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REVIEW ARTICLE

Emergence of viral diseases: mathematical modeling as a tool for infection control, policy and decision making

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Abstract

Mathematical modeling can be used for the development and implementation of infection control policy to combat outbreaks and epidemics of communicable viral diseases. Here an outline is provided of basic concepts and approaches used in mathematical modeling and parameterization of disease transmission. The use of mathematical models is illustrated, using the 2001 UK foot-and-mouth disease (FMD) epidemic, the 2003 global severe acute respiratory syndrome (SARS) epidemic, and human influenza pandemics, as examples. This provides insights in the strengths, limitations, and weaknesses of the various models, and demonstrates their potential for supporting policy and decision making.

Keywords: *Viral disease; mathematical modeling; epidemiology; infection control; regulatory policy*

Introduction

New and re-emerging viral diseases may arise from animal reservoirs when ecological or environmental changes increase opportunities for viruses to enter either human or animal populations (Woolhouse & Gaunt, 2007). During the last two decades we witnessed viral disease outbreaks caused by HIV, the Ebola virus, West Nile virus (WNV), severe acute respiratory syndrome coronavirus (SARS-CoV), foot-and-mouth disease virus (FMDV), and avian influenza (AI) (Murphy 2008). We are now confronted with the recently emerged swine-originated new influenza A (H1N1) virus (Darwood et al. 2009). Its worldwide spread urged the WHO (World Health Organisation) in June 2009 to declare the first pandemic of the twenty-first century (http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html). Practices of biomedicine such as the increased use of pathogenic viruses in research laboratories, vector viruses for gene therapy, vaccination with live-virus vaccines, and xenotransplantation also pose risks of viral outbreaks with epidemic potential (Enserink, 2007; Louz et al., 2005, 2008; Normile, 2004). Also we are faced with the threat of viruses such as smallpox as weapons of bioterrorism (Dembek, Kortepeter, & Pavlin, 2007). These threats raise challenges regarding infection control policies. Outbreaks or epidemics of communicable viral diseases can have enormous consequences for public and/or animal health and may have enormous economical, social, and even political consequences affecting many countries worldwide (Bender, Hueston, & Osterholm, 2006). To mitigate both spread and impact, it is necessary to timely implement and/or develop infection control measures. Policy makers nowadays face important questions regarding trade-offs between different response strategies and degrees of mitigation to implement. Given the scale, speed, and complexity of epidemics in a globalized world, simulation of transmission scenarios, and evaluation of infection control measures becomes a necessity (Jones et al., 2008). Mathematical models are now increasingly used for this

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purpose (Grassly & Fraser, 2008). The use of mathematical models for quantitative epidemiology of infectious diseases has a long history. Mathematical models have been widely used to study and understand the spread of viral diseases. They have also been successfully used for development and evaluation of antiviral therapy and vaccination policies against viral diseases such as AIDS and measles (Baggaley, Ferguson, & Garnett, 2005; Gay, 2004). However, their use to inform and guide infection control policy, risk assessment, and decision making during the course of an outbreak or epidemic or for contingency planning is rather recent and less well known among regulatory authorities and policy and decision makers. The transmission potential of an infectious disease is commonly quantified by the basic reproduction number R_0 (Anderson & May, 1991; Dietz, 1993). R_0 is defined as the average number of secondary cases generated by a single infectious person in a totally susceptible population. R_0 has a threshold value that equals 1. In general if $R_0 \geq 1$ then an outbreak will lead to an epidemic. If $R_0 < 1$, an outbreak will fade out. In practice efficacy of infection control measures can be measured in terms of the ability to reduce R_t, the reproduction number of a disease at a given time, to a value below 1.

In this review we discuss modeling studies on emerging communicable viral diseases that can have a major impact on both public and animal health in light of infection control and policy and decision making. In the first part we provide an introductory outline on mathematic modeling and important concepts. In the second part we focus on studies of the 2001 UK foot-and-mouth (FMD) outbreak, the 2003 global SARS epidemic and future human influenza pandemics with emphasis on predicting transmission potential, the course of the epidemic, and assessment of effectiveness of infection control measures. The purpose of this paper is to demonstrate the application of mathematical models and illustrate their potential as a tool for policy and decision making.

Mathematical models: model structure, model building, and use

When an outbreak of a communicable disease occurs, mathematical models can be used to describe the spread in a community and to understand infection dynamics. The models can also be used to forecast characteristics of the outbreak (e.g., size and duration), to build epidemic scenarios and to model the impact of possible interventions. In addition, they can provide guidance to control strategies and policy decisions. Models allow estimating important epidemiological parameters from the outbreak data. Furthermore, the models can be used for preparedness and mitigation planning of future outbreaks or epidemics and retrospective analysis in support of policy development. To facilitate mathematical models for these purposes it is necessary to conceptualize the dynamic epidemic process and quantify disease transmission. For that it is important to choose the modeling procedure, to design the model structure and define underlying biological and epidemiological assumptions and parameters. Two main types of models are commonly distinguished: deterministic and non-deterministic or stochastic. The models can range from simple compartmental deterministic models to complex spatially stochastic and (individually) social-based network models (Koopman, 2005). The choice of model, its complexity and which parameters to specify is context dependent and largely driven by the type of disease, available data, the main purpose, the questions to be answered, and the expertise available (Keeling & Rohani, 2008). In general, a useful model should be fitted to its purpose, include all necessary features and be parameterizable from available data (Keeling & Rohani, 2008). Which details and complexities to incorporate to the models' purpose can be a skillful and complex task.

Policy decisions may require the results of more than one type of approach or model. The choice of what control measures and response strategies to implement is context dependent and is usually a compromise between the magnitude of intervention and their logistical and economical feasibility (Wearing, Rohani, & Keeling, 2005).

In the following section we provide an outline of basic concepts and approaches common to mathematical modeling and parameterization of disease transmission. This provides understanding of how mathematical models can be constructed and used as a tool for infection control and decision making.

The basic SIR model and model formulation

The majority of the models in epidemiology are compartmental and based on systems of differential equations reflecting disease dynamics and rates of flow of a population from one epidemiological state (compartment) to another. These compartmental models can be either deterministic or stochastic (see below). The classic prototype, the so-called deterministic compartmental SIR (susceptible-infectious-recovered) framework, was first introduced by Kermack and McKendrick in the 1930s (Kermack & McKendrick, 1991). In addition to the SIR model two other basic models, i.e., SI (susceptible-infectious) and SIS (susceptible-infectious-susceptible) are commonly distinguished. The SIR model is regarded as the foundation for almost all mathematical epidemiological

models. The SIR model classifies host populations in susceptible S (individual hosts that are susceptible for the disease), infectious, I (individuals that are infectious) or recovered/removed, R (individuals that recovered with immunity or are classified as removed by either death or isolation) compartments (Figure 1). S(t), I(t), and R(t) represent the actual number of individual hosts at time t per compartment. This framework is made mathematically by formulating a set of non-linear differential equations:

$$\frac{ds}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma l$$
$$\frac{dR}{dt} = \gamma l$$

These equations describe the transmission dynamics of the infection (flow) from one compartment to another that are governed by rate coefficients leading to a flow chart as shown in Figure 1 (Anderson & May, 1991; Hethcote, 2000). The SIR model is based on the so-called mass action principles of reaction kinetics. In epidemiological terms the SIR model in its most elementary form is based on the following assumptions: (1) all susceptible individual hosts in the population are equally at risk for infection which is known as "homogeneous mixing", (2) the infectiousness of all infected individual hosts is presumed to be equal and constant, (3) the total population size is fixed, i.e., a "closed population" as no demographic turnover (birth or death) is taken into account (Roberts & Heesterbeek, 2003). Since demographic effects are ignored, by definition S(t)+I(t)+R(t) equals N(t) which represents the total population size. Therefore the third equation is redundant. Analogous to the mass-action principles, contacts between susceptible and infectious hosts are assumed to take place at a rate proportional to their numbers in the population. Flow charts usually display rates of flow rather than absolute numbers that move from one compartment to the next. In practice often the simplifying assumption is made that the recovery rate γ of infected hosts (Keeling & Rohani, 2008) is constant, leading to exponentially distributed infectious periods. The mean infectious period, i.e., the average time that individuals remain in compartment I is equal to $1/\gamma$. The rate of new infections can be defined as βI with a contact rate β. (see Figure 1). The parameter values for β and γ are determined from field data or through literature review.

