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Mathematical Models in Infectious Disease Epidemiology

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KEY CONCEPTS

- Mathematical modeling of infectious diseases has a long history, and is increasingly used to understand transmission patterns, better understand natural history, plan studies and public health interventions, evaluate interventions, and plan for and respond to outbreaks and epidemics.
- Modeling is required to account for the 'natural dynamics' arising from the transmission process: the incidence of infection (the rate of new infections arising) depends upon the prevalence (the proportion of the population that is infectious), and the prevalence depends upon the incidence – there are dynamic feedback interactions between population-level prevalence of infection and individual-level risk.
- Population-level transmission-dynamic effects can be beneficial: it is not necessary to vaccinate everyone in the population to prevent an epidemic: if vaccination coverage is sufficiently-high then 'herd immunity' prevents epidemics occurring, which protects those who are not vaccinated.
- Population-level transmission-dynamic effects can be harmful: reducing rates of transmission through vaccination can produce a net increase in disease due to an increase in the average age at infection unless mitigating action is planned and implemented.
- Multiple interacting factors affect infection-transmission patterns, so modeling requires many sources of data, and the input of professionals from multiple disciplines.
- Economic analysis of infectious disease interventions needs transmission-dynamic modeling to account for infections *averted*, which can be the major health benefit, and can result in net cost savings.
- There is no one 'correct' transmission-dynamic model for a disease: different types of models are appropriate for the same disease, depending upon the available data, the question being addressed, the time-frame of the work and other factors.

The first mathematical model of infectious disease transmission was constructed by Bernoulli in 1760[1] to determine the impact of variolation, a crude form of smallpox vaccination, on life-tables used for actuarial purposes.

Models are tools used throughout science and medicine – they are used to interpret results, formulate hypotheses and devise experiments to test them, derive diagnoses from observed signs and symptoms and test results, and guide decision-making. Formulating models *mathematically* facilitates rigorous analysis and allows quantitative predictions to be made of trends in disease burden and the impact of interventions.

Mathematical models of infectious disease transmission are increasingly being used to guide public health policy. Examples include the control of an epidemic of foot-and-mouth disease in the UK in 2001,[2] the outbreaks of severe acute respiratory syndrome (SARS)[3] and Middle East respiratory syndrome coronavirus (MERS-CoV),[4] planning control strategies for tuberculosis (TB), human immunodeficiency virus (HIV) and sexually transmitted infections (STIs),[5-7] vaccination policy,[8] and planning for and responding to pandemic influenza,[9–11] and bioterrorism,[12] planning of intervention trials,[13,14] evaluation of intervention policy (since evaluation of interventions at close to full-scale is usually impossible),[14,15] as well as improving understanding of disease natural history, and examining general principles of disease control.[16]

Infectious disease epidemiology is inherently multidisciplinary because the transmission of infection within a population is affected not just by the biologic characteristics of the infectious agent and its host, but also by the patterns of contact between hosts (and vectors, where relevant), the environment and, for humans, their use of health services and response to public health interventions, etc. Mathematical models are used to characterize the complex interactions between these factors and to enable information from diverse sources, including social sciences, to be integrated.

Importantly, models should not be 'black boxes', but should be clearly described so that non-modelers are able to assess the validity of the model and its use of data. Modeling is the process of formalizing one's conception of a system, and the exercise should increase clarity; nevertheless, infectious disease transmission dynamics are typically inherently complex.

Dynamics of Infectious Disease Transmission

The defining characteristic of infectious diseases – that they are transmissible – means that an individual's risk of acquiring infection changes dynamically as levels of infection rise and fall in the population.

The fundamental measures in epidemiology are the incidence and prevalence. *Incidence* is the per-capita rate of new cases arising per unit time, and is usually expressed as x% of the population affected per year or x cases per 1000 per year or x cases per 100 000 per year. *Prevalence* is the proportion of the population (usually expressed as a percentage or number per 1000 or per 100 000) that are cases at a point in time. For both infectious and noninfectious diseases, prevalence is related to incidence, since newly arising incident cases become prevalent cases.

For infectious diseases, however, incidence is also related to prevalence, since it is from prevalent cases that transmission occurs, giving rise to incident cases.

The greater the prevalence of infectious individuals the more frequently (on average) a person who is susceptible to infection will encounter an infectious individual, providing an opportunity for transmission to occur.

Therefore, there is a dynamic feedback process in which incidence depends upon prevalence and prevalence depends upon incidence. This leads to infectious disease epidemics having 'natural dynamics', with incidence typically rising to a peak then declining, in the absence of any intervention.

