevalence (light grey curve) at the equilibrium point as function of the constant culling rate ($\bar{u}$). Solid lines represent the equilibria in the two-strains model, while dotted lines represent the equilibria in the one-strain model. The parameters of the function $f(u)$ have be fixed to: $a = 0.3$, and $b = 0.1$. Other parameter values as in Tab. 1.

THE COSTS OF CSF OUTBREAKS AND DISEASE ERADICATION

The transmission of CSFV from wild boar to domestic pigs may cause extensive damage to the pig industry worldwide, because in many countries, all the pigs on infected farms must be slaughtered and properly disposed of (usually burned) according to the legislations in force (see Edwards et al., 2000). Moreover, in order to reduce the risk of contamination and further economic losses to nearby farms, sanitary belts are enforced around the infected farms to prevent the movement of animals and equipment and pig trade outside the belts. (Meuwissen et al., 1999). These costs can be borne by the government to compensate for economic losses. On the other hand, depopulation of wild boar by hunting also comes at a cost, since a considerable effort in terms of the time and staff of wildlife agencies is required to cull wild boar as they become rare. Moreover, hygienic measures, such as the treatment of carcasses and the sanitary inspection of killed specimen, also increase the cost of hunting. As a result, the lower the threshold population density is for disease eradication, the higher are the culling costs.

Total costs are thus given by the sum of two factors. The first is simply the culling cost C_H and includes the cost of organizing and carrying out hunting activities, monitoring population densities, checking for disease prevalence, etc. The second comprises the damages associated with disease transmission to pig farms (from here on also referred to as sanitary costs, C_F) and includes costs for control measures (such as pig slaughtering and carcass disposal, movement restriction, supply and delivery problems and farms disinfection), missing revenues caused by the interruption of production activities, and the costs of farms repopulation (see Meuwissen et al., 1999 for a review). Generally, low culling rates imply low culling costs C_H and high sanitary costs C_F, while high culling rates imply high C_H and low C_F. As the probability of CSF spreading to pig farms increases with the number of the infected wild boar, I assumed the sanitary cost C_F is an increasing function of the total infected individuals' density, namely:

$$C_F(t) = c_F (I_1(t) + I_2(t))^{\gamma} \qquad (3)$$

where $c_F \geq 0$ is the unitary cost of an infection which takes into account the costs of control measures (see description above), the probability of transmission from wildlife to pig farms, density of pig farms and the average number of pigs per farm; $\gamma > 0$ is a shape coefficient which takes into account nonlinearities in the relationship between the level of infection and the sanitary costs. Consequently, $\gamma > 1$ ($\gamma < 1$) means that the sanitary costs increase more (less) than proportionally with the total number of infected wild boar.

The culling cost C_H is assumed to increase with culling effort ($u \geq 0$):

$$C_H(t) = c_H u(t)^{\theta} \qquad (4)$$

where $c_H \geq 0$ is the unitary cost of harvesting; $\theta > 0$ is a shape coefficient which takes into account nonlinearities in the costs of culling, $\theta > 1$ ($\theta < 1$) means that costs increase more (less) than proportionally with culling. Hence, the total cost over T years (time horizon) as a function of the culling effort, $u(t)$, can be computed as follows:

$$C_{tot}(u) = \int_0^T e^{-\delta t}(C_F + C_H)dt \qquad (5)$$

where $\delta \geq 0$ is the discount rate and C_F and C_H are computed as in (3) and (4), respectively.

2.1 The optimization problem

The aim of the present analysis is to assess: *i*) how control policies implementing time-variable culling rates perform with respect to traditional policy in which the culling effort is constant in time, and *ii*) how different assumptions about cost functions may affect the performance of alternative control policies?

Formally, the optimization problem can be stated as follows:

$$\min_{u(t)\geq 0} C_{tot}(u) \qquad (6)$$

where $u(t)$ is the culling policy that needs to be specified. In the following, I present the solution of the problem for a constant culling rate $u(t) = \bar{u}$; then, I solve the same problem when the culling rate changes over time. I analyse only a set of very simple time-variable policies based on the estimation of the host population density, the number of host carcasses, or disease prevalence. Detailed information on disease dynamics and population structure is usually relatively scarce and, most importantly, health authorities have, in general, limited organizational capacities; hence, they are only able to implement culling schemes based on simple rules. The unconstrained optimization problem provides solutions that would be seen as too complex to be implemented. I thus focus my analysis on a set of constrained culling strategies as described below.

2.1.1 Swiss Health Authority policy

The Swiss Health Authority of Canton Ticino devised a control strategy based on the following assumption (Hofmann et al., 1999): it is not convenient to implement high culling rates during the first disease epidemic phase, which is characterized by sharp increases in wild boar mortality (mainly caused by the disease), because it would not significantly influence the ratio between susceptible and infected individuals. In addition, it would increase the movement of CSF virus infected animals throughout their territory, increasing the contact rate among infected and

susceptible individuals. As a consequence, the policy implemented by the Swiss health authority of Canton Ticino can be described as follows:

- not to cull at the onset of the epidemics when disease dynamics is mainly affected by the pathogen induced mortality that eventually leads to a lower host population density;
- then, to cull at a constant rate at the end of the first epidemic wave.

Accordingly, I solved the optimization problem under the following constraints:

$$u(t) = \begin{cases} 0 & if\ t < t^* \\ u^* & if\ t \geq t^* \end{cases} \quad (7a)$$

where the optimal culling rate (u^*) and the time to start the hunting activity (t^*) need to be estimated so as to minimize $C_{tot}(u^*,t^*)$.

2.1.2 Immediate intervention policy

Notwithstanding the policy recommended by the Swiss Health Authority, it often happens that under the emotional wave of the first epidemic outbreak, the farmers' lobby calls for immediate intervention to reduce the risk of transmission from wildlife to domestic pigs. I simulate such a strategy by setting $u(t)$ as follows:

$$u(t) = \begin{cases} u^* & if\ t < t^* \\ 0 & if\ t \geq t^* \end{cases} \quad (7b)$$

where the optimal culling rate (u^*) and the time to stop the hunting activity (t^*) need to be estimated so as to minimize $C_{tot}(u^*,t^*)$.

2.1.3 Policy based on the observed prevalence of infection

In this case, culling intensity is determined on the basis of information related to the actual level of disease prevalence. Usually, during CSF epidemics, public health authorities carry out laboratory diagnoses on wild boar to detect the infection level in the population This information can be used to improve the disease control policy. However, high costs and organizational problems make it difficult to continuously monitor the disease prevalence in the population. I thus assumed the more realistic hypothesis that the census of population and the infected fraction of wild boar is carried out periodically by the public health authorities. Therefore, the culling rate has been assumed to remain constant within each census season (Ghezzi and Piccardi, 1997), as follows:

$$u(t) = u(k) \quad \forall t \in [k, k+\tau),\ k = 0, \tau, 2\tau, \ldots \quad (8)$$

where τ is the period between two censuses and $u(k)$ is a function of the disease prevalence. Under this assumption I analysed two control schemes. In the first case, wild boar are culled when disease prevalence exceed a fixed threshold, that is:

$$u(k) = \begin{cases} 0 & if \ \dfrac{I_1(k)+I_2(k)}{N(k)} < i_{th} \\ u^* & if \ \dfrac{I_1(k)+I_2(k)}{N(k)} \geq i_{th} \end{cases} \qquad (9a)$$

In the second case wild boar are removed only when disease prevalence is below a fixed threshold, that is:

$$u(k) = \begin{cases} u^* & if \ \dfrac{I_1(k)+I_2(k)}{N(k)} < i_{th} \\ 0 & if \ \dfrac{I_1(k)+I_2(k)}{N(k)} \geq i_{th} \end{cases} \qquad (9b)$$

where the optimal culling rate (u^*) and the prevalence threshold (i_{th}) in (9a) and (9b) are chosen to minimize $C_{tot}(u^*, i_{th})$.

2.1.4 Policy based on the observed population density

In this case, culling intensity is determined on the basis of information related to the actual population density of wild boar and the decision whether or not to cull is revised based on a periodic census of the population density (see (8)). Again, two simple eradication schemes have been analysed: to cull when population density exceeds a fixed threshold, that is:

$$u(k) = \begin{cases} 0 & if \ N(k) < N_{th} \\ u^* & if \ N(k) \geq N_{th} \end{cases} \qquad (10a)$$

or to cull when population density is below a fixed threshold, namely:

$$u(k) = \begin{cases} u^* & if \ N(k) < N_{th} \\ 0 & if \ N(k) \geq N_{th} \end{cases} \qquad (10b)$$

where the optimal culling rate (u^*) and the population threshold (N_{th}) in (10a) and (10b) need to be estimated so as to minimize $C_{tot}(u^*, N_{th})$.

2.1.5 Policies based on carcass counting

Usually, health officials and foresters count and remove potentially infected carcasses during CSF epidemics to reduce the risk of disease transmission to susceptible hosts. Hence, a control policy based on information about animal carcasses is certainly feasible. I have thus implemented two policies, one based on the total number of carcasses and the other on the fraction of infected carcasses. As for the disease prevalence in the population, the number of carcasses (or their prevalence) cannot be monitored in real-time because of practical reasons (as logistical and funding limitations). In order to provide realistic hypotheses, I assume that data are collected only during the census season and the culling effort is based on the acquired information. Accordingly, the number of carcasses accumulated during the *k-th* season can be computed as follows:

$$D(k) = \int_{k}^{k+\tau} \left(\mu N(t) + \alpha_1 I_1(t) + \alpha_2 I_2(t)\right) dt \qquad (11)$$

while

$$P_D(k) = \int_{k}^{k+\tau} \left(\alpha_1 I_1(t) + \alpha_2 I_2(t)\right) / \left(\mu N(t) + \alpha_1 I_1(t) + \alpha_2 I_2(t)\right) dt \qquad (12)$$

is the infected carcass prevalence during the *k-th* season.

