Chapter 5
Modelling the Dynamics of Host-Parasite Interactions: Basic Principles

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Abstract Mathematical modelling is a valuable tool for the analysis of the infectious diseases spread. Dynamical models may help to represent and summarize available knowledge on transmission and disease evolution, to test assumptions and analyse scenarios, and to predict outcomes of the host-pathogen interactions. This chapter aims at introducing basic concepts and methods of epidemiological modelling, in order to provide a starting point for further developments. After positioning modelling in the process of disease investigation, we first present the main principles of model building and analysis, using simple biological and also mathematical systems. We then provide an overview of the methods that can be employed to describe more complex systems. Last, we illustrate how the modelling approach may help for different practical purposes, including evaluation of control strategies. A brief conclusion discusses the challenge of including genetic and molecular variability in epidemiological modelling.

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5.1 Introduction

Daniel Bernoulli was the first to use a mathematical model approach for assessing the effectiveness of prophylaxis method to control the spread of an epidemic disease (Bernoulli 1766, targeted to smallpox propagation). He simplified a rather generic first model based on the fate of a cohort of individuals, keeping only what was clearly needed for his own purposes. Then, Bernoulli performed a mathematical analysis of the resulting model using a celebrated method to solve in closed form a specific class of nonlinear ordinary differential equations (sometimes referred to as Bernoulli's equations). He carried out a sensitivity analysis and evaluated the robustness of his conclusions with respect to the simplifications made and thus tested their relevance (Valleron 2000).

After Bernoulli's pioneer researches, developments in epidemiological modelling mainly occurred in the early twentieth century. Hamer (1906) was interested in the recurrence of measles epidemics. He introduced one of the fundamental ideas in epidemiology, that is, the epidemic spread depends on the rate of contact between susceptible and infected individuals. Hamer formalized this idea using the 'mass action principle', which states that the transmission rate of an infection is proportional to the product of the densities in both susceptible and infected individuals (Anderson and May 1991). At about the same period, Ross (1908) found a relationship between malaria and mosquito abundance. A few years later, the first complete formulation of a generic epidemiological model was proposed by Kermack and McKendrick (1927). The analysis of their model led to the statement of the threshold theorem: after the introduction of a few infected individuals into a fully susceptible population, an epidemic will occur provided the number of susceptible individuals exceeds a critical threshold. Finally, in 1931 Greenwood introduced the idea that chance may intervene in the process of transmission: during a given contact, transmission may occur or not with a certain probability. These three fundamental concepts, contact rate, threshold theorem and randomness in transmission, are at the origin of the modern theoretical epidemiology.

The very first analysis by Bernoulli which encompassed both observations and theoretical hypotheses to predict the effect of vaccination already showed how such an approach is useful and complementary to experimentations and observations. In order to formulate a relevant model, biologists and modellers have to work together to establish the simplest set of rules that summarizes the biological system of interest, according to the objective of the study. The biological side of model building consists in providing observed or experimental data, expert opinion, or knowledge on similar systems, while the modeller perspective is dedicated to choosing and adapting available methods or develop new ones that are appropriate to the system and questions under study. Interaction between biology and modelling is particularly

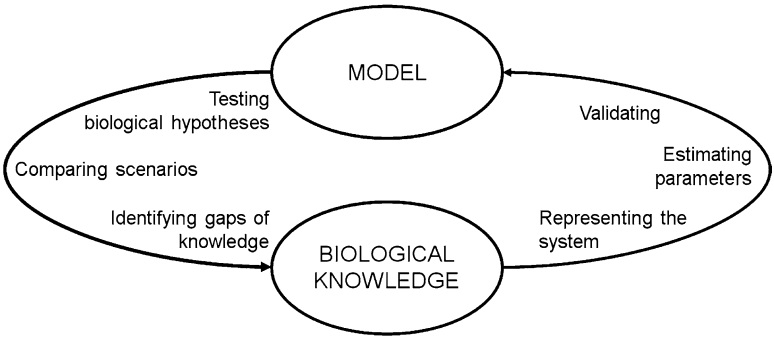

Fig. 5.1 Mutual input of biology and modelling

important to define the scale of the representation (within or between hosts, populations, etc.) and to identify established knowledge together with unlikely or controversial aspects. Hypotheses to be tested can then be formulated. This process gives rise to a mutual input: biology provides the necessary pieces to formalise and validate models, while modelling leads to the formulation of new hypotheses and to the identification of key points and gaps of knowledge that should be investigated through experimental or observational studies (Fig. 5.1).

According to what is known about the system under study and depending on the question to be answered, modelling approaches are used in a variety of manners (Becker 1979; Hethcote 2000; Valleron 2000). The first aim can consist in summarizing available knowledge and constructing a formal representation of the system, in order to facilitate the understanding of underlying complex processes and to provide general qualitative conclusions. Analytical formulations (deterministic dynamical systems, stochastic processes…), computer-based models, graphical schemes or diagrams (conceptual models) are some of possible representations. A classical example of such a descriptive model is the representation of the spatio-temporal dynamics of rabies in wild-living populations (Fig. 5.2): the paradigm of spatio-temporal waves constitutes a reasonable representation of the complex processes underlying rabies expansion, thus it was much used to summarize and explain these processes, including in communication towards non-specialists.

A second aim is to assess the relative importance (essential, secondary or irrelevant) of each of the various mechanisms involved in the system dynamics. With such an objective, an accurate description of the system with clearly stated assumptions and biologically relevant parameters is necessary. Then the model may be used to test biological hypotheses (such as those justifying the structure, parameter values, or the form of transition functions of the model), by comparing the dynamical behaviour of different sub-models including the hypothesis or not. As an example, in order to test whether immune protection or age-dependent infection rates are important processes in the transmission of *Theileria equi* and *Babesia caballi* among horses, Rüegg et al. (2008) compared the goodness-of-fit of predictions issued from

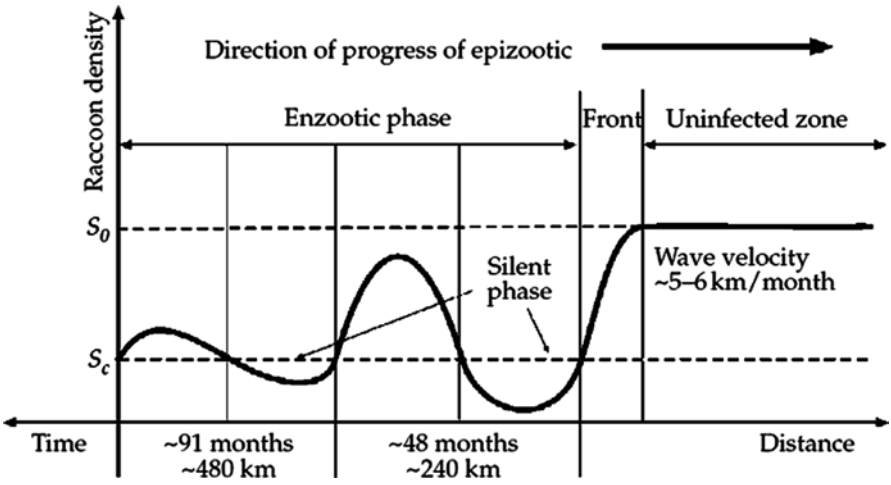

Fig. 5.2 Description of racoon rabies spatio-temporal dynamics through the evolution of host density. Time increases to the *left* of the epidemic front, while distance increases to the *right* of the front (From Real and Childs 2006)

different models. They showed that both mechanisms are important in the transmission dynamics of *B. caballi* (*i.e.*, their inclusion significantly improved the quality of model prediction), but not for *T. equi*.

