Covid-19: Simulation models for epidemics

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No human brain has the capacity to think through all possible outcomes of an epidemic. A simulation model can keep track of many individuals and factors that influence the course of the epidemic; however, simulation models can never fully replicate reality.

The healthcare service needs answers to a number of questions when epidemics threaten. How many will be infected? How many will require intensive care treatment? How many will die? Should we close schools? Should all those who can, stay home from work? Who should be tested for the infection? Who should be quarantined? How might a vaccine affect the course of the epidemic? These types of questions cannot be answered by searching for randomised trials or registry studies if what we are facing is, as now, a new virus with unknown characteristics. Increasingly, statistical modelling – so-called infectious disease models – are being used nationally and internationally to understand and manage epidemics and the challenges related to infection outbreaks (1).

Modelling infections

Epidemic models are a type of infectious disease models and are based on theories of infectious diseases and knowledge of previous epidemics. Such models simulate the spread of disease from person to person with the aid of computer models or mathematical systems of equations (Figure 1). The starting point is that a single person can infect one or more others. This is quantified as the basic reproduction number, R_0. R_0 is defined as the average number of new cases generated by one infected individual in a fully susceptible population. R_0 increases with the number of persons the infected individual comes into contact with, the transmission probability of each contact, and the length of time the infected individual is infectious. During the swine flu epidemic (H1N1pm09), R_0 was calculated to be 1.35 (2). R_0 is believed to be 5–7 for chickenpox and 16–18 for measles (3). Early in an epidemic when the proportion of susceptible individuals in the population is high, the number of infected individuals will increase exponentially (Figure 2).
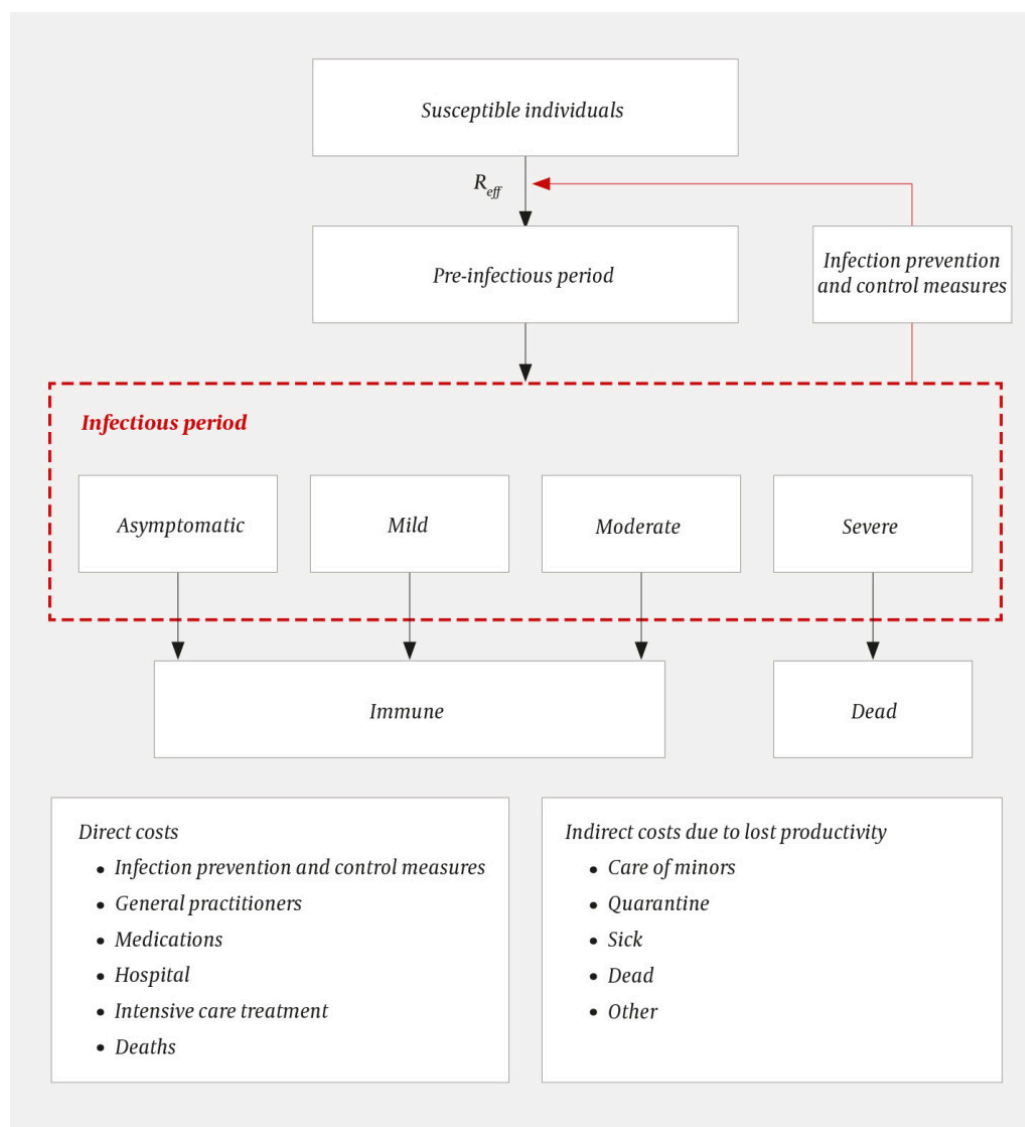
Figure 1 Schematic overview of a simple infectious disease model. Individuals start out as susceptible with a certain risk of being infected based on the effective reproduction number (Reff). Infected individuals can be asymptomatic or symptomatic, after which each individual either becomes immune or dies. The costs to society can be divided into direct costs and indirect costs (lost productivity).
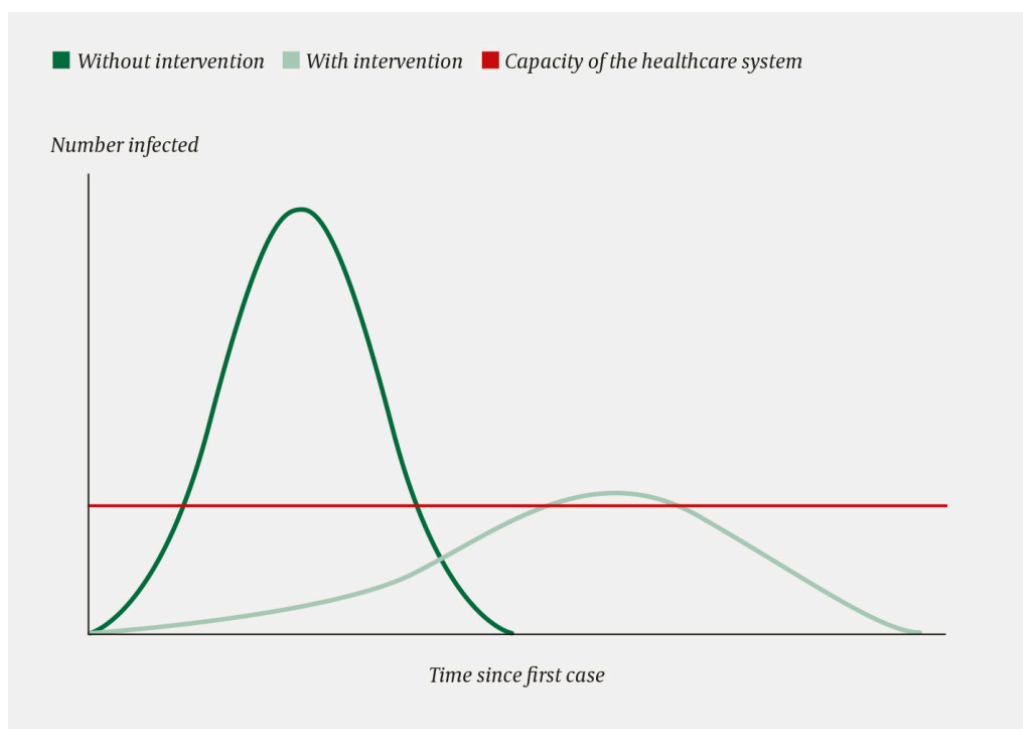
Figure 2 Number of infected individuals with and without societal interventions during an epidemic.