A TYPICAL EPIDEMIC

In a typical epidemic, without any intervention, prevalence rises initially as infection spreads. This causes an increase in incidence, which in turn causes prevalence to increase even faster – so the epidemic accelerates. Consequently, the supply of susceptible individuals becomes depleted (by their becoming infected) and the incidence falls,

even though prevalence may continue to rise for a time. Eventually, the fall in incidence leads to a fall in prevalence because infections are 'lost' from the population (due to recovery, death or emigration) faster than they are replaced by the spreading of infection. In the longer term, the infectious agent may be able to persist in the population (i.e. become endemic) if there is a high-enough rate of resupply of susceptible individuals due to birth, immigration, recovery from infection (if there is no lasting immunity) or waning of immunity (if applicable); otherwise the infectious agent will go extinct locally.

These *population-level effects* have important consequences. For example, vaccinating individuals or treating infectious individuals benefits not only the individual patient directly but also benefits others in the population indirectly by reducing their risk of acquiring infection through the reduction in the prevalence of infection in the population. (Quarantine and isolation typically benefit the population more than the affected individuals.) Vaccination against pneumococcus caused the incidence of infection with 'vaccine' serotypes to fall in those who did not receive the vaccine because they were older than the target group for vaccination, as well as in those who were vaccinated.[17]

It is important that economic evaluation of potential interventions takes account of infections *averted*, which benefits health and saves money by averting the need for treatment, by using mathematical models.[8,14]

Insights from Transmission-Dynamic Modeling

Importantly, population-level effects due to infectious disease transmission dynamics mean there is typically a complex nonlinear relationship between the size of an intervention and the outcome.

Typically, as the scale of an intervention (e.g. vaccination coverage or provision of treatment) increases from a low level, the benefits – reductions in levels of disease – accrue 'faster' than the costs, until disease has been reduced to a low level or even eliminated; further increasing the intervention further produces a diminishing incremental benefit. Vaccinating just a small proportion of the population mostly benefits only those who receive the vaccine because it does little to interrupt transmission. Vaccinating a large-enough proportion of the population to achieve 'herd immunity' prevents epidemics, providing a large 'indirect' benefit to those not vaccinated. Another example is in the control of curable infections (e.g. STIs) through treatment: if treatment capacity is inadequate then there is a 'vicious circle' where failing to control transmission in the present results in more infections in the future, maintaining the inadequacy of treatment capacity.[6] Conversely, making a concerted effort to increase capacity can break this vicious circle and create a virtuous circle, where promptly treating a large-enough proportion of infections reduces transmission, reducing the need for treatment, leading to significant cost savings.[6]

However, 'indirect' population-level effects can also be harmful.[18] Whilst reducing levels of infection in the population through vaccination protects those who are not vaccinated as well as those who are vaccinated by reducing the overall rate of infection, those who do still get infected are older on average when they get infected and this can lead to more severe outcomes for some diseases (e.g. congenital rubella syndrome). Therefore, vaccination can increase the overall rate of *disease* – either transiently, until infection is eliminated from the population, if there is high-enough coverage – or indefinitely, if vaccine coverage is persistently low.[18] Mathematical models can help predict these effects and aid the design of strategies to mitigate them, e.g. ensuring sufficient vaccination coverage and identifying the at-risk age range.

Use of Models for Analysis of Epidemics and Interventions

Observing a decline in incidence following an intervention is not sufficient evidence to demonstrate its effectiveness.[15] Conversely, in some circumstances it is even possible to observe incidence continue to rise despite an *effective* intervention, due to an increase in prevalence.[19]

Models can evaluate interventions that have been implemented by allowing comparison with the 'counterfactual' – the modelled scenario of what would have happened in the absence of the intervention.[14,15]

Crucially, quantitative analysis can determine if a putative cause for an observed effect would have been strong enough to cause the effect – e.g. a modeling of the Ugandan HIV epidemic found that several modes of behavior change (delaying sexual debut, reducing numbers of sexual partners, increasing condom use) must have occurred to explain the observed decline in prevalence. No single behavior change was sufficient to account for the observed reduction.[15]

Models can help set priorities for empirical research by determining the importance of different 'gaps' in knowledge. This is done by testing the 'sensitivity' of a model's behavior to changes in the values of parameters that are poorly estimated by current data to see how much they affect predicted levels of disease or the predicted effectiveness of different interventions. Typically, some parameters are highly influential, so ideally would be known with high precision, whilst others are less influential.

