Measurement and Modeling: Infectious Disease Modeling

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What Is Infectious Disease Modeling?

In recent years, mathematical models have been used increasingly to support public health policy making in the field of infectious disease control. Especially in developing public health response plans for a future pandemic outbreak of a new strain of influenza A, a mathematical and computer modeling has been applied to investigate various intervention scenarios ranging from ring prophylactic treatment with antivirals to increasing social distance by school closure. There are several reasons to use mathematical modeling as a tool for an analysis of policy options. One is the complexity of infectious disease dynamics: as transmission of infections involves contact between infectious and susceptible persons, the spread of an infectious disease depends on contact patterns in the population in combination with biological characteristics of the host–pathogen interaction. Second, it is not possible by pure reasoning to decide between a variety of different intervention strategies or possibly combinations of these strategies, because their effectiveness depends on many interrelated factors. Third, to conduct a sound cost-effectiveness analysis, the impact of intervention on the prevalence and incidence of an infectious disease should be taken into account, which requires quantitative estimates of the impact of different intervention options.

The central idea about transmission models as opposed to statistical models is a mechanistic description of the transmission of infection between two individuals. This mechanistic description makes it possible to describe the time evolution of an epidemic in mathematical terms and in this way connect the individual level process of transmission with a population level description of incidence and prevalence on an infectious disease. The rigorous mathematical way of formulating these dependencies leads to the necessity to analyze in much detail all dynamic processes that contribute to disease transmission. Therefore, developing a mathematical model helps to focus thoughts on the essential processes involved in shaping the epidemiology of an infectious disease and to reveal the parameters that are most influential and amenable for control. Mathematical modeling is then also integrative in combining knowledge from very different disciplines such as microbiology, social sciences, and clinical sciences.

The first roots of mathematical modeling go back to the eighteenth century, when Daniel Bernoulli used mathematical methods to estimate the impact of smallpox vaccination on life expectancy (Dietz and Heesterbeek, 2000). Later, Hamer (1906) used mathematical reasoning to argue that an epidemic can come to an end before all susceptible persons in the population have been infected, even without a decrease in virulence of the pathogen. A rigorous mathematical framework was first worked out by Kermack and Mckendrick in 1927 (Kermack and McKendrick, 1991a,b,c). Their model has been the basis of all further modeling and is nowadays best known as 'Susceptible-Infected-Removed model' or 'SIR model,' even if the theory developed by Kermack and McKendrick is much richer than what is usually meant by the SIR model. In their work, the central notion of the threshold value that determines whether a disease spreads or goes extinct is first introduced. This threshold value is now better known as the basic reproduction number and will be explained in more detail below. Research in mathematical modeling of infectious diseases increased and expanded out of the applied mathematics community into the public health community in the 1980s with the advent and problems posed by the spread of HIV/AIDS. But only in recent years has mathematical modeling been recognized as a valuable tool for public health policy makers and has the interaction between modelers and policy makers become direct and intense. Starting with the outbreak of SARS in 2003, and the need to design response plans for renewed smallpox outbreaks, the collaboration between mathematical modeling and policy makers was intensified during the 2009 outbreak of pandemic influenza, when in many countries modeling was used to support decisions about vaccination strategies. Also, the World Health Organization (WHO) initiated a network or mathematical modelers, who helped analyzing epidemiological data in real time and assessing effectiveness of interventions (Van Kerkhove and Ferguson, 2012). More recently, similar efforts are taking place in face of the large outbreak of Ebola in West Africa (WHO Ebola Response Team, 2014), where modeling helps to project how the outbreak will develop in the future and what intervention effort is needed for control. Experience with such collaboration has shown public health policy makers the power of using models to test intervention strategies in the face of infectious disease threats that are newly emerging or yet to come.

The SIR Model and the Basic Reproduction Number R_0

The so-called SIR model contains all essential elements of a mathematical model for the transmission of an infectious disease. Its basic assumption is that the human population is subdivided into three groups or compartments: the group of susceptible persons (denoted by S), the group of infected persons (denoted by I), and the group of removed persons (removed from the process of transmission by immunity) (denoted by R). The mathematical model provides a precise description of the movements in and out of the three compartments. Those movements are birth (flow into the compartment of susceptibles), death (flow out of all compartments), transmission of infection (flow from S into I), and recovery (flow from I into R) (**Figure 1**).

