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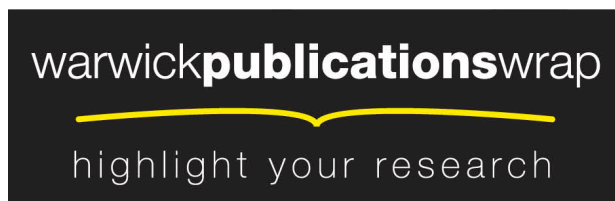http://wrap.warwick.ac.uk/51880

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Controlling infectious disease outbreaks: Lessons from mathematical modelling

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Abstract

Epidemiological analysis and mathematical models are now essential tools in understanding the

dynamics of infectious diseases and in designing public health strategies to contain them. They

have provided fundamental concepts, such as the basic and effective reproduction number,

generation times, epidemic growth rates and the role of pre-symptomatic infectiousness, which

are crucial in characterising infectious diseases. These concepts are outlined and their relevance

in designing control policies for outbreaks is discussed. They are illustrated using examples from

the 2003 severe acute respiratory syndrome (SARS) outbreak, which was brought under control

within a year, and from pandemic influenza planning, where mathematical models have been

used extensively.

Introduction

The study of infectious diseases has been transformed by the use of mathematical models to gain insight into the dynamics of epidemics, to identify potential public health interventions and to assess their impact (1). Mathematical models have been useful in informing policy during the foot and mouth disease outbreak in the UK in 2001, during the severe acute respiratory syndrome (SARS) outbreak in 2003, and in recent planning of responses to potential smallpox or pandemic influenza outbreaks. These analyses and subsequent ongoing research have led to insights into epidemic dynamics and control which have informed public health policy in this field. However, these results can be presented in a technically complex or intimidating fashion, making the field inaccessible to non-specialists. This paper is designed to provide a non-technical summary of the core results and concepts for the non-specialist.

Mathematical models of epidemics rigorously represent our knowledge and assumptions about disease transmission. Models can range from simple systems of ordinary differential equations to complex individual-based stochastic simulations of millions of people (2). Depending on the quality and detail of data available, the models can represent variability in the disease course of individuals, as well as variability in spatial structure, demographic structure, population density, travel patterns or treatment protocols (3). Model complexity is not, in itself, a virtue and indeed may not be necessary. The more intricate a model becomes the more realism it can aspire to, but estimating parameters and interpretation of results is also increasingly difficult.

Models must be designed to make effective use of the available (and reliable) data and they

must be tailored to answer clearly defined scientific or policy questions in a timely fashion.

Epidemiological analyses allow quantification of characteristics such as mortality rates,

incubation periods and transmission rates and identification of disease transmission route(s),

heterogeneities and risk factors for disease spread and the effectiveness of disease-control/risk-

reduction policies. Analysis of well constructed models can provide insight into the course of an

epidemic and can be used to test 'what if' scenarios to inform the development of policy.   In

this paper I outline important concepts of and insights on outbreaks of directly transmissible

infections provided by quantitative approaches and epidemiological models, using examples

from the 2003 SARS outbreak and recent analyses of a potential pandemic influenza outbreak.

Severe Acute Respiratory Syndrome (SARS)

The world health organisation (WHO) issued a global alert for SARS on March 12 2003, at which

point there were 150 suspected cases in seven countries (4). Although the disease had already

spread to several countries across the globe, the epidemic was brought under control within a

few months, with most of the 27 affected countries reporting fewer than 10 suspected cases

(Figure 1). Epidemiological analysis and mathematical models played a crucial role in informing

public health policy and contributing to the control of the outbreak (5-7). Effective international

collaboration and data sharing facilitated rapid completion of most of the essential tasks,

including identification of the aetiological agent (8).

Influenza

The global spread of the highly pathogenic H5N1 influenza virus amongst wild fowl and

domestic poultry flocks and the continuing occurrences of human cases (4) poses the threat of

a global influenza pandemic, should a strain emerge which is transmissible between humans.