Epidemiologic Data

Incidence can be measured directly in longitudinal cohort studies, following a group of subjects through time, or can be calculated from a series of cross-sectional prevalence surveys.[20] Case notifications from surveillance systems are often used as a proxy for incidence (but not all infections may be detected and without laboratory confirmation some cases might be misreported); long-term datasets are available for a large number of infectious agents due to mandatory (notifiable) disease surveillance schemes. Analysis of past influenza pandemics has contributed greatly to preparedness for future pandemics (www.who.int/influenza/preparedness/pandemic/en/).

Serological studies often provide valuable data, particularly when complemented by clinical investigations (e.g. see http://consise.tghn.org/) – for example in informing on the proportion of infections that are symptomatic, since it is typically only symptomatic infections that are detected in surveillance systems.[21]

Reproduction Numbers

The key measure of an infectious agent's ability to spread in a population is the reproduction number (sometimes called the net reproduction number or effective reproduction number), $R(t)$, which is the mean number of new infections caused by a typical infected individual in the population of interest.[22] (Note that '(t)' indicates that the value can change with time – see below.) A related quantity is the *basic* reproduction number R_0,[18] which is defined as the mean number of new infections caused by a typical infected individual in a population of wholly susceptible individuals, i.e. R_0 is what the value of $R(t)$ would be if the population were totally-susceptible. It is important to understand that $R(t)$ is specific to the particular infectious agent in the particular population at the particular time, and can be changed by interventions. $R(t)$ depends upon the average rate of transmission from an infectious individual and the average duration of infectiousness. An epidemic requires that $R(t)>1$, so that the prevalence of infection increases because more than one new infection arises from the average infected person before that person is 'lost' from the infected population. In the typical epidemic described above, depletion of the 'supply' of susceptible individuals causes $R(t)$ to fall, even though R_0 does not change. In fact, $R(t)$ falls even as incidence rises; the initial increase in incidence is driven by the increase in prevalence, with the proportionate increase in prevalence being greater than the proportionate reduction in transmission from the average prevalent case, caused by the reduction in the number who remain susceptible.

Public health interventions aim to reduce and maintain $R(t)$ below 1, which may be achieved by reducing the average infectious period (e.g. through treatment or isolation) or the transmission rate (e.g. by closing schools and workplaces to combat SARS or influenza,

or promoting condom use and reductions in numbers of sexual partners to combat STIs) or using vaccination or prophylaxis to 'remove' people from the susceptible population. Generally, the higher the value of R_0, the harder an infection will be to control. In a homogeneous population (one where everyone has the same average risk of acquiring and transmitting infection) the relationship between R_0 and $R(t)$ is $R(t) = R_0 \times s$ where s is the proportion of the population that is susceptible. To prevent an epidemic by vaccination requires that s be reduced so that $R(t) < 1$ (i.e. that s be reduced below $1/R_0$), hence the greater the value of R_0 the smaller s must be. The critical vaccination threshold is the proportion of the population that must be successfully immunized to prevent an epidemic; for childhood infections such as measles, which have high typical R_0 values, this is typically >90% or even >95%.

There are various ways to estimate R_0 and $R(t)$, depending upon the available data.[4,18,22,23] It is important to realize that R_0 alone does not provide complete information on the transmission dynamics of an infectious agent.[3,16] A highly infectious agent that spreads rapidly but has a short infectious period could have the same R_0 as another infectious agent that is much less infectious but has a longer infectious period – the latter would tend to spread more slowly but for longer.

Structure of Models of Infectious Diseases

All models of infectious disease transmission use a simplified representation of the key features of the natural history of the infection, and of the patterns of contact through which transmission occurs.[18,22,23] The design of the model used is determined by the question being addressed, the availability of data, computing resources available, speed of analysis required, and other factors – there is no 'right' model for a particular disease.

Important characteristics of the natural history include the incubation period (the time from the point of infection until the appearance of symptoms) and the latent period (the time from infection to becoming infectious). These vary greatly (from days to years, depending upon the infection) and either can be longer than the other. For SARS the latent period is longer than the incubation period, with people becoming unwell before they become infectious; for HIV the opposite is the case (ignoring brief seroconversion symptoms), but for pulmonary TB they can be the same, with people becoming infectious at the time they become unwell.