Transitions between compartments are governed by rates, which in the simplest version of the model are assumed constant in time. The birth rate ν describes the recruitment of

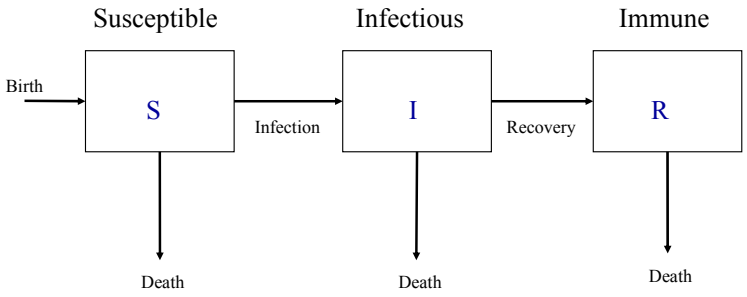

Figure 1 Flow chart of the SIR model.

new susceptibles into the population, the death rate μ the loss of individuals due to disease-unrelated background mortality, and γ denotes the recovery rate of infected individuals into immunity. The key element of the model is the term describing transmission of infection according to a rate β using a mass action term. The idea behind using a mass action term to describe transmission is that individuals of the population meet each other at random and each individual has the same probability per unit time to meet each other individual. Therefore, for a susceptible person the rate of meeting infected persons depends on their density or prevalence in the population, or in mathematical terms $\lambda = \beta I$, where λ is the so-called force of infection. The force of infection is a measure for the risk of a susceptible person of becoming infected per unit time. It depends on prevalence, either in an absolute sense on the number of infected people in the population, or in a relative sense on the fraction of infected people in the population. In the latter case, we would get $\lambda = \beta I/N$ with N denoting the total population size. The parameter β is a composite parameter measuring the contact rate κ and the probability of transmission upon contact q, so $\beta = \kappa q$. The flow chart in Figure 1 can be translated into a system of ordinary differential equations as follows:

$$\frac{dS}{dt} = \nu - \beta S\frac{I}{N} - \mu S$$
$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

with $N = S + I + R$. For a full definition of the model, the initial state of the system has to be specified, i.e., the numbers or fractions of the population in the states S, I, and R at time $t = 0$ have to be prescribed. Values for the parameters ν, μ, γ, and β have to be chosen, either based on estimates from data or based on assumptions. Then standard numerical methods are used to compute the time evolution of the system starting from the initial state.

The above model describes disease transmission without any possible intervention. We now show how to incorporate vaccination of newborns into this simple system and to obtain some important insights into the effect of universal newborn vaccination. We denote the fraction of newborns that are vaccinated immediately after birth by p. Then instead of having a recruitment rate of ν, the recruitment is now $(1-p)\nu$ into the susceptible compartment, while $p\nu$ is recruited directly into the immune compartment. In terms of model equations this leads to

$$\frac{dS}{dt} = \nu(1-p) - \beta S\frac{I}{N} - \mu S$$
$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I - \mu I$$
$$\frac{dR}{dt} = \nu p + \gamma I - \mu R$$

with $0 \le p \le 1$. We will now derive some basic principles using this model as an example.

Basic Concepts: Reproduction Number, Endemic Steady State, and Critical Vaccination Coverage

The most important concepts of epidemic models can be demonstrated using the SIR model. Let us first consider an infectious disease, which spreads on a much faster timescale than the demographic process. On the scale of disease transmission, the birth rate ν and the death rate μ can be considered to be close to zero. When can the prevalence in the population increase? An increase in prevalence is equivalent with $dI/dt > 0$, which means that $\beta SI/N > \gamma I$. This leads to $\beta S/N > \gamma$ or equivalently to $\beta S/(\gamma N) > 1$. In the situation that all individuals of the population are susceptible we have $S = N$; this means that an infectious disease can spread in a completely susceptible population if $\beta/\gamma > 1$. The quantity $R_0 = \beta/\gamma$ is also known as the *basic reproduction number* and can in principle be determined for every infectious disease model and can be estimated for every infectious disease. In biological terms the basic reproduction number describes the number of secondary infections produced by one index case in a completely susceptible population during his entire infectious period (Diekmann et al., 1990, 2012).

