Wrong but Useful — What Covid-19 Epidemiologic Models Can and Cannot Tell Us

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Amid enormous uncertainty about the future of the Covid-19 pandemic, epidemiologic models are critical planning tools for policymakers, clinicians, and public health practitioners. Some models with apparently conflicting conclusions have received substantial press coverage, giving the impression that mathematical models are in general unreliable or inherently flawed. But infectious disease modeling is an expansive field with a long history, encompassing a range of methods and assumptions that are not necessarily directly comparable, or even designed for the same purpose (see box).

Covid-19 modeling studies generally follow one of two general approaches that we will refer to here as forecasting models and mechanistic models. Although there are hybrid approaches, these two model types tend to address different questions on different time scales, and they deal differently with uncertainty.

Forecasting models are often statistical in nature, fitting a line or curve to data and extrapolating from there — like seeing a pattern in a sequence of numbers and guessing the next number, without incorporating the process that produces the pattern. Well-constructed statistical frameworks can be used for short-term forecasts, using machine learning or regression, for example, to crunch epidemiologic data from the past or a different location and project SARS-CoV-2 cases into the future. These models yield quantitative projections that policymakers may need in the short term to allocate resources or plan interventions.

The original versions of the controversial model from the Institute for Health Metrics and Evaluation (IHME) fell into this category, approximating the shape of the epidemic curve from outbreaks in China and Italy and applying it elsewhere (see table). Since purely statistical approaches don't account for how transmission occurs, they are generally not well suited for long-term predictions about epidemiologic dynamics (such as when the peak will occur and whether resurgence will happen) or for inference about intervention efficacy.[1] Several forecasting models therefore limit their projections to one week or a few weeks ahead.

Mechanistic models, like the Susceptible–Exposed–Infectious–Recovered frameworks, mimic the way SARS-CoV-2 spreads and can be used to forecast or simulate future transmission scenarios under various assumptions about parameters governing transmission, disease, and immunity. Unlike purely statistical models, mechanistic approaches include important nonlinear feedback — the more people become infected, the faster disease spreads. Because these models reflect the underlying transmission process, the disease-specific parameters driving it can be modified to test how the pandemic may change under various assumptions about the disease and implementation of control measures.

Mechanistic modeling is one of the only ways to explore possible long-term epidemiologic outcomes. For example, the model

Five Questions to Ask about Model Results.

1. What is the purpose and time frame of this model? For example, is it a purely statistical model intended to provide short-term forecasts or a mechanistic model investigating future scenarios? These two types of models have different limitations.
2. What are the basic model assumptions? What is being assumed about immunity and asymptomatic transmission, for example? How are contact parameters included?
3. How is uncertainty being displayed? For statistical models, how are confidence intervals calculated and displayed? Uncertainty should increase as we move into the future. For mechanistic models, what parameters are being varied? Reliable modeling descriptions will usually include a table of parameter ranges — check to see whether those ranges make sense.
4. If the model is fitted to data, which data are used? Models fitted to confirmed Covid-19 cases are unlikely to be reliable. Models fitted to hospitalization or death data may be more reliable, but their reliability will depend on the setting.
5. Is the model general, or does it reflect a particular context? If the latter, is the spatial scale — national, regional, or local — appropriate for the modeling questions being asked and are the assumptions relevant for the setting? Population density will play an important role in determining model appropriateness, for example, and contact-rate parameters are likely to be context-specific.

Referenced Covid-19 Pandemic Models.	
Model	**Source**
IHME COVID-19 Predictions	https://covid19.healthdata.org
Los Alamos National Laboratory COVID-19 Confirmed and Forecasted Case Data	https://covid-19.bsvgateway.org
University of Geneva and Swiss Data Science Center, COVID-19 Epidemic Forecasting	https://renkulab.shinyapps.io/COVID-19-Epidemic-Forecasting
Ferguson et al., Imperial College Covid-19 Response Team, Report 9	www.imperial.ac.uk/media/imperial-college/medicine/mrc-gida/2020-03-16-COVID19-Report-9.pdf
Kissler et al., Projecting the transmission dynamics of Covid-19 through the postpandemic period	https://doi.org/10.1126/science.abb5793
Aleta et al., Modeling the impact of social distancing, testing, contact tracing and household quarantine on second-wave scenarios of the COVID-19 epidemic	https://cosnet.bifi.es/wp-content/uploads/2020/05/main.pdf
Hellewell et al., Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts	https://doi.org/10.1016/S2214-109X(20)30074-7

from Ferguson et al. that has been used to guide policy responses in the United States and Britain examines how many Covid-19 deaths may occur over the next 2 years under various social distancing measures. Kissler et al. ask whether we can expect seasonal, recurrent epidemics if immunity against SARS-CoV-2 functions similarly to immunity against the milder coronaviruses that we transmit seasonally. In a detailed mechanistic model of Boston-area transmission, Aleta et al. simulate various lockdown "exit strategies." These models are a way to formalize what we know about viral transmission and explore possible futures of a system that involves nonlinear interactions, something that is almost impossible to do using intuition alone.

