bear a disproportionate burden (*15*). The social determinants of HIV and TB will need to be carefully monitored to assess the impact of COVID-19. The effect of the lockdown on the economy, including declining taxes, is also likely to negatively affect funding for HIV and TB programs, among many others.

New and ongoing research on HIV and TB prevention and treatment have been severely affected by the COVID-19 epidemic. At the initiation of the lockdown in South Africa, the National Health Research Ethics Committee suspended all medical research, including clinical trials. Research progress on these two conditions has also slowed because several of the country's AIDS and TB researchers are redirecting their efforts to COVID-19. However, COVID-19 research efforts have increased collaboration and created new approaches to speed up therapeutic and vaccine development and testing, which will likely have long-term benefits for medical research beyond COVID-19. Several countries in Africa have well-developed HIV and TB clinical trial infrastructure that could contribute to COVID-19 vaccine trials. Past investments in infectious disease training and research have generated handsome returns to the COVID-19 response, highlighting the importance of maintaining these investments in the future. ■

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CORONAVIRUS

Mathematical models to guide pandemic response

Models can be used to learn from the past and prepare for the future

By **C. Jessica E. Metcalf[1,2], Dylan H. Morris[1], Sang Woo Park[1]**

The ongoing coronavirus disease 2019 (COVID-19) pandemic has put mathematical models in the spotlight. As the theoretical biologist Robert May wrote: "the virtue of a mathematical model...is that it forces clarity and precision upon conjecture, thus enabling meaningful comparison between the consequences of basic assumptions and the empirical facts" (*1*). On page 413 of this issue, Walker *et al.* (*2*) use a mathematical model to study the impact and burden of COVID-19 across a wide range of socioeconomic and demographic settings, with a focus on low- and middle-income countries (LMICs). Their analyses show that limited health care capacity in LMICs could counterbalance the benefits of a generally younger population. Unless these countries control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, high disease burdens are likely. This work adds to a growing corpus of disease modeling designed to inform and guide the pandemic response.

Following the emergence of a previously unknown pathogen like SARS-CoV-2, mathematical models can be used to estimate parameters of pathogen spread, explore possible future scenarios, evaluate retrospectively the efficacy of specific interventions, and identify prospective strategies (see the figure). At every stage, communicating the scope of a model's aims and the uncertainty in its outputs is essential to ensure that models effectively inform public health policy.

In early 2020, it was important to assess the global risk posed by SARS-CoV-2 (*3*). Models provided estimates of R_0 (the average number of new infections caused by each infectious individual when no one in the population is immune) and the infection fatality ratio (IFR), clarifying ambiguities in the latter due to asymptomatic infections and delays between infection and death (*4*). Models also provided estimates of the incubation period (the time from infection to symptom onset), allowing public health agencies to decide on 14 days for quarantine of exposed individuals (*5*). However, this illustrates the need for careful communication: 14-day quarantine and isolation can effectively reduce disease spread on average, but some individuals may spread the disease beyond 14 days.

Building on growing knowledge of mechanisms and parameter estimates allowed researchers to explore possible future scenarios, including worst-case outcomes, and determine the implications for precautionary action (*6*, *7*). The results provided in Walker *et al.* fit within this class of analyses. Of note, the authors do not seek to provide a precise prediction of the epidemic trajectory, but rather to highlight key areas of concern for LMICs and evaluate mitigation measures.

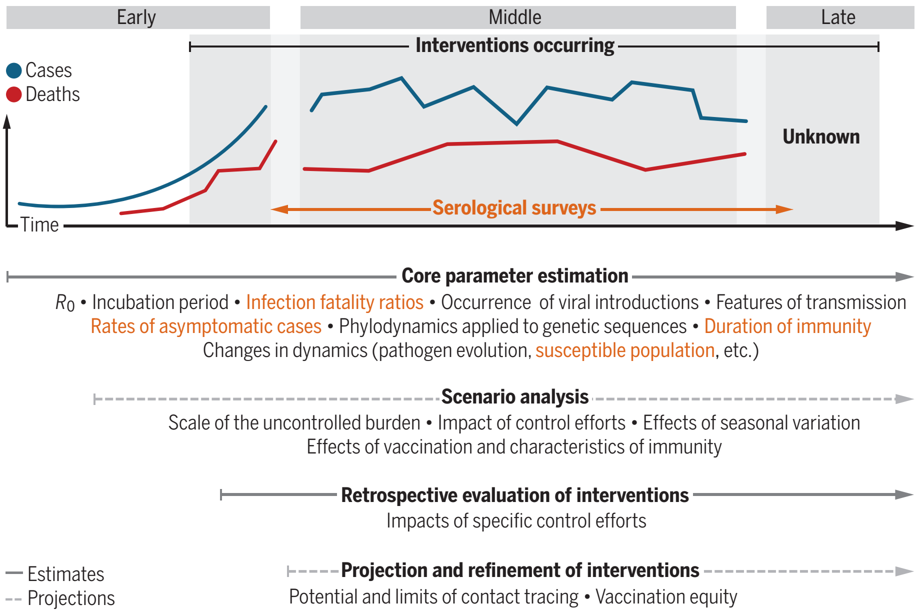
As initial pandemic responses are put in place and data accumulates, the focus shifts to retrospective estimates of the efficacy of particular strategies. Using statistical inference algorithms, researchers can fit core epidemiological models to case data and data on the timing and nature of control interventions. This allows them to account for unknown aspects of underlying transmission dynamics, to tease out the individual effects of interventions, and to quantify the degree of uncertainty in these estimates (*8*). The amount of mechanistic detail included in such a model depends on its aims. For example, accounting for age-dependent transmission and susceptibility is critical when building models for retrospective estimation of the impact of school closures (*9*), but that level of detail might be omitted when studying larger-scale interventions, such as contact tracing or bans on travel.