If $R_0 > 1$ the infection can spread in the population, because on average every infected individual replaces himself by more than one new infected person. However, this process can only continue as long as there are sufficiently many susceptible individuals available. Once a larger fraction of the population has gone through the infection and has become immune, the probability of an infected person to meet a susceptible person decreases and so does the average number of secondary cases produced. If, as we assumed above, there is no birth into the population, no new susceptible individuals are coming in and the epidemic outbreak will

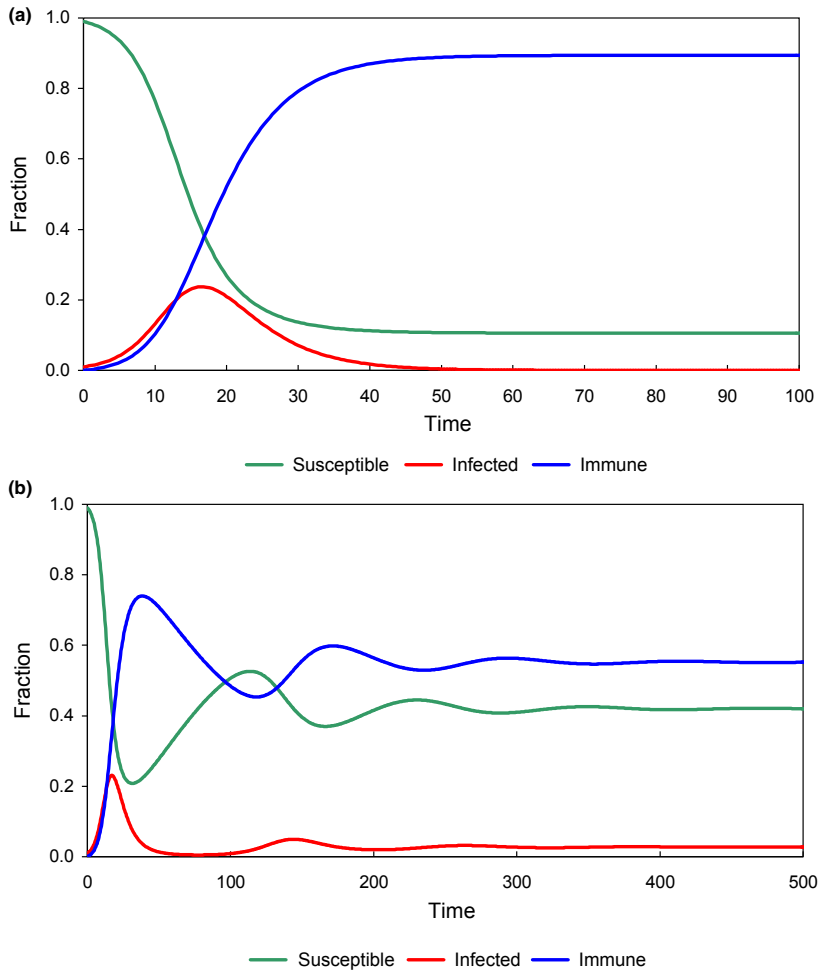

Figure 2 (a) The epidemic curve for $R_0 = 2.5$ in a population without birth and death. (b) The convergence to the endemic equilibrium for a population with birth and death.

invariably end (Figure 2(a)). Analysis of the model shows, however, that the final size of the outbreak will never encompass the entire population, but there will always be a fraction of susceptible individuals left over after the outbreak has subsided. It can be shown that the final size A_∞ (attack rate in epidemiological terms) is related to the basic reproduction number by the implicit formula $A_\infty = 1 - \exp(-R_0 A_\infty)$. In other words, if the basic reproduction number of an infectious disease is known, the attack rate in a completely susceptible population can be derived.

