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Mathematical Epidemiology: Past, Present and Future

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ABSTRACT

Mathematical Epidemiology is a growing area nowadays. In this paper, I give a brief outline of some of the important aspects of the development of mathematical epidemiology.

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INTRODUCTION

Communicable diseases have always been an important part of human history. Since the beginning of recorded history there have been epidemics that have invaded populations, often causing many deaths before disappearing, possibly recurring years later, possibly diminishing in severity as populations develop some immunity. For example, the "Spanish" flu epidemic of 1918–19 caused more than 50,000,000 deaths worldwide, and there are annual influenza seasonal epidemics that cause up to 35,000 deaths worldwide.

The Black Deaths (probably bubonic plague) spread from Asia throughout Europe in several waves during the fourteenth century, beginning in 1346, and is estimated to have caused the death of as much as one-third of the population of Europe between 1346 and 1350. The disease recurred regularly in various parts of Europe for more than 300 years, notably as the Great Plague of London of 1665–1666. It then gradually withdrew from Europe.

There are also diseases that have become endemic (always present) in some populations and cause many deaths. This is especially common in developing countries with poor health care systems. Every year millions of people die of measles, respiratory infections, diarrhoea, 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 life span and of disease debilitation and mortality on the economy in afflicted countries are considerable. The World Health Organization has estimated that in 2011 there were 1,400,000 deaths due to tuberculosis, 1,200,000 deaths due to HIV/AIDS, and 627,000 deaths due to malaria (but other sources estimate the number of malaria deaths to have been more than 1,000,000). In 1980 there were 2,600,000 deaths due to measles, but the number of measles deaths in 2011 was reduced to 160,000, primarily because of the development of a measles vaccine.

The goal of epidemiologists is first to understand the causes of a disease, then to predict its course, and finally to develop ways of controlling it, including comparisons of different possible approaches. The first step is obtaining and analyzing observed data.

HISTORY

Mathematicians and biologists, including medical scientists, have a long history of working successfully together. Sophisticated mathematical results have been used in and have emerged from the life sciences. Examples are given by the development of stochastic processes and statistical methods to solve a variety of population problems in demography, ecology, genetics and epidemics, and most joint work between biologists, physicists, chemists and engineers involves synthesis and analysis of mathematical structures. Pythagoras, Aristotle, Fibonacci, Cardano, Bernoulli, Euler, Fourier, Laplace, Gauss, von Helmholtz, Riemann, Einstein, Thompson, Turing, Wiener, von Neumann, Thom, and Keller are names associated with both significant applications of mathematics to life science problems and significant developments in mathematics motivated by the life sciences.

The study of infectious disease data began with the work of John Graunt (1620–1674) in his 1662 book "Natural and Political Observations made upon the Bills of Mortality". The Bills of Mortality were weekly records of numbers and causes of death in London parishes. The records, beginning in 1592 and kept continuously from 1603 on, provided the data that Graunt used. He analyzed the various causes of death and gave a method of estimating the comparative risks of dying from various diseases, giving the first approach to a theory of competing risks.

What is usually described as the first model in mathematical epidemiology is the work of Daniel Bernoulli (1700–1782) on inoculation against smallpox. In the eighteenth century smallpox was endemic. Variolation, essentially inoculation with a mild strain, was introduced as a way to produce lifelong immunity against smallpox, but with a small risk of infection and death. There was heated debate about variolation, and Bernoulli was led to study the

question of whether variolation was beneficial. His approach was to calculate the increase in life expectancy if smallpox could be eliminated as a cause of death. His approach to the question of competing risks led to publication of a brief outline in 1760 (Bernoulli, 1760) followed in 1766 by a more complete exposition. His work received a mainly favorable reception but has become better known in the actuarial literature than in the epidemiological literature. However, more recently his approach has been generalized (Dietz & Heesterbeek, 2002).