Eventually, as the proportion of susceptible individuals in the population decreases, the effective reproduction number R_{eff} falls, where R_{eff} is R_0 multiplied by the proportion of susceptible individuals (Figure 2). An epidemic dies out when R_{eff} becomes lower than 1. The total proportion of infected individuals in a population ('attack rate') will be higher when the basic reproduction number is higher. When R_0 is above 3, more than 90 % will become infected, unless effective interventions reduce the transmission chain of infection. Information on the basic reproduction number is important early on in the initial phase of an epidemic, which helps informs policy makers about how extensive the measures needed to control the epidemic must be.

The simplest epidemic models, so-called SIR models, are based on the premise that a population can be divided into three groups: susceptible, infected, and immune or recovered (dead). Based on the basic reproduction number and a number of other parameters, one can calculate the number of asymptomatic and clinical cases, and the number of hospitalised and deceased individuals. A key element is data on the extent to which the groups 'schoolchildren', 'workers' and 'older people' interact with each other and with other members of their respective groups. Such data are necessary to simulate the spread of infection and can be obtained from social contact studies (contact tracing). National contingency plans should, as far as possible, be based on local data because differences in these contact patterns can give rise to substantial variation in the development of epidemics.

Simpler models, such as cancer models, assume that the risk factors remain constant by time and place, and that the disease in one individual does not affect the risk of disease in others. However, with infections, the likelihood of events change over time and from one place to another such that one individual

or group of individuals can affect the risk of disease in others. Infectious disease models are thus said to be dynamic, which makes developing this type of model far more demanding.

«For all simulation models the same rule applies: the results are no more reliable than the input data supplied»

Sensitivity analyses are important in all modelling studies. Sensitivity analysis involves running numerous simulations while changing various parameters in the model, such as R_0 or the risk of death in infected individuals. This provides information on the extent to which the uncertainty in the data entered into the model affects the results of the simulations. It may also be appropriate to examine whether changes in the logical structure of the model affect the results.

Once an infectious disease model has been developed, it must be validated to verify that it contains no miscalculations and that its predictions are in line with reality. As new data become available, the models must be updated and re-validated to ensure that they are consistent with the status quo, to the extent that this is known at any given time. During an epidemic in which new measures are being introduced on an ongoing basis, developments in the spread of the infection and the effective reproduction number must be continuously monitored to evaluate the effectiveness of the measures taken and the need for new interventions.

Predicting and evaluating effects of interventions

An infectious disease model can have many applications. During an epidemic, knowledge of the likely consequences of the outbreak is required. The healthcare authorities need to know how the number of infected people is likely to develop over time, how many may require hospitalisation or respiratory support, and how many may die. In the course of a typical epidemic, there is a period of exponential growth in the number of infected individuals, after which the proportion of susceptible individuals in the population falls (R_{eff} decreases) and the epidemic dies out (Figure 2). It is also possible to simulate the effects of interventions such as quarantine, school closures, drug treatment and vaccines where appropriate (Figure 2).

Linking epidemic models with health economic models can provide a framework that may assist in making health policy decisions. It can provide, for example, some indication of the need for hospital beds, medicines and intensive care units, and of the cost-effectiveness of interventions.

School closures and sick leave

Yiting Xue and colleagues studied the costs and benefits of school closures during influenza pandemics in Norway (4). They assumed that individuals infected with influenza could either remain asymptomatic, develop mild to

moderate disease, develop serious disease requiring hospitalisation, or die as a result of the influenza. The outcomes were 'translated' into loss of quality-adjusted life years. Reductions in morbidity or mortality as a result of interventions could thus be measured in terms of quality-adjusted life years. The model captured the costs avoided by the healthcare service as a result of school closures, including lost productivity to society due to individuals caring for children at home. It also captured the value of lost teaching, but interestingly enough, there are almost no data on what pupils lose out on as a result of short-term absence from school. The results indicated that it is profitable to close schools for students who will not require supervision at home during the closure. For younger children, the results depended on the severity of the epidemic and on whether lost productivity to society due a child's guardian requiring time off work was taken into account.

A related issue is the guidelines for sick leave in cases of suspected influenza (5). Edwards and colleagues estimated the associated costs and benefits based on a study of sick leave in cases of influenza-like symptoms (6). The analysis varied the proportion of individuals who stayed away from work due to symptoms, and the duration of their absence. The study indicated that it would be socio-economically profitable for a high proportion of employees to promptly take sick leave, especially for an infection with high morbidity and mortality. Somewhat surprisingly, sick leave was most cost-effective in epidemics with a low basic reproduction number.