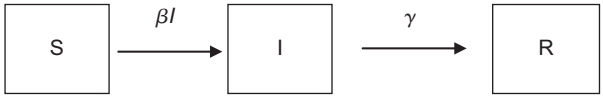

Figure 1. Flow chart of the basic SIR model. Boxes represent the different epidemic states or compartments. Arrows indicate the movement or flow between the compartments. The flowchart can be translated into the accompanying set of differential equations as displayed in the text.

Practical application and extensions of the SIR model

The basic SIR model assumes a uniform population and homogeneous mixing with no demographics. For most epidemics this is unrealistic and a simplification of real epidemic spread. Nevertheless it can for instance be applied to viral epidemics of which the time scale is much shorter than the time scale of births and deaths, conferring immunity to individuals after recovery (e.g., measles and influenza) (Keeling & Rohani, 2008). Furthermore, SIR models can be relatively easy adjusted to account for demographic turnover when this becomes important, e.g., for HIV given the long epidemiological time scale of AIDS. Despite limitations, the basic SIR model can lead to potent qualitative results and often serves as a basis to (understand) more complex models or to gain analytical insights into the behavior of models, e.g., threshold analysis (Hethcote, 2000). Although basic SIR models can generate qualitative insights in the dynamics of infection and immunity and their effect on epidemic patterns, they are not useful to determine quantitative effects of, e.g., intervention strategies on the course of an epidemic.

Depending on the nature of the viral outbreak or epidemic and the purpose of the model, more compartments reflecting different states of the infection process, e.g., exposed (E) or passive immune (M), may be added to the model structure. By this way a series of conventional deterministic compartment models have been introduced over the last century and successfully applied ever since. Commonly used acronyms and extensions of basic SI, SIS and SIR models are SEIR, SEIS and MSEIRS (Hethcote, 2000; Keeling & Rohani, 2008). The simplest SI model (referred to as the 'simple epidemic') can capture infection where no recovery is possible (e.g., early stages of the HIV/AIDS epidemic). The SIS model can deal with infection where recovery is possible and where recovered hosts are immediately susceptible without immunity from reinfection (e.g., common cold viruses). In the SIR model recovery is possible with lifelong immunity from reinfection. The SEIR model incorporates an E compartment for the time period during which individuals have been infected but are not yet infectious, i.e., the time from infection to infectiousness (e.g., childhood viral diseases such as measles and rubella). The MSEIR model incorporates a state M where hosts, e.g. infants, have passively acquired (maternally derived) immunity for the first months of life before becoming susceptible (e.g., measles).

Table 1. Values of the basic reproduction number R_0 for various viral diseases.

Disease	R_0	REFERENCE
1918 Spanish Flu	1.5-3.5	(Mills, Robins, & Lipsitch 2004)
2009 pandemic influenza	1.4-1.6	(Fraser et al. 2009)
AIDS	1-6	(http://www.who.int/hiv/strategic/en/wpraids2001.pdf)
Foot-and-mouth disease	3.5-4.5	(Ferguson, Donnelly, & Anderson 2001)
Influenza (seasonal)	0.9-2	(Chowell, Miller, & Viboud 2008)
Measles	16-18	(Anderson & May 1991)
Polio	5-7	(Dowdell et al. 2001)
SARS	2-4	(www.who.int/csr/sars/en/WHOconsensus.pdf)
Smallpox	3.5-6	(Gani & Leach 2001)

Addition of realism and complexity

Disease transmission in real populations often involves complex social and spatial structures characterized by heterogeneity in contact networks and accordingly in the impact of control measures (Colizza et al., 2007). To add realism and more detail, newer generations of models include additional compartments or subclasses representing e.g. age structure, social behavior, socio-economical demographics, spatial elements, and/or control strategies such as quarantine and isolation. Inclusion of more elements of complexity requires more parameters, variables, and detailed assumptions about the nature of the underlying processes and tends to introduce more unknown parameters. This inevitably introduces stochastic heterogeneity and uncertainty and often involves the transition from deterministic to stochastic or individual- and network-based approaches. More complex models usually require numerical solutions (to differential equations) or stochastic simulations for analysis (see below) (Koopman, 2005). It should be mentioned that conceptually more complex models are not necessarily mathematically more difficult to resolve. The use of more complex and detailed models generally leads to greater resolution and accuracy of modeling results which is necessary for, e.g. control policy guidance (Keeling & Rohani, 2008). However, the use of more simple models may be sufficient for gaining, e.g., insights of general infection dynamics. Thus depending on their purpose and preciseness or generality of the questions to be answered, models can vary in the level of detail they incorporate. A trade-off exists between simplicity, the absence of details, and whether inclusion of additional parameters and complexity will lead to improvement of predictive power (Koopman, 2005). When little is known of the disease and its parameters and parameter values, the use of simple (basic deterministic compartmental) models may represent an effective tool as an initial step. Subsequently, more complexity can be added to suit the model's purpose and the questions to be answered (Arino et al., 2006). However, the lack of data as such does not justify model simplicity or preclusion of analysis using more realistic assumptions.

Deterministic versus stochastic models

Although deterministic compartmental models form the basis of mathematical modeling, they are based on assumptions that are usually epidemiologically unrealistic as aforementioned. Typically individual hosts differ in susceptibility to infection and infectivity and are usually part of structured and heterogeneous populations. In addition, susceptibility and infectivity can be affected by age, gender, genetic, physiological and social differences, immune and vaccination history, and infection control measures (Boëlle, Cesbron, & Valleron, 2004; Kwiatkowski, 2005; Lloyd-Smith et al., 2005; Quinn & Overbaugh, 2005; Woolhouse et al., 1997). Therefore heterogeneities in host populations can affect the dynamics of infection. As viral transmission between individual hosts is stochastic by nature, deterministic models can become too elementary to describe a complex viral outbreak as they do not take into account chance events. Deterministic models produce a single output result per scenario for each set of expected or average input parameter values. Therefore they are not useful for small and non-homogenous populations. Additionally they are not useful to capture extreme variation and dynamics that can be inherent to viral infection, persistence, and extinction as often witnessed at the beginning or end of an epidemic. An example of unusual dynamics is "superspreading" as observed during the, 2003 SARS epidemic (Galvani & May, 2005). Despite such limitations to capture and resolve population structures and other heterogeneities at the individual level, deterministic models have been shown to be useful and of predictive value for, e.g., establishing factors affecting the epidemic growth rate and for estimations of the final size of epidemics (Anderson & May, 1991; Mollison, Isham, & Grenfell, 1994). Although some deterministic models can incorporate spatial elements, in most cases they are non-spatial. In general, they are more suited to capture and describe the overall pattern of infection dynamics or to model separate stages of an epidemic (Daley & Gani, 1999).

