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PANDEMIC INFLUENZA: MODELLING AND PUBLIC HEALTH PERSPECTIVES

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Abstract. We describe the application of mathematical models in the study of disease epidemics with particular focus on pandemic influenza. We outline the general mathematical approach and the complications arising from attempts to apply it for disease outbreak management in a real public health context.

1. **Introduction.** A standard scientific practice is to formulate an explanation for an observed phenomenon and then test this formulation by projecting the outcome of various experiments under pertinent conditions. Projections are generally compared with experimental data. If there is agreement, the explanation can be accepted as a valid theory, whereas discrepancies point to a need for reformulation of the explanation. A model that describes the main features of the phenomenon, often represented mathematically, can frequently be used for this purpose. If the phenomenon is the spread of an infectious disease in a population, a model may provide an explanation that may be applicable to a future epidemic with similar characteristics or for near-future or real-time forecasting. Experiments with disease transmission are, to a large extent, impossible. While small-scale animal experiments have been performed, they generally fail to represent a true picture of population-wide spread, and experiments with human diseases are ethically challenging. As a consequence, the experimental data for model input generally originate from past documented epidemics. For example, concern about an influenza pandemic led to much study of the 1918 influenza pandemic [68].

Although models for disease outbreaks [36, 63] were originally developed by public health physicians, the mathematical and public health approaches to the formulation of such models have diverged over the years, and a communication gap has developed. Recently, especially following the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003, there have been strenuous efforts to bridge this gap. The magnitude of such efforts is highlighted particularly for pandemic influenza planning through the development of mathematical models for evaluation of disease mitigation strategies. Participants at a Canadian pandemic preparedness workshop held in 2008 noted that models are most useful when they are developed in synergistic cooperation between modellers, public health planners, and policy decision makers [52].

Modellers, public health planners, and policy decision makers may have different perspectives and goals. Modellers may be mainly interested in answers to mathematical questions and better understanding of the mechanisms of disease transmission from a scientific standpoint, while public health planners would need detailed estimates for specific scenarios in order to answer policy questions. Policy decision makers are usually influenced by political considerations, and need sound scientific information to factor into their decisions. Collaboration is needed so that modelling activities will be directed towards addressing the right questions to support complex decision making, and it is also crucial for a timely response to emerging infectious diseases such as the 2009 crisis of pandemic influenza A virus (H1N1).

This essay attempts to provide an overview of fundamental principles of disease modelling, with application of mathematical models to a pandemic scenario, but contains more mathematical details than an earlier overview [58] that was targeted

at an audience with a rather scant mathematical background. It is divided into sections on principles of epidemic modelling, model fitting to data, models for pandemic influenza, treatment possibilities for influenza, multiple pandemic waves, and conclusions.

2. **Principles of epidemic modelling.** Daniel Bernoulli's study of smallpox [8] was probably the first example of a compartmental disease transmission model. Bernoulli was not primarily interested in explaining recurrent outbreaks or in predicting the inter-epidemic interval that have received a great deal of attention more recently. His motivation was to predict the expected gain in life expectancy that would result from smallpox control measures. One of his statements, "I simply wish that, in a matter which so closely concerns the well-being of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide", summarizes the arguments in favor of making use of mathematical models for studying disease transmission.

Over many centuries pathogens have invaded human populations, transmitted from one population to another by some form of contact, spread through a part of the population and then disappeared without infecting the entire population. The simple model first introduced by Kermack and McKendrick in 1927 [36] exhibits this behavior. They assumed only that the invading disease could be transmitted to a susceptible person by a person who is infectious during a period of time (referred to as the infectious period). Their model consisted of two differential equations describing the rate at which disease-susceptible individuals become infected through contact with infectious individuals and the rate at which infected individuals recover with immunity against re-infection.

The Kermack-McKendrick model is a *compartmental* model, dividing the population into compartments of susceptible (not infected but could be infected by contact), infectious (infected and able to pass on infection by contact with susceptibles), and removed (immune, because of recovery from infection, vaccination, death from disease, or naturally immune from previous exposure) members. Modellers have been accustomed to use the term infective to describe individuals who transmit infection, but we will use the term infectious to conform to public health terminology. We may also speak of infected members, meaning people to whom infection has been transmitted but who may not yet be able to pass the infection on to others.

The model assumptions describe the rates at which individuals flow from one compartment to another, and these assumptions lead to the differential equations that express the model mathematically. During the course of an epidemic the number of new infections increases initially, and then as the number of susceptible individuals decreases, the number of new infections decreases, slowing the spread of disease and eventually ending the epidemic.

In 1911, Sir R.A. Ross introduced the concept of the basic reproduction number, denoted by $\mathcal{R}_0$, defined as the average number of new infections caused by a single infected individual introduced into a wholly susceptible population over the duration of the infection of this individual [63]. The Kermack-McKendrick model implies a fundamental property of the basic reproduction number, namely that in general the disease outbreak will not develop into an epidemic if $\mathcal{R}_0$ is less than one, while an epidemic will occur whenever $\mathcal{R}_0$ exceeds one. Thus, measures that decrease the basic reproduction number below 1 may bring an epidemic under control even if

they do not prevent all new infections. This insight, that it is not necessary to treat every individual in order to control a disease outbreak, has a great practical value. It is generally difficult, if not impossible, to vaccinate or treat everyone successfully, but the properties of the basic reproduction number imply that it is not necessary to do this to control a disease outbreak.

