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Invited Commentary: Real-Time Tracking of Control Measures for Emerging Infections

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Health officials faced a daunting task with the emergence of severe acute respiratory syndrome (SARS) last year: forecasting the trajectory of an emerging infectious disease and implementing effective control measures, even as the etiologic agent was still being identified. Investigators initially had little to go on beyond crude epidemiologic data such as the timing of new cases (the epidemic curve). With such limited data, it was difficult to disentangle two fundamental epidemiologic quantities: the time from one transmission of the infection to the next, known as the serial interval or generation time, and the average number of secondary cases resulting from each infection, known as the reproductive number.

A simple example illustrates the problem. Compare two idealized diseases, A and B. Disease A has a short generation time of 4 days but has relatively low transmissibility, such that each primary infection generates two secondary infections. Disease B has a longer generation time of 8 days but is more transmissible, such that each primary infection generates four secondary infections. The initial epidemic curves for these two infections will be nearly superimposable, with approximately a doubling of new cases every 4 days. (These calculations are approximate. In fact, the generation time for any given transmission will be a random variable, with some distribution. This distribution will affect the precise doubling time of the epidemic and will also affect the shape of the epidemic curve in the period before the epidemic enters an exponential growth phase (1–3).) Thus, investigators cannot separate generation time from reproductive number on the basis of the epidemic curves alone. As a result, they are limited in their ability to predict the efficacy of potential interventions. Despite nearly identical epidemic curves, an outbreak of disease A can stemmed by an intervention that reduces transmission threefold, while disease B will continue to spread even with such control measures in place.

In the current issue of the *Journal*, Wallinga and Teunis (4) present a statistical escape from this analytical Catch-22. Their approach is this: Once epidemiologists have traced the chains of transmission in a single isolated outbreak, they can use the transmission network to infer the distribution of generation times for that disease. This distribution, which results from the biology of host-pathogen interaction, should be relatively constant in comparison with transmission rates, which will vary from location to location and over the course of an epidemic as the pool of susceptible persons declines and as control measures are implemented. Therefore, investigators can use this generation time distribution as a grounding point from which to infer the reproductive number, R, from epidemic curves observed in other settings where extensive contact tracing may not have been achieved. Most importantly, Wallinga and Teunis describe an elegant method for following the instantaneous reproductive number as it evolves over time in a single epidemic. They provide a means of transforming the time series of cases, along with a "known" distribution for the generation time, into a time series of estimated values for the instantaneous reproductive number on each day.

This method allows nearly real-time tracking of the effect of control measures and other changes in an epidemic on the level of transmission ongoing in the population. Estimates are not precisely real-time, because accurate estimates of the instantaneous reproductive number on a given date cannot be made until some time after that date. Specifically, one can only estimate the number of persons a given case has infected when a sufficient amount of time has passed that all patients with secondary cases generated by that case (and by other, surrounding cases) have become infected, become symptomatic, and had their infections reported. While this lag period (slightly more than the generation time, plus the incubation period, plus the reporting delay) could be decades long for diseases with extended latency periods such as human immunodeficiency virus disease, in the case of SARS the lag period is a matter of a few weeks, and the information provided is as fresh as one could obtain, given the available data.

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Wallinga and Teunis's elegantly simple approach is related to more complex applications of back-calculation that have been used to derive incidence of infection from data on disease prevalence or incidence in human immunodeficiency virus disease (5) and to derive annual average reproductive numbers from case data in the United Kingdom epidemic of bovine spongiform encephalopathy (6). The present work is distinguished by its real-time applicability to a rapidly transmitted disease and its requirements for only the serial interval distribution and the epidemic curve as inputs.

In their report (4), Wallinga and Teunis demonstrate the power of this analytical approach by improving our understanding of the 2003 SARS outbreaks in Hong Kong, Vietnam, Singapore, and Canada. The authors find that despite the very different epidemic curves observed in each location, pre-intervention reproductive numbers appear to have been similar. Furthermore, they infer that control interventions appear to have reduced transmission rates approximately fourfold in each location—enough to stop the epidemics, but only barely.