Models which take chance and variability into account are known as probabilistic or stochastic. Analogous to compartmental deterministic models, stochastic models also divide host populations into compartments. However, the infection process is described using

discrete numbers and variables and process rates have been replaced by process probabilities (Isham, 2005). Stochastic models incorporate chance variation in exposure risks, disease transmission, and other (heterogeneous) factors within and between individual hosts of a certain population. Stochastic models are best applied for small populations, e.g., during the early and late phases of an epidemic when chance fluctuations or heterogeneities have to be accounted for in the model structure. The models are characterized by a probability distribution of all possible outcomes of the infection process of which the value of input parameters vary (Daley & Gani, 1999). In addition the occurrence of chance events is randomized. Therefore different values for the same input parameters are run on a computer to produce a range of outcome-based probabilities and confidence intervals for (both statistical and uncertainty) analysis. The methodology that is used for estimating parameters from sampling probability distributions (based on constructing a Markov chain) for this purpose is known as Markov chain Monte Carlo (MCMC) simulation (Daley & Gani, 1999). The use of MCMC methods and alternative computer-intensive methods for analysis of stochastic epidemic models is becoming more widespread (Gibson & Renshaw, 2001; O'Neill, 2002). Stochastic models can be hard to construct and to obtain useful results many simulations are usually necessary requiring computationally intensive methods for analysis (Isham, 2005). Such models can become mathematically very complex. In the past complexities that are associated with fitting stochastic models to epidemiological data to estimate transmission parameters, have limited their use. However due to modern statistical methods and computational power such models are now increasingly used (Matthews & Woolhouse, 2005).

Parameterization of models

The main input to epidemic models requires descriptive data of the natural history of the disease and is commonly based on assumptions on the distributions of time periods. Depending on the disease these include incubation times, latency times, infectious times and infectiousness (Giesecke, 2002). These are parameters or concepts (epidemiological determinants) that are related to the course and progress of disease within individual hosts and the time they spend in different states before proceeding to the next as illustrated in Figure 2. The proper estimation and use of these parameters is essential as it determines model outcomes. Moreover it provides insight into the transmission dynamics of the disease and can guide infection control policy (Anderson & May, 1991). This is in particular important at the beginning of an outbreak or epidemic when swift appropriate action regarding containment must be taken. Parameter values are usually assessed from surveillance data. In the best case estimations may be retrieved from useful contact-tracing field data but this can be difficult and may not always be feasible. In general obtaining field data is not an easy task and may be affected by heterogeneities in disease transmission or hampered in case of e.g. rapidly spreading viral diseases such as influenza. Alternatively, for retrospective analysis in light of preparedness and mitigation planning, historical data from past outbreaks or epidemics can be used to estimate parameters and parameter values. In the following section key parameters and concepts that are commonly used are discussed.

The basic reproduction number R_0

Central to the parameterization of epidemic mathematical models is the basic reproduction number R_0. This key epidemiologic variable characterizes the transmission potential of a disease within a population. R_0 is defined as the average number of secondary cases generated by an initial single infectious case in a totally susceptible population in the absence of infection control measures (Anderson & May, 1991). R_0 has a so-called threshold value that equals 1. In general, it is assumed that if $R_0 \geq 1$ then an outbreak will lead to an epidemic. If $R_0 < 1$, an outbreak will fade out. R_0 provides a basis for comparing transmission potential

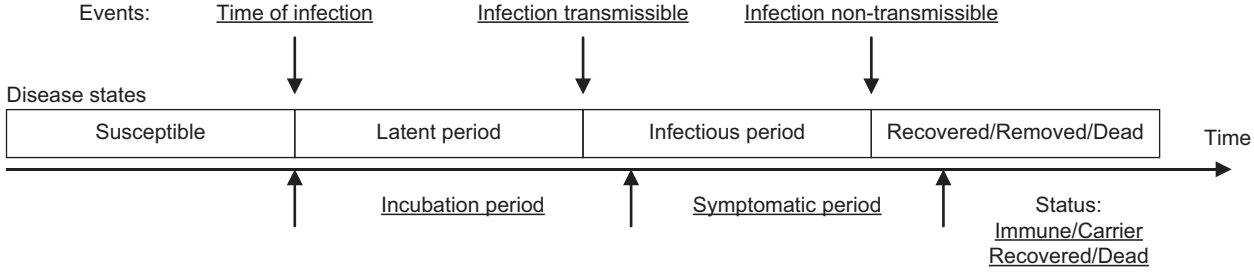

Figure 2. An illustration of relevant disease states, time periods, events and disease status and their relationship to the course of infection and disease within an individual host. The different states of disease are boxed (Compiled from Daley & Gani 1999; Aragon 2004 (http://www.idready.org/slides/conducting-investig.pdf)).

between different viruses and other infectious diseases. Estimated values for R_0 for various viral diseases are shown in Table 1. R_0 does however have limitations. For a particular disease R_0 is not a fixed property but defined for a certain host population governed by a specific contact (behavioral) pattern, duration of infectiousness, and probability of transmission: for the same disease different populations may be associated with different values of R_0. Furthermore, R_0 is a dimensionless quantity that can provide an indication of the risk of an epidemic as well as the intensity of measures needed for infection control (Heffernan, Smith, & Wahl, 2005). Under the assumption of homogenous mixing the basic formula for R_0 is defined as $R_0 = \beta cD$ in which β is the likelihood of transmission per contact: c is the number of contact per time unit and D is the average duration of infectiousness (Dietz, 1993). These different parameters can be altered by applying control measures. Mathematical models can be used to estimate R_0 (from modeling transmission). This is however not straightforward and modeling context dependent and many different approaches and methods exist for this purpose (see below). Additionally, mathematical models can be used to identify factors in controlling viral spread by examining the effect on R_0.

The efficacy of infection control measures can be measured in terms of the ability to reduce R_0 to a value below 1. When an infection is spreading it is more convenient to use R_t (or R), the effective reproduction number, which is defined as the actual average number of secondary cases per primary case at time t during the epidemic. The value of R_t is usually smaller than the value of R_0 reflecting the impact of infection control measures or build-up of immunity. For a homogenous population $R_t = fR_0$ applies, in which f is the proportion of susceptible individual hosts at time t (Bauch et al., 2005). Several methods have been developed to determine R_t during an epidemic (Heffernan, Smith, & Wahl, 2005; Cauchemez et al., 2006). Both R_0 and R_t are often expressed as combinations of parameters describing SIR model transmission dynamics and then estimated by fitting models to epidemiological data. However, the estimation of R_0 or R_t is not straightforward (Roberts & Heesterbeek, 2007; Breban, Vardavas, & Blower, 2007). Estimating R_0 or R_t can become complex when models account for more heterogeneity (Hyman & Li, 2000). Recently, prompted by the current new influenza A (H1N1) virus pandemic, more recent (and elaborated) approaches and methods estimating the (basic) reproduction number have been published (Fraser et al., 2009; Boëlle, Bernillon, & Desenclos, 2009; Silva et al., 2009; http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f-77d4-4ad8-b6d6 bf0f23083f30&ID=641&MasterPage=1&PDF=true).