Another valuable contribution to the understanding of infectious diseases even before there was knowledge about the disease transmission process was the knowledge obtained by study of the temporal and spatial pattern of cholera cases in the 1855 epidemic in London by John Snow, who was able to pinpoint the Broad Street water pump as the source of the infection (Johnson, 2006; Snow, 1855). In 1873, William Budd was able to achieve a similar understanding of the spread of typhoid (Budd, 1873). In 1840, William Farr studied statistical returns with the goal of discovering the laws that underlie the rise and fall of epidemics.

BEGINNING OF COMPARTMENTAL MODELS

In order to describe a mathematical model for the spread of a communicable disease, it is necessary to make some assumption about the means of spreading infection. The modern view is that diseases are spread by contact through a virus or bacterium. The idea of invisible living creatures as agents of disease goes back at least to the writings of Aristotle (384 BCE–322 BCE). The existence of microorganisms was demonstrated by van Leeuwenhoek (1632–1723) with the aid of the first microscopes. The first expression of the germ theory of disease by Jacob Henle (1809–1885) came in 1840 and was developed by Robert Koch (1843–1910), Joseph Lister (1827–1912), and Louis Pasteur (1822–1875) in the late nineteenth and early twentieth centuries.

In 1906 W.H. Hamer proposed that the spread of infection should depend on the number of susceptible individuals and the number of infective individuals (Hamer, 1906). He suggested a mass action law for the rate of new infections, and this idea has been basic in compartmental models since that time. It is worth noting that the foundations of the entire approach to epidemiology based on compartmental models were laid, not by mathematicians, but by public health physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, and W.O. Kermack between 1900 and 1935.

A particularly instructive example is the work of Ross on malaria. Dr. Ross was awarded the second Nobel Prize in Medicine in 1902 for his demonstration of the dynamics of the transmission of malaria between mosquitoes and humans.

It was generally believed that so long as mosquitoes were present in a population malaria could not be eliminated. However, Ross gave a simple compartmental model (Ross, 1911) including mosquitoes and humans which showed that reduction of the mosquito population below a critical level would be sufficient. This was the first introduction of the concept of the basic reproduction number, which has been a central idea in mathematical epidemiology since that time. Field trials supported this conclusion and led to sometimes brilliant successes in malaria control.

The basic compartmental models to describe the transmission of communicable diseases are contained in a sequence of three papers by Kermack and McKendrick (1927, 1932, 1933). The first of these papers described epidemic models.

STOCHASTIC MODEL

There are serious shortcomings in the simple Kermack-McKendrick model as a description of the beginning of a disease outbreak, and a very different kind of model is required. The simple Kermack-McKendrick compartmental epidemic model assumes that the sizes of the compartments are large enough that the mixing of members is homogeneous. However, at the beginning of a disease outbreak, there is a very small number of infective individuals and the transmission of infection is a stochastic event depending on the pattern of contacts between members of the population; a description should take this pattern into account.

The process to be described is known as a Galton-Watson process, and the result was first given in Galton, Watson and Galton (1874). There was a gap in the convergence proof, and the first complete proof was given much later by Steffensen (Steffensen, 1930; Steffensen, 1931). The result is a standard theorem given in many sources on branching processes, for example (Harris, 1963), but did not appear in the epidemiological literature until later. To the best of the author's knowledge, the first description in an epidemiological reference is (Metz, 1978) and the first epidemiological book source is the book by Diekmann and Heesterbeek (2000) in 2000.

A stochastic branching process description of the beginning of a disease outbreak begins with the assumption that there is a network of contacts of individuals, which may be described by a graph with members of the population represented by vertices and with contacts between individuals represented by edges. The study of graphs originated with the abstract theory of Erdös and Rényi of the 1950's and 1960's (Erdös & Rényi, 1959, 1960, 1961), and has become important more recently in many areas, including social contacts, computer networks, and many other areas as well as the spread of communicable diseases. We will think of networks as bi-directional, with disease transmission possible in either direction along an edge.

An edge is a contact between vertices that can transmit infection. The number of edges of a graph at a vertex is called the *degree* of the vertex. The degree distribution of a graph is {pk}, where pk is the fraction of vertices having degree *k*. The degree distribution is fundamental in the description of the spread of disease. We assume that all contacts between an infective and a susceptible transmit infection, but this assumption can be relaxed.

