MATHEMATHICAL MODELLING AND PREDICTION IN INFECTIOUS DISEASES

Prof.univ.Asoc. Dr.Nicolae Steiner
Doctor of Medical Sciences
Member of Health Security Committy of E.U.
Member of World Society of Disaster Medicine and Emergency Medicine (WADEM)
Member of European Crises Management Academy
Member of International Society of Disaster Medicine
Honorary member of National Disaster Medical System of U.S.A.
Process manager for emergency situations, crises and pandemics within "Stamina" group of Romanian Academy Virology Institute "Ștefan S. Nicolau" Bucharest

Abstract

We discuss to what extent disease transmission models provide reliable predictions. The concept of prediction is delineated as it is understood by modellers, and illustrated by some classic and recent examples. A precondition for a model to provide valid predictions is that the assumptions underlying it correspond to the reality, but such correspondence is always limited—all models are simplifications of reality. A central tenet of the modelling enterprise is what we may call the 'robustness thesis': a model whose assumptions approximately correspond to reality will make predictions that are approximately valid. To examine which of the predictions made by a model are trustworthy, it is essential to examine the outcomes of different models. Thus, if a highly simplified model makes a prediction, and if the same or a very similar prediction is made by a more elaborate model that includes some mechanisms or details that the first model did not, then we gain some confidence that the prediction is robust. An important benefit derived from mathematical modelling activity is that it demands transparency and accuracy regarding our assumptions, thus enabling us to test our understanding of the disease epidemiology by comparing model results and observed patterns. Models can also assist in decision-making by making projections regarding important issues such as intervention-induced changes in the spread of disease.

Keywords: Epidemic modelling, HPV, model prediction pandemic, influenza reproductive number, SIR

1. Introduction

Can mathematical models in the field of infectious diseases provide predictions? We argue that they can and do, provided that the scope of the notion of prediction is suitably qualified. Below, we will delineate the

concept of prediction as we believe it is understood by mathematical modellers, illustrating it by some classic and recent examples.

A mathematical model is an imaginary microworld consisting of entities behaving according to precisely specified rules. Mathematics provides us with a language for formulating these rules of behaviour in a concise and unambiguous way, thus forcing and helping us to clearly state our assumptions. Once a mathematical model is constructed, mathematical analysis, often combined with computer simulations, helps us to investigate the global behaviour of the model, drawing out the consequences of the assumptions that we have made. Thus, within the context of the model, we can make predictions of the future of our imaginary world and also study how these predictions change as the rules governing the entities described by the model are varied

Thus, a mathematical model for the spread of an infectious disease in a population of hosts describes the transmission of the pathogen among hosts, depending on patterns of contacts among infectious and susceptible individuals, the latency period from being infected to becoming infectious, the duration of infectiousness, the extent of immunity acquired following infection, and so on. Once all of these factors are formulated in a model, we can make predictions about the number of individuals who are expected to be infected during an epidemic, the duration of the epidemic, the peak incidence, and, indeed, we can predict the entire epidemic curve, providing us with the expected number of cases at each point in time.

Clearly, for the precise predictions made within the model's virtual world to be relevant to reality, the model itself needs to correspond to or represent what is occurring in the real world—one cannot expect to obtain good predictions from false assumptions. However, modellers are well aware of the fact that all models are, at best, partial descriptions of the mechanisms operating in reality, containing various layers of simplification, idealization, approximation, and abstraction. Indeed, much of the discussion and debate among modellers involves the nature of these simplifications and their appropriateness. Thus, a central tenet of the modelling enterprise is what we may call the ‘robustness thesis': a model whose assumptions approximately correspond to reality will make predictions that are approximately valid. If one accepts this general (and admittedly vague) idea, then even highly simplified models—which clearly overlook or even contradict some aspects of reality—can provide some valuable predictions, as long as their assumptions mirror some central aspects of reality. Deciding which of the predictions of a simple model are robust, in the sense that they can be applied with confidence to reality, can be a difficult question. An important procedure that modellers use to test the robustness of predictions made by a mathematical model is to compare different models [1, 2, 3]. Thus, if a highly simplified model makes a prediction, and if the same or a very similar prediction is made by a somewhat more elaborate model that includes some mechanisms or details that the first model did not, then we gain some confidence that the prediction is robust.