As in previous control policies, I implement two alternative management schemes: only culling if the number of carcasses exceeds a fixed threshold:

$$u(k) = \begin{cases} 0 & if\ D(k) < D_{th} \\ u^* & if\ D(k) \geq D_{th} \end{cases} \qquad (13a)$$

or to cull only when the number of carcasses is below a fixed threshold:

$$u(k) = \begin{cases} u^* & if\ D(k) < D_{th} \\ 0 & if\ D(k) \geq D_{th} \end{cases} \qquad (13b)$$

where the optimal culling rate u^* and the number of carcasses D_{th} need to be estimated so as to minimize $C_{tot}(u^*, D_{th})$.

In the case where the prevalence of infected carcasses is used as a control parameter, the two management strategies are to only cull if the prevalence of infected carcasses exceeds a fixed threshold:

$$u(k) = \begin{cases} 0 & if\ P_D(k) < P_{D\,th} \\ u^* & if\ P_D(k) \geq P_{D\,th} \end{cases} \qquad (14a)$$

or to cull only when the carcass prevalence is below a fixed threshold:

$$u(k) = \begin{cases} u^* & if\ P_D(k) < P_{D\,th} \\ 0 & if\ P_D(k) \geq P_{D\,th} \end{cases} \qquad (14b)$$

where the optimal culling rate u^* and the carcasses prevalence P_{Dth} need to be estimated so as to minimize $C_{tot}(u^*, P_{Dth})$.

2.2 Further assumptions

Control policies have been evaluated over a 50 year period and with a discount rate $\delta = 4\%$ (see (5)). I chose a finite time horizon for my analysis since forecasts for a longer period would be of little significance due to uncertainties in epidemic processes resulting from factors such as long term demographic trends in wild boar populations not accounted for in the model or changes in future land uses. Moreover, recent advances in vaccine technology for CSF may eventually lead to different and more sophisticated control policies (Oirschot, 2003; Kaden et al., 2004a). A period of 50 years from the onset of the epidemics is long enough to encompass several epidemic waves and to account for the effects of strain competition. However, in section 4.1, I also discuss the sensitivity of optimal policy performance to changes in the length of the time horizon. I assumed that one individual infected with each strain is introduced into a healthy population at its carrying capacity (i.e., $S(0) = 600$, ($I_1(0) = 1$ and $I_2(0) = 1$) and that a census of the host population is carried out every 3 months.

Several published studies provide estimates of the economic costs and losses caused by classical swine fever epidemics in European pig farms (see Vanthemsche, 1995; Saatkamp et al., 1997; Meuwissen et al., 1999). However, little information is available about the probability of wildlife-domestic transmission, how transmission translates into potential damages to pig farm activities, especially in developing countries, and about the costs of hunting wild boar. In the absence of quantitative information, I simply assumed that the sanitary and culling costs have the same order of magnitude, i.e., that their contributions to the total costs are comparable. Furthermore, I used two different shapes for the cost functions in the optimization problem: the case in which sanitary and culling costs scale linearly with disease transmission to pig farms and harvesting rate (from here on referred to as the linear cost case, $\gamma = \theta = 1$ in eqs.(3) and (4)) and the case in which both scale quadratically ($\gamma = \theta = 2$ in eqs.(3) and (4)).

For each culling scheme, parameter values that allow the minimization of the overall costs have been estimated using the Matlab optimization toolbox (The MathWorks, Inc.).

RESULTS

The total cost, $C_{tot}(u)$, vs. constant culling effort for the linear and quadratic cost-scaling relationships are shown in Fig 2a and 2b, respectively. In both cases, the total costs function $C_{tot}(u)$ has two minima: the first one corresponds to the stability frontier between the presence of the more virulent strain alone and the coexistence behaviour (strain 2 - coexistence edge in Fig. 1), the second minimum corresponds to disease eradication (strain 1 edge in Fig. 1). As expected from the analysis carried out by De Leo and Guberti (2003), the total costs associated with classical swine fever in domestic pigs also show a local maximum for intermediate values of the culling rate. This is a consequence of concurrently increasing both the infected individuals and the culling effort up to $\bar{u} \cong 0.18$ y^{-1}.

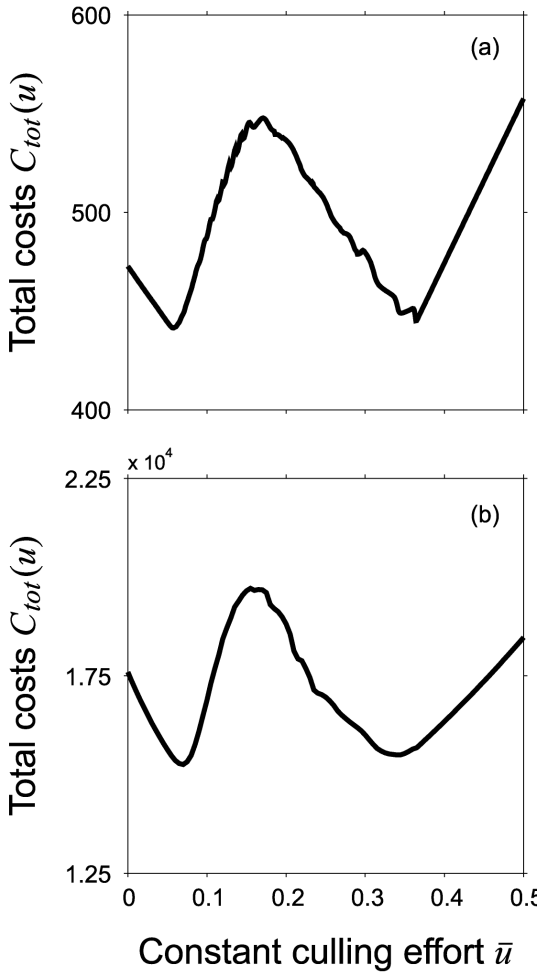

Fig. 2: The total costs C_{tot} (computed as in (5)) as a function of the constant culling rate ($\bar{u}$) when (a) sanitary and culling costs scale linearly with disease transmission to pig farms and harvesting ($\gamma = \theta = 1$ in eqs.(3) and (4)) and (b) the case in which both scale quadratically ($\gamma = \theta = 2$ in eqs.(3) and (4)). Cost functions parameters have be fixed to: $\delta = 0.04$, $c_F = 4$, $c_H = 40$ (in Fig. 2a), and $c_H = 1300$ (in Fig. 2b). Values of model parameter as in Fig. 1.

As reported in Tab. 2, all time-variable hunting policies investigated in the present chapter allow for a reduction of the overall costs relative to the optimal control policy in which hunting is held constant. Yet, in the case of time-variant culling strategies the choice of the optimal control rule clearly depends upon the shape of the cost functions (3) and (4). For instance, when the culling decision is based on the observed prevalence in the host population (section 3.1.3), the optimal strategy for the linear cost function ($\gamma = \theta = 1$), is to cull when disease prevalence in the population exceeds the threshold $i_{th} = 1.7\%$ (with c set to about 0.4 year^{-1}) as shown in Fig. 3a. On the other hand, if the cost function is quadratic ($\gamma = \theta = 2$), the optimal strategy is to cull with lower culling effort ($c \sim 0.1$ year^{-1}) only when the disease prevalence is below $i_{th} = 2\%$, as shown in Fig. 3b.

Therefore, not only does the optimal value of the culling effort change with the shape of the cost function, but also the type of culling strategy (i.e., (9a) vs. (9b)). Furthermore, I notice that in the case of control policy (9a) the density of infected

individuals during the first inter-epidemic period is remarkably smaller than in the case of control policy (9b), thus increasing the probability of stochastic fade-out of the pathogen (i.e., the parasite stochastic extinction caused by environmental noise; de Castro and Bolker, 2005).

Culling Policy	Linear cost function ($\gamma = \theta = 1$)			Quadratic cost function ($\gamma = \theta = 2$)		
		Optimal value of control variables	ΔC_{tot}		Optimal value of control variables	ΔC_{tot}
Swiss Health Authority policy	(7a)	$u^* = 0.4$ $t^* > 5.45$	-1.4%	(7a)	$u^* = 0.28$ $t^* > 4.27$	-3.1%
Immediate intervention policy	(7b)	$u^* = 1.09$ $t^* < 0.53$	-0.6%	(7b)	$u^* = 3.37$ $t^* < 0.17$	-68.5%
With information on prevalence	(9a)	$u^* = 0.41$ $i_{th} > 0.017$	-7.7%	(9b)	$u^* = 0.095$ $i_{th} < 0.02$	-1.1%
With information on population density	(10a)	$u^* = 0.4$ $N_{th} > 331$	-1.3%	(10a)	$u^* = 1.32$ $N_{th} > 355$	-38.8%
With information on number of carcasses	(13a)	$u^* = 0.39$ $D_{th} > 8.13$	-7.5%	(13b)	$u^* = 0.34$ $D_{th} < 5.05$	-11.9%
With information on infected carcasses	(14a)	$u^* = 0.32$ $P_{Dth} > 0.02$	-6.5%	(14b)	$u^* = 0.17$ $P_{Dth} < 0.068$	-17.4%

Tab. 2: Summary of the control policies performances. ΔC_{tot} represents the relative change in total costs with respect to the optimal time-invariant policy. Numbers in square brackets refer to the function defining the culling schemes.

I found similar results when the culling strategy is based on the number of carcasses discovered or the prevalence of CSF among dead individuals (as in section 3.1.5). The optimal policy for the linear cost function is to only cull when the number of carcasses or the disease prevalence in carcasses exceeds the fixed threshold. While in the case of a quadratic cost function culling occurs when the number of carcasses or the disease prevalence in carcasses is below the threshold.

Interestingly, when the decision whether or not to cull is taken on the basis of population density (as in section 3.1.4), the assumption about the shape of the cost functions does not affect the type of optimal control policy to be implemented. In both cases, the best strategy is to cull when the population density exceeds a fixed threshold (eq.(10a)). Yet, the optimal level of culling effort is remarkably different in the two cases, that is $c \sim 0.4$ y^{-1} for $\gamma = \theta = 1$ and $c \sim 1.5$ y^{-1} for $\gamma = \theta = 2$. The optimal culling strategies based on host population density are reported in Fig. 4.