The 1918 influenza epidemic spread extremely rapidly and killed 20-40 million people

worldwide. The world population has more than tripled since 1918, so current high population

densities, as well as increasing domestic and international travel, may facilitate the spread of

such a pandemic. Improved surveillance, technological advances and an increased

understanding of epidemiology together enable societies to prepare for a range of possible

pandemic scenarios. National governments and the WHO are monitoring human and avian

cases of H5N1 and other novel strains (4), antiviral treatments are being produced in large

quantities for stockpiling by governments (9) and novel vaccines are being developed to protect

against the avian form of the virus and are also being stockpiled by governments (9). Despite

these precautions, the exact characteristics of a potentially pandemic strain which may emerge

cannot be predicted exactly, although ranges can be estimated from previous pandemics (10-

12). Therefore, it is essential to understand how the effects of such an outbreak might be

contained, or at least mitigated, for a range of scenarios. Complex, often individual-based,

models of influenza outbreaks, informed by re-analysis of previous pandemics, are being used

to inform the design of public health strategies should a strain emerge which is capable of

human-to-human transmission (2).

Key epidemiological quantities

When faced with an emerging or re-emerging outbreak of an infectious disease, it is important

to quantify the characteristics of the disease in order to evaluate the level of threat, the

timescales over which the threat is likely to develop and to consider possible methods of

control. Accurate estimation of these characteristics is reliant on real time centralised collation

of epidemiological information.

Basic reproduction number, R_0

The basic reproduction number, R_0, is typically defined as the mean number of new infections

caused by a single infectious individual in a wholly susceptible population (1) (the definition is

slightly different for heterogeneous populations (13)). If each infected individual on average

infects more than one other individual, i.e. if R_0 is greater than one, then a small number of

cases in a population will usually lead to an epidemic. However, when there are small numbers

of cases and R_0 is large, there is a small probability that the epidemic will 'fade-out' after only a

few infections because the early cases recover prior to infecting enough other individuals

(Figure 2a). This probability of fading out before the epidemic takes off becomes smaller as R_0

gets larger If R_0 is less than one the outbreak will die out. Infections with reproduction numbers

close to, but exceeding, one are potentially easier to control than infections with reproduction

numbers much larger than one.

The basic reproduction number for a particular infection is dependent on the biological

characteristics of the disease and on the behavioural patterns of a population. The higher the

transmission rate of the disease per unit time and the longer the duration of the infectious

period, the larger the R_0. A disease which is highly infectious for a short period of time may have

the same basic reproduction number as a disease that is not as infectious but has a much longer

infectious period. For diseases with similar characteristics, the basic reproduction number is

different for each population, since the opportunities for onward infection are affected by the

contact patterns of a population. For example, in a city where most people commute to work by

public transport, the opportunities for onward transmission of an airborne pathogen may be

much greater than in less densely populated areas. For many directly transmitted diseases, such

as measles (1), pandemic influenza (10), and , R_0 is usually assumed to be similar in

unvaccinated populations. For sexually transmitted diseases large differences in sexual

behaviour within populations can lead to estimates of R_0 for heterosexual populations from 2

for low risk populations (14) to over 10 for high activity groups and sex workers (15) .

Generation time, serial interval, T_g,

Alongside the basic reproduction number it is important to have some estimate of how quickly

the number of cases a novel infection will grow and how long an outbreak will last The

generation time, T_g, is defined as average time from an individual being infected to that

individual infecting others (1, 13, 16, 17). This includes any latent period when the infected

individual may not show symptoms or may not be infectious, and excludes any period when

infected individuals may be showing symptoms but are no longer infectious. It is often assumed

to be equivalent to the serial interval, which is the average time from when one person shows

symptoms until the person they infect shows symptoms (17). For SARS this was initially

estimated as 8 to 12 days (6, 18).

Estimating R_0 from the epidemic growth rate, r

When a novel infection is introduced to a population, there is a finite probability that it may not

take hold in this population and die out, even if R_0>1, due to the chance events when there are

small numbers of infected individuals (Figure 2b). If, however, the infection takes hold, the

number of new cases grows exponentially(1). The rate at which the number of cases will grow

during this early stage, *r*, is dependent on both the reproduction number and the generation

time of the infection and can therefore be used to estimate the basic reproduction number.

There are different models which can be used to estimate this relationship, but for a

homogeneous population with onward infection occurring throughout the infectious period as

$R_0 = rT_g +1$, but there are other formulations *(1, 16, 19, 20)*. As for the basic reproduction

number, the relationship between the epidemic growth rate, the serial interval and the basic

reproduction number is more complex for heterogeneous populations (13, 16). In Figure 2c I

have used this equation to estimate R_0 from first month of the SARS outbreak in Hong Kong in

2003 (Figure 2c). The best fitting straight line to the log incidence data gives a growth rate, *r*, of

0.15 per day (equivalent to a doubling time 4.6 days). The generation time of *SARS*, T_g, has been

estimated to be 10 days from data on the number of days between the start of symptoms for

individuals who infected each other (6, 21). We can now use the equation above to get an

estimate of the basic reproduction number for SARS as R_0=1+0.15*10=2.5. This relatively simple

calculation gives a similar to estimate to those made by more sophisticated methods (6, 18, 22).