The same kind of analytical models may also be used to compare different scenarios, and thus answer 'what if' questions. For instance, infection dynamics in different host populations (with different structures, sizes, etc.), in different regions, at different periods, for different variants of a pathogen, etc. can be compared (Becker 1979). Such comparisons cannot generally be carried out in the field or in the laboratory, whereas numerous numerical experiments can be performed by simulation. As an example, Ezanno et al. (2008) evaluated the influence of herd structure on the spread of bovine viral diarrhoea virus within a dairy herd: enhancing contacts between young animals before breeding or isolating lactating cows from other groups both decreased virus spread compared to a herd with a typical structure with indirect contacts between groups.

A last context to use analytical models is the estimation of key parameters from data. For example, the spatial variation of the infection probability for foot-and-mouth disease has been estimated by modelling (Gerbier et al. 2002). Control points of the system and factors of uncertainty that may decrease our confidence in estimations can be identified. Models can also help guiding further data collection in order to improve estimation accuracy.

Third, if the model has been validated against data, it can be used to predict future states of the system depending on observed past ones and on assumptions on mechanisms acting in the future. Whereas quantitative predictions are still subject to some uncertainty even after model validation, qualitative forecasts can be provided for a

variety of situations. For instance the assessment of the relative effectiveness of interventions used to control infectious diseases spread may help to design optimal strategies. This approach was largely used for a variety of diseases such as the foot-and-mouth disease (Ferguson et al. 2001), avian influenza (Boender et al. 2007; Le Menach et al. 2006) and human pandemic influenza (Ferguson et al. 2006; Flahault et al. 2009; Kernéis et al. 2008; Longini et al. 2005 amongst many others).

5.2 Principles of Model Formulation for a Single Homogeneous Population

The formulation and analysis of epidemiological models include several steps: definition of the model structure involving a preliminary choice of a formal representation, analysis of model properties and outputs and identification of thresholds which determine radical changes in model dynamics depending on whether they are exceeded. If an analytical representation of the system in question is chosen, a mathematical formalism should be specified with respect to the context and the question motivating the study. Deterministic or stochastic models in discrete or continuous time are possible representations. Both approaches have their strengths: deterministic models are appropriate in large populations where fluctuations have relatively little overall impact whereas stochastic formulations are more suited for small populations and rare events where randomness has large effects. Although most theoretical aspects presented in this chapter are valid for both categories of models, examples are often related to deterministic models that are more easily described in short terms and appropriate for an introductory text. Stochastic modelling is by no means less relevant for the study of diseases spread and we invite the reader to refer to excellent monographs specifically developing this methodology (Andersson and Britton 2000; Daley and Gani 1999; Keeling and Rohani 2008 to quote only a few). A brief overview of simple prototypes of epidemiological models illustrated by examples is provided in this section, where all the basic models assume a single homogeneous population.

5.2.1 Model Structure

Most epidemiological models start from the description of the infection dynamics at the individual level (Fig. 5.3) to infer pathogen spread at the population level.

At least two individual states should be defined with respect to the disease: susceptible (S) and infected (I). The implicit assumptions when limiting to a two state model are a negligible latency period and an instantaneous return to the susceptible state after infection (this corresponds to the SIS model; Fig. 5.4) or life-lasting infection (the SI model).

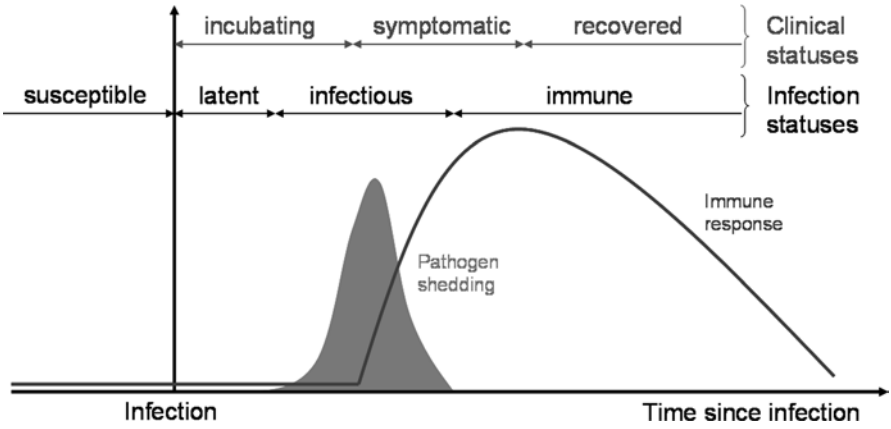

Fig. 5.3 Definition of the individual infection status *vs*. clinical status during a much simplified infection process (Modified from Keeling and Rohani 2008). It has to be noted that the symptomatic period is not necessary simultaneous to the infection status

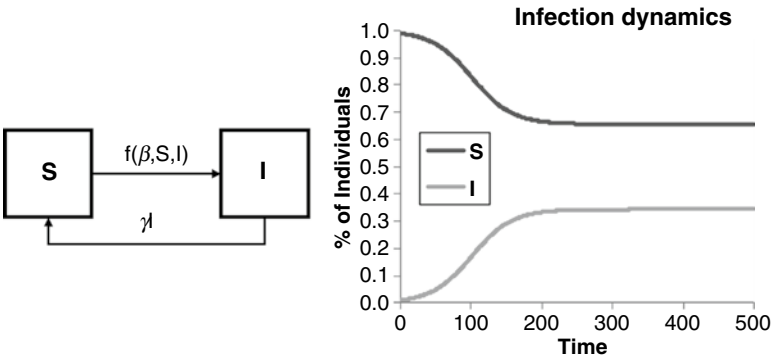

Fig. 5.4 Diagram of a SIS model (susceptible – infected – susceptible) (*left*) and example of simulated dynamics (*right*). The transition from S to I corresponds to the infection process and depends on the transmission rate β, and on the numbers of S and I individuals, f being the force of infection. The transition from I to S corresponds to a recovery (without immunisation) and depends on the mean infection duration ($1/\gamma$ if the sojourn time in compartment I is exponentially distributed)