One way to calculate this number is from knowledge of the rate of contact between individuals and the rate of recovery from the disease. These two rates can in turn be estimated from seroprevalence and attack rate data, and knowledge of the disease natural history.

The simplest version of the Kermack-McKendrick epidemic model is the system of two ordinary differential equations for the susceptible population size $S(t)$ and the infectious population size $I(t)$,

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \alpha I. \end{aligned} \qquad (1)$$

Here, the mean number of contacts per individual in unit time is βN (N is the total population size, here assumed constant), new infections arise from a contact between susceptible and infectious individuals, and α is the recovery rate so that $1/\alpha$ is the mean infectious period. The units of both α and βN are $1/(time)$. For the model (1) the basic reproduction number is given by

$$\mathcal{R}_0 = \frac{\beta N}{\alpha}.$$

The Kermack-McKendrick model is not a good description of the beginning of a disease outbreak because one of its underlying assumptions is that there is complete (homogeneous) mixing between susceptible and infectious members of the population, and at the start of a disease outbreak, given stochasticity, this assumption is not necessarily valid. To describe the beginning of a disease outbreak, it is more realistic to examine the network of person to person contacts. *Network models* trace the flow of infections through a population and their recent use has led to significant improvements in understanding of the development of epidemics [48, 49, 50, 54, 55]. One of the consequences of considering the network of contacts of the first few cases of infection and stochastic effects early in the outbreak is that, even if the basic reproduction number is greater than 1, it is possible that there will be only a minor outbreak without developing into a full-blown epidemic. An elementary description of the fundamentals of the network approach to disease transmission models may be found in [48].

While the basic reproduction number provides information on the development of an epidemic, knowledge of the generation time is also necessary to predict the rate of growth of an epidemic. The generation time, which introduces a time scale into the development of an epidemic [71], is the average time from onset of infection in an individual to the onset of infection in a secondary case caused by this individual. In an epidemiological context, this is referred to as the *serial interval*.

Infectious diseases may have a more complicated compartmental structure than that of the model (1). There may be an exposed period between the acquisition of infection and the ability to transmit infection; there may be a sequence of infectious periods with different transmissibilities and durations, and some members of the population may be removed from one compartment to another compartment due to

application of some form of intervention, such as treatment. All of these possibilities can be included in the form of the model that was initially introduced by Kermack and McKendrick. A model involving the time since becoming infected, known as the *age of infection*, can be written in the form

$$\frac{dS}{dt} = -\beta S(t)\varphi(t) \tag{2}$$

$$\varphi(t) = \varphi_0(t) + \int_0^t \beta S(t-\tau)\varphi(t-\tau)A(\tau)d\tau.$$

In this model, $\varphi(t)$ represents the total infectivity at time t of all infected members of the population, $\varphi_0(t)$ represents the total infectivity at time t of all members of the population who were already infected at time $t = 0$, and $A(\tau)$ represents the mean infectivity of all members who were originally infected at τ time units previously, including those who are no longer infected. The basic reproduction number of the model (2) is given by

$$\mathcal{R}_0 = \beta N \int_0^\infty A(\tau)d\tau.$$

While this expression is deceptively simple, the calculation of the integral may be quite complicated [13].

The severity of a disease may be described by the attack rate, or attack ratio (the term attack ratio would be more appropriate since it is dimension-free, but the term attack rate is more commonly used), defined as the fraction of the susceptible population infected during the entire course of an epidemic [11, 46]. The attack rate is given by the expression

$$A = 1 - \frac{S_f}{N},$$

where S_f is the number of susceptible individuals at the end of the epidemic. There is a mathematical relationship between the basic reproduction number and the attack rate, the so-called final size relation, given by

$$\ln \frac{S_0}{S_f} = \mathcal{R}_0 A = \mathcal{R}_0 \left[1 - \frac{S_f}{N} \right].$$

where S_0 is the number of susceptible individuals at the start of the epidemic (presumably approximately equal to N). This relation holds not only for the simple model (1) but also for the more general model (2). A more thorough description of the mathematical analysis of compartmental epidemic models may be found in [12]. The final size relation is represented graphically in Figure 1, in which the calculations have been made with 1 initial infectious member in a population of total size 1000. For example, if the basic reproduction number $\mathcal{R}_0$ of a disease is 1.5, a value comparable to estimates for various influenza epidemics, the corresponding attack rate is approximately 0.58. If control measures can reduce the reproduction number to 1.2, the corresponding attack rate is approximately 0.32, a decrease of 45%.