The basic reproduction number for influenza has been estimated to be as high as 21(23), but recent reanalysis of pandemic outbreaks estimate R_0 for pandemic influenza to be in the rage 1.4-3.0 (10, 11, 24), which is similar to that for SARS. The generation time for influenza is, however, much shorter than that for SARS, approximately 4-6 days (10, 24), which gives a doubling time of the epidemic of 1 to 4 days, much faster than was observed for SARS. This means that control of an outbreak of pandemic influenza will require very swift implementation of public health measures.

Effective reproduction number, R

During the course of an epidemic the effective reproduction number, *R*, is the average number of secondary cases per primary case at that point in the epidemic (Figure 2a). Estimation of this number during an epidemic facilitates quantitative assessment of the effectiveness of intervention strategies, with reduction below one meaning the outbreak being brought under control (22, 25). During the course of the SARS epidemic in 2003, mathematical modelling was an essential tool in showing that intervention methods gradually brought the epidemic under control in Hong Kong, Special Administrative Region of China, and Singapore (6, 7, 22, 25), or controls appear to have been lifted too early in Toronto, Canada (26). Reanalysis of the 1918-19 influenza pandemic shows that public health measures were effective in containing this outbreak (27-29).

Whilst R is an estimate of average transmission at a population level, individuals vary both in

how they respond to an outbreak of a novel infection (such SARS) or an outbreak of a known

infection (such as pandemic influenza) and in their behaviour in terms of the number of

contacts that they make (13). Some individuals, termed 'superspreaders', may transmit to many

others either because of some characteristic of their infection, because of their contacts, or

purely by chance - being in the wrong place at the right stage of their infection (6, 7, 30-32).

Care should be taken when gathering and interpreting data on possible exposures because they

may be subject to bias towards previously identified sources and away from transmission from

casual contacts and may neglect asymptomatic transmissions.

Case fatality rate and age-distribution of cases

In assessing the potential consequences of an infectious disease outbreak, one of the most

important concerns of policy makers is the number of fatalities. The case fatality rate (CFR) for a

particular aetiological agent is the proportion of those who acquire the disease who will

eventually die from it. In the early stages of an outbreak there will be many new cases of the

disease for whom the outcome is not yet known and therefore estimates of the case fatality

rate must be carefully calculated (5, 31). In 2003 the WHO initially reported a CFR of 5% (4), in

fact the CFR for SARS was a much higher 15% overall (5).

The overall case fatality rate often hides large variations, with the young and the elderly often at

highest risk. In the 2003 SARS outbreak in Hong Kong the CFR was very low amongst the young

(<1% for ages <30 years) and increased to 55% for patients over 60 years of age(31). Very few

cases were admitted to hospital amongst the very young (5), which is unusual because children

are often considered to be the group with the highest rate of transmission of directly

transmitted pathogens, whilst also serving as a source of infection for their parents and other

adults (sometimes called a 'core group') (1). Serological surveys show little evidence to support

asymptomatic cases amongst this age group.

In the influenza outbreak of 1918, the CFR was much higher (~3%) in young adults aged 20-40

than in non-pandemic years (<0.5%). Also, those aged 5 to 14 contributed disproportionately to

the numbers of cases (~25%), but not to the numbers of deaths (33). There could be many

possible explanations for these distributions, such as previous exposure to the pandemic strain,

environmental factors, or the patterns of mixing and transmission due to the world war (33), or

due to biological factors which could have made the virus so pathogenic overall (such as those

discussed by Loo et al (34)). High numbers of cases and fatalities amongst the 20-40 age group

are likely to have huge economic impact since they form an important part of the workforce,

and are primary carers for children.