The generation time

The generation time is another important parameter which is usually defined as the average time necessary for secondary cases to become infected (Svensson, 2007). In concert with R_0, the generation time can provide a picture of the dynamics of the epidemic over time. Although methods have been developed, estimating the generation time is not straightforward (Wallinga & Lipsitch, 2007; Kenah, Lipsitch, & Robins, 2008). As the generation time refers to actual infection events that are usually not observable, in practice the serial time is used as a proxy (Scalia Tomba et al., 2009). The serial time is defined as the time between the onset of symptoms in an index case and a secondary case (Svensson, 2007). Together, the generation time and R_0 can provide a rough indication for the speed by which control measures should be implemented: a viral disease that has a small generation time and a moderate to high R_0 (R_0: 10–15) is likely to spread before infection control measures are put into place as for less infectious diseases (R_0: 2–10) that have a larger generation time (>20 days), the timely use of appropriate control measures can be sufficient to achieve containment provided the viral outbreak is detected early (Anderson et al., 2004).

Infectious period

The infectious period or duration of infectiousness is defined as the time period during which contact with an (symptomatic or asymptomatic) infected host may lead to an infection (Barreto, Teixeira, & Carmo, 2006). During this time infected hosts can transmit the viral disease, shed the virus into the environment and susceptible hosts can become infected. This probability depends on the clinical manifestation of the disease, route of transmission, concentration of virus shed, population density, and social behavior of both infected and non-infected hosts (Fine, 2003). Estimation of this time period requires detailed contact-tracing or shedding data. Obtaining good estimates for the incubation period may be compromised as the timing of the infection event and the timing of disease onset may be difficult to retrieve (Fine, 2003). The infectious time determines the time course of the infection pattern and is of importance for, e.g., isolation and quarantine policies.

The incubation period

The incubation period is defined as the time from infection to the onset of clinical symptoms (Giesecke, 2002). The length of the incubation period is influenced by determinants such as age, infectious dose, host genetics, and immune status of individual hosts (Fine, 2003). Therefore the incubation period for any disease is not a fixed number but is represented by an interval. During

this period infected hosts can be infectious. The incubation time influences the generation time as it influences the timescale of the development of the epidemic. Early estimation of this parameter during a newly emerging disease provides insight into the mechanisms of disease transmission and into the type of control measures to implement (Tam & Wong, 2007; Lessler, 2009). Knowledge of the incubation period is of importance for contact tracing and quarantine policies.

The latent period

The latent period is defined as the time from infection to acquisition of infectiousness (Fine, 2003). This time interval is difficult to measure as infection transmission events are seldom observed and (shedding) data is hard to collect. Nevertheless its importance as a key epidemiological determinant has been demonstrated (Wearing, Rohani, & Keeling, 2005). Fitting models to initial outbreak data without taking the latent period into account or without incorporating realistic assumptions of the latent and infectious period, will lead to an underestimation of the transmission potential (R) of the infection. With the incubation period, the latent period supports estimation of the (theoretical) efficacy of control measures against symptomatic individual hosts (Fraser et al., 2004).

The proportion of transmission prior to symptoms θ

This relative new parameter, denoted as θ is the proportion of asymptomatic infections that occurs prior to the onset of symptoms. This parameter gives an indication of the efficacy for symptom-based (simple) public health measures such as isolation of symptomatic individuals and tracing and quarantining of their contacts (Fraser et al., 2004). Estimations of θ can indicate whether nosocomial transmission should be included in the mathematical model (Bauch et al., 2005). Transmission will be more widespread for diseases with a large θ. In such cases quarantine of pre-symptomatic individuals would be more effective to prevent an epidemic then isolation or contact tracing. Small θ values implicate a more important role for nosocomial transmission in transmission dynamics as individuals become infectious after displaying symptoms and being hospitalized. In such cases early quarantine would be less effective (Bauch et al., 2005).

Network, spatial, and metapopulation models

Heterogeneity in disease transmission dynamics at the individual level can significantly influence disease dynamics at the population level which has implications for infection control policy (Keeling & Eames, 2005). Disease transmission often occurs through populations via contact networks that are formed by physical contacts between individual hosts. The patterns of these contacts are heterogeneous, involve various (specific) types of interactions, and can cross social structures, physical locations and different spatially geographical locations. Therefore mathematical epidemiologists are increasing utilizing individual- and network-based epidemiology for modeling disease spread. Such models explicitly consider population and spatial heterogeneity, which cannot be captured by 'homogeneous-mixing' compartment models, incorporating stochasticity (Bansal, Grenfell, & Meyers, 2007). They are best applied when behavioral characteristics of individuals regarding, e.g., 'mixing' behavior and migration have to be accounted for. Such models usually require detailed empirical data input and may be difficult to construct. Commonly used types such as contact network, spatial and metapopulation models are addressed below.

Contact network models

In contact network models, not only the properties of individual hosts but also the nature of the network of connections between them determine the course of an epidemic (Bansal, Grenfell, & Meyers, 2007). These models commonly consider disease spread by close contact and not transmission related to geographical space (Parham & Ferguson, 2006). Different approaches of contact network models include micro-simulation and agent-based models in which individual hosts reside in, e.g., the household, schools and workplaces to form contact networks (Ferguson et al., 2005).

Spatial models

Explicit spatial models are used to account for behavior of individual hosts with regard to (geographical) space and movement (migration and mixing patterns). This may involve capturing both disease dynamics at a large geographical scale as well as on a more local scale where transmission patterns between individuals are defined by a contact network-like structure (Keeling et al., 2001; Lipsitch et al., 2003; Eubank et al., 2004). Spatially explicit models are useful for, e.g., evaluating the effects of movement control measures or (local) contact tracing. Spatial models have been used for modeling disease dynamics and effects of control measures in both human and animal populations, e.g., pandemic influenza and Foot-and-mouth disease (FMD) (Riley, 2007).

Metapopulation models

Human populations are often structured in communities that represent geographical locations, subpopulations or

'patches' such as cities (Leibold et al., 2004). A metapopulation is a group of subpopulations each with their own dynamics. Within a metapopulation framework the spread of the viral disease is usually modeled within a subpopulation or alternatively between subpopulations (Colizza & Vespignani, 2007). For this purpose several approaches and methods exist. In general, the models rely on spatial structure of the environment and knowledge of transportation infrastructures and movement patterns (Colizza & Vespignani, 2007). Metapopulations are usually complex and hard to build as they aim for increasing model realism and therefore inclusion of many details. Nevertheless metapopulation models are regarded as a compromise between the use of simple compartment models and detailed complex contact network models. They are best used when the population structure has a known large influence on spreading patterns and transmission dynamics (Grenfell & Harwood, 1997).

Mathematical modeling of human and animal viral diseases: FMD, SARS, and pandemic influenza

Mathematical modeling of viral disease has become an important tool for public and animal health authorities to understand a viral disease outbreak and to formulate and implement infection control policies. The prevention and control of disease transmission can be achieved by a variety of both nonpharmaceutical as pharmaceutical interventions such as isolation, quarantine, contact tracing, movement and travel restrictions, culling (restricted to animal diseases), and the use of vaccines or antiviral drugs. In this section we discuss relevant modeling literature of the 2001 UK FMD outbreak, the 2003 SARS global epidemic and future influenza pandemics. We address the utility of mathematical models in providing information on the course of the epidemic, their (predictive) value in controlling the epidemic and contribution to policy and decision making.