Another quantity that is important for knowing how easily an outbreak can be controlled is the proportion of transmission caused by an individual that occurs before the individual exhibits symptoms [29]. It is harder to control an infection through isolation, quarantine, or even treatment, if significant transmission has already occurred by the time that an infected case is identified. This is a common
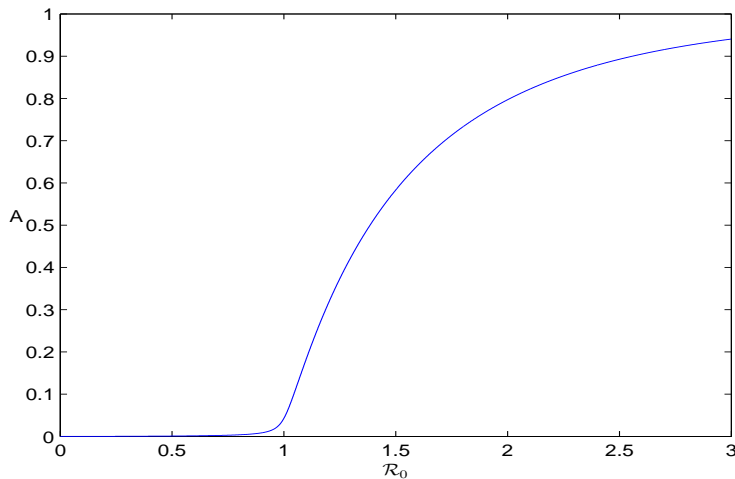
FIGURE 1. Graph of attack rate A as a function of basic reproduction number $\mathcal{R}_0$

situation in influenza infections, referred to as pre-symptomatic infection, where infected individuals become infectious prior to the onset of disease symptoms.

The models (1) and (2) assume that infected individuals can spread the infection uniformly across the population. However, these models discount some important details, including heterogeneity of contact patterns, the local nature of infectious interactions, and differences in social behaviour. In addition, the public health response and the evolution of behavior in response to an epidemic can affect significantly the spread of disease in the population. These model deficiencies were highlighted during the SARS epidemic, where estimates of the basic reproduction number led to predictions of epidemic size that far exceeded what was observed [7, 49].

To overcome the limitations imposed by the assumption of homogeneously mixing patterns, models have been developed to account for heterogeneity of interactions between individuals. Many factors may be considered in these models, such as different rates of contacts among individuals belonging to different age groups that may also represent different susceptibilities to infection. In addition, modes of communications and transportations are essential in determining who acquires infection from whom within and between communities [53]. Thus, a better understanding of the epidemic behaviour would require the development of models with more complex structures, but this would also require more information and data pertinent to the characteristics of a particular disease and population demographics. Ideally, the choice of model for studying an epidemic should reflect not only the amount of data available, but also the questions being asked and the nature of information to be drawn from model outputs (these criteria may not be compatible). Models incorporating heterogeneity of behavior may be compartmental, network, or even *agent-based models* that give simulations considering each individual separately.

Compartmental models that separate the population into subgroups also have a final size relation, but now there is a set of equations determining the final epidemic size in each subgroup [5]. The final size relations depend not only on the basic

reproduction number but also on a matrix describing the development of secondary infections caused in one group by infectious members of another group, the so-called *next generation matrix* [22, 23, 70]. The elements of the next generation matrix are all non-negative, and the matrix has properties ensuring that it has a positive eigenvalue which is larger in absolute value than all other eigenvalues, and the basic reproduction number $\mathcal{R}_0$ is this eigenvalue.

When factors aimed at controlling the spread of disease are incorporated into a model, it is no longer quite correct to speak of the basic reproduction number, since control measures generally lead to a decrease in the reproduction number and therefore in the number of secondary infections. We speak, instead, of a *control reproduction number*, often denoted by $\mathcal{R}_c$. Models provide a systematic way to estimate the control reproduction number of an infectious pathogen, which is crucial for determining the type of public health measures required for disease control, and evaluating their impact on infection transmission [62]. This is particularly important when there are multiple intervention strategies available, each with certain costs, benefits, and potentially adverse epidemiological and clinical consequences. An example is the level of drug use for treatment of ill individuals when there is a danger of developing drug-resistant strains of the pathogen.

As more data become available during the course of an epidemic, it should be possible to refine the models being used in order to make better predictions. For example, when there are enough data to identify the susceptibility of different age groups to infection, it may be possible to use this information to decide optimal allocation of (often limited) treatment resources.

The SARS epidemic of 2003 brought the study of epidemics to public attention, and resulted in a large number of modelling studies. Since SARS was a previously unknown disease with no tools available for pharmaceutical management, social distancing measures including isolation of diagnosed infectious cases and quarantine of suspected carriers of disease were the only public health means to cope with its spread [17, 33, 40]. While different groups of researchers were assembled to investigate strategies for the management of SARS, the rapid spread of disease through the worldwide air travel network, and the lack of proper understanding of the pathogen behaviour and its epidemiological characteristics posed significant challenges for the development and application of mathematical models. These difficulties, in addition to the lack of timely access to critical data, alarmed public health planners everywhere and produced recognition that confronting the threat of emerging infectious diseases requires collaborative efforts through engagement of scientific, administrative, and political communities across disciplines. Arguably, this has been the most important lesson learned from SARS as the first major infectious disease threat of the 21st century, and its effect has flourished in modelling influenza pandemic preparedness.