Public health interventions

Isolation and contact tracing

Isolation of symptomatic individuals together with tracing and quarantine of their contacts are

major weapons in the armoury of public health outbreak control measures. The success of these

strategies has been shown to be crucially dependent on the proportion of transmissions which

occur prior to infected individuals showing symptoms (23). . Isolation of a proportion of

symptomatic individuals can control an outbreak provided this proportion is large enough for

that infection (23). Normally circulating influenza is believed to be infectious prior to the

infected individual showing symptoms (35), which makes control extremely difficult. However, if

the disease is mainly transmitted to close contacts, for example family members, then contact

tracing may be manageable and effective. If transmission is likely for more casual contacts,

contact tracing is much more difficult. Contact tracing , has also been shown to depend on the

degree of variability in the timing of infectiousness between different infected people in the

population (36, 37). It may be important to assess the effectiveness of such a policy early in an

epidemic through analysis of transmission chains and the impact of the intervention on the

effective reproduction number before large amounts of resources are allocated.

Vaccination and prophylactic treatment

Both vaccination and prophylactic treatment with anti-viral drugs or antibiotics restrict the

spread of an infectious disease by limiting the number of individuals to whom the infection can

be transmitted. Such strategies do not have to eliminate susceptibility from the population, but

merely need to reduce the number of susceptible individuals so that the epidemic cannot be

sustained. The minimum proportion of the population which must be vaccinated to prevent a

large outbreak is $1-1/R_0$ for homogeneous populations (1) (there are expressions for

heterogeneous populations (38)). This proportion is higher for diseases with large R_0. The whole

population need not be vaccinated as those who are not vaccinated are protected by 'herd

immunity', i.e. the fact that the epidemic cannot be sustained in the population because there

are so few susceptible individuals.

Limited vaccine and antivirals stockpiles available to governments may be targeted in a number

of ways, at those most at risk, at key workers or to contain an outbreak. If antivirals are to be

distributed prophylactically to prevent the spread of disease, rather than to treat cases, then

containment may be possible, provided (i) there are enough doses or courses of treatment, (ii)

the programme is implemented extremely rapidly and (iii) cases are situated in a limited

geographic region (10, 12, 37). The evolution of drug resistance would, of course, be a concern if

large scale prophylaxis were implemented. Due to the short doubling time of influenza

epidemics, these strategies would have to be implemented when there were very few cases.

One such responsive strategy of implementing travel restrictions and prophylactic treatment of

everyone within 10km ring of each case and would require a stockpile of approximately 3

million courses of antiviral drugs to contain an outbreak of pandemic influenza (10). Following

the publication of this analysis by Ferguson *et al*, Roche donated 3 million doses of their antiviral

drug to the WHO for this very purpose and the WHO has set up project to develop protocols for

practical implementation of containment.

Travel advisories and screening of passengers

International air travel greatly facilitates global spread of infectious diseases such as SARS and

influenza (39-42). The SARS epidemic of 2003 spread across the globe within a matter of days,

eventually affecting 27 countries, with suspected cases reported in every populated continent

(Figure 1). Public health measures, including screening and travel restrictions can be put in place to slow this spread. However, the effectiveness of such methods is dependent on the characteristics of the disease. If an infection has an incubation period which is longer than the duration of a flight then infected people are unlikely to develop symptoms during a flight and so even 100% effective entry screening is unlikely to be useful in identifying cases (42). Imported SARS cases caused new outbreaks only in the early stages of the global outbreak, because of effective exchanges of information about the disease, the lack of pre-symptomatic infectiousness, and local outbreak control. If an outbreak is uncontrolled, then the number of new cases continues to grow exponentially and sheer weight of numbers means that cases will be exported. Travel reductions of greater than 99% will be required to slow the spread of influenza (40, 41, 43, 44). Strategies aimed at protecting the public from pandemic influenza should focus resources on surveillance and rapid control of outbreaks wherever potentially pandemic strains arise (45).

Summary

Epidemiological analyses and mathematical models are essential tools in understanding and controlling outbreaks of directly transmissible pathogens. There are many clinical and biological tasks to be completed, such as formulating a case definition and treatment strategies, identifying the aetiological agent and developing diagnostic tests. Alongside these tasks the estimation of key parameters, such as the basic and effective reproduction numbers, the generation time, and the proportion of transmissions occurring prior to symptoms are essential to characterise an outbreak and its potential scope. Estimation of the effective reproduction

number during an ongoing outbreak also provides an early indication of whether an infectious

disease outbreak is under control or not. Case fatality rates are an important consideration in

public policy and must also be estimated accurately.