The situation changes when we consider the system on a demographic timescale where births and deaths play a role (Figure 2(b)). Assuming now that ν and μ are positive, with the same arguments as above we get that $R_0 = \beta/(\gamma + \mu)$. Now if $R_0 > 1$ the system can develop into an equilibrium state where the supply of new susceptible persons by birth is balanced by the transmission process and on average every infected person produces one new infection. This so-called endemic equilibrium can be computed from the model equations by setting the left-hand sides to zero and solving for the variables S, I, and R in terms of the model parameters. First one obtains the steady-state population size as $N^* = \nu/\mu$ (the superscript * denotes the steady-state value). The steady-state values for the infection-related variables are then given by,

$$S^* = \frac{(\gamma + \mu)\nu}{\beta\mu} = \frac{\nu}{\mu R_0}$$

$$I^* = \left(\frac{\nu}{\mu}\right)\left(\frac{\mu}{\gamma + \mu}\right)\left(1 - \frac{1}{R_0} - p\right)$$

$$R^* = \frac{\nu}{\mu} - S^* - I^*$$

Hence the fractions of the population that are susceptible, infected, and recovered in an endemic steady state are given by,

$$\frac{S^*}{N^*} = \frac{\gamma + \mu}{\beta} = \frac{1}{R_0}$$

$$\frac{I^*}{N^*} = \left(\frac{\mu}{\gamma + \mu}\right)\left(1 - \frac{1}{R_0} - p\right)$$

$$\frac{R^*}{N^*} = 1 - \frac{S^*}{N^*} - \frac{I^*}{N^*}$$

Note that the fraction of susceptible individuals S^*/N^* in the endemic steady state is independent of the vaccination coverage p. On the other hand, the prevalence of infection

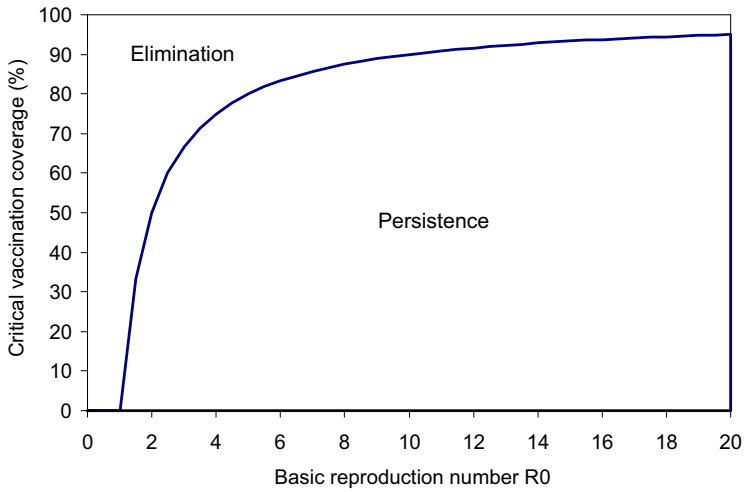

Figure 3 The relationship between the basic reproduction number R_0 and the critical vaccination coverage p_c.

I^*/N^* depends on p: the prevalence decreases linearly with increasing vaccination coverage until the point of elimination is reached. This means we can compute the critical vaccination coverage p_c, i.e., the threshold coverage needed for elimination from $0 = 1-1/R_0-p_c$ as $p_c = 1-1/R_0$. In other words, the larger the basic reproduction number, the higher the fraction of the population that needs to be vaccinated in order to eliminate an infection from the population. For an infection such as smallpox with an estimated basic reproduction number of around 5, a coverage of 80% is needed for elimination; while for measles with a reproduction number of around 20, the coverage has to be at least 96%. This provides one explanation for the fact that it was possible to eradicate smallpox in the 1970s whereas we are still a long way from measles eradication. There are some countries, however, that have been successful in eliminating measles based on a consistently high vaccination coverage (Peltola et al., 1997). A graphical representation of the relationship between the basic reproduction number and the critical vaccination coverage is shown in Figure 3.

Advanced Models

Building on the basic ideas of the SIR framework, numerous types of mathematical models have been developed in the meanwhile, all incorporating more structure and details of the transmission process and infectious disease dynamics.