Like any model, this one has some limitations, which the authors note. First, the method makes the simplifying assumption of independence of transmission events—that the assignment of a source to any case A is independent of the assignment of the source to each other case B. This is, at best, an approximation. For example, if different persons vary in their degree of infectiousness (e.g., because of differences in viral shedding) or in their duration of infectiousness, the numbers of secondary infections per individual will be overdispersed (even within the same short time period). Put another way, if we know that case i was still infectious at a time when case j became infected, we know that case i is a likely candidate for having infected other secondary cases around the same time. Second, the method assumes that interventions do not affect the generation time of the pathogen. In reality, when interventions involve improved monitoring followed by either isolation or effective treatment, most transmissions will occur early, before detection. As a result, the mean generation time will be reduced, and the algorithm presented here could lead to an overestimate of the instantaneous transmission rate for the period subsequent to intervention.

So will Wallinga and Teunis's approach work despite these limitations? Computer simulations offer some limited evidence that it will, but further study is warranted to assess its performance under various departures from its assumptions. If the method proves robust, it will be a very useful tool for policy-makers in the midst of an outbreak. Rapid assessment of the reproductive number of an emerging infection in the absence of interventions is a crucial first step in understanding and controlling the disease.

Control of a disease in a population requires that the reproductive number be brought below 1 and kept there. By assessing the initial reproductive number (before the implementation of control measures), health officials can estimate the magnitude of the control measures that will be necessary. As the infection spreads in a particular population and as control measures are instituted, real-time tracking is needed to establish the impact of control. The success of a control program for a disease like SARS, in which isolation of symptomatic patients and quarantine of contacts were the key control measures, can be measured in part by "process" indicators, such as the time from the onset of symptoms in a case to the isolation of that case to prevent transmission, or the fraction of incident cases that were identified by contact tracing prior to symptom onset. However, real-time measurements of disease transmission, using methods like the one developed by Wallinga and Teunis, will provide "bottom-line" evidence of whether an epidemic is being brought under control. During the 2003 SARS outbreak, health officials used a conservative definition—no new cases in a time span exceeding twice the longest known incubation period for the infection—to declare an epidemic fully controlled in a particular jurisdiction, but health officials responsible for daily control efforts need a more immediate and quantitative measure of the effects of control measures as they work toward the goal of eliminating the local epidemic. Wallinga and Teunis' method of tracking the instantaneous reproductive number provides just such a measure.

More broadly, new tools are needed to facilitate data entry, management, visualization, analysis, and forecasting in the early days of an outbreak. For example, epidemiologists attempting to track a natural outbreak of a disease like SARS or pandemic influenza or the deliberate release of a biologic agent would benefit from the ability to manipulate a rapidly changing database with ease, to map spatial and temporal patterns in disease incidence according to the home, school, hospital, or workplace of cases, and to perform key analyses in ways that have been thought through and validated in advance. As data become available during the course of an epidemic, public health officials should have at their disposal tools to allow the integration of these data into real-time predictions of the relative costs and benefits of potential control strategies. Many such tools were developed in real time during the 2001 epizootic outbreak of foot-and-mouth disease in the United Kingdom (7), and since then, refined methods for "predictive" vaccination strategies have been proposed (8). It would be encouraging to see similar effort being put toward planning for human disease outbreaks.

Spurred by the perceived threat of biological terrorism, current epidemiologic efforts to prepare for outbreaks have taken two major forms. The first is the development of "syndromic surveillance" systems designed to detect the first anomalous cases and alert health officials that an outbreak is under way (9). While they are well suited to this purpose, such systems are not designed to provide much additional information once the outbreak has been identified. Other efforts have concentrated on modeling particular attack scenarios with different pathogens, particularly smallpox (10, 11) and anthrax (12, 13). These models provide valuable a priori guidance about the range of possible responses to given scenarios, but they require, of necessity, untestable assumptions about the size and nature of the outbreak; moreover, to some degree, each of these models gives results whose application is limited to the pathogen under consideration or pathogens that closely resemble it. As with syndromic surveillance, the usefulness of such models is greatest prior to or at the moment of an attack, but unless the models are designed to incorporate up-to-the-minute data on

the state of the outbreak, they will provide limited real-time assistance once an outbreak is under way.

Given the indisputable creativity of Nature and the potential creativity of biologically sophisticated evildoers, we cannot expect to have an appropriate a priori model for every outbreak. Therefore, development of tools for understanding and responding to a novel outbreak as it unfolds is a pressing task, and one that differs from those that have received the most epidemiologic attention thus far. Transmission models, as well as the spatial-temporal analysis tools used in syndromic surveillance, may be readily adapted to meet the need for analysis of and response to an outbreak in progress, but the adaptation requires additional work. The technique described by Wallinga and Teunis would be a valuable component of a suite of tools that should be made available to public health officials before the next important outbreak occurs.

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