One of the lessons learned from SARS is that because of the worldwide air travel network, a disease could spread very rapidly to any part of the world, and this stimulated interest in *metapopulation models*, that is, models for collections of sub-populations (cities) with links (transport connections) between them [37]. This has been noted for SARS and influenza, and is in fact an important feature of many communicable diseases.

A general data analysis problem became apparent during the SARS epidemic. During the course of an epidemic the number of cases and disease deaths to date are reported. Then the case fatality rate, defined as the number of disease deaths

divided by the number of cases, is calculated. As with the attack rate, the case fatality rate is a dimensionless ratio rather than a rate, but the term case fatality rate is standard. Because such running reports do not include individuals already infected who will die of disease later, the case fatality rate will normally appear to increase over the course of an epidemic until the number of new cases begins to decrease. This may raise unfounded fears that the disease has evolved into a more lethal form.

It is therefore important to make strong efforts to communicate to the public and the news media the differences between statistical effects and actual developments. News media are under pressure to over-simplify and sensationalize information, and it is paramount that information supplied by scientists use plain language to explain complex issues. Descriptions including a system of differential equations would not be convincing, or even informative, to decision makers, news media, or the general public.

There are a number of different strategies that can be followed to facilitate this communication. Firstly, modelling teams can select key individuals to serve as media expert contacts to explain issues and address any existing knowledge gaps a reporter may have. These media expert contacts should have training in media relations, that is, these contacts should be familiar with the way in which media stories are written, the time pressures of media personnel, and should have a capacity to explain complex material in plain language. Early identification of these media contact people is imperative. Secondly, presenting risk information in different formats (visual/diagrammatic examples, numbers, scenarios) can help improve understanding of the epidemic state and efforts for its management, in particular for people who learn best by such diverse strategies. Thirdly, if any risk comparisons are used to help put risk information into a proper context, it is imperative that these comparisons are scientifically/ mathematically appropriate (i.e., based on the same kind of evidence or measured in the same way). Moreover, a risk comparison may not necessarily increase public acceptance, and may run the risk of trivializing public concern [20].

3. **Fitting models to data.** Ideally, we would like to have a model describing the course of the spread of an infectious disease, depending on some parameters, and enough data to make it possible to estimate some important parameters, and be able to use the model to make projections. However, there are some basic underlying problems in this process. Models are based on events that may not be observable at the time, such as the transmission of infection from one individual to another, the beginning and end of the ability of an infected individual to transmit infection, and the serial interval, defined as the gap between the infection times of two linked individuals. Data, on the other hand, are based on observable events, typically collected through epidemiological and clinical manifestations. The clinical serial interval is not necessarily the same as the serial interval in the sense of the model. There are also differences in terminology. Public health professionals speak of the incubation period of an infection, meaning the time from exposure to onset of clinical symptoms, while modellers speak of the latent period, meaning the time from exposure to infectiousness. Incorrect or inconsistent use of these terms may lead to confusion. For influenza there seems to be an infectious pre-symptomatic period, so that the latent period is shorter than the incubation period.

An additional problem is that there are various kinds of bias that may arise in the collection of data. Analysis of clinical data is complicated by administrative factors such as reporting delays and inconsistencies in classification of clinical cases. This is particularly important for a disease such as influenza in which many cases are asymptomatic or sufficiently mild and therefore not diagnosed or reported, and the definition of reportability may vary from one location to another.

Modellers may fit models to data in order to obtain a curve describing the course of a disease and to estimate some key transmission parameters, such as the basic reproduction number. However, fitting curves to data is valid only if the model produces a curve with the same meaning as the data, and often a model curve may not give a true picture of observations: this process often amounts to trying to compare apples to oranges. Epidemic data gives a curve representing the number of reported cases of infection, while a model attempts to produce a curve representing the number of actual cases. During a public health crisis such as a pandemic, it is necessary to blur important distinctions in order to obtain applicable results quickly, but it is also important to re-examine the results and ask some deeper questions after the crisis passes.

One common use of data collected for an epidemic is to estimate the basic reproduction number based on the observed initial exponential growth rate of infectious cases. For the simplest compartmental model (1), this rate r is given by the relation

$$r = \alpha(\mathcal{R}_0 - 1).$$

If the initial exponential growth rate can be measured, this provides an easy way to estimate the basic reproduction number. However, if there is an exposed or latent period between the transmission of infection and the ability to pass an infection on, a different model (of $SEIR$ type) is needed and the relation between the initial exponential growth rate and the basic reproduction number is quite different. For the age of infection model (2), it is known [71] that the exponential initial growth rate r is the solution of the equation

$$\beta N \int_0^\infty e^{-r\tau} A(\tau) d\tau = 1.$$

The relation between this rate, the serial interval, and the basic reproduction number depends very much on the model, and therefore the use of an overly simplified model or form for $A(\tau)$ can lead to erroneous estimates of important parameters.

