

Modeling infectious disease dynamics

The spread of the coronavirus SARS-CoV-2 has predictable features

By Sarah Cobey

The emergence of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) has offered the world a crash course in modern epidemiology, starting with lessons in case detection and exponential growth. It has also reminded scientists of the challenges of communicating effectively during uncertainty. The current pandemic has no parallel in modern history, but the new virus is following rules common to other pathogens. Principles derived from influenza virus infections and other infectious diseases offer confidence for two predictions: SARS-CoV-2 is probably here to stay, and the high transmission rate will continue to force a choice between widespread infection and social disruption, at least until a vaccine is available. The difficulty of this choice is amplified by uncertainty, common to other respiratory pathogens, about the factors driving transmission. This pandemic presents a broader opportunity to interrogate how to manage pathogens.

Modern history is riddled with pandemics that have shaped the study of infectious disease. In the past 200 years, at least seven waves of cholera, four new strains of influenza virus, tuberculosis, and HIV have spread across the world and killed at least 100 million people. Virtually all transmissible diseases continue to evolve and transmit globally once established, blurring the conceptual boundaries between a pandemic and a particularly bad flu season. More than a century studying the size and timing of outbreaks, including which interventions are effective in stopping them, has given rise to a well-founded quantitative and partially predictive theory of the dynamics of infectious diseases.

An epidemic dies out when an average infection can no longer reproduce itself. This occurs when a large fraction of an infected host's contacts are immune. This threshold—between where an infection can and cannot reproduce itself—defines the fraction of the population required for herd immunity. It can be calculated precisely if the epidemiology of the pathogen is well known, and is used to guide vaccination

strategies. Herd immunity is constantly eroded by the births of new, susceptible hosts and sometimes by the waning of immunity in previously infected hosts. The durability of immunity to SARS-CoV-2 is not yet known, but births will promote virus survival. Thus, like other transmissible pathogens, SARS-CoV-2 is likely to circulate in humans for many years to come.

If sufficiently fast and widespread, declines in the availability of susceptible individuals or the transmission rate can drive pathogens extinct. For example, in 1957 and 1968, resident seasonal influenza virus strains died out because cross-immunity between these strains and emerging pandemic strains reduced the number of susceptible individuals (1). Four lineages of coronaviruses already circulate in humans.

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The genetic differences between these viruses and SARS-CoV-2 and its rapid spread suggest that they do not compete with one another for susceptible hosts, in contrast to influenza virus. Current interventions, such as social distancing, aim to reduce transmission of SARS-CoV-2. Human behavior can have both subtle and obvious effects on transmission. For example, the schedule of school holidays, which modulate contacts between susceptible and infected children, influenced the timing of historic measles epidemics in England and Wales (2).

Regional efforts to drive SARS-CoV-2 extinct may not be successful in the long term owing to seasonal factors that influence susceptibility or transmission. Influenza viruses flow from tropical to temperate regions and back in each hemisphere's respective winter. Within tropical and subtropical populations, influenza viruses move less predictably among interconnected cities and towns (3). These desynchronized dynamics limit opportunities for global population declines. SARS-CoV-2 and influenza virus are epidemiologically similar in that they are both highly transmissible by the respiratory route, they both cause acute infections, and they both infect and are transmitted by adults. This suggests that in

the absence of widespread, carefully coordinated and highly effective interventions to stop SARS-CoV-2 transmission, the virus could persist through similar migratory patterns, assuming it is influenced by similar seasonal forces.

This assumption is tentative because exactly why most respiratory pathogens exhibit prevalence peaks in the winter of temperate regions is a long-standing puzzle. Experiments in ferrets showed that lower absolute humidity increases influenza virus transmission rates, and recent experiments showed higher humidity improves immune clearance of influenza virus in the lungs of mice (4, 5). But although drops in temperature and humidity are correlated with the onset of influenza seasons in the United States (6), annual seasonal influenza epidemics often start in the muggy southeast of the United States, not in the colder and dryer north. There is no clear evidence suggesting a lower incidence of influenza virus infection in tropical compared with temperate populations. Disentangling the environmental from the endogenous immune drivers of infectious disease dynamics has been a long-standing statistical challenge (7).

The early spread of SARS-CoV-2 has revealed critical information about the potential size of the pandemic, if it were allowed to grow unchecked. This information has mathematical foundations developed from modeling other infectious diseases (see the figure). The total number of people infected in a population is determined by the intrinsic reproductive number, R_0 . This number is the expected number of secondary cases caused by an index case in an otherwise susceptible population. Equivalently, R_0 can be expressed as the transmission rate divided by the rate at which people recover or die. It is most accurate to describe R_0 in reference to a pathogen and host population, because the number is partially under host control. It also partly determines the average long-term prevalence in the population, assuming new susceptible individuals prevent the disease from dying out. As an epidemic progresses and some of the population becomes immune, the average number of secondary cases caused by an infected individual is called the effective reproductive number, R_t .