Epidemiological parameters cannot be estimated for outbreaks with new influenza strains until

they actually emerge, but mathematical models can be used to investigate the likely

consequences of a future influenza pandemic, based on analysis of previous epidemics and of

current population structures and behaviours. Integration of epidemiological and statistical

approaches increases the power of such analysis and the usefulness of models. Both statistical

analyses and models require high quality epidemiological data, collected and collated centrally

whilst the onbreak is ongoing and made available for analysis. Prediction of the exact progress

of an epidemic will never be possible due to the variability of human behaviour. Nonetheless,

mathematical models which precisely represent knowledge and assumptions about disease

transmission add significant insight into the dynamics of infectious diseases and are increasingly

recognised as a vital part of any public health policy development.

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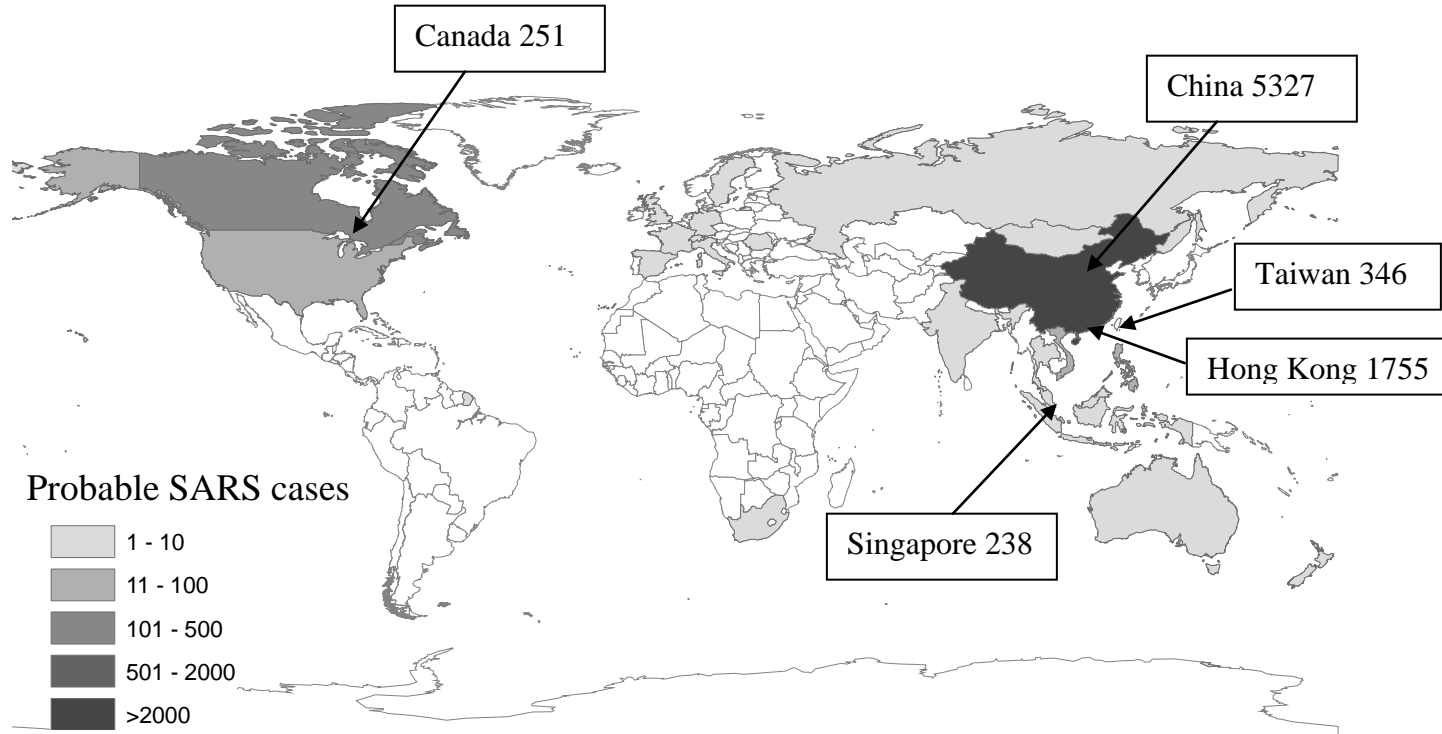
Figure 1

Canada 251

China 5327

Taiwan 346

Hong Kong 1755

Singapore 238

Probable SARS cases

1 - 10
11 - 100
101 - 500
501 - 2000
>2000

Figure 2

a

| Infections | 1 | 2 | 1 | 2 | 4 | 5 |
| R | 1 | 2/1 | 1/2 | 2/1 | 4/2 | 5/4 |

b

c