REVIEW ARTICLE

Influenza—Insights from Mathematical Modelling

Rafael Mikolajczyk, Ralf Krumkamp, Reinhard Bornemann, Amena Ahmad, Markus Schwehm, Hans-Peter Duerr

SUMMARY

Background: When the first cases of a new infectious disease appear, questions arise about the further course of the epidemic and about the appropriate interventions to be taken to protect individuals and the public as a whole. Mathematical models can help answer these questions. In this article, the authors describe basic concepts in the mathematical modelling of infectious diseases, illustrate their use with a simple example, and present the results of influenza models.

Method: Description of the mathematical modelling of infectious diseases and selective review of the literature.

Results: The two fundamental concepts of mathematical modelling of infectious diseases—the basic reproduction number and the generation time—allow a better understanding of the course of an epidemic. Modelling studies based on past influenza epidemics suggest that the rise of the epidemic curve can be slowed at the beginning of the epidemic by isolating ill persons and giving prophylactic medications to their contacts. Later on in the course of the epidemic, restricting the number of contacts (e.g., by closing schools) may mitigate the epidemic but will only have a limited effect on the total number of persons who contract the disease.

Conclusion: Mathematical modelling is a valuable tool for understanding the dynamics of an epidemic and for planning and evaluating interventions.

Key words: influenza, epidemic, disease course, infection control, prevention

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The outbreak of any new infectious disease poses questions as to the expected course of the disease, and as to the most effective interventions to protect the general population and individuals. The mathematical modelling of infectious diseases can produce important results, allowing understanding of the evolution of epidemics as well as gauging the efficacy of interventions (1, 2). This article presents basic concepts of mathematical modelling and a selective literature review of modelling studies related to influenza. Key concepts are illustrated by using a very simple model to show the progression of a fictitious influenza epidemic. The goal of this article is not to predict the course of the current H1N1 epidemic, rather to facilitate a general understanding of models which can be incorporated into decisions regarding preventative strategies.

Basic concepts relating to the mathematical modelling of infectious diseases

Latent period versus incubation period

After infection with a pathogen it is important to distinguish between the incubation period (the time until the onset of clinical symptoms) and the symptomatic phase of the disease. The latent phase, by contrast, is the time between infection and that individual becoming infectious, which can be the case during the incubation period or after the onset of symptoms. The duration of infectiousness can vary between diseases and individuals. The relationship between the incubation and latent phases has relevance to the potential containment of any outbreak, because symptomatic patients are more easily identified than those who remain without clinical signs (3).

Basic model for directly transmissible infections

A simple mathematical model for the spread of infectious diseases divides the population into four groups:

- Susceptible (individuals with no established immunity to the pathogen)
- Exposed—the infected individual in the latent period
- Infectious
- Removed (immune)

(SEIR [susceptible-exposed-infectious-removed] Model).

When an infective agent is first introduced into a population, the whole population is susceptible.

a) The typical course of an influenza epidemic in a fully susceptible population. The curves show the proportion of the population which is severely ill or convalescing on varying days—based on the assumption that only a third of all infected individuals would become severely ill (source: www.influsim.de). The basic reproduction numbers for the curves are (from left to right): 3.0 (Grey), 2.0 (Red), 1.5 (Green), 1.3 (Blue) and 1.2 (Yellow).

b) The proportion of the population who would be infected during the course of an epidemic dependant on the various basic reproduction numbers

Through contact with the first affected case (the index case) a secondary wave of infection begins. Infected individuals then move into the “exposed” category until they themselves become infectious and go on to infect others. The course of the epidemic is best quantified by the expansion rate, which is dependant partly on the generation interval and partly the basic reproduction number R_0 . R_0 indicates how many individuals one infected person can infect, on average, in a susceptible population. The generation time is the average time between the infection of the index case and secondary cases. The generation time is variable according to the duration of the latent and the infectious periods.

The basic reproduction number R_0 in the context of epidemic progression

With the help of R_0 it is possible to predict the course of an epidemic at its very beginnings. For a disease where $R_0 = 2$, the number of infected individuals in each generation increases by a factor of 2. In the process of the analysis the first generation of infected individuals denotes all individuals who were infected by the index case, the second generation all those infected from a person of the first generation and so on. In the course of an epidemic the number of susceptible individuals steadily diminishes, so that eventually fewer than two susceptible individuals per index case will be infected. Later on in the epidemic, when a newly infected individual infects less than one person on average, the number of new infections falls.

Figure 1a demonstrates the course of an epidemic for differing values of R_0 , allowing for an average generation time, typical for seasonal influenza, of 3 days. The larger R_0 is, the more rapidly the epidemic grows from one generation to the next and therefore more susceptible individuals will be infected in the course of the epidemic (Figure 1b).

Figure 2 posits $R_0 = 2$ (within the range typical of influenza) and shows the number of infected individuals in the first two months of an epidemic for varying generation intervals. This figure demonstrates how the duration of the epidemic is dependant upon the duration of the latent and infectious periods.