In modeling there is a trade-off between complexity/realism and the ability to understand the model's behavior. Since even simple models can have complex dynamics it is important to make the model as simple as possible, whilst still capturing the essential features of the infection. For example, for genital *Chlamydia trachomatis* the incubation period is often omitted from models[6] because it is short relative to the infectious period – and so has little effect on the dynamics of infection – while HIV's incubation period is long compared with the symptomatic late-stage period and so it is usually incorporated into models.[24] In the case of TB, most people with infection never develop infectious disease (they remain latently infected) and so models distinguish between these states.[25] Modeling of HIV and of TB have been reviewed by Johnson and White[7], and White and Garnett[25], respectively.

All models of infectious disease transmission need to represent changes in the infection status of persons in the population, but models vary in how they represent the population and patterns of contact within it. Most commonly, the population is represented in aggregate, with the population notionally assigned to 'compartments' representing different infection states and the model 'keeping track' of changes over time in numbers of individuals in each of these different states (see example below and Figure 5-1). However, other types of model represent each person in the population as a discrete individual, and are able to 'track' each individual's history, as well as individual-level variation in different traits – these models are typically very computationally demanding.

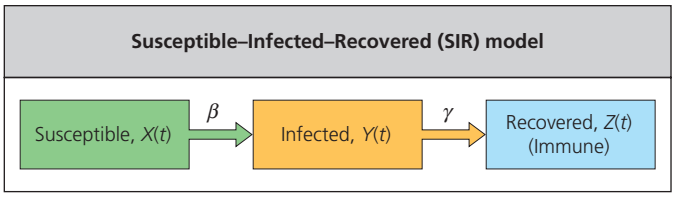

Figure 5-1 Susceptible–infected–recovered (SIR) model. The population is notionally divided into three compartments according to whether they are Susceptible to infection, Infected (and infectious) or have Recovered from infection and are immune. Individuals who become infected move from the Susceptible compartment to the Infected compartment; the process of recovery subsequently moves them from the Infected compartment to the Recovered compartment. The parameters β and γ affect the rate of transmission of infection and the rate of recovery, respectively.

The population can also be stratified by age, sex, co-morbidities, or other characteristics of interest.

Representations of contact patterns within populations vary in the level of detail used (in part determined by the model structure), from simple homogeneous mixing, to dividing the population into smaller aggregate groups (e.g. age categories or geographically distinct subpopulations), to having separate households, or even having explicit networks of contacts between discrete individuals (e.g. sexual-contact networks). Models can also represent movement patterns, e.g. commuting to work, or air travel within and between countries.

Models can be *deterministic*, meaning that they do not explicitly represent randomness arising from the probabilistic nature of transmission and other events, or *stochastic*, meaning that they do.[22] Deterministic models, which represent expected 'average' behavior, are more common because they are simpler and less computationally demanding to analyze, but stochastic models are more appropriate to analysis of outbreaks, emergence of novel strains (e.g. with antibiotic resistance), or patterns occurring in small populations because they capture the expected variance due to random events.

EXAMPLE COMPARTMENTAL MODEL OF INFLUENZA

For a directly transmitted pathogen such as influenza, where acquired immunity (to a particular strain) is lifelong, the host population can be represented by three compartments containing the number of Susceptible, Infected (and infectious) and Recovered (immune, non-infectious) individuals. In this example, the latent period is ignored, so individuals become infectious as soon as they become infected. This so-called 'Susceptible–Infected–Recovered' (or 'SIR') model approach was first developed by Kermack and McKendrick in 1927,[26] elaborated upon by Anderson and May,[18] and now forms the basis for many modern-day models of epidemics.

A simple SIR-type model (see Figure 5-1), can be applied to data from an outbreak of influenza in a boarding school in England.[27] Since the outbreak is short-lived, the population is regarded as 'closed': no one enters or leaves, and there was no mortality due to infection. (Often, one has to consider immigration, emigration, birth and death – and if the infection being modeled causes mortality then Infected individuals have an additional disease-induced mortality rate to be considered.) Additionally, there is only one age group – models of influenza in the general population typically distinguish age groups, due to differences in social contact rates, immunity due to past exposure to flu strains, and risk of severe illness if infected.

Each compartment has a state variable 'keeping track' of the number of individuals in that compartment, which can change through time. In this case, the state variables are $X(t)$ for the Susceptible individuals, $Y(t)$ for Infected individuals and $Z(t)$ for Recovered individuals, where '(t)' indicates that the values can change with time. The total population size is $N(t)$, where $N(t) = X(t) + Y(t) + Z(t)$. The model consists of a set of differential equations describing the rates that individuals flow between different compartments as they become infected, recover, die (not applicable here), etc. The net rate of change in $X(t)$ is

described by the differential equation $dX(t)/dt$, etc. In this example, there are two processes: infection and recovery.