Model accuracy is constrained by our knowledge of the virus, however. With an emerging disease such as Covid-19, many biologic features of transmission are hard to measure and remain unknown. The most obvious source of uncertainty, affecting all models, is that we don't know how many people are, or have been, infected. Ongoing issues with virologic testing mean that we are certainly missing a substantial number of cases, so models fitted to confirmed cases are likely to be highly uncertain (as demonstrated by Lu et al.).[2] The problem of using confirmed cases to fit models is further complicated by the fact that the fraction of cases that are confirmed is spatially heterogeneous and time-varying. Covid-19 hospitalizations and deaths are more reliable data — though they may still underestimate disease burden — but assumptions must then be made about how they relate to cases in the community.[3]

In fact, many parameters associated with Covid-19 transmission are poorly understood. The resulting model uncertainty is not always calculated or reported in a standardized way. Consumers of epidemiologic results should know that confidence intervals presented in figures or dashboards may not adequately capture the model's many uncertain aspects; indeed, usually only one kind of uncertainty is presented, which may create an inflated sense of confidence in the results. In statistical models, the uncertainty of the prediction is generally presented as statistically computed prediction intervals around an estimate — as in the IHME model. Given that what happens a month from now will depend on what happens in the interim, the estimated uncertainty should increase as you look further into the future — as shown in the Los Alamos National Laboratory model, which incorporates the uncertainty of the timing of epidemic growth as well as measurement uncertainty.

In mechanistic models, uncertainty in a key epidemiologic parameter or set of parameters — the duration of infectiousness, for example — may be presented as a range around a mean trajectory, reflecting simulations across the plausible or measured values of a parameter, or as separate simulations. These sensitivity analyses provide insight into how robust the model findings are to particular inputs. Both the mean trajectory and the upper and lower bounds may be useful in different ways — for example, we may be interested in knowing the maximum number of cases that could reasonably result from what we

know about a particular parameter. Confidence intervals from a mechanistic model may also represent the results under a single set of parameters but across multiple simulations with randomness or stochastic processes included — as in the Hellewell and Aleta models of intervention efficacy. Less often presented, but equally important, is the uncertainty associated with the model structure itself — the extent to which our description of transmission reflects the truth about how the virus spreads. Together, these uncertainties reflect data gaps and inherent uncertainties about future human behavior and interventions.

Three model parameters in particular limit our ability to predict the future of the Covid-19 pandemic. First, we remain uncertain about the extent of protective immunity.[4] If SARS-CoV-2 infection produces strong, long-lasting immunity, then the risk of recurrent, annual outbreaks is lower. If there is waning, only partially protective, or no immunity, then epidemics may recur frequently or seasonally, as the Kissler model explores. Most models (such as the Ferguson, Aleta, and Hellewell models) assume that immunity completely protects against infection for at least a year or two — often the duration of the simulation. Until we have better data on antibody kinetics and protection against reinfection, models will be useful for exploring possibilities rather than making strong predictions about longer-term disease dynamics.

An audio interview with Dr. Buckee is available at NEJM.org

Second, the extent of transmission and immunity among people with no or minimal symptoms (including children) plays an important role in predictions: if there is very little asymptomatic infection, we are probably still far from the epidemic peak. If there is a lot of asymptomatic transmission, there are many unobserved cases, but we may be further along the epidemic curve than we thought — assuming some protective immunity. Carefully designed serologic surveys will clarify this issue, but meanwhile models vary in their assumptions, primarily affecting estimates about the peak's timing and the epidemic's duration.

Third, it remains extremely challenging to measure and model contact rates between susceptible and infectious people, not only under physical distancing policies but also in various reopening scenarios. Models must make assumptions about how people interact with others, and they often do so on the basis of diary studies conducted in different countries at different times.[5] Contact rates will be hard to predict during such a rapidly changing crisis and are therefore a key source of model uncertainty.

In all mechanistic models, epidemics can die away in two ways: either the disease runs out of fuel because there are no longer enough susceptible people to infect, or something changes to slow or halt transmission — for example, the number of contacts is reduced by dramatic physical distancing interventions. Since this latter mechanism slows the spread of disease without changing the number of people at risk, Covid-19 models agree that almost all populations are at risk of disease resurgence when societies reopen. Recent serosurveys indicate that even where this pandemic has been most severe, we remain far from starving it of susceptible hosts and must continue to control spread with contact-reduction measures.

Unlike other scientific efforts, in which researchers continuously refine methods and collectively attempt to approach a truth about the world, epidemiologic models are often designed to help us systematically examine the implications of various assumptions about a highly nonlinear process that is hard to predict using only intuition. Models are constrained by what we know and what we assume, but used appropriately and with an understanding of these limitations, they can and should help guide us through this pandemic.

Disclosure forms provided by the authors are available at NEJM.org.

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