Necessary vaccination coverage

When R_0 is known, an estimate can be made of the proportion of the population who should be immunized against the infection, in order to hinder the progress of the epidemic. If, for example, only half of the population were susceptible, infected individuals would only transmit disease to a proportion of the population equivalent to $R_0/2$, even in the beginning of the epidemic. In order to stem an outbreak, the number of susceptible individuals must be so greatly reduced, that on average each affected individual infects less than one other person. Therefore if the number of susceptible people in the population is less than $1/R_0$ this is sufficient. If, in another example, $R_0 = 10$ and 90% of the population were immunized, the infection could not spread

Isolation of infected individuals, and contact tracing

For novel infectious agents vaccines are not immediately available. In cases of severe illness one should seek to isolate sick individuals or even suspected cases, in order to prevent further spread of infection. Transmission can frequently be controlled sufficiently if contacts of the infected individuals are also promptly isolated. If most transmissions occur before the onset of clinical symptoms however, this may possibly not be sufficient to halt an outbreak.

Contact reduction

Contact reduction is an intervention which can be universally implemented. The definition of a contact depends on the specific mode of transmission for a particular disease. For infections that are spread by droplets or aerosol anyone who has been in the same room as the infected individual can be considered a contact. If everyone reduces their contact with others by 10%, the reproduction rate is reduced by 10%. Although at first glance this may appear to be negligible, it can have substantial effects for infectious diseases where R_0 is only marginally greater than 1. The epidemic will grow more slowly, have a later and lower peak, and more individuals will be spared infection. It is precisely this flatter curve that can lead to a profound reduction of the burden on a healthcare system.

Validation of mathematical models

Mathematical models for infectious diseases are generated on the basis of a mechanistic understanding of the transmission of infections (for example likelihood of transmission per contact, contact rate, duration of the infectious period). Additional parameters are obtained by fitting models to data from previous epidemics so that the simulated course generated by the mechanical model reflects the course of the observed epidemic under study. A mathematical model can give a representation of how the current situation has evolved, in contrast to a statistical model which merely describes a situation. Therefore an agreement between the observed and simulated course of the epidemic means at the same time that the model is likely to correctly explain the causal mechanisms according to which the epidemic evolves. Repeated, successful application of the same mathematical structure to various historical epidemics indicates that the model reproduces and predicts the underlying biological mechanisms correctly. Further validation can be obtained through short term predictions in the course of evolving epidemics: After the corresponding parameters have been estimated on the basis of the first cases, events in the coming days and even weeks can be predicted (4, 5). Longer term predictions can be made subject to the caveat that the conditions (parameters such as viral characteristics, restrictions imposed on human contact, or successful preventative measures) remain the same. Interventions, for example the availability of a useable vaccine, can be incorporated into the model to show progression of the epidemic in the presence of such measures. At the onset of an epidemic only a prediction as to the possible course can be made. Despite these restrictions mathematical models are extremely useful for investigating the hypothetical course of epidemics and for testing the potential effects of various interventions.

Example of the course of an influenza epidemic

In the following paragraph an example of the course of a possible influenza epidemic in Germany will be demonstrated. In this simple form, the object is not to predict the actual course of an epidemic but to illustrate the applications of modelling. This model is not prospectively validated.

In *Figure 3* a slightly broader model is demonstrated and in *Figure 4* this model is applied to a fictitious epidemic. Assumptions are as follows:

- a fully susceptible population
- a latent period of two days
- an infectious period of six days
- an incubation time of four days
- a symptomatic illness lasting for five days (figures for varying influenza strains are in [6])
- an R_0 of 2—in the region of that estimated for H1N1 (7–9).

Furthermore it is assumed that the asymptomatic and symptomatic phases are equally infectious. Symptomatic individuals do in fact potentially excrete more

The number of infected individuals in the course of an epidemic. The basic rate of reproduction R_0 is set at 2.0 for all of the curves, the duration of the latent and infectious periods varies. Red curve: 1 day latent, 2 days infectious. Green Curve: 1.5 days latent, 3 days infectious. Blue Curve: 2 days latent, 4 days infectious.

virus, but due to their manifest illness, have fewer contacts to whom they can pass on the disease. The asymptomatic cases are not represented explicitly, but are considered as a part of the continuum of those with mild symptoms.

In the course of the epidemic, the total number of sick individuals remains relatively small for a long time. This is followed by a sharp increase in the number of infected individuals, and at the peak of the epidemic approximately 15% of the population is infected, constituting 5% in the asymptomatic and 10% in the symptomatic phase. In the whole of Germany this would equate to approximately 12 million concurrently infected individuals. If we assume that 5% of people in the symptomatic phase—i.e., around 400 000 people—will require hospitalization, it is clear that demand for hospital beds would quickly outstrip available supply. Furthermore consider that of these patients with severe disease around 2% will die (assuming a mortality of 0.1% of all infected individuals), the resulting

Expanded SEIR (susceptible-exposed-infectious-removed) Model (the infectious group in this model is composed of groups A, M and H)