4. **Models for pandemic influenza.** Influenza is a very old disease that remains a new threat every year. It causes more than 2000 deaths annually in Canada [65], and more than 36,000 deaths in the U.S. [69]. Usually the strains that circulate are related to strains that have been circulating in the past, and many individuals may have some residual immunity. Gene reassortment with an animal virus may lead to a strain readily transmissible between humans for which there is no pre-existing immunity; this may lead to a pandemic that may spread to many countries and may also result in a high case fatality rate. Also, in a pandemic, the age distribution of cases may be quite different from the age distribution of cases in seasonal influenza. It appears that model parameters for influenza are strongly age-dependent, and planning requires enough data on age dependence to support *age-structured models.*

Soon after the SARS epidemic, concerns developed about the possibility of a new influenza pandemic with viruses that have crossed species barriers and caused

deadly disease in humans [57]. Triggered by poultry outbreaks of avian influenza
A virus H5N1 that have been recurring sporadically since 1997, a large number
of epidemiological, clinical, public health and modelling studies were conducted.
Stochastic models were employed in 2005 to simulate potential outbreaks of the
influenza H5N1 strain in rural Southeast Asia and assess the effectiveness of antivi-
ral drugs for treatment of infectious cases and prophylaxis of their close contacts
[27, 44]. Based on social networks and close contacts in household clusters, schools,
workplaces, and other social settings, these models predicted that a pandemic could
be contained at the origin through a combination of targeted blanket prophylaxis
and social distancing. A key assumption was that the virus would remain less
transmissible than pandemic viruses of the last century, so that the basic repro-
duction number of disease transmission would stay below 1.8. The predictions of
these models, however, depend strongly on the specific location of an initial out-
break, patterns of exposure to infection in localities, and how quickly infected cases
are diagnosed and treated, and their contacts offered prophylaxis. Since then, the
modelling literature on evaluation of various containment strategies in general and
also in the context of specific population settings has expanded greatly.

It was recognized that because the basic reproduction number of an emerg-
ing infection could not be known in advance, plans for coping would have to
be developed for a range of reproduction numbers. The hope was that early in
an epidemic the basic reproduction number could be estimated and then policies
formulated in advance could be adopted and implemented, and therefore many
countries developed pandemic preparedness plans on the basis of mathematical
models. Most of the pandemic plans relied on simulations of very complicated
models, which divided the population into multiple groups and took into account
the contacts and variability in susceptibility to infection of the various groups
[18, 19, 25, 26, 27, 28, 31, 34, 42, 43, 61, 62, 66]. These models were also used
to compare the results of different management approaches. The advantage of us-
ing a model with detailed structure is that it is possible to draw detailed conclusions
on the effects of treating different portions of the population in different ways. How-
ever, it can be more difficult to understand the relationship between model inputs
and outputs without rigorous sensitivity or uncertainty analysis, and this can be a
difficult task that is not always carried out.

Some useful conclusions may be drawn from simpler models such as systems of
a small number of differential equations [4], although detailed planning requires
more complex models, which could be systems of many differential equations, inte-
gral equations, partial differential equations, or stochastic models. The usefulness
of any model depends on the accuracy of the data used for estimation of param-
eters of the model. Thus, it would appear that early collection of usable data,
and methodologies for dealing with parameter uncertainty are the keys to provide
recommendations for effective management of an influenza pandemic.

However, as the contemporary philosopher Yogi Berra has said, "In theory, theory
and practice are the same. In practice, they're different". Early in an epidemic
data are incomplete and unreliable. This was a major problem with SARS, where
many early cases were misdiagnosed, and this will inevitably be the case for a new
disease. For influenza, it is an even more serious problem because many cases
are asymptomatic or mild enough that they are not diagnosed and therefore not
reported in data. Influenza-like illnesses (ILIs) generally constitute a significant
proportion of cases of respiratory diseases and can lead to overestimates of the

burden of influenza infection. They can also lead to the diversion of resources such as clinical tests being performed for individuals who do not have influenza. The influenza H1N1 epidemic of 2009, with a new strain combining avian, swine, and human strains, appears to have begun in Mexico and some cases may have been confused with a seasonal strain. Early in the epidemic it appeared that the case fatality rate was much higher in Mexico than when it appeared later in other countries, and this created major fears of a pandemic causing a very large number of deaths. However, influenza has some properties not shared by all epidemic diseases. Not all infected individuals develop symptoms; a significant fraction of infected individuals are asymptomatic and able to transmit infections without showing any signs of illness. Also, many cases are mild enough not to be reported, and influenza data will always be incomplete. The number of cases becomes too large to count early in a pandemic, making it even more difficult to estimate the number of "true" cases. As a result, only laboratory-confirmed cases are counted, and it is very difficult to estimate how many cases there are in a community per confirmed case; in 2009 expert opinion ranged from 10 to 500 cases per laboratory-confirmed case.