The 2001 UK foot-and-mouth disease (FMD) outbreak

The 2001 UK FMD epidemic devastated the livestock industry and caused severe economical damage (Kao, 2003). Although FMD does not directly affect human health the 2001 UK outbreak exerted significant social pressure by disrupting (local) economies (Bender, Hueston, & Osterholm, 2006). The viral disease exemplifies the strong relationship between animals and humans as humans that come in contact with infected animals can serve as mechanical vectors. Foot-and-mouth disease virus (FMDV) is a highly transmissible virus. The virus infects many cloven-footed mammals including sheep, cattle, pigs, and goats (Alexandersen et al., 2003). The virus is spread in droplets from infected to in-contact animals, by feeding animals with infected products and by mechanical spread through fomites. The incubation period can last 3–11 days including a presymptomatic phase during which the animals are infectious. The virus has the potential of air- and windborne transmission over long distances which require particular (climatic) circumstance (reviewed in (Sobrino et al., 2001) and (Moutou, 2002)). The, 2001 FMD epidemic was primarily restricted to sheep and cows. Different antigenic types of the virus that consist of multiple strains exist in different parts of the world. It is assumed that the particular virulent FMDV type O Pan Asia strain entered the UK via illegally imported contaminated food products (Rossides, 2002). Over the course of the epidemic animals on 9900 premises (including over 7500 that were not infected) were culled including 3.3 million sheep, 500000 cattle, 143000 pigs to bring the epidemic to a halt (http://www.defra.gov.uk/footandmouth/). With an additional 2.5 animals culled on welfare grounds, the total number of animals culled was about 6.5 million (Scudamore & Harris, 2002). Current control policies in Europe are based on strict import and quarantine regulations as routine vaccination ended in, 1994 (Council Directive, 2003/85/EC). In general, the execution of control policies regarding FMD is complicated due to the variation in the severity of the disease, display of symptoms, the duration and level of infectiousness, and excretion among different target animal species (Donaldson & Alexandersen, 2001; Donaldson et al., 2001). Within weeks after the, 2001 UK outbreak, infection control was compromised by the extent of the outbreak (Kitching, Thrusfield, & Taylor, 2006). The initial applied traditional "stamping out policy," i.e., the culling of infected premises together with animals at premises classified as "dangerous contacts" proved to be inadequate. It should be noted that there was an initial delay before the suspected disease was reported and positively confirmed (http://www.defra.gov.uk/footandmouth/). As a result when the outbreak was officially confirmed on February 20th the disease had already spread. To guide UK government policy during the epidemic, a number of mathematical models were developed by different teams of mathematical modelers. This was one of the first examples of computer-based (predictive) mathematical modeling in the UK and in the rest of the world for this purpose. The models ranged from a deterministic differential equation model with inclusion of spatial variables (Ferguson, Donnelly, & Anderson, 2001a; Ferguson, Donnelly, & Anderson, 2001b) to the use of a spatially detailed complex micro-simulation model (Morris et al., 2001) and a spatially explicit Monte Carlo computer simulation (Keeling et al., 2001). The different modeling approaches and techniques used have been described

and compared in detail elsewhere (Keeling, 2005). All models were based on the same data with the aim to identify containment strategies to minimize the size and the length of the epidemic. Despite the differences in approaches, the models made similar predictions about the type of control that was needed to stop spread of the disease: a more intensive culling strategy was needed as the epidemic had gone out of control. Based on these models policy was revised and the "24/48" policy of contiguous culling without vaccination was implemented: in addition to rapid culling of susceptible animals on confirmed infected premises (IPs) and premises confirmed as dangerous contacts (DCs) within 24 hours of reporting, rapid culling on premises contiguous to IPs (CPs) and DCs within 48 hours after reporting (known as "pre-emptive culling") was implemented. The estimation of R_0 has proven to be of importance for taking on the revised culling policies. For the UK setting R_0 was defined as the average number of farms infected by one farm in a totally susceptible population of farms. One modeling team derived a R_0=4.5 that was reduced to R=1.6 after inclusion of control measures (movement restrictions) (Ferguson, Donnelly, & Anderson, 2001a). Interestingly, although the study showed that culling all animals within 24 hours after case reporting would significantly slow down the epidemic, R was not reduced below one indicating the necessity of more intensive control strategies. The pre-emptive culling policy was thought to be crucial in bringing the epidemic eventually to an end in September 2001 (Woolhouse et al., 2001). However, the revised policy caused criticism and controversy over the decision to rely on pre-emptive culling as the sole option as it led to the destruction of many healthy animals (reviewed in (Sutmoller et al., 2003). This led to an inquiry ordered by the UK government into the lessons to be learned (http://www.defra.gov.uk/footandmouth/). In addition the modeling approaches have been scrutinized and re-evaluated and the models' appropriateness, validity, and predictive value to guide policy were questioned (Haydon, Kao, & Kitching, 2004; Kao, 2002; Rossides, 2002). Some of the criticism involved the quality of data and epidemiological knowledge that were used for model building and parameterization, in particular regarding viral transmission characteristics, distribution of initially infected farms and livestock and target species involved (Kitching, Thrusfield, & Taylor, 2006). In addition, retrospective analysis implied that the predictive power of the models (regarding both transmission dynamics and the effect of control measures) had been affected by two major forms of heterogeneity (Green & Medley, 2002; Woolhouse, 2003). First, spatial heterogeneity was caused by a rapid depletion in the number of susceptible animals around an infected farm. Second, heterogeneities were caused by differences in the composition of livestock between farms. In addition FMD transmission dynamics was subject to spatial and temporal heterogeneities caused by variations in weather conditions and farming practices. This resulted in epidemic parameters that varied in time and space as the epidemic changed geographically. Probably model misspecification compromised translating modeled predictions to control policies as the models' validity became influenced by spatial and temporal variation in transmission dynamics.

In conclusion, the 2001 UK FMD epidemic was the first time that real-time predictive mathematical modeling influenced crucial decisions, driving control policies to end the epidemic. Mathematical modeling was a new analytical tool to policy and decision makers at the time. During and after the epidemic the appropriateness of the models was questioned, suggesting that the adopted revised control policies had resulted in unjustified excessive culling of uninfected animals. In hindsight however, the models' predictions generally appeared to be correct and the implementation of the revised control policies led to a halt of the epidemic (Woolhouse et al., 2001; Kao, 2002; Chis Ster, & Ferguson, 2007; Tildesley et al., 2008). Furthermore, the models all provided useful and important insights for policy makers into FMD transmission dynamics in real time during the epidemic both qualitatively and quantitatively. Some controversy still exists over whether different strategies would have resulted in a better epidemic control, in particular regarding the number of culled animals (Kao, 2003; Honhold et al., 2004; Taylor et al., 2004, Kitching, Thrusfield, & Taylor, 2007). The 2001 UK FMD outbreak emphasized the importance of accurate data input and model validation in order for models to be used as a reliable tool in support of policy decisions but not as a substitute for policy making (Green & Medley, 2002; www.defra.gov.uk/science/documents/publications/2003/UseofModelsinDiseaseControlPolicy.pdf; Kitching, 2006; Kitching, Thrusfield, & Taylor, 2006). It highlighted difficulties, complexities and (future) challenges with regard to capturing spatio-temporal variation of infection dynamics and the necessity for the development and use of rigorous modern statistical methods to estimate parameters (Chis Ster, & Ferguson, 2007). Importantly, it demonstrated the usefulness and potential of mathematical modeling for retrospective analysis, contingency planning and policy development. This gave incentive for (further) development and improvement of new and existing models and approaches (Keeling, 2005; Parham, Singh, & Ferguson, 2008: Tildesley et al., 2009; Tildesley et al., 2009).