2.3 Sensitivity analysis

A sensitivity analysis has been performed with regards to the cost parameters c_F and c_H, as these are among the most difficult to estimate. Specifically, I investigated how the optimal solutions change as a consequence of substantial variations in c_F and/or c_H. In particular I look at the effects for sanitary and culling costs that are 25% larger or smaller than the values used to derive the results reported on Tab. 2. For each case, I computed the relative variation in the total costs $\Delta C_{tot}(u)/C_{tot}(u)$, and the relative change of the control parameters $\Delta u^*/u^*$ and $\Delta i_{th}/i_{th}$. Results are reported in Tab. 3 for the culling policy based on disease prevalence in the host population, (9a), and when the cost function is quadratic. In general, uncertainty in the estimation of the cost functions would translate into negligible changes in both the cost-effectiveness and the optimal value of the control parameters. The only exception is when sanitary costs increase by 25% and hunting costs decrease by 25%. In this case, the optimal hunting effort would be three times larger and the intervention threshold 18% smaller. Nevertheless, under this circumstance, the change in the overall costs would still be negligible (~ 3%).

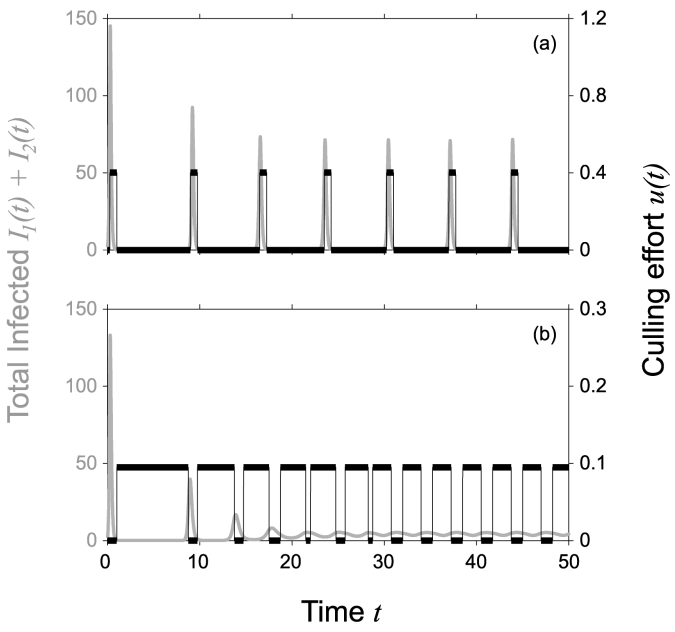

Fig. 3: The total infectious densities, $I_1(t) + I_2(t)$ (grey curves), obtained with model (2) and time-variable culling efforts, $u(t)$, (black curves) calculated by using information on disease prevalence in host population (see section 3.1.3). (a) Sanitary and culling costs are linear functions of infected individuals and control effort, respectively ($\gamma = \theta = 1$). (b) Sanitary and culling costs are quadratic functions of infected individuals and control effort, respectively ($\gamma = \theta = 2$). Other parameter values as in Fig. 2.

Finally, I analysed the sensitivity of optimal policy performance with respect to changes in the time horizon (T) in eq. (5). For all six types of control policies I computed the optimal solution when T = 100 years and T = 150 years respectively. In both cases, the total costs, $C_{tot}(u)$, do not increase by more than 1%, and the variation of the optimal value of the control parameter is smaller than 1%. In fact, the majority of the costs are suffered during the first epidemic wave and the discount rate further reduces the burden of costs perceived in the distant future.

3 DISCUSSION AND CONCLUSIONS

The present chapter shows that, regardless of the shape of the cost functions analysed, all the time-variable control policies are more cost effective than the best strategy based on implementing a constant culling rate. For the nonlinear cost functions, time-variable control strategies generally perform much better than the constant culling protocol (see Tab. 2). This is not true in the linear case, where the improvement in term of costs reduction is only marginal.

Ranking the different culling strategies according to their cost effectiveness strongly depends upon the specific shape of the cost function (see Tab. 2). For instance, for the linear cost function, the Swiss Health Authority policy (7a) performs slightly better than an immediate intervention policy (7b). On the other hand, when the shape of the cost function is quadratic, the immediate intervention policy is substantially better than the Swiss Health Authority policy. Similarly, the strategy (10b), based on host population density, allows for a significant reduction of the overall cost of disease control only in the case of quadratic costs.

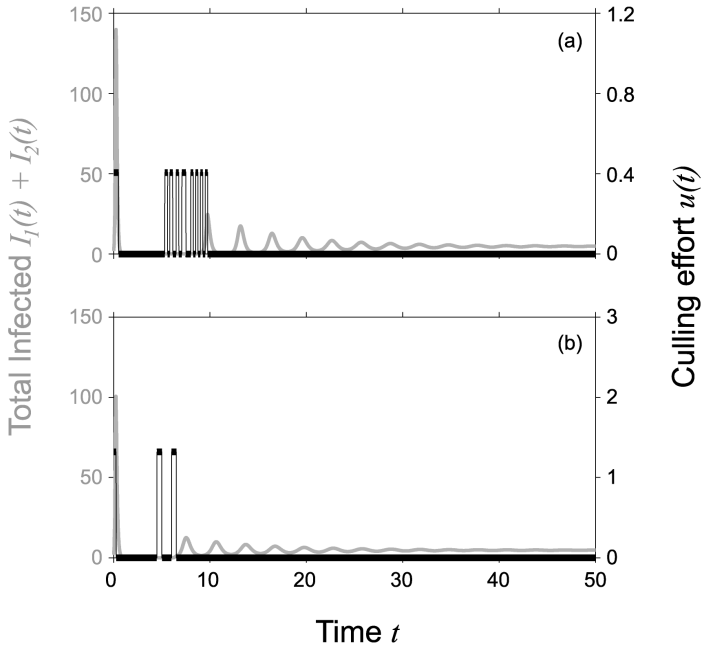

Fig. 4: The total infectious densities, $I_1(t) + I_2(t)$ (grey curves), obtained with model (2) and time-variant culling efforts $u(t)$ (black curves) calculated by using information on host population density (see section 3.1.4). (a) Sanitary and culling costs are linear functions of infected individuals and control effort, respectively ($\gamma = \theta = 1$). (b) Sanitary and culling costs are quadratic functions of infected individuals and control effort, respectively ($\gamma = \theta = 2$). Other parameter values as in Fig. 2.

Further analyses, not reported here, show that the optimal control policy is only affected by the shape of the sanitary cost function C_F (eq.3), while the optimal control policy is rather insensitive to the actual shape of the culling cost function C_H (eq.4). As a consequence, a great deal of effort in future researches needs to be devoted to explore the route of infection from wildlife to livestock and the relationship between disease prevalence and consequent costs.

In the case of a quadratic cost function, the immediate intervention policy and those based on estimations of the host population density through periodic censuses perform

significantly better than the other policies analysed here. On the other hand, these policies require a large culling effort (Tab. 2) and countries without organized veterinary authorities may face critical problems implementing them effectively.

In the case of the linear cost function, policies based on carcass sampling and disease prevalence among live or dead animals perform better than other policies, even though the reduction of costs in the linear case is remarkably lower than in the nonlinear case.

In this chapter I used a very simple strains-competition model without considering age structure, acquired immunity of the host population, or stochasticity in the infection dynamics – which are important elements in understanding epidemic evolution – to point out the mutual interactions between the persistence of classical swine fever strains in wildlife and the costs of disease control by culling.

$\Delta C_{tot}/C_{tot}$		$\Delta c_F/c_F$		
		-25%	**0**	**+25%**
$\Delta c_H/c_H$	**+25%**	0.25%	0.22%	0.21%
	0	0.044%	--	0.18%
	-25%	0.062%	0.067%	2.6%

$\Delta u^*/u^*$ $\Delta i_{th}/i_{th}$		$\Delta c_F/c_F$		
		-25%	**0**	**+25%**
$\Delta c_H/c_H$	**+25%**	+0.32% -7.0%	+0.32% -7.5%	+0.32% -7.5%
	0	-2.5% -6.5%	--	+0.32% -6.0%
	-25%	+0.21% -3.0%	+0.21% -3.0%	+297% -18.4%

Tab. 3: Relative increase of the total cost, $C_{tot}(u)$, (above) and relative variation of the optimal value of the control variables u^* and i_{th} (below) due to uncertainty in the estimation of the unitary costs c_F and c_H. The optimal control problem has been solved for quadratic cost functions ($\gamma = \theta = 2$) as in Fig. 3b for the policy in which the culling decision is based on the disease prevalence in the host population (equation (9b)).

The next step should be the introduction of stochastic processes in the epidemic dynamics in order to take into account the possibility of stochastic fade-out of the disease during the inter-epidemic periods.

Moreover, it should be interesting to introduce host age/stage structure to the model to investigate how hunting activities modify the population structure and to understand how the selective culling of the young individuals – which are the main virus targets – or the young adult females – which are the most fecund individuals – can improve the disease control. Nevertheless, I are confident that the analysis presented here may be very useful in highlighting the importance of cost estimation in the design and implementation of eradication strategies in the wildlife.

CHAPTER 5 REFERENCES

Anderson, R.M., Jackson, H.C., May, R.M. and Smith, A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-771.

Artois, M., Delahay, R., Guberti, V. and Cheeseman, C. (2001) Control of infectious diseases of wildlife in Europe, *Veterinary Journal* **162**(2):141-152.

Aubert, M., Picard, M., Fouquet, E., Conde, J., Cruciere, C., Ferry, R., Albina, E., Barrat, J. and Vedeau, F. (1994) Classical swine fever in European wild boar, *Annales de Medicine Veterinaire* **138**(4):239-247.

de Castro, F. and Bolker, B. (2005) Mechanisms of disease-induced extinction, *Ecology Letters* **8**:117-126.