The initial data from Mexico reported mainly severe cases. Thus the number of cases was much higher than what was believed originally and the case fatality rate was much lower. In fact, it was very similar to what was observed later in other countries. However, this analysis was not available until the epidemic had been building for at least a month [30]. This indeed attests to the fact that it is very difficult to estimate some key parameters of a suitable model quickly. It required more than a month to obtain good estimates for the influenza epidemic that began in Mexico, and control measures for an epidemic must be implemented quickly to be effective. As a result, it is possible, even probable, that control strategies must be adopted based on a profile of the epidemic that is different from what eventually turns out to be the case. To paraphrase the warnings of Peter Sandman, "At the beginning of an epidemic the situation looks exactly like a developing catastrophe. It also looks exactly like a potential false alarm. As the epidemic proceeds, it may be possible to get a better idea which it is. The approach must be to hope for the best but prepare for the worst". Nevertheless, work is underway to develop novel approaches to the analysis of data in order to estimate parameters more rapidly [60].

In such situations where data are initially limited, techniques of uncertainty and sensitivity analyses may be useful to determine which information is most crucial for reliable projection of outcomes. In uncertainty analysis, the impact of unknown parameters or missing data on the model outputs is investigated. In the closely-related method of sensitivity analysis, the variation of model outputs in response to changes in input parameter values is investigated. Both methods are widely used in decision analysis and are now gaining traction in infectious disease modelling, where they can help to identify which parameter values most influence model projections and hence are most urgently needed [9]. The use of sensitivity and uncertainty analyses has grown in parallel with the development of more complicated models, as both often require computer-intensive simulations.

Because there are many asymptomatic and mild cases, possibly one third to one half of all cases, if not more [30], the danger of an influenza pandemic may be overstated by news media. Thus the symptomatic attack rate (the fraction of the population that develops symptoms) is considerably less than the clinical attack rate (the fraction of the population that becomes infected and can be identified

by clinical tests, including individuals who do not develop symptoms). A clinical attack rate of 0.6 translates into a symptomatic attack rate of 0.3 to 0.4 (assuming a fraction 1/2 to 2/3 of clinical cases becoming symptomatic) and a much smaller attack rate of serious cases. It is also important to note that a pandemic concerns wide spread of disease, and does not necessarily imply a high case fatality rate (the fraction of individuals who are infected that die of the disease). The 2009 H1N1 pandemic appears to have a case fatality rate of less than 1% [30], which is even slightly less than the case fatality rate reported for some seasonal influenza epidemics. In evaluating news media reports of the number of influenza cases in an epidemic or pandemic, it is also important for everyone to remember that most cases are very mild and may be asymptomatic. In most influenza epidemics many of the deaths are associated with individuals who suffer from underlying health problems.

5. **Intervention strategies for influenza.** There are generally two approaches against the spread of influenza. The first is containment, and attempts to limit the spread of disease outside a known source area. In this stage, travel restrictions and non-pharmaceutical interventions may be effective. The ideal would be to contain a pandemic at the source before it has a chance to spread to other locations [27, 44], but this may be impossible, as was observed in the 2009 H1N1 influenza pandemic. Frequently, an epidemic starts in a remote location and it is not possible to diagnose the first cases quickly or to bring the necessary resources to the source before the disease spreads. This is especially significant for a disease like influenza where a significant fraction of transmission is caused by individuals who do not show or do not yet have symptoms, and the difficulty is compounded by the fact that there is usually a delay in identifying the disease. The challenges are even greater when the disease begins to spread in a community that has limited health care resources, and may even lack sanitary systems or running water. This stage is really a pre-pandemic scenario during which the number of point sources is limited enough that there is hope of wiping out the epidemic there.

In the second stage, there is widespread propagation of disease in many locations. Containment becomes impossible and we move into a mitigation mode. There are three main kinds of mitigation strategies, namely behavioural changes (e.g., social distancing), vaccination before and during an epidemic, and treatment and prophylaxis during an epidemic.

Some of the decisions on how to deal with an epidemic, especially behavioural changes such as increased hand washing, covering of coughs, avoidance of large public gatherings and school closures are mainly made to decrease contacts that are likely to contribute to disease transmission [14, 26, 59]. They may be encouraged by public service announcements. In the 1918 influenza pandemic, although no vaccines or antiviral drugs were available, non-pharmaceutical interventions appeared to be effective in decreasing the number of infections [10].

Other decisions are made by political leaders, presumably guided to some extent by the advice of public health experts. It would be beneficial if this advice is based in part on the results of model analysis, but modellers should not expect model analysis to influence political leaders directly. It is important to improve communication between modellers and public health officials so that modellers understand what results would be useful, and public health officials also recognize the potential and limitations of modelling.

If persons who are infected stay home from work, transmission of infection is reduced, but there are economic costs and people may be unwilling to stay home. Cancellation of large public gatherings and closing of public facilities also decrease the transmission of infection but has economic costs. Interventions that have been considered in published mathematical models of influenza transmission include several social distancing measures. For example, school closures may be implemented during pandemic outbreaks in order to diminish contacts between children and therefore reduce transmission in the wider community. However, this strategy may result in redistribution of contacts in the venues where children may gather (e.g., day care centers, cinemas, churches, food stores, malls, and athletic arenas). Parents might need to stay home from work to care for children, which could result in high absenteeism rates and stress in critical services, including health care [21, 34, 64]. Travel restrictions may also be considered for interruption of disease transmission and prevention of case importation, but the associated societal and economic costs could be staggering.