If, on the other hand, a certain prediction is highly dependent on the details of a particular model, then, as we never expect the model to be more than an approximate description of reality, we cannot have much faith in that particular prediction.

2. The SIR model

Let us illustrate some of the above considerations by reference to the most famous and paradigmatic model in mathematical epidemiology, the simple SIR model of Kermack and McKendrik [4]. In this model, a population is divided into susceptible, infective and recovered individuals, with the functions $S(t)$, $I(t)$ and $R(t)$ denoting their respective fractions in the populations at time t (measured, for example, in days). The evolution of these quantities is described by the differential equations:dSdt=-βSIdIdt=βSI-γIdRdt=γI
where the derivatives dS/dt, dI/dt and dR/dt measure the rates of change of the quantities $S(t)$, $I(t)$, and $R(t)$. The transmission parameter β is the average number of individuals that one infected individual will infect per time unit, assuming that all contacts that this individual makes are with susceptible individuals. Thus, a more highly infectious disease has a higher β. The number γ is the rate of recovery, so that 1/γ is the average time period during which an infected individual remains infectious. The product $\beta S(t)\, I(t)$ is the total infection rate, the fraction of the population that will be infected per unit time at time t. To understand this, note that, if a fraction $I(t)$ of the population is currently infected, then they would infect a fraction $\beta I(t)$ of the population per unit time if all of their contacts were with susceptible individuals, but as only a fraction $S(t)$ of the population is currently susceptible, they will only infect $\beta I(t)\, S(t)$ per unit time.
The ratio β/γ is also known as the basic reproductive number R_0, which is an important index for quantifying the transmission of pathogens. R_0 is defined as the average number of people infected by an infected individual over the disease infectivity period, in a totally susceptible population.
This simple model, which is the basis for many elaborations, turns out to provide some quite striking predictions. By entering the above differential equations into any software for the numerical solution of differential equations, and choosing some values for β and γ together with the initial values $S(0)$, $I(0)$, and $R(0)$, it is possible to generate an epidemic curve corresponding to this model, that is a prediction for the fraction of the population that will be infected on each day of the epidemic. Moreover, analytical tools allow us to draw some general conclusions about the model's solutions. The most important conclusions are as follows:
1. The epidemic threshold: if the inequality $S(0)\, R_0 > 1$ holds, then the number of infected individuals will rapidly decrease; that is, no epidemic will occur. Note that, if $S(0)\, R_0 > 1$, then an epidemic will occur, no matter how small the initial number of infected individuals.

2. The size of the epidemic, when it occurs, will not depend on the initial number of infectives, but it will depend on the initial fraction of susceptibles, $S(0)$, and on R_0. An important point here is that the final size of the epidemic (the fraction of the population infected) will always be strictly smaller than the initial fraction of the population that was susceptible, $S(0)$, so that there will always remain a subpopulation of susceptible individuals who have not been infected.
These conclusions, in so far as they apply in reality, have some crucial implications. Most notably, the epidemic threshold implies that, if we vaccinate a fraction of the population prior to the arrival of the pathogen, so as to reduce the initial fraction of susceptibles to $S(0) < \gamma/\beta$, then we will have prevented an epidemic. This result underlies the concept of herd immunity, whereby prevention of an epidemic can be achieved if a sufficiently large fraction of the population is vaccinated. If we do not achieve sufficiently high vaccination coverage, then we will have only reduced the size of the epidemic, and not have prevented it. Other ways to achieve the condition $S(0) < \gamma/\beta$, and thus to eliminate an epidemic are: (i) reducing the transmissibility parameter β by isolation of infectives or social distancing measures; and (ii) increasing the recovery rate γ by treatment of infectives. Should the predictions from this very simple model be trusted in policy-making?