The 2003 SARS global epidemic

The 2003 outbreak of sever acute respiratory syndrome (SARS) is an example of how rapidly a new viral infectious

disease can spread in a globalized world. The 2003 SARS epidemic was caused by a newly identified coronavirus SARS-CoV resulting from cross-species transmission from civet cats or raccoon dogs on open food markets that are associated with the selling of live animals out in the open, so-called "wet markets" (Poon et al., 2004). The virus originated in the province of Guangdong, Republic of China causing more than 8000 infections affecting 29 countries worldwide, resulting in approximately 800 deaths. Within one month after its recognition SARS spread across the world causing epidemics in China, Hong Kong, Taiwan, Vietnam, and Canada (http://www.who.int/csr/sars/country/table, 2004_04_21/en/index.html). As SARS became a global hazard the World Health Organization (WHO) initiated a worldwide campaign to combat SARS. In the absence of a diagnostic test, prophylaxis therapy, or vaccines the epidemic was eventually relatively quickly controlled fast in July 2003 using traditional or non-medical public health infection control measures (Bell, 2004). These measures varied from one geographical location to another. They included the rapid identification and isolation of cases and tracing and quarantining of their contacts, community-related measures to increase social distances such as cancellation of mass gatherings and closing schools, travel restrictions regarding domestic and international travel by issuing travel advisories and fever surveillance on, e.g., airports, and recommendations to the public for improved personal hygiene and the use of personal protective equipment such as masks (Poutanen & McGeer, 2004; Bell, 2004). Some of these measures were implemented consistent with WHO recommendations. Others were implemented by authorities and public health officials on their own initiative (Bell, 2004). SARS-CoV is primarily transmitted by respiratory droplets and close contacts are important. Transmission through contaminated environmental surfaces and fomites may also have played an important role (Poutanen & McGeer, 2004). Still, the exact patterns of transmission of the SARS virus remain an enigma (Krilov, 2004). Remarkably, more than 57% of all reported cases of SARS worldwide acquired the infection in a hospital setting. Health care workers constitute approximately a third of these cases (Lee & Sung, 2003). This indicated that the virus was unable to establish and to maintain itself within the community at large (Low & McGeer, 2003). SARS did not become communicable before the onset of symptoms and infectivity of the virus increased as patients became more ill. For SARS an incubation time of 4–7 days has been determined. This was followed by the onset of symptoms for 1–15 days (Krilov, 2004). Despite a worldwide susceptible population SARS did not result into a pandemic. The SARS epidemic was eventually effectively controlled as a result of an almost simultaneously implementation of multiple infection control measures in the countries that were affected. The timely and vigorous use of isolation and quarantine measures that restricted movement and limited contact mixing proved to be crucial (Anderson et al., 2004; Baric, 2008). The effectiveness of this policy was supported by the fact that the onset of symptoms preceded infectiousness of patients. While the epidemic was unfolding (in the early to mid stages) two different research groups developed mathematical models to predict whether the epidemic would evolve into a pandemic and to evaluate control measures. The first group determined R_0 for SARS for data in Hong Kong, Singapore, and Canada using both a deterministic and stochastic compartmental model (Lipsitch et al., 2003). An R_0 ranging from 2.2–3.6 was estimated for the deterministic approach. A wide range of 1.5–7.7 with an expected value of 3.5 was derived for R using a stochastic approach. This variation was likely due to effects of heterogeneity in transmission dynamics. The second group using a stochastic metapopulation-compartmental model, derived an R_0 for data in Hong Kong ranging from 2.1–3.7 (Riley et al., 2003). A median value for R_0 of 2.7 was derived with exclusion of superspreading. These initial estimates for R_0 were all above 1, but classified SARS as relative low to moderate transmissible, less transmissible than most respiratory infections and therefore potentially more susceptible to infection control measures (Pennington, 2004). Another 'early' study using a stochastic simulation model used a range of values for R_0 corresponding to data for different cities (Lloyd-Smith, Galvani, & Getz, 2003). In this study quarantine and isolation as control measures were evaluated with emphasis on data for Hong Kong using 3.0 for R_0. All three (independent) modeling studies implied that a combination of isolation and quarantine, contact tracing, improved infection control procedures, surveillance, or stringent hygienic procedures, would be effective in controlling spread provided they were implemented timely. Importantly, the results also implied that if left uncontrolled, the virus would infect the majority of the population upon its entrance. These conclusions offered useful guidance for public health policies and WHO (http://www.who.int/csr/sars/en/WHOconsensus.pdf). Moreover these results supported public health policies such as isolation and quarantine already put in place in affected countries. The results were also viewed with some caution and called for vigilance for acceptance by policy and decision makers (Dye & Gay, 2003). The models were conceived as conceptually complex and field data used for these studies suffered (with varying degrees) from deficiencies (Donnelly et al., 2004; Dye & Gay, 2003; Heffernan, Smith, & Wahl, 2005). The early phases of an outbreak (in particular of a previously unknown viral disease like SARS) are often hindered by inaccuracies and incompleteness of data. At the time several aspects, parameters and parameter values of SARS such as mode of transmission, incubation time, infectivity, virulence,

and persistence were unknown or uncertain. Population heterogeneity is likely to have caused a substantial variation of the estimates of R_0. In addition, so-called superspreader events contributed to the observed heterogeneities in transmission dynamics (Lloyd-Smith et al., 2005). Also spatial (geographical) variation in transmission has contributed to this (Galvani, Lei, & Jewell, 2003). Despite moderate values of R_0 well above 1, the SARS epidemic did not develop into a pandemic. The observed discrepancy between the estimates of R_0 and the epidemiology may have resulted from early implementation of infection control measures and intervention resulting in a decrease of R (Meyers et al., 2005). Interestingly, based on an R_0 value of 2.2–3.6, a total of 30000 to 10 million cases should have been expected in China (Meyers, 2007). At the end of the epidemic only 782 cases had been reported suggesting a R_0 of about 1.6 from SARS. Field data used for these early models were primarily derived from hospital or closed community settings such as apartment buildings. However, outside of the hospital setting and with the exception of superspreading events, R_0 has been shown to be less than 1 (Low, 2004). Most of the 'early studies were based on homogeneous mixing' compartmental models. It was therefore suggested that population heterogeneity may not have been properly captured resulting in (biased) outcomes for R_0 not representative of the population at large (Meyers et al., 2005). During the epidemic an additional five studies regarding SARS transmission and the effect of infection control were published for data in Hong Kong, Beijing, Toronto, Singapore, and Vietnam (Chen, 2003; Lin, Jia, & Ouyang, 2003; Wang & Zhao, 2003; Chowell et al., 2003; Shi, 2003). These models predominantly consisted of deterministic SEIR models considering key epidemic variables with respect to both public health and hospital based control measures and estimations of R. All the same, estimates of R in these studies grossly fell within the range of values mentioned for SARS above.