De Leo, G.A. and Guberti, V. (2003) Effetti dell'abbattimento controllato sulla evoluzione della virulenza: Il caso della Peste Suina Classica, *Journal of Mountain Ecology* **7**(Suppl.):107-118. (in Italian, with English abstract).

De Vos, C.J., Saatkamp, H.W. and Huirne, R.B.M. (2005) Cost-effectiveness of measures to prevent classical swine fever introduction into The Netherlands, *Preventive Veterinary Medicine* **70**(3-4):235-256.

Edwards, S., Fukusho, A., Lefèvre, P.-C., Lipowski, A., Pejsak, Z., Roehe, P. and Westergaard, J. (2000) Classical swine fever: the global situation, *Veterinary Microbiology* **73**:103-119.

van Gennip, H.G.P., Vlot, A.C., Hulst, M.M., de Smit, A.J. and Mooremann, R.J.M. (2004), Determinants of virulence of classical swine fever virus strain Brescia, *Journal of Virology* **78**:8812-8823.

Ghezzi, L.L. and Piccardi, C. (1997) PID control of a chaotic system: An application to an epidemiological model, *Automatica* **33**:181–191.

Guberti, V., Cossu, P., Bozzi, F., Cabras, P., Ruiu, A., Pirino, A., Mereu, G., Bassu, M. and Firinu, A. (1996) Aspetti demografici della popolazione di cinghiale nella provincia di Nuoro: effetti del modello di gestione. *I Convegno programmi di ricerca finalizzati degli Istituti Zooprofilattici Sperimentali*. Istisan Congressi (46):87. (in Italian).

Guberti, V., Rutili, D., Ferrari, G., Patta, C. and Oggiano, A. (1998) Estimate the threshold abundance for the persistence of classical swine fever in the wild boar population of the Eastern Sardinia, *Proceedings of the meeting Measures to control classical swine fever in the European wild boar*, Perugia, Italy 6-7 April 1998, European Commission, doc. VI/7196/98, pp. 54-61.

Hassell, M.P., Lawton, J.H. and Beddington, J.R. (1977) Sigmoid functional responses by invertebrate predators and parasitoids, *Journal of Animal Ecology* **46**:249-262.

Hofmann, M.A., Thur, B., Vanzetti, T., Scleiss, W., Schmidt, J. and Griot, C. (1999) Classical swine fever in wild boars in Switzerland, *Schweizer Archiv fur Tierheilkunde* **141**(4):185-190.

Kaden, V., Schurig, U., Lange, E., Steyer, H., Fischer, U. and Strebelow, G. (1997) Evaluation of the oral immunization of wild boars against classical swine fever in Mecklenburg-Westernpomerania with respect to investigations in three selected areas, *Proceedings of the*

meeting on control of classical swine fever in wild boar population. Isle of Riems, 25-26 June 1997.

Kaden, V., Lange, E. and Steyer, H. (2004a) Does multiple oral vaccination of wild boar against classical swine fever (CSF) have positive influence on the immunity?, *Deutsche Tierarztliche Wochenschrift* **111**(2):63-67.

Kaden, V., Lange, E., Polster, U., Klopfleisch, R. and Teifke, J.P. (2004b) Studies on the virulence of two field isolates of classical swine fever virus genotype 2.3 *Rostock* in wild boars of different age groups, *Journal of Veterinary Medicine B* **51**:202-208.

Karsten, S., Rave, G. and Krieter, J. (2005a) Monte Carlo simulation of classical swine fever epidemics and control - I. General concepts and description of the model, *Veterinary Microbiology* **108**(3-4):187-198.

Karsten, S., Rave, G. and Krieter, J. (2005b) Monte Carlo simulation of classical swine fever epidemics and control - II. Validation of the model, *Veterinary Microbiology* **108**(3-4):199-205.

Kermack, W.O. and McKendrick, A.G. (1927) A contribution to the mathematical theory of epidemics, *Proceedings of the Royal Society of London B* **115**:700-721.

Maillard, D. and Fournier, P. (1995) Effects of shooting with hounds of size of resting range of wild boar (*Sus scrofa*) groups in Mediterranean habitat, *Journal Mountain Ecology* **3**:102-107.

Matthews, L., Haydon, D.T., Shaw, D.J., Chase-Topping, M.E., Keeling, M.J. and Woolhouse, M.E.J. (2003) Neighbourhood control policies and the spread of infectious diseases, *Proceedings of the Royal Society of London B* **270**(1525):1659-1666.

Meuwissen, M.P.M., Horst, S.H., Huirne, R.B.M. and Dijkhuizen, A.A. (1999) A model to estimate the financial consequences of classical swine fever outbreaks: principles and outcomes, *Preventive Veterinary Medicine* **42**(3-4):249-270.

Nowak, M.A., and May, R.M. (1994) Superinfection and the evolution of parasite virulence, *Proceedings of the Royal Society of London B* **255**(1342):81-89.

van Oirschot, J.T. (2003) Vaccinology of classical swine fever: from labs to field, *Veterinary Microbiology* **96**:367-384.

Pan, C.H., Jong, M.H., Huang, T.S., Liu, H.F., Lin, S.Y. and Lai, S.S. (2005) Phylogenetic analysis of classical swine fever virus in Taiwan, *Archives of Virology* **150**:1101-1119.

Saatkamp, H.W., Dijkhuizen, A.A., Geers, R., Huirne, R.B.M., Noordhuizen, J.P.T.M. and Goedseels, V. (1997) Economic evaluation of national identification and recording systems for pigs in Belgium, *Preventive Veterinary Medicine* **30**:121-135.

Sodeikat, G. and Pohlmeyer, K. (2002) Temporary home range modifications of wild boars family groups (*Sus scrofa L.*) caused by drive hunts in Lower Saxony (Germany), *Zeitschrift fur Jagdwissenschaft* **48**(Suppl. S):161-166.

Stadejek, T., Vilcek, S., Lowing, J.P., Ballagi-Pordany, A., Paton, D.J. and Belak, S. (1997) Genetic heterogeneity of classical swine fever virus in Central Europe, *Virus Research* **52**:195-204.

Vanthemsche, P. (1995) Experiences with Swine Fever control in Belgium, in: Dijkhuizen, A.A. and Davies, G. (Eds.), *Proceedings of a Workshop on Animal Health and Related Problems in Densely Populated Livestock Areas of the Community*, 22-23 November 1994, Brussels. European Commission, Office for Official Publications of the European Communities, Luxembourg, pp. 69-79.

Verhulst, P.F. (1838) Notice sur la loi que la population suit dans son accroissement, *Correspondance mathématique et physique* **10**:103-121.

Wilpshaar, H., Meuwissen, M.P.M., Tomassen, F.H.M., Mourits, M.C.M., van Asseldonk, M.A.P.M. and Huirne, R.B.M. (2002) Economic decision making to prevent the spread of infectious animal diseases. 20th Conference of the O.I.E. Regional Commission for Europe, Finland,16p.

6

Transmission heterogeneity and control strategies for infectious disease emergence

Published Chapter: Luca Bolzoni, Leslie Real, and Giulio A. De Leo, Transmission heterogeneity and control strategies for infectious disease emergence, PLoS ONE, 2(8):e747.

ABSTRACT

Background

The control of emergence and spread of infectious diseases depends critically on the details of the genetic makeup of pathogens and hosts, their immunological, behavioural and ecological traits and the pattern of temporal and spatial contacts among the age/stage-classes of susceptible and infectious host individuals.

Methods and Findings

I show that failing to acknowledge the existence of heterogeneities in the transmission rate among age/stage-classes can make traditional eradication and control strategies ineffective, and in some cases, policies aimed at controlling pathogen emergence can even increase disease incidence in the host. When control strategies target for reduction in numbers those subsets of the population that effectively limit the production of new susceptible individuals, then control can produce a flush of new susceptibles entering the population. The availability of a new cohort of susceptibles may actually increase disease incidence. I illustrate these general points using Classical Swine Fever as a reference disease.

Conclusion

Negative effects of culling are robust to alternative formulations of epidemiological processes and underline the importance of better assessing transmission structure in the design of wildlife disease control strategies.

INTRODUCTION

Historically, models for infectious diseases considered populations of host and pathogen to be well-mixed with homogeneous disease transmission among susceptible and infected individuals. In recent years, however, I have recognized that transmission may not be constant but may vary with time, social structure, and/or age/stage-class. In human epidemiology it is well known that transmission may indeed change substantially among social groups and age classes, as observed, for instance, in the early phases of HIV epidemics (Castillo-Chavez, 1989; Hethcote and Van Ark, 1992). Recently, different works emphasized the roles of superspreaders in the dynamics of SARS, sexually transmitted and childhood diseases (Galvani and May, 2005; Lloyd-Smith et al., 2005). However, there is only anecdotal information about variation in transmission rate by age/stage structure in wild animals or the implication of such variation on disease dynamics in zoonotic reservoirs (Heesterbeek and Roberts, 1995), while few information exist in the case of domestic animals (see e.g., Matthews et al., 2006). This is unfortunate since the majority of emerging infectious diseases are zoonotic and it is well know that many species exhibit a high degree of heterogeneity in their spatial, social and age/stage structure. It is highly likely that age/stage-dependent behavioural differences in reservoir contact rates may significantly affect disease transmission between and within different age/stage classes and, as a consequence, the effectiveness of disease control policies.

While the science of infectious diseases has made tremendous progress in the last several decades thanks, in part, to advances in molecular biology, immunology, medicine and mathematical modelling, the eradication of pathogens and parasites in wildlife relies very often only on two simple strategies, namely vaccination and culling, i.e., the removal of animals to push host population density below the threshold for disease invasion (Grenfell and Dobson, 1995). Quarantine and isolation through the construction of sanitary containments are rare options in the control of wildlife diseases and are applied primarily to domestic animals and farms such in the case of the foot-and-mouth epidemics in UK (Gilbert et al., 2005) and of avian flu epidemics in Asia (Ellis et al., 2004) often at the cost of huge economic losses.