We think of a small number of infectives in a population of susceptibles large enough that in the initial stage we may neglect the decrease in the susceptible population. We assume that the infectives make contacts independently of one another and let pk denote the probability that the number of contacts by a randomly chosen individual. In other words, {pk} is the degree distribution of the vertices of the graph corresponding to the population network.

DEVELOPMENTS IN COMPARTMANTAL MODELS

In the mathematical modeling of disease transmission, as in most other areas of mathematical modeling, there is always a trade-off between simple, or strategic, models, which omit most details and are designed only to highlight general qualitative behavior, and detailed, or tactical, models, usually designed for specific situations including short-term quantitative predictions. Detailed models are generally difficult or impossible to solve analytically and hence their usefulness for theoretical purposes is limited, although their strategic value may be high.

For example, very simple models for epidemics predict that an epidemic will die out after some time, leaving a part of the population untouched by disease, and this is also true of models that include control measures. This qualitative principle is not by itself very helpful in suggesting what control measures would be most effective in a given situation, but it implies that a detailed model describing the situation as accurately as possible might be useful for public health professionals.

It is important to recognize that mathematical models to be used for making policy recommendations for management need quantitative results, and the models needed in a public health setting require a great deal of detail in order to describe the situation accurately. For example, if the problem is to recommend what age group or groups should be the focus of attention in coping with a disease outbreak, it is essential to use a model which separates the population into a sufficient number of age groups and recognizes the interaction between different age groups. The increased availability of high - speed computing in recent years has made use of such models possible.

Many of the early developments in the mathematical modeling of communicable diseases are due to public health physicians. The first known result in mathematical epidemiology is a defense of the practice of inoculation against smallpox in 1760 by Daniel Bernoulli, a member of a famous family of mathematicians (eight spread over three generations) who had been trained as a physician. The first contributions to modern mathematical epidemiology are due to P.D. En'ko between 1873 and 1894 (En'ko, 1889), and the foundations of the entire approach to epidemiology based on compartmental models were laid by public health physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick, and W.O. Kermack between 1900 and 1935, along with important contributions from a statistical perspective by J. Brownlee.

The development of mathematical methods for the study of models for communicable diseases led to a divergence between the goals of mathematicians, who sought broad understanding, and public health professionals, who sought practical procedures for management of diseases. While mathematical modeling led to many fundamental ideas, such as the possibility of controlling smallpox by vaccination and the management of malaria by controlling the vector (mosquito) population, the practical implementation was always more difficult than the predictions of simple models. Fortunately, in recent years there have been determined efforts to encourage better communication, so that public health professionals can better understand the situations in which simple models may be useful and mathematicians can recognize that real - life public health questions are much more complicated than simple models.

In the study of compartmental disease transmission models the population under study is divided into compartments and assumptions are made about the nature and time rate of transfer from one compartment to another. For example, in an SIR model we divide the population being studied into three classes labeled *S*, *I*, and *R*. We let S(t) denote the

number of individuals who are susceptible to the disease, that is, who are not (yet) infected at time *t*. I(t) denotes the number of infected individuals, assumed infectious and able to spread the disease by contact with susceptibles. R(t) denotes the number of individuals who have been infected and then removed from the possibility of being infected again or of spreading infection.

In many diseases infectives return to the susceptible class on recovery because the disease confers no immunity against reinfection. Such models are appropriate for most diseases transmitted by bacterial or helminth agents, and most sexually transmitted diseases (including gonorrhea, but not such diseases as AIDS from which there is no recovery). We use the terminology SIS to describe a disease with no immunity against re-infection, to indicate that the passage of individuals is from the susceptible class to the infective class and then back to the susceptible class.

We will use the terminology SIR to describe a disease which confers immunity against re-infection, to indicate that the passage of individuals is from the susceptible class *S* to the infective class *I* to the removed class *R*. Usually, diseases caused by a virus are of SIRtype.