In conclusion, several generally considered state-of-the-art models with different structures were developed during the 2003 global SARS epidemic to predict the effect of control measures, eliciting renewed interest in modeling human infectious diseases for this purpose. These studies were of great value to understand SARS transmission dynamics, informing control policies and strategies. They also offered the opportunity to compare models and explore the effect of model structure on possible outcomes. Estimated values for R_0 derived from the early studies suggested that SARS was controllable and that a timely implementation of control measures was crucial to stop the epidemic. Considerable variation for R_0 was found not only in early studies during the epidemic but also in modeling studies that were performed in retrospect after the epidemic (summarized in Bauch et al., 2005). This implies that the estimated R_0 values depended on the model structures, input parameters, and on the methods used to estimate R_0 (Donnelly et al., 2004; Bauch et al., 2005). Moreover, in general the models' predictive value seemed to considerably depend on their architecture, assumptions, the choice of epidemiological parameters and quality of field data (Wallinga, Teunis, & Kretzschmar, 2006; Pitzer, Leung, & Lipsitch, 2007). In addition transmission dynamics of SARS was complex and found to be subject to considerable heterogeneity in time and space, population heterogeneity, and geographical variation which may compromise the models' predictive capacity (Chowell et al., 2003; Bauch et al., 2005). This prompted the development and use of (more complex) models capable of capturing more detailed population (social) structure, temporal variability, and spatial heterogeneity to evaluate combinations of control measures (Colizza et al., 2007; Pitzer, Leung, & Lipsitch, 2007; Cori et al., 2009). The unprecedented global spread of SARS demonstrated the importance of inclusion of spatio-temporal effects and geographical movement of individuals on a global scale and long-range transportation (civil aviation) networks to understand and forecast worldwide geographical spread of epidemics (Hufnagel, Brockmann, & Geisel, 2004; Colizza et al., 2007). The SARS epidemic also highlighted the need for models capable of evaluation of control measures in real time in case insufficient data is available regarding viral transmission characteristics and clinical features of the disease (Pourbohloul et al., 2005; Cauchemez et al., 2006; Hsieh et al., 2007).

Future influenza pandemics

During the last century we have been confronted with three pandemics, namely the, 1918 ("Spanish Flu"), 1957 ("Asian Flu"), and 1968 ("Hong Kong Flu") pandemic that resulted in millions of deaths worldwide (Poland, Jacobson, & Targonski, 2007). Analysis revealed that both the 1957 and the 1968 pandemics have been caused by reassortant influenza A viruses, containing a mixture of human and avian influenza genome segments (Horimoto & Kawaoka, 2005). Influenza pandemics are characterized by the worldwide spread of novel influenza strains for which most of the population lacks substantial immunity. As a result such pandemic strains typically cause a significant increase in morbidity and mortality compared to common seasonal influenza epidemics (Monto & Whitley, 2008). Common seasonal influenza A epidemics result from the spread of antigenically new subtypes that are generated through small mutations ("antigenic drift"). Partial immunity due to previous infections by a similar subtype is thought to limit the size of these epidemics. Every few decades a subtype is generated through more substantial genetic changes, reassortment ("antigenic shift"), resulting in a pandemic (Nicholson, Wood, &

Zambon, 2003). We are now confronted with the recently emerged swine-originated new influenza A (H1N1) virus that is spreading globally (Flahault, Vergu, & Boëlle, 2009; Garten et al., 2009). Nevertheless the unprecedented spread of highly pathogenic avian influenza virus (HPAI) subtype H5N1 among birds and mammals in the past decade and hundreds of reported zoonotic transmissions directly from birds to humans with a high case fatality rate still warrants caution and the need for worldwide preparedness and mitigation planning (Monto & Whitley, 2008). Cross-species transmission of HPAI H5N1 can potentially lead to the occurrence of a new influenza A pandemic through adaptive mutations and/or reassortment with human influenza A virus (Peiris, de Jong, & Guan, 2007). Although H5N1 causes disease in human, the virus is yet not efficiently transmissible and sustainable among humans. However if such a virus would acquire the ability to transmit readily from person to person it could spread worldwide within months or weeks due to globalization and the rapidity and high frequency of modern transport such as international air travel (Gust, Hampson, & Lavanchy, 2001). Common seasonal influenza A virus is in most cases transmitted by droplets through coughing and sneezing of infected persons but can also be spread by direct physical contact between individuals or by transfer to persons via fomites (Brankston et al., 2007). Future or new pandemic influenza A viruses are thought to be transmitted in a similar way. Typically upon infection with seasonal influenza A virus, an individual has a short latent period of about 2 days before becoming infectious for 2–3 days with shedding starting a day before symptoms appear in case of a symptomatic infection (Carrat et al., 2008). Although the characteristics and origin of a new pandemic cannot be predicted WHO has recommended nations to prepare contingency plans (http://www.who.int/csr/disease/influenza/pipguidance2009/en/index.html). Several countries have used mathematical models to predict the viral spread and to evaluate the feasibility to contain an influenza pandemic at the national level (e.g., http://www.health.gov.au/internet/main/publishing.nsf/Content/ mathematical-models). There are two types of strategies of prevention and intervention. Nonpharmaceutical measures include basic public health measures such as isolation and quarantine of suspected cases, increased hygiene and use of protective devices such as masks (World Health Organization Writing Group, 2006). Pharmaceutical measures include vaccines and antiviral drugs (Hota & McGeer, 2007). In the event of a pandemic, control will be hampered by a limited vaccine supply at least during for the first wave, therefore multiple control measures have to be considered (Nguyen-Van-Tam & Hampson, 2003). Many modeling studies have simulated pandemic spread and assessed intervention strategies for controlling pandemic influenza at both local and global levels based on historical data from the three pandemics of the last century. With its unprecedented estimated number of 50 million deaths worldwide (Johnson, 2002), the, 1918 pandemic serves as a worst-case scenario for pandemic planning. Several studies have estimated R_0 for the, 1918 pandemic. One study using historical data from 45 cities in the United States estimated a median value for R_0 of 2.9 for the 1918–1919 strain with a range of 1.5–3.5 (Mills, Robins, & Lipsitch, 2004). In another study using data from San Francisco, R_0 was estimated 2.0–3.0 using four modeling approaches (Chowell, Nishiura, & Bettencourt, 2007). Values for R_0 ranging from 2.6–10.6 and from 2.4–4.3 were determined for confined and community settings respectively (Gani et al., 2005). Other studies estimated a range for R_0 of 1.5–3 for both seasonal and pandemic influenza A (including 1957 and 1968 strains) (Longini et al., 1984). These results demonstrated that the reproduction number for the, 1918 influenza strain, was not large relative to other viral diseases like SARS, measles, or polio (Table 1). Several studies have also evaluated control strategies for pandemic influenza based on historical, 1918 pandemic data. By fitting a deterministic SEIR model to historical data from 45 cities in the United States, one study estimated that a pandemic can be controlled by public health interventions if these interventions would be applied early (Mills, Robins, & Lipsitch, 2004). By using an individually based spatially explicit simulation for data in Thailand, another study suggested that control would be feasible with the use of targeted antiviral therapy together with social distancing provided that R_0 is below 1.8, the pandemic is detected within the first weeks of its emergence and control measures are implemented early (Ferguson et al., 2005). Another study using a stochastic simulation model for rural Southeast Asia, showed that for a R_0 value below 1.6 the use of targeted antivirals would have a high probability of controlling viral spread (Longini et al., 2005). For a value of 2.4 for R_0 viral spread became uncontrollable. However, when in the same study a R_0 of 2.4 was used in scenarios evaluating combinations of targeted prophylaxis, quarantine, and pre-vaccination, control could also be achieved. In other studies it was demonstrated that the use of a pre-pandemic vaccine before or soon after the onset of a pandemic together with other control measures can be effective in reducing the clinical attack rate (Ferguson et al., 2006; Germann et al., 2006). These studies also modeled the impact of a variety of levels and combinations of antiviral agents, vaccines, and reduced social mobility at large scale within the United Kingdom and United States (including school closure and travel restrictions), demonstrating feasibility of reducing speed and magnitude of viral spread. A recent study focused on data for the United States, examined combinations or so-called targeted layered containment (TLC) of antiviral