Oral vaccination, on the contrary, is a quite widespread technique for disease eradication and control: it has been applied in the USA to control the westward expansion of rabies virus in raccoon hosts and has effectively eliminated rabies in coyotes in Texas (Real et al., 2005; Sidwa et al., 2005). In Germany, oral vaccination is used to control classical swine fever virus exposure in wild boars (Kaden et al., 2005). The drawbacks of oral vaccination mainly consist in the difficulty of producing, at a reasonable price, a sufficient amount of a vaccine able to persist long enough in baits so as to be picked up by a suitable fraction of susceptible animals. Moreover, vaccination

might be less effective than expected, as older animals – who may have antibodies resulting from prior infection – are often more aggressive in ingesting baits than younger more susceptible individuals.

Culling is usually the most simple and economical measure to control diseases spread in wildlife and its application is strongly supported as an emergency procedure for disease eradication. It has been historically applied to control different domestic and wildlife diseases with the aim to reduce host population or to put down infected individuals, such as for bovine tuberculosis in badgers (Donnelly et al., 2006) and foot-and-mouth disease in cattle in the UK (Haydon et al., 2004), avian flu in waterfowl birds and poultry in Asia and classical swine fever in wild boars and domestic pigs in Europe . Albeit, sport hunting *per se* is certainly not aimed at preventing disease spread, it usually exerts effects similar to those of culling in terms of population density reduction. The same is true also for illegal hunting (poaching).

Despite its simplicity and alleged cost effectiveness, there is some evidence that under a variety of circumstances culling may not generate the benefits anticipated (Donnelly et al., 2003; Woodroffe et al., 2004; Shirley and Rushton, 2005). Selective hunting may interfere with establishment of herd immunity inducing faster turnover of the population and decreasing host life expectancy. Furthermore, it may induce long distance host movement, increasing contacts between different groups of animals (Laddomada, 2000), and it may affect the evolution of some host species traits (Coltman et al., 2003). Finally, culling often affects age/stage structure by preferentially removing older and less susceptible individuals. This is important, as the basic theory for Susceptible-Infected-Recovery (SIR-like) compartmental models of a self-regulating host suggests that disease prevalence in a homogenous population should monotonically decrease with increasing culling rate (as in Anderson et al., 1981; Coyne et al., 1989). However, as we will see, the existence of age/stage structure in transmission rate may significantly alter this conclusion

In the present chapter I show (using very general assumptions about life history traits of host species) that the presence of age-dependent heterogeneity in the transmission rate may produce the counter-intuitive result that disease prevalence increases over a range intermediate levels of culling. I recast a simple SIR model for wildlife disease with two age/stage classes, namely, pre-reproductive juveniles and adults and sub-adults (see Material and Methods). Numerical characterization of the problem was examined for the specific case of classical swine fever in wild boar (see Protocol S1 in Supporting Information). I chose CSF as reference disease because it caused serious economic losses in Europe from spillover infection to pig farms over the last twenty years (Saatkamp et al., 1997) and it is still endemic in Asia and South America and in some regions of Eastern Europe and Italy (Sardinia). Also, Choisy and Rohani (2006) have recently illustrated

similar points using CSF but with a different model structure. Comparison across model structures for the same disease will lead to an increased robustness in any general characterization of optimal strategies for control.

While the ideas being investigated in the present chapter are based on a detailed understanding of wild boar biology, the epidemiological model itself has been simplified to address the following key question: how do age-dependent heterogeneities in transmission interact with culling rate in the control of disease prevalence?

To answer this question, I extend the classical SIR model of infection to allow for an age structured wildlife population. In this simple model, host population is divided into two age classes, juveniles and adults. I assumed that juveniles are highly susceptible to infection with associated high mortality and negligible recovery rates. On the other hand, infected adults and sub-adults exhibit negligible mortality and can recover with life-long immunity (see Material and Methods for details).

RESULTS

I have computed disease prevalence in the population at equilibrium as a function of culling rate or hunting mortality for different values of age-dependent heterogeneity in transmission, called $\Delta\beta=\beta_a-\beta_j$ (where, β_a is the transmission rate between adults and β_j is the transmission rate between juveniles). I held constant the basic reproduction number R_0 in model (1) to keep the same level of infection in the population for each value of $\Delta\beta$ when culling is absent (see details in Protocol S2 in Supporting Information).

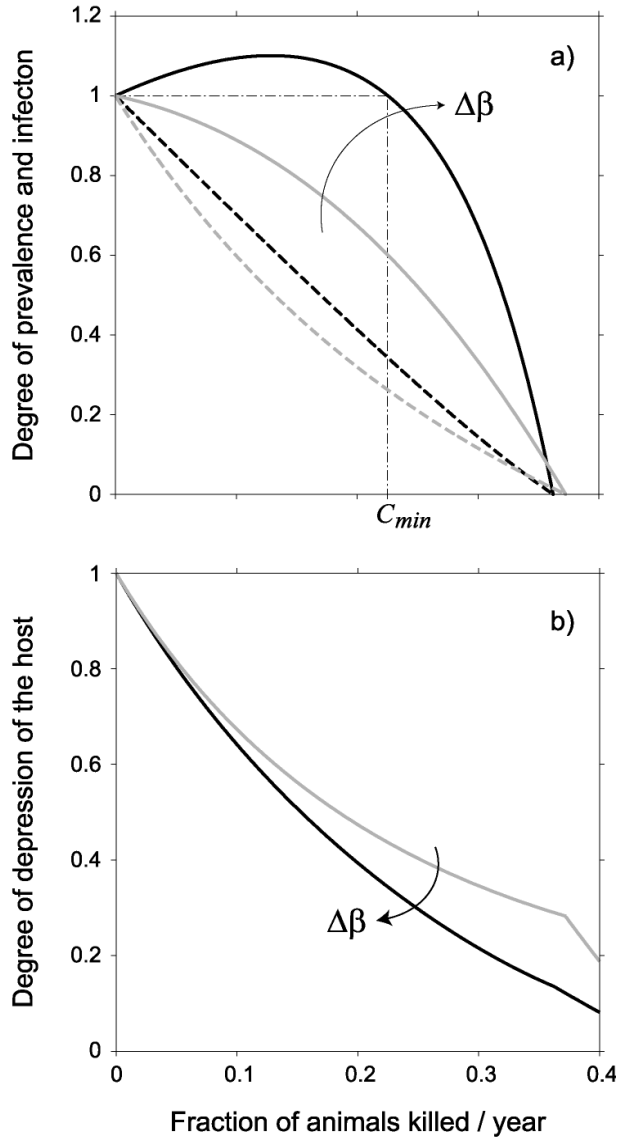

Fig. 1: Effects of age/stage transmission on culling - a) Solid lines represent disease prevalence as function of the fraction of animals killed through culling scaled with respect to prevalence at equilibrium in the absence of culling; dotted lines refer to the number of infected individuals as functions of the fraction of animals killed through culling scaled with respect to prevalence at equilibrium in the absence of culling; grey lines $\Delta\beta = 0$ ($\beta_a = \beta_j = 0.2856$); black lines $\Delta\beta = \beta_a - \beta_j = 0.31$ ($\beta_a = 0.32$; $\beta_j = 0.01$). In both cases $R_0 = 9$. - b) Degree of depression of population abundance as a function of culling rate c under the same condition than above . Other parameter values have been set as follows: ν=1.25 years^{-1}, μ_j=0.9 years^{-1}, μ_a=0.4 years^{-1}, γ= 0.0067 (#individual^{-1} * 220 km^2 * years^{-1}), α=25 years^{-1}, ρ=2 years^{-1}, δ=17.4 years^{-1}.

When the within class transmission rate for adults is larger than that within juveniles, the disease prevalence can actually increase with culling or hunting rate instead of decreasing as expected under the assumption of homogenous mixing (Fig. 1a); disease prevalence eventually peaks for intermediate values of culling and then decreases only for high level of animal removal. Moreover, the absolute number of infected individuals is larger in the case of heterogeneous mixing relative to the number under conditions of homogenous mixing at all levels of culling. The explanation for this effect is that at low and intermediate levels of culling, by removing older resistant individuals, population age structure is skewed in favour of highly susceptible juvenile hosts thus making culling ineffective. The minimum culling rate C_{min} required to bring disease prevalence below the value attained in the absence of culling can be fairly high, as depicted in Fig. 1a. As a consequence, as long as $c < C_{min}$, culling actually performs worse, in terms of disease

control, than the do-nothing alternative ($c=0$). The dynamics of infection also reveal that the population density at equilibrium decreases with culling more quickly in the presence of in transmission heterogeneity (see Fig. 1b) even though, for intermediate values of culling, the actual number of infected hosts is larger in the case of heterogeneous transmission.

I also performed a sort of sensitivity analysis in the transmission parameters by estimating the values assumed by C_{min} for a broad range of R_0 and $\Delta\beta$ values. Fig. 2 shows that, in the case of quite large transmission heterogeneity, relatively low R_0 values are sufficient to obtain $C_{min} > 0$, then a reduction of culling effects compared to the homogeneous case.

