EPIDEMIOLOGY

Modeling the SARS Epidemic

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As molecular biologists put the finishing touches to the genome sequence of a new coronavirus (*1*, *2*), epidemiologists were still contemplating a list of basic questions about how and why the disease caused by this coronavirus—severe acute respiratory syndrome (SARS)—has been spreading through populations in Asia and elsewhere. What is the period of time between infection and the onset of infectiousness? For how long do patients remain infectious? How many further infections will each patient produce? How many people will get infected during the epidemic? Will the current public health measures be enough to bring SARS under control? Is SARS here to stay? The epidemiology is difficult, in part because of the variable response by individuals, institutions, and governments to a new and dangerous disease. Nonetheless, a coherent picture of the epidemic is beginning to emerge. By piecing together preliminary data on the course of infection, and by making use of accumulating case notifications, two studies reported by Lipsitch *et al*. (*1*) on page 1966 and Riley *et al.* (*2*) on page 1961 of this issue give the first quantitative assessment of the epidemic potential of SARS, and the effectiveness of control measures. Their main message is that this new coronavirus is sufficiently transmissible to cause a very large epidemic if unchecked, but not so contagious as to be uncontrollable with good, basic public health measures.

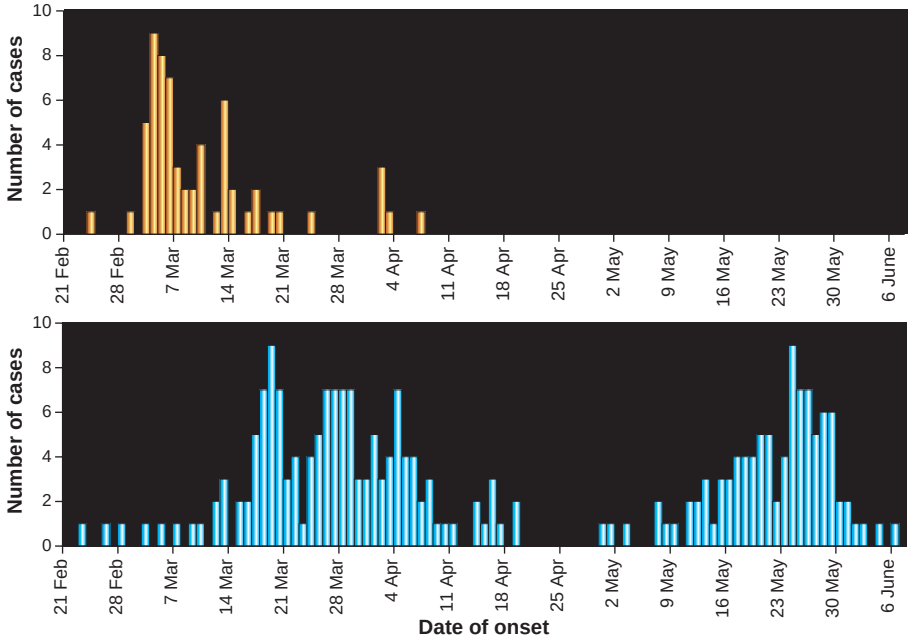
Both groups of researchers make use of dynamic mathematical models in which individuals progress through mutually exclusive classes containing susceptible, exposed (latent), infectious, and recovered (immune) individuals (SEIR). As inputs, both groups have used the available data for SARS, such as they are, on latent, incubation and infectious periods. Both have fitted their models to data describing the number of cases observed over time. Both calculate that the basic case reproduction number (R_0)—the fundamental epidemiological quantity that determines the potential for disease spread—is on the order of 2 to 4 for the Hong Kong epidemic. Both draw the conclusion that the SARS coronavirus, if uncontrolled, would infect the majority of people wherever it was introduced.