therapy and prophylaxis and quarantine, isolation, school closure, community, and workplace social distancing for a range of R_0 values (Halloran et al., 2008). The outcome of this study suggests that in the absence of a efficacious vaccine a timely implementation of a combination of targeted household antiviral prophylaxis and social distancing measures could reduce the clinical attack rate. Other recent modeling studies involved analyses of the occurrence of antiviral drug-resistant influenza strains, and the influence of air transportation between countries on viral spread and pandemic control. In the event of a pandemic the widespread use of antiviral drugs as a prophylaxis or on a therapeutic basis is likely to select for resistant influenza strains (Regoes & Bonhoeffer, 2006). Transmission of such strains could limit the effectiveness of these drugs as a first line of defense. Therefore to constrain the emergence and spread of resistant strains the use of two different types of antiviral drugs is advocated (McCaw et al., 2008; Lipsitch et al., 2007). Several studies addressed the importance of local control measures and air travel restrictions with regard to the influence of (international) air travel on the spread of a pandemic. The results of these studies suggest that such control measures are not likely to (substantially) delay the spread of a pandemic (Epstein et al., 2007; Colizza et al., 2006).

In conclusion, mathematic modeling has provided valuable insights in the dynamics of (past) influenza pandemics and the potential of (combination of) different intervention strategies. Depending on the modeling techniques and assumptions made, variability for estimated values of R_0 was found. In addition, sources of historical data differed from one study to the next. Past pandemics have varied considerably with regard to epidemiological characteristics, pathogenicity, virulence, and pre-existing immunity (Oxford et al., 2006). As a consequence current contingency planning based on mathematical models must consider the possibility that transmission dynamics of a future pandemic can differ substantially both temporally and geographically from previous pandemics (Mills et al, 2006; Smith, 2006). Nevertheless, modeling studies based on using historical data can offer useful insights of influenza dynamics to develop relevant intervention strategies and policies (Morse, 2007). The results derived from the different modeling studies should however be used with some caution and vigilance in (support of) preparedness planning. Furthermore, given the unpredictability and uncertainty of the characteristics of a future pandemic contingency planning will probably need constant re-evaluation and adjustment in real time as the pandemic progresses (Hall et al., 2007). Although it is now widely accepted that a combination of measures will be necessary to sufficiently control viral spread, precise planning may be hampered by key unknowns, uncertainties and limitations as mentioned above. It should be mentioned that in light of H5N1 preparedness planning several countries have considered stockpiling antiviral drugs and pre-pandemic vaccines (based on a currently circulating strain of HPAI H5N1) for population priming. Important questions however remain, for instance which combinations of interventions will be most effective? or to what extent will asymptomatic infections, the existence of pre-existing and waning immunity and/or antigenic drift affect spread and control measures? (Mathews et al., 2007; Ferguson, Galvani, & Bush, 2003). This emphasizes the necessity to further develop models incorporating such aspects in scenario simulations of multi-component strategies (Flahault et al., 2006; Halloran et al., 2008). Such simulations will provide further insight into the best ways to develop strategies and allow to choose and implement the most successful control measures (Cooper et al., 2006; Colizza et al., 2007). This also advocates further research and modeling studies with regard to the sources and spread of avian influenza, the contribution of contact structures such as workplaces and schools to the overall spread of influenza and the feasibility and effectiveness of social distancing measures (Flahault et al., 2006; Halloran et al., 2008).

Concluding remarks: implications for translation to infection control policies

Mathematical modeling now plays an increasingly important role in contingency and preparedness planning ("what-if" scenarios), risk assessment and policy and decision making. In addition mathematical models have become useful tools to analyze the underlying disease dynamics of epidemics in real-time as highlighted by the current new influenza A (H1N1) pandemic (http://www.who.int/wer/2009/wer8434.pdf). Mathematical models can provide insights into infectious disease epidemiology and can be applied to evaluate the effects of infection control measures. Mathematical analysis can lead to the identification of important thresholds that determine whether, e.g., an outbreak will die out or will develop into an epidemic. When developing infection control policies, policy makers face different questions, trade-offs, and uncertainties that are associated with different strategies to implement to combat a viral outbreak or epidemic. In the past important decisions regarding trade-offs and implementation were primarily based on previous experience (from other countries) or the consensus opinion of expert scientific committees. Nowadays mathematical models and simulation of scenarios are increasingly used for this purpose.

In this review we discussed a number of studies with regard to (predictive) modeling of the course of the epidemic and evaluating various (combinations of) control measures of the 2001 UK FMD outbreak, the 2003 SARS global epidemic, and future influenza pandemics. It is

important that policy and decision makers that use the results of model prediction understand both the strengths and limitations of the models applied (May, 2004). As models are abstractions and simplifications of the real world the results they generate will always be approximations. The models are designed for particular situations using the information that is available and making assumptions where information is lacking and should therefore be used with some caution and vigilance. The assumptions can have a significant effect on the models' outcomes, their interpretation and their predictive power (Wearing, Rohani, & Keeling, 2005; Drake, 2006). Because models are always based on some extrapolation, uncertainty is to some level inherent to all models. Validation of the models by, e.g., ascertaining the quality of model fit to the observed data using statistical methods or by establishing the robustness of the conclusions by uncertainty and sensitivity analysis is therefore essential (Blower, 2004).

Properly constructed and well-parameterized models can be important and useful tools for infection control. Policy makers and public health officials should therefore be aware of their availability, potential, and the existence of a wide range of methods and approaches. The models can provide a basis for infection control measures which can be tested experimentally or empirically, e.g., predict the size and area spanning the epidemic so that resources and logistics can adequately be made available (Keeling, 2005). As they provide quantitative understanding of disease dynamics, models can be used to suggest, select, and evaluate control policies by simulating scenarios. Furthermore, models can suggest criteria for the evaluation of infection control measures not only by identifying key parameters but also by identifying uncertainties and gaps of knowledge of transmission dynamics. Infection is a stochastic process and viral epidemics often develop in a non-linear fashion characterized by complex epidemiology (Anderson & May, 1991). A variety of models exist ranging from very simple to highly complex to capture infection dynamics. The choice of model and its complexity is context and setting dependent and is largely determined by the type of disease, its purpose, and user. It should be mentioned that several "user-friendly" simple models are available for regulatory authorities to input data and observe the effects. These applications do not necessarily need experts to be used appropriately. However, it is clear from the modeling studies of FMD, SARS, and pandemic influenza discussed here, that models have evolved from simple compartmental models into complex approaches in which incorporation of, e.g., host population heterogeneities, greater individual variability, and spatial elements into the modeling structure have become more and more important. Addition of more elements of complexity increases realism which can lead to, e.g., greater accuracy of forecasts. On the other hand this inevitably introduces more parameters and thus uncertainty. It is therefore important to achieve a right balance between model purpose, model complexity and model validation (Ferguson et al., 2003). Importantly, modeling results should be interpreted with acknowledgement of model assumptions and limitations. In support of informed decision making or control policy guidance, modeling results should therefore be critically approached and evaluated with some caution. As decisions can have important consequences and implications this should preferably take place in a multidisciplinary setting using appropriate expertise in amongst others mathematical modeling, epidemiology, veterinary and human medicine and policy making.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the writing and content of this paper

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