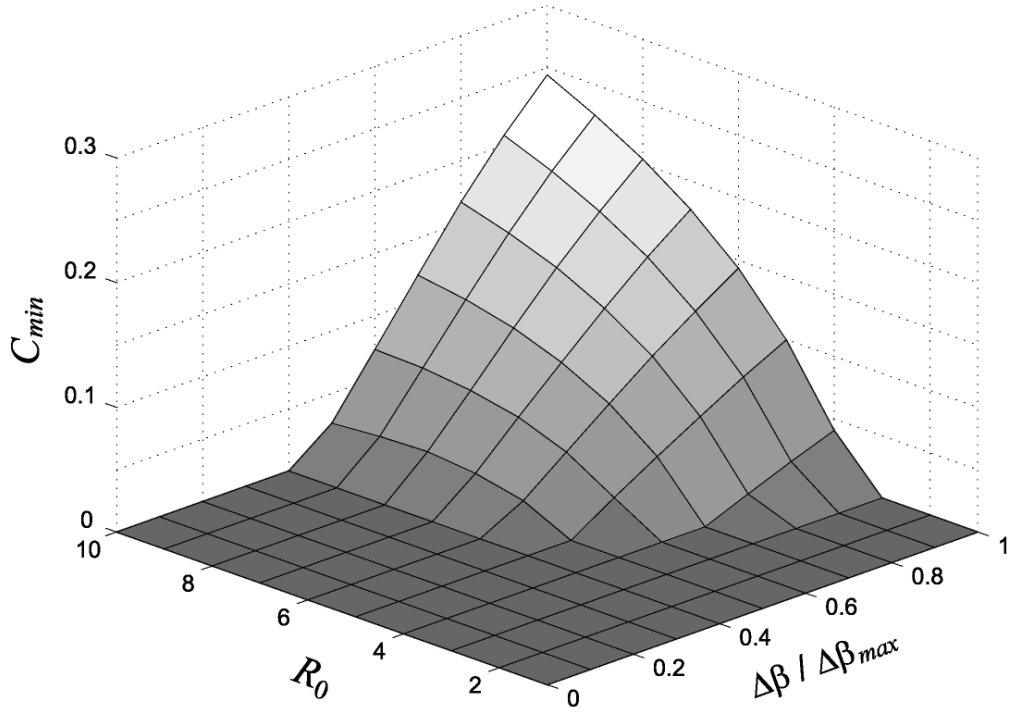

Fig. 2: Value of the minimum culling rate C_{min} required to bring disease prevalence below the value attained in absence of culling as a function of the basic reproduction number (R_0) and the age-dependent heterogeneity in transmission ($\Delta\beta = \beta_a - \beta_j$) renormalized by the maximum heterogeneities in transmission ($\Delta\beta_{max}$) allowed at each level of R_0 (see Protocol S2).

DISCUSSION

The pattern revealed in Fig. 1a suggests that if the culling rate for disease eradication is computed by assuming homogenous mixing while transmission rate is actually age dependent, then classical culling strategies may prove to be ineffective: in fact, even though the host population is even more depressed then expected under homogeneous mixing, not only will the disease not be eradicated from the population but prevalence can be even higher than in the absence of culling. As a consequence, unless it is possible to guarantee a sufficiently high removal of adult individuals, the do-nothing alternative is more effective and less costly than an intermediate culling strategy. For example, in the case of classical swine fever, to move from c=0 to C_{min} requires removing at least 22.5% of individuals in the population; consistent results may be obtained for a broad range of the parameter setting (see Fig. 2). Similarly, intermediate levels of hunting pressure, especially when not aimed at disease control, might actually increase disease prevalence as well as the number of infected individuals.

On the other hand, the maintenance of a high level of culling that guarantees disease eradication is not always feasible in practice. In fact, if the host population is very small, culling might generate conservation concern, as the removal of a large fraction of individuals might drive the host to the brink of extinction, as argued by Dobson and Meagher (1996) for the eradication of Brucellosis in Yellowstone National Park bison. On the contrary, if the host population is very large, it might be impossible to cull a large enough fraction of individuals. This may correspond to the case, for instance, for huge colonies of bats in central Africa suspected of being the reservoir of Ebola and Marburg viruses (Leroy et al., 2005) or populations of small rodents in North America, that comprise the main reservoirs for Hanta viruses or the vectors of Lyme disease (Oliver et al., 2003).

The results presented in Fig. 1 contain an important insight concerning the potential for disease to spill-over into domestic animals. If transmission between wildlife and domestic animals is density-dependent, the risk of spill-over decreases for increasing culling rates even though it is higher than in the case of homogenous mixing (dotted lines in Fig. 1a); while if transmission between wildlife and domestic animals is frequency dependent, the risk of spillover can substantially increase for intermediate values of culling rate with respect to the case of homogenous mixing (solid lines in Fig. 1a). Therefore, it is crucial to articulate and understand the exact mechanisms by which infectious wild hosts interact with susceptible domestic animals and humans susceptible in order to predict the effects of wildlife culling on the risks of spillover.

I thus conclude that age/stage structure of transmission rate can be crucial in our understanding of disease pattern and the implementation of control policies. This conclusion likely

applies to other wildlife diseases in which age/size structure is an important component of population dynamics.

Recently, Choisy and Rohani (2006) presented a model of wildlife disease that focused on the effects of strong density-dependence and seasonality on culling and equilibrium disease prevalence. Their model was different from mine in that it was not age-structured and culling was random over the population of hosts. Nonetheless, they showed a similar response to culling with intermediate levels of culling producing a counter-intuitive increase in disease prevalence. Given the explicit difference in model structures it is instructive to speculate on how two very different models can generate the same over all effect. As Choisy and Rohani indicate, the result of their model is driven by culling releasing the population from density-dependent reductions in the birth rate thereby producing a flush in new susceptible in the population. In my model I have a similar effect but driven by a completely different mechanism. The age-dependent culling coupled to the intrinsic heterogeneity in transmission similarly produces a flush in the relative abundance of the young susceptible class. I imagine that other mechanisms besides age/stage structure (as in my model) or strong density-dependence and seasonality (as in the Choisy and Rohani model), may interact with culling to produce similar patterns of prevalence.

Given the implications of transmission heterogeneities on dynamics and control, more detailed studies are thus necessary to assess these heterogeneities when structuring control strategies in current and ongoing wildlife epizootics (Coyne et al., 1989; Donnelly et al., 2003; Donnelly et al., 2006). What appears certain is that the negative effects of culling are robust to alternative model formulations and highlight the importance of better assessing transmission structure, seasonality, and population regulatory processes in the design of wildlife disease control strategies.

MATERIAL AND METHODS

The model is characterized by five classes: susceptible juveniles and adults, infected juveniles and adults and recovered (immune) adults. The infection dynamics in this age-structured population are described by:

$$\begin{aligned}
\dot{S}_j &= \nu(S_a + R_a) - (\mu_j + \gamma A)S_j - \rho S_j - \beta_j S_j I \\
\dot{I}_j &= \beta_j S_j I - (\alpha + \mu_j + \gamma A)I_j \\
\dot{S}_a &= \rho S_j - \mu_a S_a - \beta_a S_a I - cS_a \\
\dot{I}_a &= \beta_a S_a I - (\mu_a + \delta)I_a - cI_a \\
\dot{R}_a &= \delta I_a - \mu_a R_a - cR_a
\end{aligned} \qquad (1)$$

where $S_{j(a)}$, $I_{j(a)}$, and R_a refer to susceptible juveniles (adults), infected juveniles (adults), and recovered adults, respectively. The system parameters ν, μ_j, μ_a, and ρ represent the host birth rate, the juveniles mortality rate at low population density, the adults mortality rate, and the rate at which juveniles pass into adulthood, respectively. I assume that host population is self-regulating with density-dependent mortality in juveniles (γ) affected by total adults density ($A=S_a+I_a+R_a$). The force of infection for susceptible juveniles (adults) individuals is $\lambda_{j(a)}= \beta_{j(a)}I$, where $I=I_j+I_a$ is the total infectious density in the population. Parameters α and δ represent the disease-induced mortality in juveniles, and the adult recovery rate, respectively. Finally, c is the control parameter and represents the culling effort over the adults population. Only adult and sub-adult individuals are here assumed to be culled either because of conservation measures or, in the case of hunting, because of the preference for large trophies. Moreover, culling is not usually allowed in spring when peak fertility occurs and when most juveniles are born. By the onset of the hunting season, at the beginning of autumn, juveniles have already moved into the sub-adult age class.

Contact rate among adults increases dramatically during mating season (when males roam considerable distances in search of reproductive females). Consequently, within adult transmission rate is assumed to be larger than within juvenile transmission. It is this variation in the within-class transmission rates that forms the basis of transmission heterogeneity. I assign the magnitude of this heterogeneity in age-specific transmission as a new variable, $\Delta\beta=\beta_a-\beta_j$ (≥ 0) assessing the marginal increase of adult transmission rate (β_a) relative to that of juveniles (β_j).

CHAPTER 6 REFERENCES

Anderson R.M., Jackson H.C., May R.M. and Smith A.M. (1981) Population dynamics of rabies in Europe, *Nature* **289**:765-771.

Castillo-Chavez C. (1989) *Mathematical and Statistical Approaches to AIDS epidemiology*, New York.

Choisy M. and Rohani P. (2006) Harvesting can increase severity of wildlife disease epidemics, *Proceedings of the Royal Society B* **273**:2025-2034

Coltman D.W., O'Donoghue P., Jorgenson J.T., Hogg J.T., Strobeck C. and Festa-Bianchet M. (2003) Undesiderable evolutionary consequences of trophy hunting, *Nature* **426**:655-658.

Coyne M.J., Smith G. and McAllister F.E. (1989) Mathematical model for the population biology of rabies in raccoons in the mid-Atlantic states, *American Journal of Veterinary Research* **50**:2148-2154.

Dobson A. and Meagher M. (1996) The population dynamics of Brucellosis in the Yellowstone National Park, *Ecology* **77**:1026-1036.

Donnelly C.A., Woodroffe R., Cox D.R., Bourne J., Cheeseman C.L., Clifton-Hadley R.S., Wei G., Gettingby G., Gilks P., Jenkins H., Johnston W.T., Le Fevre A.M., McInerney J.P. and Morrison W.I. (2006) Positive and negative effects of widespread badger culling on tuberculosis in cattle, *Nature* **439**:843-846.

Donnelly C.A., Woodroffe R., Cox D.R., Bourne J., Gettingby G., Le Fevre A.M., McInerney J.P. and Morrison W.I. (2003) Impact of localized badger culling on tuberculosis incidence in British cattle, *Nature* **426**:834-837.

Ellis T.M., Bousfield R.B., Bissett L.A., Dyrting K.C., Luk G.S.M., Tsim S.T., Surm-Ramirez K., Webster R.G., Guan Y. and Peiris J.S.M. (2004) Investigation of outbreaks of highly pathogenic H5N1 avian influenza in waterfowl and wild birds in Hong Kong in late 2002, *Avian Pathology* **33**:492-505.