In order to describe the flows of individuals between compartments within the simplest mathematical framework, additional assumptions have to be made: homogeneous population (*i.e*., in a SI model, all S individuals are of identical susceptibility, all I individuals have identical infectiousness), homogeneous contacts between individuals, a short infection period relatively to the host life expectancy (which allows to neglect population vital dynamics), and a transition from I to S that does not depend on the time since infection. Based on these assumptions, a model may

be formulated in discrete time (*e.g.* the Reed-Frost first models, Daley and Gani 1999; Thrusfield 1995) or continuous time (*e.g.* through a system of ordinary differential equations). When one or several of the above assumptions are not valid, the model should be modified. Typically, if two compartments are not sufficient to describe the infection process, other states may be defined. A recovered (R) status indicates a non negligible delay between the end of the infectious period and the moment individuals lose their immunity (SIRS model). An exposed status (E) is to be considered when there is a non negligible delay between infection and infectiousness. Classically, the probability of recovery per unit of time is constant, which corresponds to an exponential distributed infectious duration (a classical assumption routinely used for mathematical tractability-based reasons). However, more realistic probability distributions can be used. For instance, a gamma distribution can be assumed for the infectious duration by replacing the single previous I compartment by a series of n stages, where the rate of transition between stages is equal to $n\gamma$ (the mean duration of the infectious period being still equal to $1/\gamma$, according to the known property stating that the sum of n equally exponentially distributed variables of mean $1/n\gamma$ is a gamma distributed variable of mean $1/\gamma$).

5.2.2 Model Analysis

The qualitative behaviour of the analyzed system may first be deduced from the mathematical properties of the model. For both discrete and continuous time system models, the resulting mathematical analysis fits into the framework of dynamical systems, a well known and developed branch of mathematics. An important preliminary question is the non-negativity of solution components that is also part of the validation of the rationale underlying model building. Forward invariance is a convenient tool to answer this question.

A second step is the understanding of the population dynamics behaviour before the parasite introduction. Various paradigms are available: constant population size, logistic or mono-stable behaviour (regulation toward a limited carrying capacity), Allee effect or bi-stable behaviour (existence of a population size threshold separating population extinction *vs.* regulation), as well as exponential growth or time-periodic dynamics, to name a few. The exploration of population dynamics requires sorting stationary states (constant solutions) of the model, that can be achieved either in closed form or by using suitable software for numerical or algebraic computation.

Then, a local stability analysis (LAS) should be developed. This consists in assessing whether a small initial departure from a given stationary state will result into the model driving back the population to the original stationary state, or else, driving it toward a new stationary state or to some new horizon, *e.g.* periodic *vs.* chaotic dynamics. A generic mathematical methodology goes through devising a dedicated matrix made of partial derivatives of the model system – referred to as Jacobian matrix of the system evaluated at the given stationary state – and then

computing its spectrum, that is its real and complex eigenvalues. The system is locally stable when all eigenvalues are negative or have negative real parts. Global stability analysis (GAS), that is stability for any nonnegative departure from a given stationary state, is much more complicated since it requires more sophisticated mathematical tools such as building Lyapunov functional. Although complex eigenvalues can make non-mathematician modellers feel uneasy, they are a nice tool to support the existence of oscillatory behaviours in transient solutions as well as to exhibit periodic solutions when time gets large (*e.g*. Hopf biburcation).

The main step now arises: what are the likely outcomes after introducing an infective individual into a naive population? From a mathematical point of view, most questions and answers are identical to those in the foregoing paragraph: stationary states, stability analysis, transient and long time behaviour, put in a somewhat different setting. A first question is whether infection will persist after the introduction of a few infective individuals, *i.e*., LAS of the stationary state without any latent, infectious and immune individuals, the so-called disease free equilibrium (DFE). Computing eigenvalues of a suitable Jacobian matrix will yield an answer (see above). Mathematically this will select a (nonlinear) combination of the parameter set from the model that is to be compared to 0, negativity implying LAS while positivity yields instability (see also R_0 in the next subsection). Heuristically, one may expect the emergence of a LAS endemic stationary state (with infectious individuals) as soon as the DFE becomes unstable, due to one or several parameter(s) variation. This step requires looking for all possible LAS endemic states. What is mostly expected is a *forward bifurcation*, that is the emergence of a unique LAS endemic stationary state when the DFE looses its stability. Dynamics can be much more complex with a *backward bifurcation*, that is the existence of an extraneous LAS endemic state right before the DFE looses its stability (see also the R_0 limit in the next subsection). This means that two different dynamics and LAS regime can coexist: a DFE one and an endemic one, which could make the control of the disease quite uneasy. It may also happen that a LAS endemic state may loose its stability yielding oscillations and time periodic dynamics (cf. rabies model). Numerical simulations can be supported by a suitable mathematical analysis (*e.g*. Hopf bifurcation). For exponentially growing populations (before introduction of the disease) no DFE can exist but the actual question is whether the disease can control and regulate the given population. For time periodic population dynamics (before introduction of the disease), the existence and stability of both DFE and periodic endemic states is challenging to prove from a mathematical point of view, though sophisticated theoretical and numerical tools are available (Bacaër and Gernaoui 2006).

Besides mathematical analysis, numerical simulations are conveniently used to observe or guess transient and long-time dynamics, especially for models using a large number of parameters and state variables. As an example, studying host-macroparasite systems, Rosà et al. (2003) showed that, while a deterministic system predicts oscillatory behaviour, taking into account stochastic events in the system dynamics leads to larger oscillations that may threaten parasite or host persistence (Fig. 5.5). Interactions between model components can be studied, which may give rise to unexpected behaviours. Simulations first require adequate parameterisation of the model, using demographic or epidemiological data (Becker 1989). Then a

