Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Mathematical prediction in infection

Neil M Ferguson

Abstract
It is now increasingly common for infectious disease epidemics to be analysed with mathematical models. Modelling is possible because epidemics involve relatively simple processes occurring within large populations of individuals. Modelling aims to explain and predict trends in disease incidence, prevalence, morbidity or mortality.

Epidemic models give important insight into the development of an epidemic. Following disease establishment, epidemic growth is approximately exponential. The rate of growth in this phase is primarily determined by the basic reproduction number, \( R_0 \), the number of secondary cases per primary case when the population is susceptible. \( R_0 \) also determines the ease with which control policies can control an epidemic. Once a significant proportion of the population has been infected, not all contacts of an infected individual will be with susceptible people. Infection can now continue only because new births replenish the susceptible population. Eventually an endemic equilibrium is reached where every infected person infects one other individual on average. Heterogeneity in host susceptibility, infectiousness, human contact patterns and in the genetic composition of pathogen populations introduces substantial additional complexity into this picture, however — and into the models required to model real diseases realistically.

This chapter concludes with a brief review of the recent application of mathematical models to a wide range of emerging human or animal epidemics, most notably the spread of HIV in Africa, the 2001 foot and mouth epidemic in British livestock, bioterrorism threats such as smallpox, the SARS epidemics in 2003 and most recently the use of modelling as a tool for influenza pandemic preparedness planning.

Keywords basic reproduction number; epidemic; epidemiology; emerging infections; HIV; mathematical model; smallpox; SARS

An epidemic is a chain reaction of disease spread within a population. Epidemics can be described and sometimes predicted by mathematical models because they involve relatively simple processes occurring within large populations of individuals. ‘Simple’ means that infection and disease progression can be characterized by the transition of an individual from one state to another; for example, from a state of being uninfected and susceptible to infection, or to an infected state following contact with an infectious individual, or from the infected to the recovered state following recovery from infection and the acquisition of immunity. Defining a model therefore involves classifying the possible infection states of an individual and the processes causing movement between those states. The aim then is to predict changes through time in the proportions of the population in different infection states, and the incidence of disease-related events. This contribution discusses the modelling of epidemics, but similar techniques can be used to study the pathogenesis of viral or bacterial infections within an infected individual.

The dynamics of epidemics
An understanding of basic concepts is informed by consideration of the spread of a new infectious disease within a large population with no prior exposure. This process can crudely be divided into three phases (Figure 1).

Establishment — the epidemic grows from the first infected individual to a point at which sufficient individuals are infected that random extinction of the disease is unlikely. Many epidemics can die out after infection of only one or two individuals, if the last infected individual recovers (or dies) before infecting anyone else. This randomness means that the establishment phase can be relatively long and is variable in duration — a possible explanation for the several decades that passed between HIV entering the human population before 1950 and the recognition of a large-scale epidemic in the early 1980s.

Exponential growth — growth of epidemics is approximately exponential following disease establishment. How fast an epidemic grows is largely determined by two factors — the number of secondary cases generated by one primary case when the epidemic starts (the basic reproduction number, \( R_0 \)) and the average time taken for secondary cases to be infected by a primary case (generation time, \( T_G \)). \( R_0 \) characterizes the

![Epidemic process](image)

The ‘chain reaction’ nature of the process results in exponential growth (once infected numbers are great enough to make random effects small), until there are no further susceptible contacts.

![Figure 1](image)
intrinsic transmissibility of infections and depends on both disease biology (determining infectiousness) and host population structure (determining contact rates). $T_c$ is largely determined by the incubation period of the disease and the duration of infectiousness. $R_0 > 1$ is essential to epidemic growth because, for an infection to be self-sustaining, every infected individual must infect at least one other. The target of vaccination campaigns is to reduce $R_0$ below 1, thereby driving the disease extinct.

**Endemicity** — once a significant proportion of the population is immune, dead or chronically infected, not all contacts of an infected individual are with susceptible people. Hence, the number infected by one individual is now reduced by the proportion of the population that is no longer susceptible. This causes the incidence of new infections to decline, and when the susceptible population is exhausted, the primary epidemic is over. Disease extinction is again possible by chance, particularly in small populations. Otherwise, infection continues, with new births replenishing the susceptible population, and eventually an endemic equilibrium is reached in which every infected person infects one other individual on average. From the definition of $R_0$, this occurs when $1/R_0$ of an individual’s contacts are susceptible at any point in time, and thus $R_0$ not only determines the epidemic growth rate, but also the proportion of the population that are infected by the disease, and the steady-state incidence of infection.

