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Review

Mathematical epidemiology is not an oxymoron

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Abstract

A brief description of the importance of communicable diseases in history and the development of mathematical modelling of disease transmission is given. This includes reasons for mathematical modelling, the history of mathematical modelling from the foundations laid in the late nineteenth century to the present, some of the accomplishments of mathematical modelling, and some challenges for the future. Our purpose is to demonstrate the importance of mathematical modelling for the understanding and management of infectious disease transmission.

Introduction

Communicable diseases such as measles, influenza or tuberculosis are a fact of modern life. Some diseases, such as chicken pox, usually have mild symptoms and vanish of their own accord. Others, such as Ebola (recurrently) and SARS, have appeared, causing a significant number of deaths, and then disappeared, but not before giving rise to fears of catastrophic spread. The prevalence and effects of many diseases in resource-constrained countries are probably less well-known but may be of even more importance. Every year, millions of people die of measles, respiratory infections, diarrhea and other diseases that are easily treated and not considered dangerous in the Western world. Diseases such as malaria, typhus, cholera, schistosomiasis and sleeping sickness are endemic in many parts of the world. The effects of high disease mortality on mean lifespans, and of disease debilitation and mortality on the economy in afflicted countries are con-

belief that epidemics represented divine retribution for sinful living. This view has not disappeared entirely. Some have described AIDS as punishment for sinful activities and such views have delayed or hampered attempts to control this modern epidemic.

In view of the importance of communicable diseases in history, it is natural that people would make efforts to understand the causes of diseases and search for treatments. This search leads naturally to an effort to construct models that focus on the main properties of a disease without necessarily attempting to include all the details.

Why should we model?

A model is an attempt to answer a question that begins with "Why?" The relation between problems and models in science may be described by the "flow chart" in Figure 1 (adapted from a similar flowchart in [2], by permission).

The normal process of scientific progress is to observe a phenomenon, hypothesize an explanation and then devise an experiment to test the hypothesis. A mathematical model is a mathematical description of the situation based on the hypotheses and the solution of the model gives conclusions which may be compared with experimental results. This comparison usually requires numerical simulations to give predictions which may be compared with observed data.

It has been observed in many epidemics that the disease spreads into a population and then disappears without infecting the entire population. Intuitively, one might think that epidemics die out because there are no people left in the location of the epidemic to be infected, but there is much evidence to contradict this explanation. In order to explain why part of the population escapes infection during an epidemic, it is natural to try to give a description of how the disease spreads. Such a description, or model, does not necessarily try to include all the details of the epidemic spread, but attempts to incorporate the factors that appear to be the most important. While a model may be a description in words, in order to compare observed results with a model prediction it is necessary to formulate the model mathematically. The general process is to make some assumptions about the way in which the epidemic spreads, formulate these assumptions in mathematical terms and translate them into a mathematical problem. This mathematical problem is a model of the epidemic.

Figure 1
Problems and Models. A "flow chart" describing the relationship between scientific problems and models.

For example, Kermack and McKendrick set out to try to explain why epidemics pass through a population without affecting the entire population [3]. Their mathematical model assumed mass-action incidence to describe the acquisition of infection followed by a period of infectivity and then recovery with immunity against reinfection. The simplest mathematical formulation of these assumptions is a pair of ordinary differential equations for the number of susceptible (uninfected) and the number of infected (and infectious) members of the population. They were able to describe the solution of this mathematical problem qualitatively, in terms of a quantity called the basic reproduction number that may be calculated in terms of the parameters of the model. This mathematical solution leads to the prediction that if the basic reproduction number is less than one, the number of infectives will tend to zero; if the basic reproduction number exceeds one, the number of infectives will increase initially before tending to zero, while the number of susceptibles decreases but never reaches zero. This prediction not only matches observations but also gives a criterion for whether a disease outbreak will develop into an epidemic or die out. In order to make more detailed predictions about the number of people infected in an epidemic, it would be necessary to make more detailed assumptions about the situation to give a more complicated mathematical model. Such a model would probably be sufficiently complicated that an exact solution would be impossible; numerical simulations would be needed to obtain predictions that could be compared with observations. Scientific experiments are usually designed to obtain information and to test hypotheses. For example, we might wish to compare two different management strategies for a disease outbreak. Experiments in epidemiology with controls are often difficult or impossible to design; even if it is possible to arrange an experiment, there are serious ethical questions involved in withholding treatment from a control group. In order to describe the course of a future disease outbreak, formulation and analysis of a mathematical model may be the only way to compare the

erations and then verified in observations. Its calculation

est. An important aspect of sexually transmitted diseases is that there is often a "core" group of very highly active individuals who are responsible for most of the disease transmission; control efforts aimed at this core group are likely to be most effective for control. This was analyzed in models in [49,50] and the translation of this analysis into action has been effective, especially for gonorrhea.