More Complex Compartmental Models

A first obvious extension is the inclusion of more disease-specific details into a model. Compartments describing a latent period, the vaccinated population, chronic and acute stages of infection, and many more have been described in the literature (Anderson and May 1991). Another important refinement of compartmental models is to incorporate heterogeneity of the population into the model, for example, by distinguishing between population subgroups with different behaviors or population subgroups with differences in susceptibility, or geographically distinct populations. Heterogeneity in behavior was first introduced into models describing the spread of sexually transmitted infections by Hethcote and Yorke (1984). Later, during the first decade of the HIV/AIDS pandemic, efforts were made to describe models with sexual activity levels and mixing patterns between subgroups of various activity levels (Koopman et al., 1988). These models are still used frequently for assessing the effects of intervention in the spread of sexually transmitted infections. Age structure has also been modeled as a series of compartments with individuals passing from one compartment to the next according to an aging rate, but this requires a large number of additional compartments to be added to the model structure. This point also shows the limitation of compartmental models: with increasing structure of the population, the number of compartments increases rapidly and with it the necessity to define and parameterize the mixing between all the population subgroups in the model. The theory of how to define and compute the basic reproduction number in heterogeneous populations was developed by Diekmann et al. (1990). Geographically distinct population groups with interaction among each other have been investigated using the framework of metapopulations for analyzing the dynamics of childhood infections.

Models with Continuous Age Structure

Age structure can best be described as a continuous variable, where age progresses with time. Mathematically this leads to models in form of partial differential equations, where all variables of the model depend on time and age (Diekmann et al., 2012). Analytically, partial differential equations are more difficult to handle than ordinary differential equations, but numerically solving an age-structured system of model equations is straightforward.

Stochastic Transmission Models

In a deterministic model based on a system of differential equations, it is implicitly assumed that the numbers in the

various compartments are sufficiently large such that stochastic effects can be neglected. In reality this is not always the case. For example, when analyzing epidemic outbreaks in small populations such as a school or a small village, typical stochastic events can occur such as extinction of the infection from the population or large stochastic fluctuations in the final size of the epidemic. Questions of stochastic influences on infectious disease dynamics have been studied in various ways, starting with the Reed–Frost model for a discrete time transmission of infection up to a stochastic version of the SIR model introduced above (Bailey, 1975; Becker, 1989). Finally, stochastic models have been investigated using simulation techniques also known as Monte Carlo simulations. An important theoretical result from the analysis of stochastic models is the distinction between minor and major outbreaks for infectious diseases with $R_0 > 1$. While in a deterministic model an R_0 larger than unity always leads to an outbreak if the infection is introduced into an entirely susceptible population, in a stochastic model a certain fraction of introductions remain minor outbreaks with only a few secondary infections. This leads to a bimodal probability distribution of the final epidemic size following the introduction of one infectious index case (**Figure 4**). The peak for small outbreak sizes describes the situation that the infection dies out after only a few secondary infections, the peak for large outbreak sizes describes those outbreaks that take off and affect a large part of the population. The larger the basic reproduction number, the larger is the fraction of major outbreaks in the susceptible population (Andersson and Britton, 2000).

Network Models

Some aspects of contact between individuals cannot easily be modeled in compartmental models. In the context of the spread of sexually transmitted infections, models were developed that take the duration of partnerships into account, the so-called pair formation models (Kretzschmar 2000). Extending those models to include also simultaneous long-term partnerships leads to the class of network models, where the network of contacts is described by a graph with nodes representing individuals and links representing their contacts. Different network structural properties have been related to the speed of spread of an epidemic through the population. In the so-called small world networks, most contacts between individuals are local, but some long-distance contacts ensure a rapid global spread of an epidemic. Long-distance spread of infections is becoming increasingly important in a globalizing world with increasing mobility as the example of the SARS epidemic in 2003 demonstrated. Recently the concept of scale-free networks where the number of links per node follows a power law distribution was discussed in relation to the spread of epidemics. With respect to the spread of sexually transmitted diseases, a network structure where some individuals have very many partners while the majority of people have only few might lead to great difficulties in controlling the disease by intervention. Network concepts have also been applied to study the spread of respiratory diseases.