FIGURE 4

Example of the possible course of an influenza epidemic (using the model from Figure 3)

death toll would be over 10 000 in Germany over a period of 160 days. By the end of the epidemic, according to this simulation, in total more than 60 000 people will have died from the infection (Figure 5). At the beginning of the epidemic, if the identified cases are effectively isolated, the outbreak can be substantially delayed. If alternatively the epidemic begins with 20 cases rather than one, the time to the 10 000th death is reduced by a quarter. This observation highlights the fact that through timely intervention at the beginning of an epidemic, time can be bought for pandemic planning, the development of intervention strategies based on the level of facts available as well as the development and production of a vaccine. Even in ideal circumstances, vaccine will only be available after four to six months (10). A general reduction in interpersonal

FIGURE 5

Hospitalization and deaths during the course of the example epidemic

contact (and thereby a reduction in R_0 from 2 to 1.5 in the example) will reduce the peak incidence and level-off the course of the epidemic (Figure 6). These measures reduce the total number of sick individuals and deaths only marginally, but can reduce the peak burden on the healthcare system.

Findings from modelling studies of influenza

A differentiated model for pandemic influenza produces statistics useful for planning, for example the expected demand for doctors during an influenza pandemic, the burden on hospital beds, or the labor shortfall created by the epidemic (11, 12). The model divides the population into six age groups and applies the varying risks, relative to age, of infection and of developing severe disease. Interventions such as interpersonal contact avoidance, treatment or prophylaxis with antiviral medication can be assessed with additional parameters and their efficacy judged.

The simulation results show, for example, that it is very difficult to contain an influenza pandemic with antiviral medications alone. The prophylactic administration of antivirals to medical personnel in hospital can delay infection but not prevent it. A widening of prophylaxis to other groups is not recommended, because this increases the danger of building resistance. The outbreak of a resistant virus in the population would make antivirals useless for the treatment of sick individuals (13, 14).

With the help of a different model it has been shown that an almost immediate and complete cessation of air travel (>99%) has no substantial (i.e. more than four months) effect in delaying an influenza pandemic (15). The efficacy of screening on arrival is questionable (16). Screening could however have a place in protecting small islands from an outbreak of a local epidemic (17, 18). The identification and isolation of contacts, despite its application at the beginning of an outbreak, cannot alone slow the course of an influenza epidemic (3, 19). To this end it must also be remembered that contact tracing is a very resource intensive measure that is only possible where there are small numbers of cases (17).

Another option is to reduce the contact rate. This can be achieved by first-line measures such as school closures but also by the avoidance of any large public gathering. The high rate of interpersonal contact between children and adolescents has been proven in empirical studies (20–23). Because of this, children function as a reservoir for rapid spread of any infection as well as being a pool of infection for other age groups. The effects of school closure can only be evaluated with models that take into account the age stratification of a society. Various authors (24–26) concluded that school closure can reduce the peak of the epidemic and constrain it to a lower level. However, Ferguson et al. (25) and Germann et al. (24) found that school closure only had a limited effect on the total number of cases during an epidemic, whereas Cauchemez et al. (e1) concluded there was a reduction of approximately

15%. An analysis of strikes by primary school teachers in Israel in 2000 showed that school closure had a substantial impact on influenza-like illness (ILI) rates (e2).

Antiviral medications can be introduced with various aims:

- post-exposure prophylaxis
- to reduce the severity of the disease
- to lower the chance of transmission of a pathogen to an uninfected individual.

A simulated study showed that if 80% of identified contacts (for example in their household, nursery, or school) were given a prophylactic dose of antivirals for eight weeks the infection rate fell from 33% to 2% (e3). A further model study showed that the stocking of antivirals for 20% to 25% of the population would be sufficient to treat all patients and to reduce the burden on hospitals by 50% to 77% (in the case of a typical epidemic involving a new influenza strain (e4). However, the positive effects of generalized prophylaxis shown in modelling studies have subsequently been questioned in view of the development of drug resistance (e5).

Conclusions

Mathematical modelling offers the opportunity to investigate potential interventions in advance of an epidemic. Alternative approaches can be simulated and assessed prospectively with regard to their effectiveness and efficiency. Mathematical models represent an idealized situation, where transmission is simplified to an algorithm. They are based on previous epidemics, for which it has been shown that the basic biological mechanisms were correctly represented in the model. For future epidemics one can investigate the effects of variations in specific parameters, observe if their effects are strong or small, and assess the range between worst and best case scenario. The basic advantage of modelling is that in the case of a new outbreak the structure of the relevant model does not need to be changed, but only the parameters updated. Later on, as the epidemic unfolds with increasing clarity as to the hospitalization rate and mortality, an estimation of the burden on hospitals as well as the total number of deaths can be made. Subsequently, decisions can be made to prioritize interventions. For these reasons, both planning for interventions in pandemic influenza and predictions of their effects are based on models such as illustrated in this article. Any model predictions, however, must be viewed with the caveat that the assumptions used in the model do not change.

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FIGURE 6

Effects of a reduction in R_0 on hospitalization rates and deaths

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Conflict of interest statement

Dr Markus Schwehm is managing director of ExploSYS GmbH, which advises health authorities on preparations for pandemics. He created and runs the website www.influsim.de, which runs the simulation programme used to model the example. Dr Reinhard Bornemann was the Robert-Koch Institute's expert in the field of Influenza Pandemic Planning. The other authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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