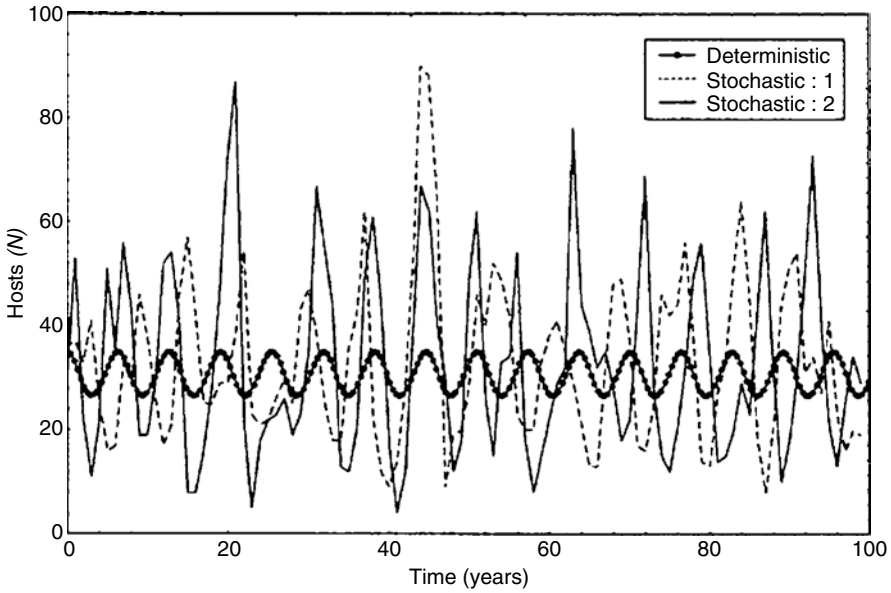

Fig. 5.5 Deterministic prediction and two stochastic simulations for the evolution of the number of hosts across time in the red grouse – *Trichostrongylus tenuis* model (From Rosà et al. 2003)

sensitivity analysis is a relevant approach to evaluate how model outputs vary according to variations in model inputs (parameter values, functions, model structure, etc.; see Saltelli et al. 2000 for a review of methods of sensitivity analysis). First, such an analysis is useful to test modelling assumptions: what if other functions had been chosen? What if the model were simpler with less state variables? etc. A sensitivity analysis also constitutes the first step before using a model to evaluate strategies of control of the system. Only parameters that significantly influence model output and can be managed on the field are potential control points of the modelled system (Ezanno et al. 2007).

5.2.3 *Reproductive Numbers: R_0 and Related Threshold Parameters*

The basic reproductive number, R_0, is one of the most important concepts in epidemiology, population dynamics and ecology provided by the mathematical thinking. Generally speaking, R_0 is the expected number of secondary individuals generated by a typical individual during its lifetime. The term "secondary" depends on context: it means "secondary cases" in epidemiology (where a typical individual refers to an infectious one) and "offspring" in ecology and demography (Heffernan et al. 2005; see Heesterbeek 2002 for a historical perspective on R_0).

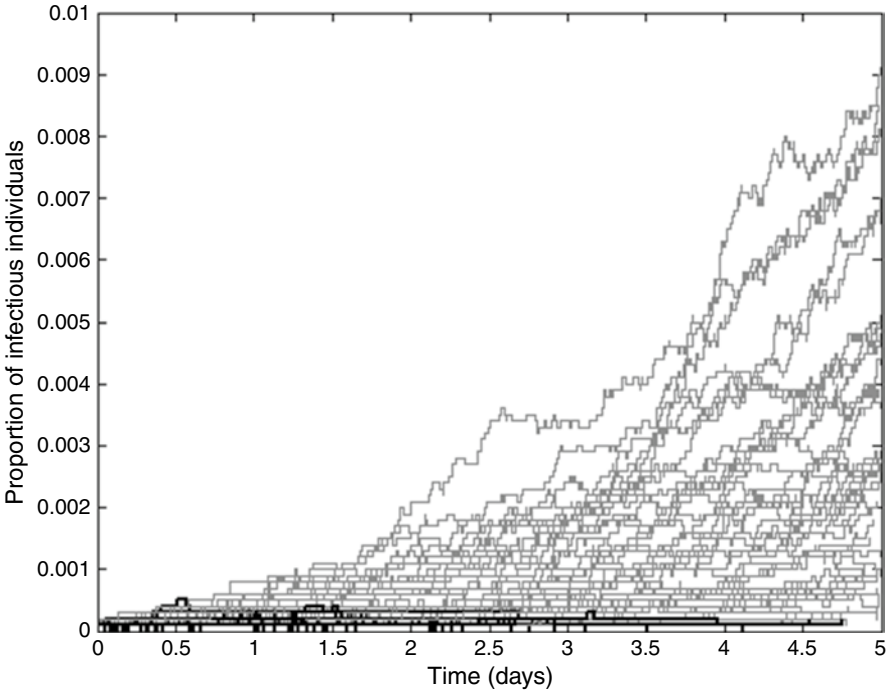

Fig. 5.6 R_0 and epidemic dynamics: proportion of infectious hosts for 100 simulations of an epidemic starting in a susceptible population of size 1,000 after the introduction of one infectious, using a SIR model with $R_0 = 2$. *Black lines* represent simulations where extinction occurs before major epidemics (defined as epidemics leading to infections of more than 90% of the initial susceptibles)

The threshold behaviour of R_0 renders this parameter very useful for predicting the emergence of a new epidemic, the outcome of a started outbreak and the efficacy of mitigation strategies. In a deterministic formulation, if $R_0 < 1$, a pathogen introduced in a completely susceptible population will not be able to invade, whereas if $R_0 > 1$ an epidemic can occur. In a stochastic framework, the interpretation of R_0 is less straightforward: a value of R_0 below 1 predicts the extinction with probability 1, whereas if $R_0 > 1$, invasion is not the only possible outcome because the probability of extinction is not equal to 0. More specifically, in the case of an entirely susceptible population where a single individual is initially introduced, and the dynamics is described by a branching process (with three state variables S, I and R), the probability of extinction before a major epidemic is equal to $1/R_0$ for $R_0 > 1$ (Fig. 5.6). Beyond the context of an entirely susceptible and homogeneous population, other formulations of the reproductive number exist, as briefly stated below.

A general method, developed by Diekmann et al. (1990) (and then described in detail in Diekmann and Heesterbeek 2000, illustrated on a number of specific models in van den Driessche and Watmough 2002 and clearly summarized in Heffernan et al. 2005) allows deriving R_0 as a function of model parameters for a variety of

situations where the population is split into disjoint classes. This method is based on the next generation matrix and R_0 is then calculated as its dominant eigenvalue. Situations as diverse as the following ones are handled by this approach (see van den Driessche and Watmough 2002 for more details): heterogeneous populations divided in several groups with specific behaviours with respect to the disease, such as sexually transmitted diseases; multi-strain systems, such as influenza spread, where several strains may co-circulate and are in competition for the same hosts; vector-borne diseases where both vectors and hosts dynamics should be considered simultaneously. For any of these types of models, a next generation matrix can be built after having identified and separated terms defining new infections. More precisely, for each compartment i, F_i is defined as the rate of appearance of new infections and V_i as the difference between out and in transfers of individuals by any other means. The next generation matrix is then equal to FV^{-1}, where F and V are the matrices of partial derivatives of F_i and V_i respectively, under some particular conditions met by F_i and V_i. Applied to a simple SIR model with no demography, this method would yield to $R_0 = \beta/\gamma$ (see Fig. 5.4 for parameter definition).