Both groups are also acutely aware that the available database is still fragile. Lipsitch *et al*. (*1*) therefore have used their model somewhat cautiously to explore the potential effectiveness of different control measures. Such control measures include early case detection, reducing the infectiousness of each patient (for example, by isolation or treatment with antiviral drugs), and quarantine for contacts. They conclude that any of these measures, on its own, could have a major impact on the epidemic. Even if these measures are implemented rather inefficiently, but in combination, the effect could still be large.

Riley *et al.* go boldly further. By examining data from Hong Kong they conclude, not just that the current public health measures could be effective, but that they actually have been effective. In their assessment, the Hong Kong epidemic was under control by early April 2003, in the sense that each case was, by then, failing to replace itself. The main reason for the success, they argue, is the reduction in the contact rate between infectious individuals and the rest of the population. Improved control measures in hospitals, quarantine of contacts of cases, and voluntary reduction in contacts in the population would all contribute to this effect. The increasingly rapid hospitalization of patients played a role but was not, they suggest, the main control mechanism.

These positive messages about the potential (Lipsitch *et al.*) or actual (Riley *et al.*) success of control measures are encouraging, but less than fully comforting. The mathematical models are complex, the data are poor, and some big questions remain. The first is about the accuracy of case reports. Underdiagnosis and misdiagnosis are almost inevitable during an outbreak of a new disease, and could affect measurements of the rate of epidemic spread. However, if the reporting of SARS improved as the epidemic proceeded, R_0 would be overestimated, and the impact of control measures therefore underestimated. Another possible bias goes in the same direction. As Lipsitch *et al.* point out, if each SARS case infects many other people, most of whom become immune without developing symptoms, we can expect a smaller epidemic for a given value of R_0. A combination of clinical and serological studies are needed to find out what proportion of infections progress to patent disease.

A more worrying problem is the evident heterogeneity in transmission. Estimates of R_0 get higher as one focuses more narrowly on subpopulations that are suffering the worst of



En route from local control to global eradication? SARS epidemics appear to have been contained in Vietnam (**top**) and Canada (**bottom**), though the resurgence of cases in Toronto during May warns of the need to maintain vigilance. [Sources: Ministry of Health Vietnam, Health Canada, and WHO]

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an outbreak. The extreme instances of SARS are the so-called superspreading events (SSEs), where single individuals have apparently infected as many as 300 others. Riley *et al.* treat them as exceptions, and exclude them from their calculations of R_0. But were these distinct epidemiological events arising, as they suggest, by different modes of transmission? Or do they simply represent the tail of some very skewed but continuous distribution of contact rates? By excluding SSEs, Riley *et al.* put the emphasis on the other, low-transmission events. And yet understanding and quantifying these SSEs is clearly vital for the containment of SARS. The general message here is that it is crucial to understand the variation around the estimated average R_0 because foci of higher transmission could lead to further local outbreaks. It is worth remembering that the rapid initial spread of SARS in Vietnam, Hong Kong, and Canada was in hospital wards.

Heterogeneity can affect the conclusions of these modeling studies in other ways. Riley *et al.* found that the contact rate fell as the Hong Kong epidemic proceeded, and attributed the fall to control measures. But a decline in the average contact rate might be due to spatial variation in transmission. Consider two linked epidemics in different subpopulations, one driven by a high contact rate and the other by a low contact rate. If we add the case data together from the two subepidemics and measure the average contact rate through time, it will be high early in the epidemic and low later in the epidemic. The fall in contact rate in this example is simply a consequence of heterogeneous transmission, and has nothing to do with control measures. The best evidence that a SARS outbreak is under control is that the number of cases continues to decline. Other indicators of progress include a fall in the time to hospitalization (*1*, *2*), and an increase in the proportion of cases occurring in quarantined contacts.

From a theoretical viewpoint, the question of SARS virus persistence threatens to be tricky. The models described by Lipsitch *et al.* and Riley *et al.* have no mechanism that allows for long-term persistence of the virus. Lipsitch *et al.* point out that the virus could persist with waning immunity, a mechanism that replenishes the susceptible pool, but it might actually persist under the assumption of permanent immunity. The question arises because other simple SEIR models, such as those for measles (*3*), have not easily been able to explain viral persistence and extinction.