Isolation of infectious cases and quarantine of potentially infectious (but asymptomatic) contacts are also measures that would decrease the spread of infection, but also have economic costs and may not be as widely adopted. Integration of economic and transmission modelling may be useful in guiding decisions about when to apply disruptive measures such as school closure and quarantine in pandemic situations [64]. Economic evaluation is useful to estimate whether an intervention, disruptive or not, gives good value for the cost.

Because the newly emerged influenza H1N1 strain spread rapidly around the globe via air travel, a frequently posed question was whether travel restriction would slow the spread of this virus. Mathematical models suggest that extremely stringent travel restrictions (i.e., a reduction of more 95%) could delay the onset of an influenza pandemic, but at best would buy time for additional preparedness activities [6, 18, 26], and could risk pushing local epidemics forward until seasonal factors result in a more severe initial wave of infection. International Health Regulations (IHR) are biased against restrictions on movements of people and goods, and the fear of such restrictions may have been a reason why the World Health Organization deferred the decision on declaring a pandemic until June 11, 2009, about three months past the emergence of the novel H1N1 virus.

If the policies adopted to try to control an epidemic are successful but involve economic costs, it is almost certain that there will be a public reaction claiming that the measures were not needed because the epidemic turned out not to be serious and the measures did not justify the costs incurred. Also, if an epidemic takes off, there will be a public reaction clamoring for control measures which would have been needed earlier to be effective and to which there would have been strong objections earlier. Public health measures in the face of a possible pandemic with substantial uncertainties, whatever decisions are made, will almost certainly be controversial. News media reporting on the progress of an epidemic will have much influence on public opinion, and it is essential that the information circulated to the media be balanced, not sensationalized, and (perhaps most importantly) able to be condensed into a succinct plain language statement. News reports that many millions will be stricken by a global pandemic without the additional information that an overwhelming majority of cases will be asymptomatic or very mild can lead to unnecessary panic. In addition, if a pandemic turns out to be less serious than originally feared, the public may dismiss warnings about a second wave that could

be much more serious. Public response is a key ingredient to epidemic management, and must be taken into account. What is paramount is that the communication of uncertain information needs to emphasize the uncertainty and to address the fact that public health preparations are designed for the worst case scenario while hoping for the best outcome. It is important that communications between public health officials and the news media emphasize that information is based on what is known "today", and tomorrow the evidence may suggest that a different direction is needed.

A second aspect of mitigation is vaccination. Every year predictions are made about the influenza strains that are most likely to circulate during the upcoming season and a strain-specific vaccine is produced. For a new strain, such as the 2009 influenza A (H1N1), no vaccine was available, and it took about six months to develop one using egg-based technology (cell-based technology allows for more rapid development but the vaccine tends to be less efficacious [72]).

However, older people may have some residual immunity due to prior exposure to a similar strain that may reduce susceptibility or infectivity if infection occurs, and in a pandemic older people may be less susceptible than others. Questions then may arise as to which segments of the population should be prioritized to receive vaccination when a strain-specific vaccine is made available, possibly in a limited number of doses. Even after the onset of a pandemic, vaccination is still an option, as immunization programs are effective so long as protection is increased in some fraction of the population before the epidemic peaks [32].

The third aspect of mitigation is treatment after the onset of an epidemic. Without a strain-specific vaccine, antiviral drugs will be the main treatment. The use of drugs for treatment will probably take precedence over their preventive (prophylactic) use, but prophylactic treatment of contacts of index cases for about ten days may be useful [44]. Compared to vaccination, the cost of antiviral treatment or prophylaxis is prohibitive, yet far more economical than hospitalized care. Treatment of confirmed cases would normally be continued for about five days. The primary goal in treatment is to limit the severity of illness and reduce the period of infection. Initial investigations indicated that the novel H1N1 virus was susceptible to the antiviral drugs oseltamivir and zanamivir [15]. However, influenza viruses have a propensity to acquire resistance rapidly and oseltamivir resistance to H1N1 has already emerged [16, 38]; therefore strategic use of drugs is crucial for not only mitigating the disease in the short-term, but also preventing the emergence and wide-spread resistance in the longer term. Models suggest that in the absence of resistance, early and aggressive use of drugs could control influenza epidemics when $\mathcal{R}_0$ is small, but if the early control effort is not successful, the development of drug resistance may make things worse. When resistant viruses are present, more conservative initial use of drugs may be a better strategy for preventing large resistant outbreaks [3, 40, 51, 52, 62, 66].

Programmatic uncertainty can be a serious problem in considering mitigation strategies [32]. It is very important to begin mitigation measures early and effectively, before much is known about how the epidemic will develop. For example, the effectiveness of a vaccination campaign depends very critically on when the vaccine will be available for distribution, and this may not be known enough in advance to decide what other strategies might be effective. It may not be necessary to consider such possibly controversial measures as school closures if vaccination can be started early enough [32]. At the beginning of a pandemic, there may be many possible

intervention strategies, and the effects of different interventions tend to offset one another; decisions must be made in the face of considerable uncertainty.