The R_0 value derived in this way and more exactly its position with respect to 1 helps assessing questions such as the capability of a pathogen introduced into a fully susceptible population to generate an epidemic. As stated in the previous subsection, for dynamical systems, this can also be assessed by studying the LAS of the DFE which reduces to finding a relationship between parameters that makes all the Jacobian matrix eigenvalues to be negative or have negative real parts. It is important to note that, while these two approaches are qualitatively equivalent with respect to the answer concerning the invasion of the host population by the pathogen, the latter one may supply a threshold parameter different from R_0 (Roberts 2007). Roberts and Heesterbeek (2003) emphasize that if this threshold does not have the same biological interpretation as the dominant eigenvalue of the next generation matrix, it "can therefore not be called the basic reproduction ratio nor denoted by R_0". It should also be pointed out that both methods can define algebraic threshold parameters with no sound epidemiological interpretation.

If the population is not entirely susceptible, the appropriate term to be calculated is the effective reproduction number, R_{eff}, which is equal for an SIR system to $\beta S/\gamma N$, where S is the size of the susceptible population and N is the total population size. More generally, while R_0 is uniquely defined for a couple pathogen/host population, R_{eff} may change over time, as the proportion of susceptible hosts S/N varies.

Beyond derivations of R_0 and R_{eff} as combinations of model parameters in order to identify threshold criteria, various methods were also developed for estimating the value of R_0 and its related variants from data. One of the simplest methods, valid for SIR models and closed populations, connects R_0 to the final epidemic size: $R_0 = \ln\left(s\left(\infty\right)\right)/\left(s\left(\infty\right)-1\right)$ where $s(\infty)$ represents the final proportion of susceptible hosts (Diekmann and Heesterbeek 2000). This assumes that the epidemic is observed until the end which is not always the case. Moreover, it is also of great importance not only to provide a posterior characterization of the epidemic, but mostly to assess the epidemic intensity at its very beginning, in order to tailor mitigation strategies. This is possible for instance by calculating R_0 from r, the initial rate of the exponential

growth of the number of infectious individuals. Several expressions relate R_0 to r, depending on the distribution of the generation time, W (defined as the delay between the moment one individual becomes infected and he/she infects another individual; Roberts and Heesterbeek 2007; Svensson 2007; Wallinga and Lipsitch 2007; Yan 2008). For a simple SIR model and assuming a constant infectivity, $R_0 = 1 + r * T_W = 1 + r * T_I$, where T_W and T_I are the mean generation time and the mean duration of the infectious period respectively. R_0 is certainly of great interest, but it is often more convenient to focus on R_{eff}, since it reflects the actual capability of the epidemic to progress over time and provides information on the impact of control measures in real time. The estimation of R_{eff} reduces to a simple counting of secondary cases if all infected individuals are traced until their index case ("who infected whom" chain). However, most often, this information is not available. In this case, R_{eff} can be estimated for instance by fitting a transmission model to data (Riley et al. 2003). A statistical approach that avoids mechanistic assumptions was proposed by inferring "who infected whom" from the observed curve and times of symptoms by using pairs of cases instead of the entire infection network (Wallinga and Teunis 2004, estimations for the 2003 SARS epidemic in several geographic locations). The scenario where not all secondary cases have been detected was tackled through a Bayesian approach by Cauchemez et al. (2006) who estimated the reproduction number in an ongoing epidemic for the 2003 SARS epidemic in Hong Kong.

As already stated, information on R_0 and its related variants provides valuable insights mainly in two situations: for the evaluation of the invasion risk of a host population by a pathogen and for evaluating and comparing control strategies. For both cases, the choice of an appropriate method for estimating R_0 or R_{eff} should be done with respect to data and objectives and comparison of estimations to previous values and interpretation of discrepancies (if any) should also be provided.

Despite its incontestable role in handling infectious diseases spread, R_0 could sometimes be mis- or overused. Roberts (2007) draws our attention on some exceptions where the basic statements generally fulfilled by R_0 and cited in this subsection are not true (see also the backward bifurcation in the previous subsection). The author cites several mechanisms allowing persistence of an endemic infection even for $R_0 < 1$ (for example assuming that exposure to infection accelerates the transition from the exposed to the infectious state) and points out the existence of situations where the evolution of a pathogen does not necessarily maximise its R_0. Another important point raised by Roberts (2007) and initially fully described in Roberts and Heesterbeek (2003) and then in Heesterbeek and Roberts (2007) concerns structured populations where interventions are targeted at specific subpopulations. In this case, R_0 is less useful and should be replaced by T, the type-reproduction number. Both R_0 and T exhibit the threshold behaviour and are equivalent in homogeneous population, but T is more appropriate in heterogeneous populations since it summarizes the control effort required to eliminate an infection when measures are applied to a specific host type (rather than to the entire population). Finally, care has to be taken when evaluating control efficacy through R_0 values: as pointed out by

Heffernan et al. (2005), since sometimes the use of R_0 could ignore other issues such as the potential negative effect of interventions on population, it is important to simultaneously consider other indicators (the total morbidity or mortality) in addition to R_0.

5.3 More Realistic Models for Complex Situations

The simple models cited in the previous section give a very general idea of two processes involved in epidemiological dynamics: transmission and immunity. However, these may be not sufficient if pathogen dynamics is affected by other traits of the host population, such as heterogeneity among individuals, demographic processes or population structure. Here, we provide a brief overview of further possible models for more complex systems.

5.3.1 Heterogeneity Among Individuals

Individuals in a population do not equally contribute to infection dynamics. First, infectious individuals do not equally shed the pathogen, either because shedding routes are numerous and possibly not simultaneous, or because excretion depends on infection duration or other individual characteristics such as age, genetics, physiological stage, etc. Second, susceptible individuals do not have equal susceptibility, due to individual intrinsic characteristics or previous exposure to the pathogen. Compared to naïve (never exposed) individuals, those that have already been exposed to the pathogen often have a reduced susceptibility and infection duration. Depending on the reduction in susceptibility after a first infection, such a model goes from an SIS model (no protection) to an SIR model (full protection). The same approach is also adequate to represent immunity acquired by vaccination (Glass and Grenfell 2003; Greenhalgh et al. 2000). Lastly, a cross protection may arise when many variants of a given pathogen co-circulate in the population for example (Restif and Grenfell 2007). These heterogeneities in infectiousness and susceptibility interfere with pathogen spread and control both in non-structured (Lloyd-Smith et al. 2005b; Matthews et al. 2006) and structured (Ball and Lyne 2001) populations. Therefore, heterogeneity should be considered, especially when specific individuals are targeted by a surveillance or control program.