3. Let us first note some reasons for scepticism. There are many assumptions implicit in the SIR models that are not realistic, for example:

• Well-mixed population—the derivation of the term $\beta S(t) I(t)$ in the equations assumes that each individual is equally likely to come into contact with any other individual in the population. This ignores the fact that contacts are much more likely between individuals who are geographically and socially closer.
• Homogeneity of the population—the model does not allow for the fact that individuals may be different from each other in ways that are relevant to the transmission of infection. There are individuals who are more susceptible to infection or more infectious than others; and there are individuals who make more contacts than others.
• Exponentially distributed duration of infection—this refers to the fact that the model assumes both that a person becomes infectious immediately upon being infected, and that the probability of recovery per unit time does not depend on the time that has passed since infection. Both assumptions are unrealistic [5].
• Large population—the very form of the model, formulated in terms of continuous quantities (fractions of the population), implicitly assumes that the population is large (strictly speaking, infinite). In a small population (e.g. a village or school), stochastic effects are much more important, and

modelling using mean field approximations (i.e. by differential equations) becomes problematic [6].
Given all these unrealistic assumptions, which, if any, of the predictions made by the model can we take seriously? As we have indicated above, the main approach with which modellers can address this question is by constructing more elaborate models that replace some of the unrealistic assumptions with more representative ones. Those predictions that remain unchanged, or only slightly changed, even for the more realistic model, are deemed to be robust, and we gain some confidence that they can be applied to the real world. A large part of the literature on the mathematical modelling of infectious disease transmission consists precisely of relaxing the above assumptions, and some others, by constructing appropriate models, and examining how the models' behavior changes as the model assumptions are modified [6, 7, 8].
Going back to the predictions made by the simple SIR model above, we can note that the threshold property (i.e. when $S(0)R_0 > 1$, an outbreak will occur) predicted by this model holds for nearly all epidemiological models, no matter how elaborate: for each such model, one can derive an appropriate expression involving the model's parameters such that the pathogen will persist only if this combination is greater than one. For each specific model, such an analysis gives us information on how one could eliminate the pathogen within the context of the specific model. More importantly, the fact that the threshold concept is ‘universal', appearing in nearly every model (an interesting exception being the case of infection transmission models on ‘scalefree’ networks [9]), makes us confident that it is not dependent on very specific assumptions and should apply in reality. We note, however, that we should be much less confident about applying quantitative predictions obtained from the SIR model to the real world. For example, although an estimate for the vaccination coverage needed to prevent the spread of a pathogen can be obtained from the SIR model after estimating the parameters for this model from available medical and epidemiological data, we would not trust such a quantitative prediction unless it was confirmed by other more detailed models. Thus, even very simple models such as the one described above provide some valid predictions, but, in the case of such a simple model, one must restrict the scope of the notion of prediction to refer to certain key qualitative features that are robust. To obtain quantitative predictions, we must make our models more realistic, and hence more elaborate.
We next give some recent examples of some more complex mathematical models that can be used to make quantitative predictions in infectious disease epidemiology.

4. Modelling vaccination

Vaccines are considered to constitute of the best preventive measures to decrease the morbidity and mortality of infectious diseases. Nonetheless,

implementation of new vaccine policies is a complex and challenging task for health authorities. Today, modelling is a crucial element in any modern vaccination programme, and should be used to evaluate different vaccination policies [10, 11, 12, 13, 14, 15, 16]. Predicting the overall vaccine effectiveness is complicated and costly, and necessitates population-based studies, which are frequently not feasible [17]. Mathematical modelling is one of the only tools that allows quantification of the indirect protection provided by immunization. Recently, two new vaccines, one targeted at rotavirus, a leading cause of severe diarrhoea, and the other at human papilloma virus (HPV), which is the cause of approximately 5% of all human cancers [18], have been introduced. Both vaccines have been implemented in many immunization programmes in developed countries [11, 15]. In order to achieve a more complete epidemiological impact and to better understand the effects of the vaccination, many transmission models for both of these pathogens have been constructed [10, 11, 12, 13, 14, 15, 16]. Here, we focus on the recently introduced HPV vaccination programmes as an example of how models are used to study and predict the outcome of vaccination programmes. HPV raises many complex issues, as it involves sexual transmission, adolescent vaccination, and significant differences between sexes in the expected outcomes. Over the years, many models have been developed to study optimal vaccination against HPV [10, 11, 19, 20, 21, 22, 23, 24, 25]. The models were used to evaluate how variations in different biological processes, such as immunity, partnership duration, virus strains, and waning vaccine immunity, affect model predictions regarding the effectiveness of vaccination policies [26]. In addition, modelling provided insights into key questions such as the target ages of optimal vaccination, and the relevant ‘catch-up’ policy.