In addition to the basic distinction between diseases for which recovery confers immunity against reinfection and diseases for which recovered members are susceptible to reinfection, and the intermediate possibility of temporary immunity signified by a model of SIRS type, more complicated compartmental structure is possible. For example, there are SEIR and SEIS models, with an exposed period between being infected and becoming infective.

The rates of transfer between compartments are expressed mathematically as derivatives with respect to time of the sizes of the compartments. Initially, we assume that the duration of stay in each compartment is exponentially distributed and as a result models are formulated initially as differential equations. Models in which the rates of transfer depend on the sizes of compartments over the past as well as at the instant of transfer lead to more general types of functional equations, such as differential-difference equations or integral equations. One way in which models have expressed the idea of a reduction in contacts as an epidemic proceeds is to assume a contact rate of the form βSf(I) with a function f(I)that grows more slowly than linearly in *I*. Such an assumption, while not really a mechanistic model, may give better approximation than simple mass action contact to observed data.

The development and analysis of compartmental models has grown rapidly since the early models. Many of these developments are due to Hethcote (1976, 1978, 1989, 1997, 2000b). We describe only a few of the important developments. While there are three basic compartmental disease transmission models, namely the SIS model, the SIR model without births and deaths, and the SIR model with births and deaths, each disease has its own properties which should be included in a model for this disease.

For influenza, there is a significant fraction of the population which is infected but asymptomatic, with lower infectivity than symptomatic individuals. There are seasonal outbreaks which may be the same strain as the previous year but modified by mutation of the strain, and there is some cross-immunity protecting individuals who were infected by a similar strain in a previous year. Also, influenza models may include the effect of a partially efficacious vaccination before an outbreak and antiviral treatment during an outbreak. Cholera may be transmitted both by direct contact and by contact with pathogen shed by infectives in a water supply.

In tuberculosis some infected individuals progress rapidly to the infectious stage while others progress much more slowly. Also, in tuberculosis individuals who fail to comply with treatment schedules may develop a drug-resistant strain. In HIV/AIDS, the infectivity of an individual depends very strongly on the time since infection. In malaria, immunity against infection is boosted by exposure to infection.

SOME CURRENT TOPICS OF INTEREST

Frequently there have been outbreaks of new or recurring diseases, some of which have pointed to important epidemiological questions.

In their later work on disease transmission models (Kermack & McKendrick, 1932, 1933), Kermack and McKendrick did not include age of infection, and age of infection models were neglected for many years. Age of infection reappeared in the study of HIV/AIDS, in which the infectivity of infected individuals is high for a brief period after becoming infected, then quite low for an extended period, possibly several years, before increasing rapidly with the onset of full-blown AIDS. Thus the age of infection described by Kermack and McKendrick for epidemics became very important in some endemic situations; see for example (Thieme & Castillo-Chavez, 1993; Thieme et al., 1989). Also, HIV/AIDS has pointed to the importance of immunological ideas in the analysis on the epidemiological level.

Heterogeneity of mixing, cross immunity, coinfection

The SARS epidemic also pointed to the importance of heterogeneous mixing, especially nosocomial (in-hospital) transmission (Hsieh et al., 2014; Webb, Blaser, Zhu, Ardal, & Wu, 2004). During the SARS epidemic, where no treatment was available, the main management approach was isolation of diagnosed infectives and quarantine of suspected infectives. Quarantine was decided by tracing of contacts of infectives. In fact, very few quarantined individuals developed symptoms of SARS, and improvements in contact tracing are important for epidemic control.

In the models that we have been discussing, only one disease or disease strain has been involved. However, there are many situations in which more than one strain of a disease is present, and there may be cross-immunity between different strains (Andreasen, 2003; Andreasen, Lin, & Levin, 1997). This may lead to models in which there is a disease-free equilibrium, equilibria in which only one strain persists, and an equilibrium in which two strains coexist.

Another possible situation is coinfection of more than one disease requiring more elaborate models. This is a real possibility with HIV and tuberculosis (Kirschner, 1999; Naresh & Tripathi, 2005; Porco, Small, & Blower, 2001; Raimundo, Engel, Yang, & Bassanezi, 2003; Schulzer, Radhamani, Grybowski, Mak, & Fitzgerald, 1994; West & Thompson, 1997).