Such heterogeneities can be modelled through several methods. A first way is to consider as many categories of S or I individuals as necessary to describe variability in susceptibility (Fig. 5.7) or infectiousness. This has been used to model the spread of human tuberculosis considering that individual may have either a susceptible or a resistant phenotype, assumed to be consistent for an individual over time (Murphy et al. 2003). Another way is to use partial derivative equations when susceptibility or infectiousness continuously varies among individuals (Novozhilov 2008; Veliov 2005).

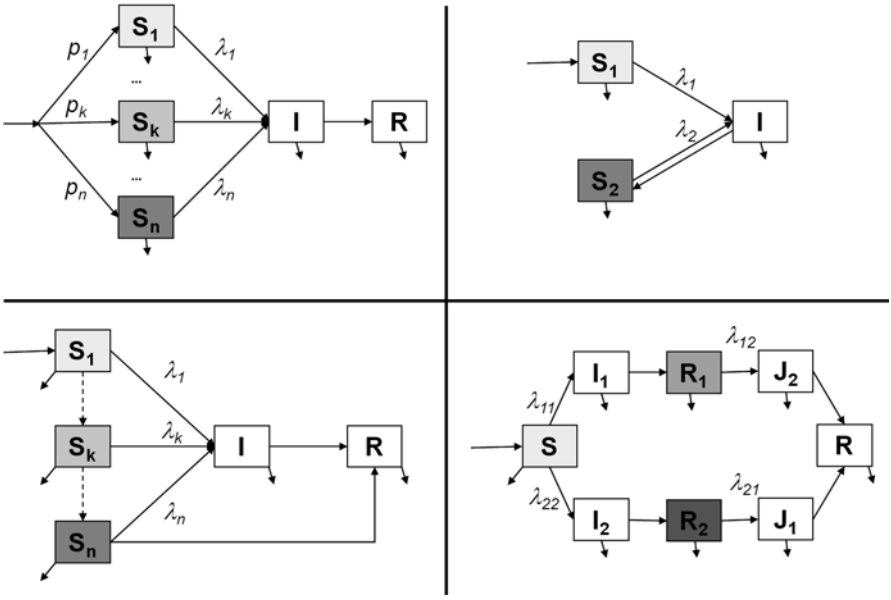

Fig. 5.7 Diagrams of SIR models accounting for heterogeneity in susceptibility. *Top left*: the level of susceptibility varies among individuals but is consistent over life (a proportion p_k of individuals are born with susceptibility k and thus has a force of infection λ_k); *bottom left*: susceptibility variation over lifetime; *top right*: reduced susceptibility following exposure to infection ($\lambda_2 < \lambda_1$); *bottom right*: reduced susceptibility because of cross-protection after infection with a close variant of the pathogen

5.3.2 *Accounting for Population Dynamics*

The assumption that demographic processes may be neglected in front of epidemiological dynamics cannot hold in all situations, specifically when the duration of infection is of the same order of magnitude as life expectancy, but also when considering the long-term dynamics of the system, instead of a single epidemic process. In this case, birth, death and migratory processes should be included in the model. This may be done by adding input and output flows to each compartment.

Including demographic processes in epidemiological models may first help to investigate their influence on disease dynamics. Generally speaking, birth acts to replenish the pool of susceptible individuals and thus to favour disease spread, while mortality has the opposite effect. This has been studied in plant diseases: when crop growth is taken into account, it first entails a dilution effect on leaf lesions, followed by an increase in R_0 due to higher density in susceptible host tissue (Ferrandino 2008). The situation becomes more complex when density-dependent processes occur, which is the case in most natural-living populations: then fecundity and mortality are not independent from population sizes. This gives rise to complex effects, including the possibility that the threshold theorem is not longer valid or observable (Lloyd-Smith et al. 2005a). Disease may also be a major determinant in host

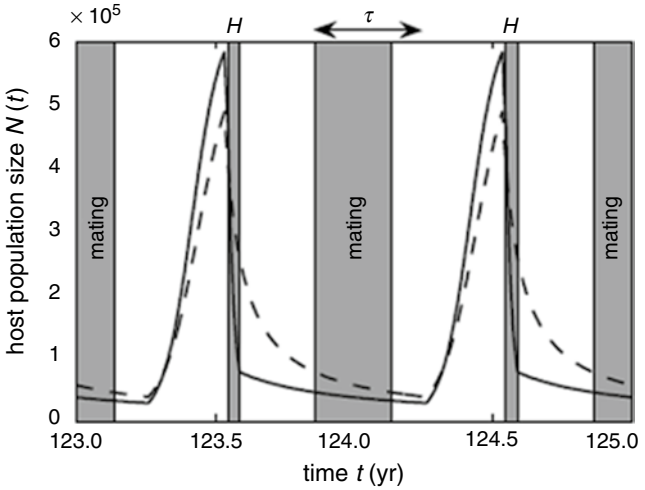

Fig. 5.8 Effect of harvesting on the total host population size in wild boar infected by Classical Swine Fever (From Choisy and Rohani 2006). Numerical solution of the model for a 2-year period, after stationary dynamics has been reached. The periods of mating and harvest (*H*) are represented in *grey*, and the duration of gestation is represented by the length of the *double arrow* above the graph. The *dashed curve* represents the total host population size in the absence of harvesting and the *full line curve* represents the dynamics of the total host population size in the presence of harvesting

population dynamics through its effect on fecundity or survival. HIV infection is one of the leading examples when population demographics need to be accounted for, the virus being able to turn population growth rates from positive to negative values (Anderson et al. 1988). Another case when host population dynamics should be considered is represented by animal populations managed by humans. Rapid changes in density, demographic parameters, spatial distribution and contact structure may result from management decisions and affect disease transmission. Complex dynamics may arise from the interactions between demographic and disease processes. A recent example is the study of hunting on transmission of classical swine fever in wild boar *Sus scrofa* (Choisy and Rohani 2006, Fig. 5.8). The model showed that the drastic reduction in population density due to harvesting results into an overcompensation due to density-dependent birth and death rates. After the next birth period, the population reaches high density, which results in a high level of disease transmission and prevalence. Overall, harvesting is predicted to increase disease spread.