Galvani A.P. and May R.M. (2005) Dimensions of superspreading, *Nature* **438**:293-295

Gilbert M., Mitchell A., Bourn D., Mawdsley J., Cliton-Hadley R. and Wint W. (2005) Cattle movements and bovine tuberculosis in Great Britain, *Nature* **435**:491-496

Grenfell B.T. and Dobson A.P. (1995) *Ecology of Infectious Diseases in Natural Populations*. Cambridge University Press, Cambridge.

Haydon D.T., Kao R.R. and Kitching R.P. (2004) The UK foot-and-mouth disease outbreak – the aftermath, *Nature Reviews Microbiology* **6**:675.

Heesterbeek J.A.P. and Roberts M.G. (1995) Mathematical models for microparasite of wildlife. In: *Ecology of Infectious Diseases in Natural Populations* (eds. Grenfell BT and Dobson AP), pp. 90-122. Cambridge University Press, Cambridge.

Hethcote H.W. and Van Ark J.W. (1992) *Modeling HIV transmission and AIDS in the United States*. Springer-Verlag, New York.

Kaden V., Hänel A., Renner C. and Gosser K. (2005) Oral immunisation of wild boar against classical swine fever in Baden-Württemberg: development of seroprevalences based on the hunting bags, *European Journal of Wildlife Research* **51**:101-107.

Laddomada A. (2000) Incidence and control of CSF in wild boar in Europe, *Veterinary Microbiology* **73**:121-130.

Leroy E.M., Kumulungui B., Pourrut X., Rouquet P., Hassanin A., Yaba P., Delicat A., Paweska J.T., Gonzalez J.-P. and Swanepoel R. (2005) Fruits bats as reservoirs of Ebola virus, *Nature* **438**:575-576.

Lloyd-Smith J.O., Schreiber S.J., Kopp P.E. and Getz W.M. (2005) Superspreading and the effect of individual variation on disease emergence, *Nature* **438**:355-359

Matthews L., Low J.C., Gally D.L., Pearce M.C., Mellor D.J., Heesterbeek J.A.P., Chase-Topping M., Naylor S.W., Shaw D.J., Reid S.W.J., Gunn G.J. and Woolhouse M.E.J. (2006) Heterogeneous shedding of *Escherichia coli* O157 in cattle and its implications for control, *Proceedings of the National Academy of Sciences of the United States of America* **103**:547-552.

Oliver J.H., Lin T., Gao L., Clark K.L., Banks C.W., Durden L.A., James A.M. and Chandler F.W. (2003) An enzootic transmission cycle of Lyme borreliosis spirochetes in the southeastern United States, *Proceedings of the National Academy of Sciences of the United States of America* **100**:11642-11645.

Real L.A., Russell C., Waller L., Smith D. and Childs J. (2005) Spatial dynamics and molecular ecology of North American rabies, *Journal of Heredity* **96**:253-260.

Saatkamp H.W., Dijkhuizen A.A., Geers R., Huirne R.B.M., Noordhuizen J.P.T.M. and Goedseels V. (1997) Economic evaluation of national identification and recording systems for pigs in Belgium, *Preventive Veterinary Medicine* **30**:121-135.

Shirley M.D.F. and Rushton S.P. (2005) Where diseases and networks collide: lessons to be learnt from a study of the 2001 foot-and-mouth disease epidemic, *Epidemiology and Infection* **133**:1023-1032.

Sidwa T.J., Wilson P.J., Moore G.M., Oertli E.H., Hicks B.N., Rohde R.E. and Johnston D.H. (2005) Evaluation of oral rabies vaccination programs for control of rabies epizootics in coyotes and gray foxes: 1995-2003, *JAVMA - Journal of the American Veterinary Medical Association* **277**:785-792.

Woodroffe R., Cleaveland S., Courtenay O., Laurenson M.K. and Artois M. (2004) Biology and conservation of wild canids. In: *Biology and conservation of wild canids* (eds. Macdonald DW and Sillero-Zubiri C), pp. 123–142. Oxford University Press, Oxford.

CHAPTER 6 SUPPORTING INFORMATION

Protocol S1: Details about the setting of epidemiological and demographic parameters in model (1) for classical swine fever in wild boar.

Protocol S2: Details about calculation of the basic reproduction number for model (1).

PROTOCOL S1:

Details about the setting of epidemiological and demographic parameters in model (1) for classical swine fever in wild boar:

Wild boar populations are characterized by a well-defined social structure with closely related adult females (1 years old or more) and sub-adult females (6-12 months old) grouping together with their piglets (0-6 months old). Young males and females become sub-adults after about six months. Sub-adult males leave the herd and roam around in search of new territory in the fall at the beginning of the hunting season. Adult males tend to be more sedentary but they wander over considerable distances during the mating season, thus greatly increasing their contact rate with respect to that of piglets. This difference in movement patterns between piglets and adult individuals may obviously affect disease transmission among different age classes similarly to what has been observed for humans (see for example Anderson and May, 1991).

Vital parameters of the host population have been set in accordance with field studies on the ecology of wild boar: Fenati and Guberti estimated that potential number of daughters produced by an adult sow per year is about 2.5 individuals/year (Fenati, M. and Guberti, V., unpublished data). As the observed rate of increase of the population at low densities in absences of harvesting is about 2.5, I have set the birth rate ν at 1.25 year^{-1}. Bieber and Ruf (2005) estimated that piglets survival in the first year of life ranges between 25-52% with mean value around 40%. As a consequences the natural mortality rate at low density μ_j is equal to 0.9 year^{-1} for individuals with age<6 months. The parameter μ_a (adult mortality rate) can be easily calibrated as the inverse of the average life expectancy of an adult host, namely about 2-3 years. Guberti et al. (1998) estimated the carrying capacity of a Sardinian wild boar population in 600 individuals on a surface of 220 km^2 which yield to instraspecific competition coefficient γ equal to 0.0067 (220 km^2 years^{-1}).

The main means of viral transmission is by direct contact between infected and susceptible animals. Once infected, wild boars become infectious after a short latent period of 2-6 days. Young individuals die between 10 and 20 days post-infection, while most adults recover after 3 weeks. Even though the issue is very controversial, wild boar have been considered the reservoir of the disease (Laddomada, 2000) and, consequently, eradication policies in recent years have been based essentially on vaccination and culling, that is, the removal of animals to push population density

below the threshold for disease invasion Culling has been widely implemented throughout Europe in the 1990s and is still considered a central component of national control plans of the disease in the wildlife in many Member States of the European Union (Laddomada, 1999).

Disease induced mortality in piglets (α) has been estimated as the inverse of the average time spent by a juvenile in the infected class before dying, that is about 15 days. The recovery rate of infected adults wild boar (δ) has been estimated as the inverse of the average time spent by adult in the infectious class I_a before recovering, namely about 3 weeks.

Howard and Donnelly (2000) estimated the basic reproduction number (R_0) of a wild boar CSF infection in Pakistan. Through the epidemic wave, R_0 ranges from values under unity to picks larger than 10. In my analyses I have set R_0=9 as this figure well fits the range of observed basic reproduction numbers of CSF in wild boar estimated for Italian populations by Guberti (pers. comm.).

Protocol S1 References:

Anderson R.M. and May R.M. (1991) *Infectious Diseases of Humans: Dynamics and Control*. Oxford Science Publications, Oxford.

Bieber C. and Ruf T. (2005) Population dynamics in wild boar sus scrofa: ecology, elasticity of growth rate and implications for the management of pulsed resource consumers, *Journal of Applied Ecology* **42**:1203-1213.

Guberti V., Rutili D., Ferrari G., Patta C. and Oggiano A. (1998) Estimate threshold abundance for the persistence of the classical swine fever in the wild boar population in Eastern Sardinia. In: *Measures to control classical swine fever in European wild boar* (ed. Communities CotE), pp. 54-61, Perugia, Italy.

Laddomada A. (1999) Classical swine fever in wild boar. In. Directorate-General XXIV, Scientific Committee on Animal Health and Animal Welfare, XXIV/B3/R09/1999, Brussels, Belgium.

Laddomada A. (2000) Incidence and control of CSF in wild boar in Europe, *Veterinary Microbiology* **73**:121-130.

Howard S.C. and Donnelly C.A. (2000) Estimation of a time varying force of infection and basic reproduction number with application to an outbreak of classical swine fever, *Journal of Epidemiology and Biostatistics* **5**:161-168.

PROTOCOL S2:

Details about calculation of the basic reproduction number for model (1):

I calculated the basic reproduction number R_0 for model (1) as a function of within-class disease transmission β_j and β_a.

The basic reproduction number for heterogeneous population, whose individuals are distinguishable by age or behaviour, but can be grouped in homogeneous compartments, may be calculated as suggested by van den Driessche and Watmough (2002). They define the basic reproduction number as the spectral radius of the 'next generation' matrix (FV^{-1}).