A key issue where modelling has played a major part regarding HPV vaccination policies is predicting the outcome of including pre-adolescent males in future vaccination programmes [10, 12, 26]. On the one hand, the morbidity toll of HPV is much higher in females; on the other hand, males play a significant role in virus transmission. The rationale of including males is that an intervention aimed at both sexes adds to the population-level impact (i.e. herd immunity) of targeting vaccinations at females only. Currently, more and more countries are considering the routine inclusion of males in national HPV vaccination programmes [12, 26]. Bogaards has demonstrated, using both a simple model and more complex HPV transmission model that also included a small group of males who have sex with males, that the optimal strategy (for cases where vaccines are limited or costly) in most cases is to focus on the sex with the highest pre-vaccine incidence (female vaccination is preferred, because the females often develop a persistent infection that leads to an extended recovery rate relative to males, i.e. a longer period of infectiousness) [11]. In addition, the analysis outlines the cases in which male vaccination should be reconsidered, mainly if the rate of transmission from females to males is

more than twice as high as the rate of transmission from males to females. The modellers stress that this outcome is independent of many model assumptions and therefore robust, and “provide a coherent argument in favor of increasing female vaccine coverage as far as possible, given the limits set by vaccine acceptance and economic constraints'' [11].
The consistent outcome of other HPV modelling studies was that vaccination of pre-adolescent females appears to be the preferred policy, because they have a higher risk of complication from infection (cervical cancers) and a prolonged duration of infectiousness. In general, most models show that, if moderate to high vaccine coverage of females is achieved (approximately 70%), vaccination of males will have only limited benefits [10, 19, 20], and that efforts should be focused on increasing female vaccine coverage.

5. Pandemic influenza

The emergence of a pandemic influenza strain is generally considered to be inevitable [27, 28]. At the global level, the next pandemic may cause severe morbidity, mortality and extensive economic impact in its wake. Current estimations of the mortality from the 1918 pandemic are over 50 million dead, making this pandemic the greatest natural disaster of modern times [28]. Although, because of modern technologies and medicine, future pandemics will probably have milder and less severe outcomes than the 1918 pandemic, present with present transportation systems infectious diseases are likely to propagate much more quickly across the globe. For instance, the 2009 H1N1 (‘swine flu’) pandemic is now considered to have been the fastest-moving pandemic in world history [29].
Modelling is a crucial element in any modern preparedness programme, and can be used to improve our understanding of the pathways and the dynamics of the spread of the pandemic [30, 31]. The Royal Society Committee [32] on infectious diseases concluded that “Quantitative modeling is one of the essential tools both for developing strategies in preparation for an outbreak and for predicting and evaluating the effectiveness of control policies during an outbreak … More work is required to refine the existing models and to strengthen their capacity to inform policy.”
Health policy/decision-makers are faced with a wide range of potential intervention policies regarding an influenza pandemic. A key priority is to mitigate the pandemic until a vaccine for the specific virus is developed (estimated to take approximately 6 months). One or more of the following measures can be implemented [33, 34, 35]: antiviral prophylaxis, quarantines, school closure, reduction in travel, and social distancing. Mathematical models, using appropriate inputs, which are expected to be part of ‘pandemic planning', can help to calculate the ‘optimal’ quantitative set of actions that will reduce the impact of the pandemic to a minimum, in terms of both public health and economic consequences. For instance, a

typical scenario might be one in which the availability of pharmaceuticals (e.g. antiviral medication and vaccines) is limited. Mathematical models can be used to investigate how, when and to which sectors of the population the drugs should be distributed in time [34]. As another example, it has been shown that travel and/or border restrictions will have minor benefits (given the high social cost and therefore difficulty in execution) in slowing the spread of a pandemic [36], and that efforts should be focused at containing the pandemic at the source.