The number of people becoming infected per day depends upon the *force of infection* (the risk per Susceptible individual of acquiring infection per day) and the number of Susceptible individuals available to become infected, $X(t)$. The force of infection depends upon the *prevalence* of infection, $Y(t)/N(t)$, and the transmission parameter, β, which is a combination of the rate of contact between people in the population and the probability of transmission upon contact between an Infected person and a Susceptible person. Therefore, the force of infection is $\beta Y(t)/N(t)$ and the transmission rate is $X(t)\beta Y(t)/N(t)$, which is conventionally written as $\beta\, X(t)Y(t)/N(t)$. Since infection transfers people from the Susceptible compartment ($X(t)$) to the Infected compartment ($Y(t)$), the term $\beta\, X(t)Y(t)/N(t)$ appears negatively in $dX(t)/dt$ and positively in $dY(t)/dt$. (Note that the transmission parameter, β, does not change with time; changes in the daily infection rate are due to changes in $Y(t)/N(t)$ and $X(t)$.)

The number of people recovering per day depends upon the per-capita rate of recovery, γ, and the number of people who are Infected, $Y(t)$, and is $\gamma\, Y(t)$. Since recovery transfers people from the Infected compartment ($Y(t)$) to the Recovered compartment ($Z(t)$), the term $\gamma\, Y(t)$ appears negatively in $dY(t)/dt$ and positively in $dZ(t)/dt$. (Note that the per-capita rate of recovery, γ, does not change with time; changes in the daily recovery rate are due to changes in $Y(t)$.)

The equations of the model are:

$$\frac{dX(t)}{dt} = \frac{-\beta X(t)Y(t)}{N(t)}$$

$$\frac{dY(t)}{dt} = \frac{\beta X(t)Y(t)}{N(t)} - \gamma Y(t)$$

$$\frac{dZ(t)}{dt} = \gamma Y(t)$$

$$N(t) = X(t) + Y(t) + Z(t)$$

This model is deterministic, i.e. random (stochastic) events are not considered. This is a common simplification that makes it much easier to gain insight into the fundamental dynamics of transmission because the effects of random chance, which cause fluctuations in the graph, are omitted. This model was fitted to data from an outbreak of influenza in a boarding school in England[27] (Figure 5-2) to estimate values of β and γ.

R_0 is the mathematical product of the transmission rate from a single infected individual in a wholly susceptible population and the average infectious period. The algebraic expression for R_0 depends upon the particular model. For this model, the rate of transmission from a single infected individual when the population is wholly susceptible (i.e. when $Y(t) = 1$ and $X(t) = N(t)$; we ignore the fact that really $X(t) = N(t) - 1$ because one person is infected, because we assume that $N(t)$ is large) is:

$$\frac{\beta X(t)Y(t)}{N(t)} = \frac{\beta N(t)\cdot 1}{N(t)} = \beta$$

The average infectious period is the reciprocal of the average recovery rate (the faster people recover, the shorter their infectious period), i.e. $1/\gamma$. Therefore $R_0 = \beta/\gamma$. The estimated values from fitting to data were $\beta = 1.97\text{day}^{-1}$, $\gamma = 0.47\text{day}^{-1}$ (corresponding to a mean infectious period of 2.12 days), so $R_0 = 1.97\text{day}^{-1}/0.47\text{day}^{-1} = 4.18$.

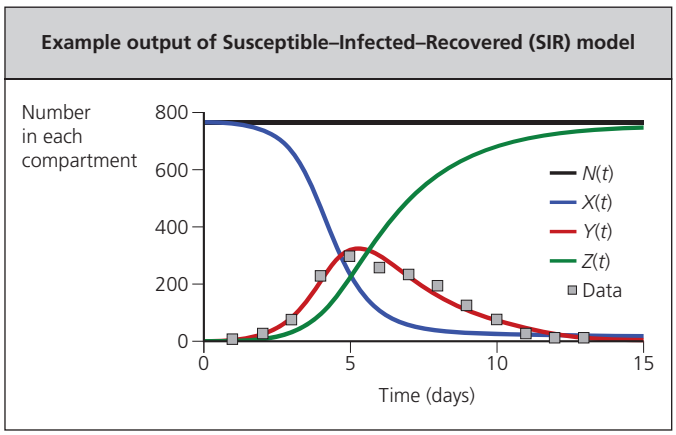

Figure 5-2 Example output of a Susceptible–Infected–Recovered (SIR) model applied to data from an outbreak of influenza. Model parameters were adjusted to fit the number of Infected individuals, $Y(t)$, to the observed data.