**Epidemiological complexity**

In theory, knowledge of $R_0$ (and the duration of infectiousness) enables simple prediction of many key aspects of epidemic and endemic disease transmission. In reality, estimation of multifactorial quantities such as $R_0$ is problematic, except in some childhood diseases (e.g. measles) for which serological data can be used. Disease epidemiology typically has many additional complexities:

- the nature of the transmission process (e.g. insect-borne, food-borne)
- heterogeneities in the pathogen population (e.g. multiple strains with different virulence and antigenic properties)
- patterns of host contact (e.g. stronger mixing within age-defined or geographically defined peer groups than without, variability in contact rates because of differences in, for example, sexual behaviour)
- long and variable incubation periods (e.g. HIV)
- seasonally varying contact rates (e.g. measles).

Incorporation of this complexity is often essential to generate a model that it is not just qualitatively reasonable (in the sense of reproducing the basic pattern of observed trends), but capable of quantitative predictions.

Sufficiently realistic models thus tend to incorporate multiple parameters that must be estimated from available epidemiological, clinical and behavioural data. Biostatistical techniques for such estimations are developing rapidly, but many problems remain, largely caused by the non-linear nature of transmission models and the extremely complex dynamics that they sometimes produce; this can include chaotic behaviour and stochastically induced intermittency in epidemic timing. Dynamic complexity can also place fundamental limits on the predictability of trends in the incidence of infectious disease. In some cases, short-term prediction of the course of an epidemic may be possible. In others, models may be predictive only in a probabilistic sense; for example, it might be possible to predict the number of epidemics of a certain size likely to occur in the next 10 years, but impossible to precisely predict weekly disease incidence over the next few months. Distinguishing these situations is a key challenge in epidemic modelling.

---

**Predicting epidemics**

In 2001, mathematical models were used to predict the course of the foot and mouth disease epidemic in UK livestock, and to evaluate the potential effect of control measures.\(^7\) The predictions above were made by a team at Imperial College London and released by the UK government in early April 2001. They indicated that additional culling or vaccination at farms neighbouring infected farms was necessary to control the epidemic; simply accelerating the slaughter of animals at infected farms was insufficient.

In 2003, models were used to analyse the SARS epidemic.\(^7\) The graph below shows the fit of a model to the epidemic in Hong Kong. This analysis showed that $R_0$ for SARS was about 3.

---

**Figure 2**
Recent developments

Despite these challenges, most infectious diseases have now been modelled, and modelling has achieved notable successes in recent years (Figure 2).

- Trends in the incidence of HIV in southern Africa in the last 10 years have validated predictions made more than 15 years ago (and then often dismissed) that AIDS would reverse population growth in sub-Saharan Africa in the 21st century.\(^1\)
- In 2001 the UK suffered the largest epidemic of foot-and-mouth disease in livestock experienced for 40 years in Europe, causing considerable economic and social disruption in rural communities. Mathematical models had a pivotal role in shaping disease-control policy during the epidemic — the first example of real-time application of such techniques.\(^2\)
- During the severe acute respiratory syndrome (SARS) epidemic in 2003, epidemiological analysis and modelling quantified key and then unknown disease parameters such as incubation period distribution, case mortality rate and transmissibility (as quantified by \(R_0\)).\(^3\)
- Greater computer power and improved statistical techniques are enabling construction of increasingly realistic simulation models, which are having a key role in contingency planning for bioterrorism\(^4\) and (following the emergence of H5N1 avian influenza) preparing for a new influenza pandemic (i.e., the global epidemic caused by the emergence of a new influenza virus from animal reservoirs into the human population).\(^5\)
- During the 2009 ‘swine’ H1N1 influenza pandemic, real-time outbreak analysis and mathematical modelling was used to give early estimates of the magnitude and speed of spread of the pandemic in different countries, to predict health impacts and evaluate the likely effectiveness of public health interventions.\(^6\) The pandemic highlighted the challenges involved in using imperfect surveillance data to evaluate the lethality of a new pathogen when severity is mild to moderate.

REFERENCES

1. Anderson RM, May RM, Boily MC, et al. The spread of HIV-1 in Africa — sexual contact patterns and the predicted demographic impact of AIDS. *Nature* 1991; 352: 581—9.
2. Kao RR. The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK. *Trends Microbiol* 2002; 10: 279—86.
3. Anderson RM, Fraser C, Ghani AC, et al. Epidemiology, transmission dynamics and control of SARS: the 2002—2003 epidemic. *Philos Trans R Soc Lond B Biol Sci* 2004; 359: 1091—105.
4. Ferguson NM, Keeling MI, Edmunds WJ, et al. Planning for smallpox outbreaks. *Nature* 2003; 425: 681—5.
5. Ferguson NM, Cummings DA, Fraser C, et al. Strategies for mitigating an influenza pandemic. *Nature* 2006; 442: 448—52.
6. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. *Science* 2009; 324: 1557—61.