In order to use mathematical models effectively for investigating the dynamics of the spread of a pandemic, including possible control strategies, there is a need to be confident that the values used for the various parameters in the model correspond to reality. Although some parameters can be determined on the basis of previous knowledge, other parameters must be estimated by fitting the model to the available data. Thus, fitting epidemiological models to real data becomes a central problem during the first phase of an outbreak [37, 38]. The 2009 pandemic has demonstrated the importance of having the capabilities to estimate parameters by developing and adapting mathematical models and statistical methods well in advance, so they can be easily implemented as early as possible to estimate the disease-specific parameters. Acting as quickly as possible and establishing rapid policy schemes is crucial. However, in many cases, such urgent decisions may have to be made under conditions of great uncertainty, owing to the lack, or poor quality, of data [29, 39]. For instance, during the 2009 pandemic, early estimates of key parameters such as R_0 were published at the first stage of the outbreak (June 2009) [40], by fitting a simple mathematical model that included two age groups and age-dependent susceptibility to data from La Gloria, Mexico, where the new H1N1 virus probably made its first appearance. As the estimates of R_0 were similar to the lower values used in previous modelling efforts that were used to develop pandemic-mitigation strategies [34, 41], it was possible to use previous results regarding the different control strategies [40] to guide decision-making.

An important role of modelling in the study of an outbreak is played by deviations between a fitted model and the observed data, as such differences can point to significant factors that were neglected by the model and need to be accounted for. During the last pandemic in Israel, when the observed incidence curves of different age groups were compared with simulations of the same age group from a model, certain deviations of the data from the model predictions were noted in the young adult age group, and were shown to be related to outbreaks among soldiers [38]. Such discrepancies need to be taken into consideration, because they can have a significant impact on the decision on where to focus mitigation efforts.

During the 2009 pandemic, considerable differences in the rates of spread of the pandemic among different geographical locations were observed in the northern hemisphere. Differences were also observed in the timing of

the outbreaks. In the USA and UK, the pandemic had a first wave in early summer, but in continental Europe the pandemic started during the autumn [1]. By the use of a complex individual-based stochastic model that was parameterized with the data collected at the first stages of the outbreak in Mexico [40], it was possible to study which elements were of most significance for the predictability of the spread of the pandemic in Europe. With the model, it was possible to demonstrate that the ingredients needed to provide predictions of the timing of the spread of the disease in different countries in Europe were: (i) the different transmission rates among different social groups; (ii) population mobility patterns; and (iii) country-specific demography. In recent years, progress has been made developing massive models of the entire world population and global transportation flows, which are hoped to significantly enhance the capacity to make predictions regarding the spread of a pandemic across the globe [42, 43]. Future studies of outbreaks (e.g. the SARS outbreak) should provide data that will enable the performance of these models to be tested.

6. Conclusions

An important advantage of using models is that the mathematical representation of biological processes enables transparency and accuracy regarding the epidemiological assumptions, thus enabling us to test our understanding of the disease epidemiology by comparing model results and observed patterns [44]. A model can also assist in decision-making by making projections regarding important issues such as intervention-induced changes in the spread of disease. A point that deserves emphasis is that transmission models are based on the current understanding of the natural history of infection and immunity. In cases where such knowledge is lacking, assumptions can be made regarding these processes. However, in such cases there can be several possible mechanisms, and therefore several different models, which can lead to similar observed patterns, so that it is not always possible to learn about underlying mechanisms by comparing model outcomes. One must then be very cautious regarding model predictions, because different models that lead to similar outcomes in one context may fail to do so in another. In such instances, it is best to conduct further epidemiological and experimental studies in order to discriminate among the different possible mechanisms. Thus, an important role of modelling enterprises is that they can alert us to the deficiencies in our current understanding of the epidemiology of various infectious diseases, and suggest crucial questions for investigation and data that need to be collected. Therefore, when models fail to predict, this failure can provide us with important clues for further research.

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