A key challenge of retrospective statistical modeling is that interventions are often entangled with each other, and with other processes. For example, several interventions may be implemented at once, making the individual impact of each intervention on transmission difficult or impossible to estimate. One solution is to compare multiple countries, regions, or municipalities that responded differently or at different times, but this approach is complicated by inevitable differences in their social and eco-

[1]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ, USA. [2]Princeton School of Public and International Affairs, Princeton University, Princeton, NJ, USA. Email: cmetcalf@princeton.edu

Modeling during an outbreak

An imagined pandemic time course shows cases (blue), deaths (red), and availability of serological data (orange). Modeling can estimate associated parameters of infection and intervention efficacy. Models can also make projections about the outbreak and the effects of interventions. Quantities that rely on, or are substantially enhanced by, serology are shown in orange.



GRAPHIC: N. CARY/SCIENCE

nomic characteristics. Such confounding factors can prevent mathematical models from providing "meaningful comparison between the consequences of basic assumptions and the empirical facts" (*1*). Robust estimates of the relative impact of different interventions could be obtained by introducing brief delays in tightening (or loosening) interventions in randomly chosen "treatment" locations. Randomization reduces the chance of systematic differences between "treatment" and "control" locations where no delay is implemented (such an approach may be ethical if the costs and benefits of interventions remain uncertain). After the delay, differences in new infections (or susceptibility) between the treatment and the control locations can be used as model inputs, and the effect of the intervention in question can be estimated (*10*). Such estimates could provide invaluable information: Knowing how well interventions work allows the determination of which costly restrictions can be loosened with least impact on transmission and case numbers.

Retrospective evaluations of specific interventions and detailed modeling efforts naturally build toward the identification of more targeted prospective strategies: Different countries, states, cities, or even workplaces vary in their capacity to respond to the pandemic and therefore require separate strategies for tightening or loosening interventions. Models can also help identify shortcomings in existing strategies, and explore opportunities for improvement or innovation. Although presymptomatic and asymptomatic transmission of COVID-19 has made contact tracing more difficult, modeling studies suggest feasibility of controlling spread through digital contact tracing, which allows for instantaneous identification of contacts (*11*). Many countries have started to develop and implement digital contact tracing apps, with varying degrees of success. However, digital contact tracing has been hampered by technical and ethical challenges, including the ability to accurately determine the proximity between individuals and to store such information in a privacy-preserving way. Thus, although models are valuable tools for testing new ideas, they must be accompanied by thorough consideration of practicalities.

Prospective modeling not only informs strategy but also guides data collection. Registers of confirmed COVID-19 cases may miss asymptomatic infections, which can bias estimates of disease severity and IFR. In principle, serological (antibody) measurements provide a more reliable indication of whether an individual has been infected. Estimates of the IFR and other key parameters can thus be improved by combining serological surveys with data on cumulative infection-associated mortality. But if serological surveys are deployed in low incidence populations, true positive tests will be a minority of all tests, and estimates of cumulative incidence will be too uncertain to produce an informative estimate of the IFR. Epidemiological models could help reduce this uncertainty.

Although valuable, mathematical models must be one facet of a diverse scientific response to a pandemic. During the early phases, models helped establish the scale of global risk and motivated action (*3*). But arguably the most critical evidence of severity was empirical data from Wuhan, Iran, and Northern Italy. Recently, establishing how best to loosen distancing restrictions has become a central challenge. Modeling can capture the benefits of specific interventions in terms of reduced transmission, but say nothing about their relative economic and psychological costs. Measurement of these costs is important to identifying which interventions work best (*10*) and which are most costly; models that encompass both epidemiological and economic aspects (*12*) are needed.

What is next in the deployment of models? Perhaps the greatest conceptual success of infectious disease modeling was revealing that because the spread of infection depletes susceptible individuals, feedbacks are inherent to disease dynamics and can produce unexpected outcomes, including multiannual cycles of outbreaks. Yet, despite the devastating burden that COVID-19 has imposed so far, most of the world is still susceptible to SARS-CoV-2 infection. Most countries have yet to see sufficient depletion of susceptibility to meaningfully reduce infection spread, but such effects are likely to shape the future. Models projecting into this future have evaluated policy scenarios (*13*) and assessed the potential impact of seasonal variation in transmission (*14*). Notably, the immunological details on which these models rely (duration of immunity, whether immunity blocks transmission or prevents disease after infection, etc.) remain unclear. Models are one tool among many for tackling the pandemic, but they are perhaps the best framework for grappling with these possible futures. ■

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