There are thus two major reasons to reduce SARS-CoV-2 transmission rates. In populations with access to advanced medical

Department of Ecology & Evolution, University of Chicago, Chicago, IL, USA. Email: cobey@uchicago.edu

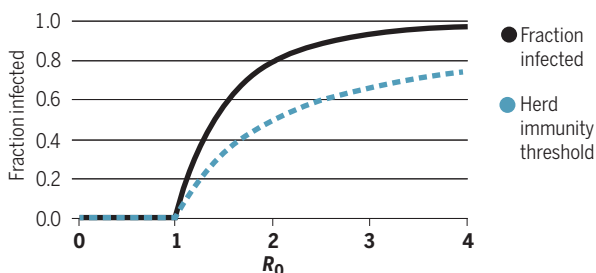
care, lowering the transmission rate can decrease mortality by increasing the fraction of severe cases receiving treatments, such as mechanical ventilation. Interventions that reduce transmission also reduce the total number of people who become infected. As a recent report warns (8), dramatic interventions to reduce R_t might not substantially change the long-term, total number of infections if behavior later returns to normal. Thus, reductions in transmission must be sustained to lower the fraction of the population that becomes infected. The high costs of current interventions underscore a need to quickly identify the most helpful measures to reduce transmission until healthcare capacity can be increased and immunity boosted through vaccination.

Comparing populations' interventions to the severity of their epidemics is one way to learn what works. Comparisons of U.S. cities' responses to the first wave of the 1918 H1N1 influenza pandemic demonstrated that social distancing—including early decisions to close schools, theaters, and churches—reduced prevalence and mortality (9, 10). Similarly, large differences are apparent in the level of SARS-CoV-2 control between countries and might be traceable to differences in diagnostic testing, contact tracing, isolation of infected individuals, and movement restrictions. Testing for SARS-CoV-2-specific antibodies, a marker of infection, in blood samples will provide important confirmation of the true numbers of people infected in different areas and can improve estimates of the effects of interventions and the potential number of future cases.

Mathematical modeling and historical influenza pandemics provide a warning about comparing the effects of interventions in different populations. A rapid decline in coronavirus disease 2019 (COVID-19) cases or a small springtime epidemic might be taken as evidence that interventions have been especially effective or that herd immunity has been achieved (11). But simple models show that epidemic dynamics become deeply unintuitive when there is seasonal variation in susceptibility or transmission, and especially when there is movement between populations (11). For SARS-CoV-2, like influenza virus, the shape of seasonal variation is uncertain. Linear correlations could lead to spurious causal inferences about which interventions work best and should not be overinterpreted. Previous influenza pandemics demonstrated regional variability in the number, timing, and severity of their pandemic waves (1, 12). Differences between populations in their preexisting

Potential pandemic size and herd immunity

The fraction of the population that becomes infected with a transmissible disease in a simple epidemic model increases nonlinearly with the intrinsic reproductive number, R_0 , and will exceed the threshold for herd immunity. R_0 is the expected number of cases caused by an index case. Interventions can reduce R_0 , the total fraction of the population infected, and the threshold for herd immunity.



immunity and seasonal factors could have contributed to this variation, even before interventions are accounted for. Such differences also caution against direct comparisons between prior pandemics and the SARS-CoV-2 pandemic, without mathematics as an intermediary.

Given uncertainty in the transmission dynamics of SARS-CoV-2 and high certainty in its virulence, it is understandable that early responses have relied on blunt interventions, such as movement bans and closures, to save lives. The scientific challenge now is to identify, through inference and simulation, measures that could provide as-good or better protection with less social cost. The effectiveness of targeted, less socially disruptive control measures depends critically on the biological parameters of the pathogen (13). Containing the SARS coronavirus in 2003 required intensive contact tracing coordinated by multiple countries. Ultimately, 8098 cases were identified, which probably represented the majority of people infected with the virus. Control was feasible because the onset of infectiousness coincided with the onset of symptoms, which were consistently severe. With SARS-CoV-2, transmission can occur before symptoms develop, and symptom profiles are heterogeneous. Substantial asymptomatic and presymptomatic transmission make containment-based interventions, especially those depending on recognition of early symptoms or limited testing, more challenging and potentially infeasible alone.

A complementary and urgent task is to identify if any subpopulations or settings contribute disproportionately to transmission and to target interventions to them. For example, school-age children tend to drive influenza virus transmission in communities, although they are underrepresented among severe clinical cases and deaths (14). Interventions to reduce influenza virus infections in children have yielded disproportional

tionate effects in reducing infections in adults. Identifying opportunities to magnify the indirect effects of interventions is particularly important if some, such as vaccination, are less effective or unavailable in vulnerable (e.g., older) populations. Population-level serological studies to estimate past infections, accompanied by household studies to measure the duration and amount of viral shedding in different people, can help identify the corresponding populations for SARS-CoV-2. These populations could shift over time if immunity to the virus is long lasting.

This pandemic illuminates choices in managing respiratory pathogens. Most people do not have access to

or opt out of the seasonal influenza virus vaccine, although influenza virus kills more than half a million people per year globally. It is not widely communicated that a typical infectious case of influenza virus does not have a fever (15), which could promote spread by people who think they only have a cold (caused by rhinoviruses, seasonal coronaviruses, and others). Populations have long differed in their formal and informal support for infection control, for example, whether people who feel ill wear face masks or can easily stay at home. The consequences are somewhat predictable. SARS-CoV-2 is an evolving virus, and whether this evolution will erode the effectiveness of a future vaccine is currently unknown. The choices faced now will continue to matter. ■

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