Drug resistance

The risk of development of resistance to drugs used in disease treatment has become a serious concern. In short-term disease outbreaks, antiviral treatment is one of the methods used to treat illness and also to decrease the basic reproduction number $\mathscr{R}0$ and thus to lessen the number of cases of disease. However, many infectious pathogens can evolve and generate successor strains that confer drug-resistance (Domingo and Holland, 1997). The evolution of resistance is generally associated with impaired transmission fitness compared to the sensitive strains of the infectious pathogen (Moghadas, 2011). In the absence of treatment, resistant strains may be competitively disadvantaged compared to the sensitive strains and may go extinct. However, treatment prevents the growth and spread of sensitive strains, and therefore induces a selective pressure that favors the resistant strain to replicate and restore its fitness to a level suitable for successful transmission (Andersson & Levin, 1999). This phenomenon has been observed in several infectious diseases, in particular for management of influenza infection using antiviral drugs (Rimmelzwaan et al., 2005).

Previous models of influenza epidemics and pandemics have investigated strategies for antiviral treatment in order to reduce the epidemic final size (the total number of infections throughout the epidemic), while preventing wide-spread drug-resistance in the population (Hansen & Day, 2011; Lipsitch, Cohen, Murray, & Levin, 2007; Moghadas, 2008; Moghadas, Bowman, Röst, Fisman & Wu, 2009; Moghadas, Bowman, Röst, & Wu, 2008). Through computer simulations, these studies have shown that, when resistance is highly transmissible, there may be situations in which increasing the treatment rate may do more harm than good by causing a larger number of resistant cases than the decrease in cases produced by treatment of sensitive infections. A recent epidemic model (Xiao, Brauer, & Moghadas, 2016) has exhibited such behavior and suggested that there may be an optimal treatment rate for minimizing the final size (Lipsitch et al., 2007; Moghadas, 2008; Moghadas et al., 2008).

In diseases such as tuberculosis which operate on a very long time scale, the same problems arise but the modeling scenario is quite different. It is necessary to include demographic effects such as births and natural deaths in a model. This means that there may be an endemic equilibrium, and that the disease is always present in the population. Instead of studying the final size of an epidemic to measure the severity of a disease outbreak, it is more appropriate to consider the degree of prevalence of the disease in the population as a measure of severity. For diseases such as tuberculosis, in which there are additional aspects such as reinfection, there may be additional difficulties caused by the possibility of backward bifurcations. The importance of understanding the dynamics of tuberculosis treatment suggests that this is a topic that should be pursued.

6.4. Slower than exponential growth

It has been standard practice in analyzing disease outbreaks to formulate a dynamical system as a deterministic compartmental model, then to use observed early outbreak data to fit parameters to the model, and finally to analyze the dynamical system to predict the course of the disease outbreak and to compare the effects of different management strategies. In general, such models predict an initial stochastic stage (while the number of infectious individuals is small), followed by a period of exponential growth. Measurement of this early exponential growth rate is an essential step in estimating contact rate parameters for the model. A thorough description of the analysis of compartmental models may be found in Hethcote (2000a).

However, instances have been noted where the growth rate of an epidemic is clearly slower than exponential. For example, the initial apparently exponential spread of the 2013–2015 Ebola epidemic in West Africa can be viewed as a composition of locally asynchronous outbreaks at local level displaying sub-exponential growth patterns during several generations (Chowell, Viboud, Hyman, & Simonsen, 2015). Specifically, if I(t) is the number of infectious individuals at time *t*, a graph of logI(t) against *t* is a straight line if the growth rate is exponential, and for some disease outbreaks this has not been true. One of the earliest examples (Colgate, Stanley, Hyman, Layne, & Qualls, 1989) concerns the growth of HIV/AIDS in the United States, and a possible explanation might be the mixture of short-term and long-term contacts. This could be a factor in other diseases where there are repeated contacts in family groups and less frequent contacts outside the home.

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