Other heterogeneities are also important. Many "childhood" diseases are transmitted mainly in school between children of the same age. Because age groups may mix heterogeneously, it may be appropriate to include age structure in epidemiological models [24,34,36,51-55]. Threshold results can be established for the existence of endemic states [56,57]. The incorporation of age structure leads to possibilities of behaviour that are not possible without the age dependence, such as sustained oscillations [19,58,59]. However, there is no indication of period-doubling or chaotic behaviour unless seasonal variation of contacts is assumed [16,60]. Age structure is an important aspect in the transmission of childhood diseases [61], e.g., for pertussis [62], rubella [29] and varicella [63]; it must be included in models designed to suggest realistic vaccination strategies. Optimal ages of

tion has been mostly about deterministic compartmental models, but stochastic models have also been important. We will not go into the description and development of such models here, but some useful references are [20,90-92,114,116-124].

Another, relatively recent, development in disease transmission modelling has been the use of network models and detailed study of the network of contacts of an individual. Again, we do not go into the description and development but merely cite references [125-131] for the theoretical background and [132-136] for some simulations using network models for predictions of influenza pandemics. There is still much to be done in validating the simulation results and relating them to the theory. The origins of the study of mathematical epidemiology come from outside mathematics. As the mathematical analysis of epidemiological models progressed, epidemiologists took less account of the contributions of mathematics to epidemiology and mathematicians have not always been responsive to the questions that concern epidemiologists. Epidemiology and mathematical epidemiology appear to have diverged, but currently there are serious attempts to improve communications.

Some of the references cited contain historical information about the development of epidemiological models. A good description of the history up to 1975 may be found in [25]. Another important source of information about mathematical epidemiology is [111], which includes both descriptions of the properties of many communicable diseases and mathematical models. However, a full, up-to-date history has yet to be written. We may hope that if mathematicians and epidemiologists can come together, a history written in a few years would be radically different from a history that might be written today.

What has modelling accomplished?

We have already mentioned two of the most striking contributions of mathematical modelling to disease management: the control of malaria through control of mosquitoes [8] and the elimination of smallpox by a sufficiently high vaccination rate [115]. Sir R. A. Ross was awarded the second Nobel prize in Medicine in 1902 for his work, beginning in 1882, in which he established that malaria was spread through contacts between humans and mosquitoes. Even though this discovery was honoured in the medical community, his conclusion that control of mosquitoes would be an aid in controlling malaria was not accepted because it was felt that it would be impossible to rid a region of mosquitoes and keep it mosquito-free. Only after Ross described a mathematical model [8] indicating that it was not necessary to remove the entire mosquito population to control the disease was this strategy adopted, with great success. In fact, Ross's model proved to be such a robust description of malaria that it remained current for about 50 years until it was updated by MacDonald [137].

Vaccination for smallpox, the world's first vaccine, was begun in 1796 by Edward Jenner, who had observed that people who had been infected with cowpox did not get smallpox. The recognition, from a smallpox model involving herd immunity, that vaccination of 70 - 80% of a population would eliminate smallpox, led to an eradication program by the World Health Organization beginning in 1967; the last case in the Americas was in 1971 and the last case worldwide was in Somalia in 1977 [8,115,138-140].

Measles is a childhood disease which is easily controlled by vaccination, but in many resource-constrained countries, few children are vaccianted against measles and there are a million deaths from smallpox worldwide. Models with age structure have compared a strategy of a single dose of vaccine to a two-dose strategy; epidemiologists have concluded that a two-dose strategy of doses at age 12 to 15 months and 4 to 6 years is more effective. However, herd immunity would require an immune fraction of at least 0.94. Since vaccine efficacy for measles is about 0.95, it is unlikely that this can be achieved [29,141]. Thus, elimination of measles is unlikely to be achievable.

Another example of an important contribution of mathematical modelling is the control of sexually transmitted diseases through concentration on the most active members of the population [49]. Others include the management of bovine hoof and mouth disease in Great Britain through a process of culling infected herds of cattle as suggested by models [142,143].

To epidemiologists, the measure of whether a disease outbreak has been controlled is whether the reproduction number has been reduced to a value less than one. During the SARS epidemic of 2002-2003, the estimation of $_0$ was the focus of many studies [144-146] and, after the epidemic had passed, models to compare the contribution of contact tracing and quarantine of suspected cases with the contribution of diagnosed infectives were studied. The conclusion appears to be that isolation was more effective and much less costly, partly because fewer than 5% of the people identified by contact tracing developed disease [147]. However, if infectivity had developed before the appearance of symptoms, which is now considered not to have been the case for SARS, contact tracing would have been more useful. The lessons learned from SARS are being applied to planning for a possible influenza pandemic.

For most disease transmission models, the expected situa-

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