Phylodynamic Models

In 2004, Grenfell and coauthors coined the term 'phylodynamics' to describe the unification of population dynamics and evolutionary dynamics of pathogens (Grenfell et al., 2004). Parallel to the rapidly advancing methods of sequencing pathogen genomes, mathematical modeling methods have been developed to incorporate information from phylogenetic trees into population dynamic models (Volz et al., 2009; Stadler et al., 2012). Genetic information complements epidemiological information and together they may result in more insight into transmission routes of pathogens and in effectiveness of interventions on the population level. Especially in situations when not all infected cases are found and diagnosed, studying the genetic composition of the pathogen population in a modeling framework may lead to insight into the proportion of undiagnosed cases (Volz et al., 2013).

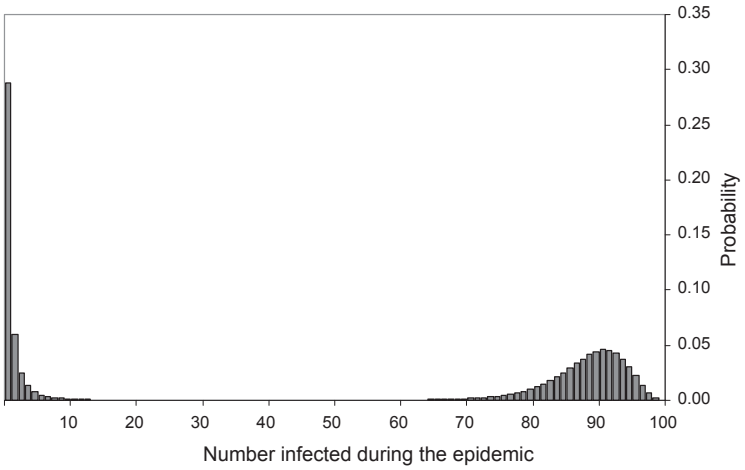

Figure 4 The probability distribution for the occurrence of minor and major outbreaks after the introduction of one infectious index case into a population of 100 susceptible individuals for an infection with basic reproduction number $R_0 = 2.5$.

Use of Modeling for Public Health Policy

Mathematical models have been widely used to assess the effectiveness of vaccination strategies, to determine the best vaccination ages and target groups and to estimate the effort needed to eliminate an infection from the population. Mathematical modeling has supported contingency planning in preparation for a possible attack with smallpox virus (Ferguson et al., 2006) and in planning the public health response to an outbreak with a pandemic strain of influenza A (Longini et al., 2004). Other types of intervention measures have also been evaluated such as screening for asymptomatic infection with *Chlamydia trachomatis*, contact tracing, and antiviral treatment in the case of HIV. The widely adopted strategy of 'treatment as prevention' to reduce the incidence of HIV by scaling up antiretroviral treatment was launched following publication of a modeling study by WHO authors (Granich et al., 2009). In the field of nosocomial infections and transmission of antibiotic-resistant pathogens, modeling has been used to compare hospital-specific interventions such as cohorting of health workers, increased hygiene, and isolation of colonized patients. In health economic evaluations, it has been recognized that dynamic transmission models are a necessary requisite for conducting good cost-effectiveness analyses for infectious disease control (Pitman et al., 2012).

It is a large step from developing mathematical theory for the dynamics of infectious diseases to application in a concrete public health–relevant situation. The latter requires an intensive focusing on relevant data sources, clinical and microbiological knowledge to make a decision about how to design an appropriate model. Appropriate here means that the model uses the knowledge available, is able to answer the questions that are asked by the policy makers, and is sufficiently simple so that its dynamics can be understood and interpreted. To link mathematical models to data, advanced statistical methodology is required, for example, using Bayesian methods and Markov Chain Monte Carlo simulation techniques. Statistical frameworks such as evidence synthesis methods (Presanis et al., 2011) have been developed to systematically link data sets from various sources to each other and to mathematical models. Also computational methods such as approximate Bayesian computation algorithms are increasingly used to deal with large simulation models. The field of mathematical modeling of infectious diseases is developing rapidly in order to further improve the performance of modeling as a public health tool.

See also: Cost-Influenced Treatment Decisions and Cost-Effectiveness Analysis.

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