5.3.3 Pathogen Spread in Structured Populations

Beside their heterogeneity, individuals are clustered in groups within which preferential contacts occur. Age, social groups, households, schools or herds strongly

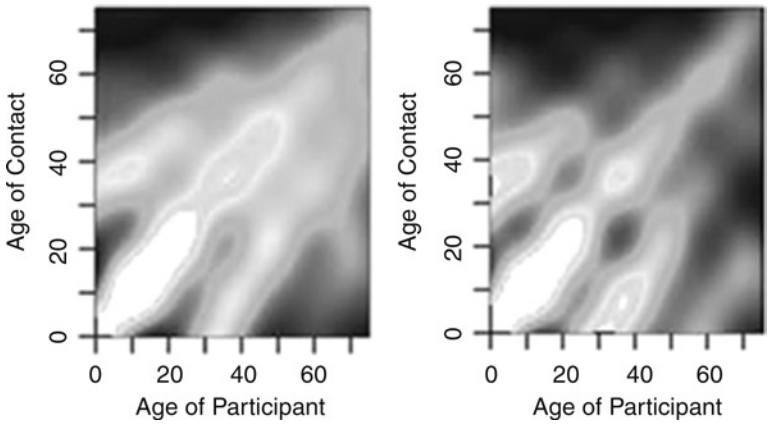

Fig. 5.9 Smoothed contact matrices among age classes in Great Britain, including all contacts (*left*) or physical contacts only (*right*) (Modified from Mossong et al. 2008). White indicates *high* contact rates, while *dark grey* stands for *low* contact rates

structure the contact network among individuals (Keeling and Rohani 2008; Mossong et al. 2008, Fig. 5.9). This structure may have spatial (due to environmental structure), behavioural (*e.g.*, related to sexual behaviour) or social components. In all cases, pathogen spread occurs at two scales: local or within-group transmission is related to direct (between individuals) or indirect (*e.g.* because of a shared environment) contacts, while between-group transmission is possible through long-distance individual movements (migration, visits, etc., Barlow et al. 1998).

It is important to understand how these structures affect pathogen invasion, spread and persistence for helping decision making in public and veterinary health (Cross et al. 2005; Grenfell and Harwood 1997; Hagenaars et al. 2004; Keeling and Rohani 2002; Lloyd and Jansen 2004). The most studied aspect is spatial structure, which has been modelled in a variety of ways, considering either continuous or discrete space, and sometimes including real environmental characteristics. One of the most widely used concepts is the metapopulation (described in the next subsection), where space is divided into discrete patches, each patch representing a potential localisation of a group of hosts.

5.3.4 Disease Spread in Metapopulations

A metapopulation structure corresponds to an inter-patches contact network in which space is either implicit or explicit (Fig. 5.10). Each unit corresponds to either an individual (Rhodes and Anderson 1996), or a local population (Cross et al. 2005; Park et al. 2002). The concept of metapopulation has been largely used in ecology and population genetics to study dynamics of fragmented populations and genes

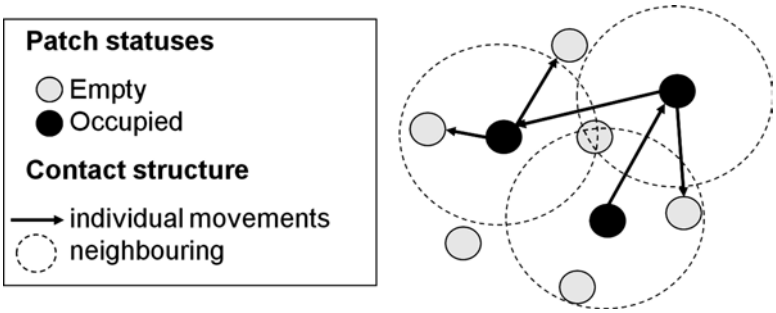

Fig. 5.10 A spatially explicit metapopulation with a contact structure based on individual movements and neighbouring relationships

flow on heterogeneous landscapes (Grenfell and Harwood 1997). Numerous epidemiological models have been developed in a context of metapopulation, accounting for patch infection dynamics in addition to the extinction-colonisation process. Hess (1996) has been a precursor by conceptualising an epidemiological model based on Levin's model: the migration of infectious individuals is a source of infection for susceptible individuals from pathogen-free populations.

Infection spread between patches has been modelled either mechanistically, *i.e.*, explicitly representing the phenomena that are at the origin of disease transmission (Cross et al. 2005; Jesse et al. 2008; Keeling and Rohani 2002), or phenomenologically, by considering that the presence of infection in a patch results in a positive force of infection on patches in contact without explicitly representing the transmission process between patches (Hagenaars et al. 2004; Keeling and Rohani 2002; Park et al. 2002).

From a mechanistic point of view, three types of metapopulations can be defined based on the type of contacts between patches (for a review, see Keeling and Rohani 2008). First, individuals do not encounter explicitly but indirect contacts exist because of the wind, a mobile reservoir, a vector, or through neighbouring contacts between adjacent populations. This mechanism is well adapted to plants which are static, but also to cases when animal diseases are vectored among herds, such as in the case of foot-and-mouth virus aerial transmission among herds, and to neighbouring populations sharing a common environment (water point, feeding area, etc.). Second, individuals may explicitly move between patches with no return to their source patch, as it is the case when individuals disperse, are sold or bought. Third, individuals may move between patches and then return to their source patch (human populations or seasonal migration). In this last case, the duration of the visit influences the number of cases generated by a visitor if infected or the probability for a susceptible visitor of being infected.

The contact pattern may be represented by a contact matrix among patches. For homogeneous networks, all patches are equally connected to each other (Hagenaars et al. 2004; Jesse et al. 2008). For heterogeneous networks, a contact matrix defines which patches are in contact (Cross et al. 2005; Park et al. 2002). In a simplistic

approach, the intensity of contacts may be equivalent for all couples of patches, whereas more refined models consider variable contact rates among patches, using observed or modelled contact networks.

Last, metapopulation models may have various levels of complexity, depending on whether they account for the within-patch infection dynamics. Metapopulations may first have no explicit within-patch dynamics (each patch is considered to have a global infection status). Such an approach has been used to study the persistence of a metapopulation when infected by a pathogen (Gog et al. 2002; Hess 1996; McCallum and Dobson 2002) or pathogen spread and persistence when local infection dynamics rapidly reaches an equilibrium (*e.g.*, avian flu: Le Menach et al. 2006; foot-and-mouth disease: Le Menach et al. 2005). When the within-patch infection dynamics is modelled, the infection status of each individual is considered (Cross et al. 2005; Hess 1996; Jesse et al. 2008; Park et al. 2002) and the status of patches is derived from patch composition. This approach is useful when there is a high variability in the within-patch prevalence among infected patches or for a given patch over time. For example, considering bovine paratuberculosis, infected animals may exit the herd long before being infectious because of a long latency period between infection and shedding (Marcé et al. 2011). These models are more realistic and give a better overview of all possible epidemiological situations, but are also far more complex.

Representing or not the within patch dynamics depends, in addition to the question under study, on the separation between time-scales of processes occurring within and between patches. If local dynamics are fast and global dynamics are slow, it is possible to neglect the first ones under certain stability assumptions and thus to reduce complexity.