Emergency Preparedness and Response

The huge growth in international travel and in population densities in many cities offers new challenges in controlling the spread of newly emerging infections. Infectious disease transmission dynamic modeling is now widely used for emergency preparedness and response. SARS, MERS-CoV and pandemic influenza are used as examples.

PANDEMIC INFLUENZA

Retrospective modeling, particularly of pandemic influenza, has been used to better understand the behavior of epidemics and the effectiveness of interventions to inform scenario modeling for planning responses to epidemics of novel pathogens, with different characteristics, and to determine the appropriate size of antiviral stockpiles, and capacity of intensive care facilities.[9,10]

In real-time during an epidemic, modeling is used for purposes such as:[21]

1. Estimation of severity at the individual level, including what proportion of infections will be symptomatic cases, and what proportions of those will be medically attended, hospitalized, admitted to intensive care, and what proportion will die. These proportions are typically age-dependent, and affected by co-morbidities.
2. Estimation of the expected ultimate size of the epidemic and its trajectory, based on the initial growth rate and accumulating surveillance data.[3,11,28] (Although R_0 varies amongst populations, similarities between populations mean that early estimates from one location can be informative for others.)
3. Estimation of the likely impact of different intervention options, and evaluation of interventions that are being implemented.

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

SARS is caused by a coronavirus (SARS-CoV) normally found in wild animals such as the palm civet cat and Chinese ferret badger.[3,29] Early cases are thought to have involved zoonotic infection, with subsequent genetic changes enabling greater human-to-human transmission, which accounted for the vast majority of cases in the global pandemic of 2002/3. SARS spread quickly from China to other parts of Asia, Europe, the Americas and elsewhere, infecting >8000 individuals in 29 countries and killing at least 774 people. Transmission was linked to close contact with cases, mostly in hospital, affecting healthcare workers or patients.[3,30]

Models of SARS transmission provided estimates of the key epidemiological parameters and showed how spreading was controlled by effective intervention. Reproduction number estimates from before the WHO global alert, for Hong Kong, Vietnam, Singapore and Canada, respectively, were 3.6, 2.4, 3.1 and 2.7, and after were 0.7, 0.3, 0.7 and 1.[31] The reduction in the reproductive number in each country reflects the effectiveness of control measures such as quarantine and travel restrictions in curbing the epidemic.

Estimating the case-fatality ratio (CFR) of newly emerged pathogens is difficult as defining true cases can be problematic.[32] The CFR may be overestimated if many subclinical infections go uncounted.

Alternatively, in epidemics where patients are hospitalized for lengthy periods before recovering or dying, a naïve real-time CFR estimate, dividing number of deaths by numbers of cases, will initially underestimate CFR, as patients will be recorded as cases before their outcome is known, and then the CFR will apparently rise over time as deaths occur and are recorded; in the 2003 SARS epidemic this apparently increasing CFR was wrongly interpreted as indicating an increase in virulence.[3]

Mathematical modeling identifies some key properties that enabled SARS to be contained effectively, in contrast to influenza. The generation time for influenza (4–6 days) is much shorter than for SARS (8–12 days),[3,16] meaning influenza will spread much quicker. Furthermore, SARS transmission occurs after the patient becomes symptomatic[16] – making it feasible to use isolation to reduce transmission – whilst influenza can be transmitted in the absence of symptoms.

MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV)

MERS-CoV was first detected in 2012, having apparently arisen from an animal reservoir. To date there has been limited human-to-human transmission; modeling[4] suggests that medical intervention reduces transmission and that currently $R(t)$ is most likely <1, although prior to medical intervention $R(t)$ might be >1, suggesting that the virus might have pandemic potential if human cases are not detected efficiently.

Future Research

There is increasing integration between infectious disease modeling and empiric research in the field and laboratory. Models can be used to help set research priorities by determining which gaps in knowledge are most important epidemiologically, and help in the design of trials.[13] Increases in computing power make it possible to develop increasingly sophisticated simulation models and to use them in real-time to analyze outbreaks to determine whether interventions are working and to guide policymakers in their response. DNA fingerprinting and now whole-genome sequencing are being used to identify 'transmission clusters' of individuals[4,33] and the developing field of 'phylodynamics'[34] synthesizes evolution and transmission dynamics. Another area of research is characterizing contact patterns between individuals in more detail[35] since this has important consequences for patterns of transmission.

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