The biggest question now about SARS is whether we can move from local control to global eradication (see the figure). On a practical level, measures to achieve this will include the early detection of new epidemics, before they overwhelm weak health services in poor countries. On a conceptual level, the next generation of SARS models may have to become yet more complex, including spatial and stochastic processes in more detail, animal reservoirs, seasonality, and different modes of transmission. These models will be hungry for the highest quality data.

References

1. M. Lipsitch *et al.*, *Science* **300**, 1966 (2003); published online 23 May 2003; 10.1126/science.1086616.
2. S. Riley *et al.*, *Science* **300**, 1961 (2003); published online 23 May 2003; 10.1126/science.1086478.
3. M. J. Keeling, B. T. Grenfell, *Science* **275**, 65 (1997).

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ASTRONOMY

Taking the Pulse of a Massive Star

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Similar to the seismic waves that provide information about Earth's inner structure, the self-excited vibrations of stars can be used to probe their interiors. It is this ability of "asteroseismology" to probe directly the interiors of stars that distinguishes it from all other astronomical techniques. For many years, the subtle variations in the brightness of the Sun, white dwarfs, and other stars with relatively low masses have provided important insights into their internal processes, origins, and futures. On page 1926 of this issue, Aerts *et al.* (*1*) extend the technique to a star that is much more massive than the Sun.

Asteroseismology has been successful for probing the Sun and white dwarfs because their periods of variation are quite short (about 5 minutes). Thus, a few weeks of observations are sufficient for identifying multiple periodicities in the star's vibrations. Through matching the observed periodicities with those predicted by stellar models, the internal structure of stars can be decoded.

Some larger and more massive stars show similar pulsations, but their periods are much longer, ranging from hours to months. Deciphering their oscillations therefore requires observations over longer time spans. But the potential payoff for patience is a detailed understanding of stars that are key to the chemical evolution of galaxies and the explosion of supernovae. Now, after accumulating over 20 years of data, Aerts *et al.* (*1*) have finally probed the interior of a star nearly 10 times as massive as the Sun during its core hydrogen-burning phase (see the figure).

In 2001, Gough (*2*) heralded the "birth of asteroseismology" in his commentary on one of the first reports on the seismology of a solar-type star (*3*). Observational asteroseismology of stars very different from our Sun has a much longer history. Over 35 years ago, Landolt (*4*) reported short-period vibrations of the white dwarf HL Tau 76. Today, more than 50 nonradially pulsating white dwarfs are known, and several have been subject to intense scrutiny by worldwide networks (*5*). Asteroseismic data have determined their compositional stratification, measured their rate of cooling, and even constrained their interior rotation rates (*6*). These results lay behind many advances in our understanding of the origin and evolution of white dwarfs.

Stars a bit more massive than the Sun, but still on the main sequence (see the figure), undergo multimode nonradial pulsations. These include the δ Scuti stars (*7*) and over 30 of the chemically peculiar Ap stars. Studies of these rapidly oscillating Ap (roAp) stars have begun to reveal details of the subsurface structure of their anomalously large magnetic fields, promising a road to the solution of this long-standing mystery (*8*).

Nine years ago, Kilkenny *et al*. discovered rapid oscillations of subdwarf B stars, which have ended their hydrogen-burning phase and, more recently, experienced the semi-explosive ignition of helium in their cores (see the figure) (*9*). At the time of this discovery, Charpinet *et al.* had just begun to explore theoretical models of subdwarf B stars and concluded that they should show pulsations, although, to their knowledge, none had yet been found (*10*). Since then, sophisticated models of subdwarf stars have been developed that explain many of the observed properties and shed some light on their origins.

The above activities, along with the efforts to probe the interior of the Sun (*2*), have focused largely on low-mass stars that are now, or were once, similar to the Sun.

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