The use of antiviral drugs is a very delicate question, and better understanding of the immunology and virology of drug resistance is needed. The allocation of antiviral drug resources, both in deciding the timing of drug treatment and in deciding who should be treated, is an important question which may be addressed by mathematical models. This is a particular concern if the supply of antiviral drugs is not sufficient to treat everyone [3]. If the drug supply runs out and if drug resistance is not a concern, then the final size of an epidemic does not depend on the rate of drug treatment [2], but the development of drug resistance could make a large difference in the size of the epidemic [2, 3]. If a second drug is available in limited supply for treatment, models can address the question of optimal timing of a switch from the primary drug to the secondary drug for minimizing the development of drug resistance [1, 35, 39].

6. **Multiple pandemic waves.** It has been observed that small seasonal variations in epidemic parameters may cause variations in the reproduction number between values above 1 and values below 1 [24]. There is evidence to indicate that transmissibility of influenza depends significantly on temperature and humidity [45]. Thus an epidemic that begins in the spring may be mild because transmission decreases early in the epidemic, but may recur, possibly in a more severe form, in the fall when transmission begins to increase again [56, 67]. In some populations, the influenza pandemic of 1918-19 began in the spring, was essentially dormant in the summer and then reappeared in a much more severe form in the fall. Also, there is a seasonal phase shift between hemispheres; the 2009 pandemic appeared in the Southern Hemisphere in June, while the first wave was fading in the Northern Hemisphere. Seasonal variations in parameters, coupled with genetic drift of influenza viruses, may be a partial explanation for second and third waves that have occurred in some pandemics [24, 43, 58]. Often, the second wave is more severe for age groups that were not hit severely in the first wave, possibly because of immunity obtained by infection and recovery in the first wave. In a second wave there may also be mutation of the influenza virus to a more lethal strain or potentially severe bacterial coinfections such as pneumococcal pneumonia that also have seasonal fall/winter peaks. This suggests that after a pandemic wave, even one that appears not to be very severe, it is important to develop a vaccine for this strain that may provide at least partial protection against a more lethal second wave. However, development of such a vaccine would use some of the resources needed for preparation of a vaccine for the next seasonal epidemic, and it would be necessary to decide how to allocate these resources without having any idea of the relative severities of the seasonal and pandemic strains. It appears that vaccine manufacturing capacity for producing both seasonal and pandemic vaccines at the same time is limited. Pandemic strains generally seem to displace the circulating seasonal strains and become the predominant strain in future influenza seasons.

One suggested explanation for a second wave in a pandemic is seasonal variation in transmissibility [56, 67], but this is by no means the only plausible explanation. Another possibility is coinfection with other respiratory diseases [47]. This means that it is not possible to rely on a model to predict when a second wave may develop or how severe it may be. Seasonal parameter variation in models will probably

become very important. Models incorporating seasonal variation are very sensitive to when during a seasonal cycle a disease outbreak begins.

While we have been considering only deterministic models, it must be recognized that there are also stochastic effects, unpredictable variations from a deterministic description. Often, the mean of the predictions of a stochastic model agrees with the prediction of the corresponding deterministic model, but there are cases in which systematic biases can result [41]. Small stochastic variations can produce resonance effects and this may be relevant to the development of pandemic waves [24].

7. **Conclusions.** Several conclusions may be drawn from the study of models for infectious diseases in general and influenza in particular.

- In order to develop a model to be used in comparing management strategies for a disease outbreak, reliable data are needed.
- Data early in a disease outbreak are almost always misleading.
- Diseases such as influenza in which a substantial fraction of transmission is by individuals without symptoms make estimation of model parameters particularly difficult.
- Uncertainty and sensitivity analyses can be used to determine which model parameters have the most impact on model projections.
- Interventions to cope with infectious diseases include social distancing measures to decrease contacts, isolation of diagnosed infectious individuals, quarantine of suspected infectious individuals, vaccines if available, and pharmaceutical treatment such as antiviral drugs. Most measures have economic costs that must be balanced against benefits. Models are useful for comparing the effects of different control strategies.
- It is important to begin control measures early, probably before the scope of the epidemic can be estimated. Programmatic uncertainty about what intervention strategies will be available is a serious problem calling for more study.
- A new virus may spread more easily and be more dangerous than a virus for which some people have residual immunity, but a pandemic that spreads widely is not necessarily more lethal than a seasonal virus.
- Influenza pandemics often have multiple waves, and in some cases a second wave has been more serious, but the interval between waves may suffice for development of a vaccine.
- Unpredictable stochastic effects and the dependence of contact rates on age and on other demographic variables may be an important factor in modelling.
- Strong integrated knowledge translation activities involving public health policy makers, public health practitioners, and mathematical modellers throughout the process are pivotal, and should be prioritized in responding to the threat of emerging infectious diseases.
- Expert media contacts with reporters should receive specific training to facilitate better communication of complex material in plain language. These media contacts need to be able to respond to media queries in ways that fit the time frame of reporters and news outlets.

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