5.4 Models for Evaluating Control Strategies of Pathogen Spread in a Population

Providing help guide for decision making about diseases spread prevention and control is one of the major purposes of epidemiological modelling. The objective of such interventions is to prevent emergence and to reduce the incidence in new cases and hence the total epidemic burden. More generally, this aims at optimizing economic animal or human-health outcomes. If we consider the case of animal infectious diseases, their control relies on three principles: increasing resistance in infection of susceptible animals (*e.g.* through vaccination or genetic selection), reducing or preventing shedding of the pathogen by infectious animals (through treatment, test-and-cull strategies), or preventing contacts between susceptible animals and pathogens (through confinement, quarantine, movement restrictions) (Garner et al. 2007). Disease control may also involve indirect measures such as acting on population dynamics (through culling, contraception, modified hunting strategy or renewal strategy in a herd) or acting on the environment (*e.g.* through sanitary fences, Ward et al. 2009). Each strategy is based on a single or a combination of measures, which may be implemented at different levels and scales.

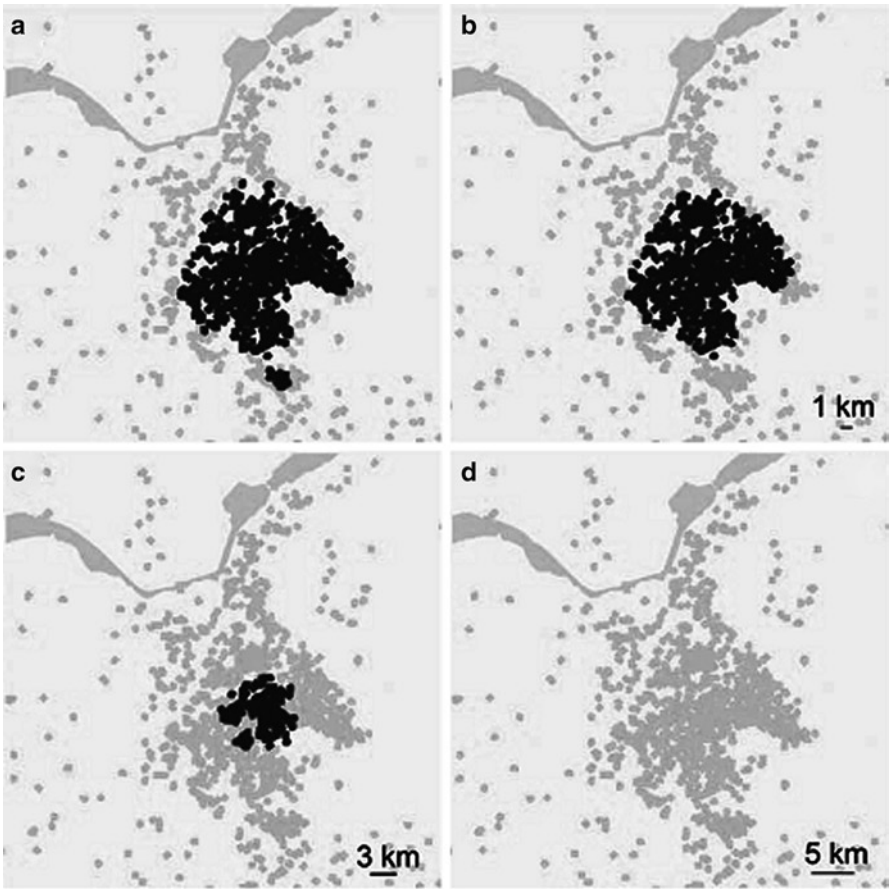

Fig. 5.11 High-risk areas for epidemic spread of the H7N7 avian influenza in poultry for various local culling strategies in the Netherlands (Modified from Boender et al. 2007). (**a**) Results for the default scenario (no culling); (**b**) Results for a scenario with immediate culling of all farms within a range of 1 km around an infected farm; (**c**, **d**) Culling is carried out in a range of 3 and 5 km around infected farms, respectively. Farms in *light grey* pose no risk of epidemic spread for the chosen control strategy, while farms in *dark grey* constitute a risk of epidemic spread even in the presence of interventions

Modelling is an adequate tool for comparing, implementing, evaluating and optimizing control strategies, by allowing to test *ex-ante* a large number of scenarios, resulting from the multiplicity of measures that can be combined and from the interaction between disease spread and population dynamics. Questions to be answered are numerous and various: what size for the zone of preventive vaccination? Which animals should be targeted by tests, vaccination?

Models – for which the consistence between outputs and expectations has been evaluated – can then be used to qualitatively compare control strategies.

For example, Wilkinson et al. (2004) compared various vaccination strategies designed to limit the transmission of bovine tuberculosis in badgers, such as proactive vaccination versus vaccination in reaction to cattle infection, or large-scale versus localized implementation. Models that have been validated on data can be used to provide predictions on the effectiveness of interventions, at least comparatively. Boender et al. (2007, Fig. 5.11) used data from a recent epidemic of avian influenza H7N7 in the Netherlands to fit an explicitly spatial model. Various levels of culling were then tested, to examine the balance between cost and effectiveness of culling.

However, using quantitative predictions requires accurate parameterisation of models and thorough validation of their forecasts using appropriate data sets which are not always recorded. In particular, when a new pathogen emerges, no historical data are available. Moreover, a reference situation in the absence of any intervention or with a perfectly known control strategy is rarely described, especially for endemic diseases. Therefore, the use of modelling approaches to evaluate control strategies should be preferentially considered for qualitative assessment of their impact.

5.5 Conclusion

Modelling is a powerful tool for representing complex systems, testing hypotheses, estimating key parameters from data and predicting the outcome of host-pathogen interactions without or in the presence of interventions. When knowledge and data are available at different scales, models also allow relating fine scales at which mechanisms are known to larger scales at which observations can be made, in order for instance to estimate parameter values (Soubeyrand et al. 2007).

Any model involves a trade-off between simplicity and mathematical tractability on one hand and complexity allowing a closer similarity to the specific problem under study on the other. In this process, taking into account the genetic and molecular variability of both hosts and pathogens is the coming challenge (Anderson 1995; Galvani 2003). Several attempts have been made to integrate the genetic diversity of strains, or represent simple selective processes. For instance, taking into account both epidemiological and molecular relationships between infected premises allowed Cottam et al. (2008) to trace back the spatio-temporal, as well as the evolutionary history of a beginning foot-and-mouth epidemic (see the following chapters). For influenza viruses, several models have been built to analyze the interaction between the pattern of reinfection and the mutation process (Gordo et al. 2009). However, classical tools of epidemiological modelling may not be relevant when genetic variability is involved. The development of specific tools is required to integrate evolutionary ecology and epidemiological patterns.

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