Interventions such as travel bans, isolation of infected individuals and school closures are intended to reduce the transmission of infection in an epidemic so that the effective reproduction number falls below the basic reproduction number. The aforementioned influenza analyses illustrate an important aspect of such interventions: they delay the epidemic and reduce the maximum number of cases at any single point in time (Figure 2). The most effective measures seem able to delay the peak of an influenza epidemic by 50–60 days, providing healthcare services with more time to prepare for the epidemic, while simultaneously reducing its peak burden.

Covid-19 modelling

Norway has a number of research communities with expertise in the modelling of infectious diseases, at institutions including the University of Oslo and the Norwegian Institute of Public Health. Researchers from these organisations have published analyses on methicillin-resistant Staphylococcus aureus (MRSA), herpes zoster, rotavirus, hepatitis C, human papillomavirus and influenza.

In 2017, the Norwegian Institute of Public Health conducted a study in which 4 300 randomly selected Norwegians were asked to complete a diary of all their contacts over the course of a single day (7). This provided data on social networks and the possibilities for spread of infection in Norwegian society.

In recent years, the Norwegian Institute of Public Health has also collaborated with Telenor and the University of Oslo on the use of mobile phone data as inputs into infectious disease models. Since February 2020, they have been working with the Norwegian Computing Center to further develop a model that can predict the spread of Covid-19 at the municipal level in Norway over the next week and the next month. The model uses Telenor's mobile phone data from Norwegian subscribers as well as daily updated epidemiological data. Many simulations are run to estimate uncertainty, and the model is adjusted to fit new data as they become available. Real-time data thus have a part to play in epidemic preparedness, but unfortunately, it is still difficult to quickly retrieve and link registry data on infections (8).

Figures from the Norwegian Institute of Public Health on March 9th suggested that Norway could end up with approximately 22 000 hospital admissions because of Covid-19 infection, of which 5 500 would be to intensive care units (9). According to the calculations, at the epidemic's peak, hospitals would face 1 700 admissions simultaneously, including 600 individuals requiring intensive care. Such figures are linked to scenario planning, in which consequences are assessed under a given set of assumptions. The assumptions must be interpreted with caution because knowledge about the virus and its spread was, and still is, limited. The Norwegian Institute of Public Health's models are updated as new information comes in. The model also makes it possible to evaluate the effectiveness of currently implemented measures.

Even though the Covid-19 epidemic has been ongoing since December 2019, at the time of writing (17 March 2020) the basic reproduction number (R_0) is still uncertain, although it is believed to be higher than for seasonal influenza. In a recent study, R_0 was estimated at 2.35 in Wuhan on 16 January, a week before restrictions were introduced. The effective reproduction number (R_{eff}) was 1.05 after measures were implemented (10). The proportion of infected individuals who die is also uncertain. The number of infected individuals is easily underestimated because some of those infected have few or no symptoms and because of insufficient contact tracing or testing capacity. Criteria for testing may vary between countries, and some countries lack the necessary equipment. Overall, this leads to the number of infected individuals being underestimated, and accordingly to the proportion of deaths due to Covid-19 being overestimated.

Discussion

For all simulation models, the same rule applies: the results are no more reliable than the input data supplied ('garbage in – garbage out'). A key limitation of infectious disease modelling is precisely the uncertainty associated with the underlying data. However, despite this uncertainty, models can provide us with useful insights, including which type of data it is important to gather. When panic over HIV prevailed in Norway in the 1980s, Hein Stigum and colleagues established a set of differential equations based on assumptions about sexual behaviour and the characteristics of HIV (11, 12). They concluded

that Norway had no reason to fear an extensive HIV epidemic. Some regarded these results as counterintuitive back then, but time would show that their assumptions and presuppositions were essentially correct.

An important insight from the modelling of infections is that no human brain has the capacity to think through all possible outcomes in the complicated chain of events seen in an epidemic. A system of equations or a computer program is able to simultaneously keep track of many individuals and factors that affect the course of the epidemic. Nevertheless, no simulation model can fully replicate reality – it is, and will remain, a model. We therefore join the statistician George Box in arguing that 'all models are wrong, but some are useful' (13).

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