$R_0 = \rho(FV^{-1})$

where F and V are defined as Jacobian matrix of new infections appearance matrix $\mathcal{F}$ and the Jacobian matrix of other rates of transfer matrix $\mathcal{V}$ calculated for infected compartments in the disease-free equilibrium (DFE) $x_0 = [K_j(c), 0, K_a(c), 0, 0]^T$. Where $K_j(c)$ and $K_a(c)$ are the carrying capacities of juveniles and adults.

$$\mathcal{F} = \begin{bmatrix} 0 \\ \beta_j S_j I \\ 0 \\ \beta_a S_a I \\ 0 \end{bmatrix} \text{ and } \mathcal{V} = \begin{bmatrix} -\nu(S_a + R_a) + (\mu_j + \gamma K_a)S_j + \rho S_j + \beta_j S_j I \\ (\alpha + \mu_j + \gamma K_a)I_j \\ \mu_a S_a + \beta_a S_a I + cS_a - \rho S_j \\ (\mu_a + \delta)I_a + cI_a \\ \mu_a R_a + cR_a - \delta I_a \end{bmatrix}$$

The infected compartments are I_j and I_a, hence:

$$F = \begin{bmatrix} \beta_j K_j(c) & \beta_j K_j(c) \\ \beta_a K_a(c) & \beta_a K_a(c) \end{bmatrix} \text{ and } V = \begin{bmatrix} \alpha + \mu + \gamma K_a(c) & 0 \\ 0 & \mu_a + \delta + c \end{bmatrix}$$

with K_j and K_a monotonically decreasing functions of the culling rate:

$$K_j = \left[\nu - (\mu_a + c)(\mu_j / \rho)\right] / \gamma$$

$$K_a = \left[\rho\nu - (\mu_a + c)(\mu_j + \rho)\right] / \left[\gamma(\mu_a + c)\right]$$

The next generation matrix is:

$$FV^{-1} = \frac{1}{(\alpha + \mu_j + \gamma K_a)(\mu_a + \delta + c)} \begin{bmatrix} \beta_j K_j(\mu_a + \delta + c) & \beta_j K_j(\alpha + \mu_j + \gamma K_a) \\ \beta_a K_a(\mu_a + \delta + c) & \beta_a K_a(\alpha + \mu_j + \gamma K_a) \end{bmatrix}$$

and its spectral radius is:

$$R_0 = \rho(FV^{-1}) = \frac{\beta_j K_j(c)}{(\alpha + \mu_j + \gamma K_a(c))} + \frac{\beta_a K_a(c)}{(\mu_a + \delta + c)}$$

Then, the basic reproduction number in host population is sum of the contribution of juveniles and adults to infection.

As a consequence, for a fixed value of R_0, the age-dependent heterogeneity in transmission ($\Delta\beta=\beta_a-\beta_j$) can range between the finite values of $\Delta\beta_{min}$ (when $\beta_a=0$) and $\Delta\beta_{max}$ (when $\beta_j=0$); at which correspond values of $\beta_j=R_0(\alpha+\mu_j+\gamma K_a(c))/K_j(c)$ and $\beta_a=R_0(\mu_a+\delta+c)/K_a(c)$, respectively.

Protocol S2 References:

van den Driessche P. and Watmough J. (2002) Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, *Mathematical Biosciences* **180**:29-48.

7

Conclusions

Ideas about threshold levels of host abundance for invasion or persistence of infectious diseases are central to the theory and practice of disease ecology (Grenfell and Dobson, 1995). These thresholds are directly related to the basic reproduction number (R_0). The disease spreads in the population if $R_0 \geq 1$. Threshold theorems are very useful in investigating disease dynamics and control policies like culling and vaccination, but their use is hampered in practice because direct measurements of the disease transmission rate are difficult, if not impossible, to obtain without extensive field data (Anderson and May, 1991; Lloyd-Smith et al., 2005). In contrast, estimates of the basic host demography (as natality rate, mortality rate, and carrying capacity) are available for many species. Extensive comparative studies (Peters, 1983; Calder, 1984) relate demographic parameters to body size and show that they scale with the host weight as simple allometric relationships. These relationships should not be interpreted as deterministic laws giving the exact transmission rate for any species, however, because other important details must be considered. We can thus derive a similar allometric relationship for the transmission rate and predict its threshold value for species over a wide range of body sizes.

My analysis of an epidemiological SEI model for rabies shows that the transmission coefficient threshold for the disease to establish in the population scales allometrically (exponent=0.45) with host size as well as the threshold at which limit cycles occur. In contrast, the analysis shows that the minimum basic reproduction number R_0 necessary to sustain epizootic cycles does not depend upon host body size or allometric formulation of model parameters, but is a function of the relative duration of the latent period and the relative mean time to death of infected individuals with respect to the mean life expectancy of a disease-free host. The model predicts that epizootic cycles cannot arise if the basic reproduction number is smaller than 5 regardless of host body size. This suggests the need of a sort of minimum activation energy (represented by the strength of R_0) for oscillation to arise, that is a structural property of the model and not of the parameters chosen. On the other hand, field observations of rabid populations in the wild show that epizootic cycles may actually occur also for R_0 as low as 1.5-2.5 (Coleman and Dye, 1996; Kitala et al., 2002). For this reason the classical homogeneous model appears unsuitable to mimic the disease dynamics in wild populations. As a consequence, it is possible that other factors, such as seasonal forcing, may actually play an important role in generating the observed patterns.

The analysis of the seasonal forced SEI model shows that, while the unforced model exhibits long-term epizootic cycles only for large values of the reproduction number R_0, the seasonally forced model can exhibit multi-year periodicity for much smaller values (< 5) of R_0. Furthermore, bifurcation analysis shows that hosts with small mean body size may exhibit complex dynamics even at small levels of

seasonal forcing. The resonance (frequency locking) is the key mechanism that determines the onset of multi-year periodic cycles for low transmission coefficients, and the larger the host the longer the oscillation period. The typical period predicted by SEI model for different species of hosts infected with rabies is in accordance with field observations

Furthermore, simple extensions of the model are particularly suitable to describe infections in wildlife communities and networks consisting of animals with a spectrum of body sizes, in order to describe spillover, multiple-host, and multiple-pathogen dynamics. I have analysed multiple host interactions in the simple case of one pathogen infecting different host species. I have put the stress on the epidemic events occurrence, deriving conditions for which epizootic cycles arise and underlining their features. I have found that, contrary to single-host models, the value of the basic reproduction number for sustained oscillation to occur strongly depends on the sizes of the two hosts (in particular on their ratio). Epidemic dynamics tends to stabilize for intermediate value of interspecific transmission if species affected by the disease have different body sizes.

In addition, for sufficiently high values of interspecific transmission and species size ratio, the host species with faster population dynamics (smaller body size) can drive the slower one (larger body size) to extinction. In practice, the smaller species acts as a disease reservoir.

I also analysed the effectiveness of disease control through culling in the presence of social structure heterogeneities and genetic heterogeneities. I show that age-dependent heterogeneity in the transmission rate and heterogeneity in strains virulence may produce counter-intuitive results on disease control. In particular, I show (using very general assumptions about life history traits of host species) that the presence of age-dependent heterogeneity in the transmission rate may produce disease prevalence increases for intermediate levels of culling. In fact, even though the host population is even more depressed then expected under homogeneous mixing, not only will the disease not be eradicated from the population but prevalence can be even higher than in the absence of culling. As a consequence, unless it is possible to guarantee a sufficiently high removal of adult individuals, the do-nothing alternative is more effective and less costly than an intermediate culling strategy.

The analysis on an epidemiological model with co-circulation of strains of different virulence suggests that depopulation through culling, in presence of super-infection mechanisms, may favour the selection of less virulent strains in wildlife diseases. This implies a decrease of the critical community size threshold for disease extinction and, consequently, an increase in the culling effort for disease eradication. Furthermore, culling policies providing intermediate level of animal removal may produce

an increase in the total prevalence in the population, with opposite results than expected. Moreover, culling effort for complete disease eradication may be unfeasible because of large cost of implementation or because of the risk for host population persistence.

To conclude, my work show that a better understanding of ecological processes in disease transmission and spread is crucial in our understanding of wildlife disease pattern and for the implementation of control policies. Lack of consideration of relevant ecological details (as seasonality, strain competition, age structure) can drive to the implementation of ineffective and, sometimes, counter-productive control strategies.

Other ecological processes than those presented in this thesis can reduce the effectiveness of disease control, such as: increase in animal contact rate that occurs during culling battues when animals are driven from their natural home range (Sodeikat and Pohlmeyer, 2002; Donnelly et al., 2006); increase frequency of mating contacts due to an increased frequency of oestrus as a consequence of fertility controls (Caley and Ramsey, 2001); decrease of the inter-epidemic period length that favour disease endemisation as a consequence of vaccination campaigns (Pulliam et al., 2007). These topics are actually object of examination in further development of this thesis.

CONCLUSIONS REFERENCES

Anderson, R.M., and May, R.M. (1991) *Infectious Diseases in Humans: Dynamics and Control*. Oxford Science Publication, Oxford, UK.

Calder, W.A. (1984) *Size, function, and life history*, Dover Publications, Mineola, NY, USA.

Caley, P., and Ramsey, D. (2001) Estimating disease transmission in wildlife, with emphasis on leptospirosis and bovine tuberculosis in possums, and effects of fertility control, *Journal of Applied Ecology* **38**:1362-1370.

Coleman, P.G., and Dye, C., (1996) Immunization coverage required to prevent outbreaks of dog rabies, *Vaccine* **14**(3):185-186.

Donnelly C.A., Woodroffe R., Cox D.R., Bourne J., Cheeseman C.L., Clifton-Hadley R.S., Wei G., Gettingby G., Gilks P., Jenkins H., Johnston W.T., Le Fevre A.M., McInerney J.P. and Morrison W.I. (2006) Positive and negative effects of widespread badger culling on tuberculosis in cattle, *Nature* **439**:843-846.

Grenfell B.T. and Dobson A.P. (1995) *Ecology of infectious diseases in Natural Populations*. Cambridge University Press, Cambridge.

Kitala, P.M., McDermott, J.J., Coleman. P.G., and Dye, C. (2002) Comparison of vaccination strategies for control of dog rabies in Machakos District, Kenya, *Epidemiology and Infection* **129** (1):215-222.

Lloyd-Smith, J.O., Cross, P.C., Briggs, C.J., Daugherty, M., Getz, W.M., Latto, J., Sanchez, M.S., Smith, A.B., and Swei, A. (2005) Should we expect population thresholds for wildlife diseases?, *Trends in Ecology and Evolution* **20**:511-519

Peters, R.H. (1983) *The Ecological Implications of Body Size*, Cambridge University Press, Cambridge, UK.

Pulliam, J.R.C., Dushoff, J.G., Levin, S.A., and Dobson, A.P. (2007) Epidemic enhancement in partially immune populations, *PloS ONE* **1**:e165.

Sodeikat, G. and Pohlmeyer, K. (2002) Temporary home range modifications of wild boars family groups (*Sus scrofa L.*) caused by drive hunts in Lower Saxony (Germany), *Zeitschrift fur Jagdwissenschaft* **48**(Suppl. S):161-166.