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Will SARS-CoV-2 become endemic?

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Reinfection, seasonality, and viral competition will shape endemic transmission patterns

Reinfection, in which an individual is subject to multiple, distinct infections from the same virus species throughout their lifetime, is a salient feature of many respiratory viruses. Indeed, the persistence and ubiquity in human society of common respiratory viruses—including influenza viruses, respiratory syncytial virus (RSV), rhinovirus, and the endemic coronaviruses—are largely due to their ability to produce repeat infection. Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic, a critical concern has been whether humans will experience reinfections with this pathogen, which might enable it to become endemic.

Typically, following an initial infection, the human adaptive immune system develops a suite of defenses, including memory B lymphocytes capable of producing neutralizing antibodies targeted to bind to that particular pathogen, and memory T lymphocytes that help regulate immune responses and induce death of infected cells. These adaptive immune components, particularly B cells, can produce sterilizing immunity in which the pathogen, if reintroduced to the host, is prevented from replicating within the body.

However, for many viruses, a number of processes, particularly insufficient adaptive immune response, waning immunity, and immune escape, can undermine or circumvent the sterilizing character of immunity and allow subsequent reinfection. In the first instance, an initial infection with a particular agent may not engender an adaptive immune response sufficient to confer sterilizing immunity. Serological studies indicate that most SARS-CoV-2 infections, regardless of severity, induce development of some specific antibodies (*1*); however, despite encouraging results from experimental vaccination of primates, it remains unclear whether those antibodies are sufficient to provide long-term effective protection or if other adaptive immune components are present and functional. Furthermore, immune response to SARS-CoV-2 infection is heterogeneous, with individuals who experience asymptomatic infections manifesting a weaker immune response than those experiencing more severe disease (*1*). It is possible that some individuals never develop sterilizing immunity following infection with SARS-CoV-2, or that multiple exposures will be needed for affinity maturation and development of long-lasting protection.

Waning immunity, in which the initial adaptive immune response is robust and protective but dissipates over time, leaving the host vulnerable to reinfection, may also undermine sterilizing immunity. Immune escape is a third process that can facilitate reinfection, in particular by viruses. Here, a virus, during its continued serial passage through a host population, accumulates point mutations. This accumulation, termed antigenic drift, may lead to conformational changes of viral surface proteins that disrupt the binding of antibodies previously generated against an earlier variant. Immune escape is a consequence of this antigenic drift that enables reinfection through the evasion of adaptive protection.

The time scales of waning immunity and immune escape differ by pathogen and have yet to be defined for SARS-CoV-2. Thus far, the mutation rate of the SARS-CoV-2 genome appears to be slower than that of influenza viruses. This lower rate may be a consequence of proof-reading during replication, which is exclusive to coronaviruses among RNA viruses. Conversely, human coronavirus (HCoV) OC43 is highly variable, particularly in genes encoding surface proteins such as the spike protein, indicating that considerable diversification can occur. To date, some evidence of SARS-CoV-2-specific antibody waning has been captured in a longitudinal study (*2*), and a few verified repeat SARS-CoV-2 infections have been documented (*3*). Although reinfections can occur, the number of reinfection cases is not currently sufficient to generalize the duration of immunity at population scales or the severity of repeat infection. Whether reinfections will be commonplace, how often they will occur, how contagious reinfected individuals will be, and whether the risk of severe clinical outcomes changes with subsequent infection remain to be understood.

Insight from other respiratory viruses points to the possibility of reinfection with SARS-CoV-2. Naturally acquired infections with the four endemic HCoVs (OC43, HKU1, 229E, and NL63) indicate that reinfections with the same HCoV type are common within 1 year (*4*); sequential infections with the same influenza virus strain can occur in less than 2 years (*5*); and reinfections of adults with RSV within 1 year have also been documented (*6*). By contrast, more pathogenic viruses that induce systemic effects on the host

may elicit a longer-lasting adaptive immune response. For example, longitudinal immune profiles from SARS survivors showed a stronger immune response with neutralizing antibodies persisting for 2 to 5 years (*7*). However, it could not be confirmed if and for how long this response conferred immunity because the SARS outbreak lasted less than 1 year.

In addition to duration of protective immunity, the long-term effects of SARS-CoV-2 on humans will depend on the severity of reinfection. Sequential infections with influenza virus have been associated with less severe symptoms (*8*), whereas no association between reinfection and symptom severity was found in recurring endemic HCoV infections (*4*). In addition, for other viruses (e.g., RSV and dengue), suboptimal binding of naturally induced or vaccine-induced antibodies can enhance infection severity upon subsequent exposure, a phenomenon called antibody-dependent enhancement (ADE) (*9*). To date, responses among the few patients with verified SARS-CoV-2 reinfection have been heterogeneous with one apparent repeat infection requiring hospitalization. Thus, thorough serological and prospective studies are needed to determine whether ADE manifests among SARS-CoV-2 infections, either because of prior homologous infection or cross-reactive antibodies from other HCoVs. This will have particular relevance for vaccines and convalescent plasma therapy.

Should reinfection prove commonplace, and barring a highly effective vaccine delivered to most of the world's population, SARS-CoV-2 will likely become endemic (*10*). The typical time scale at which individuals experience reinfection and seasonal differences in transmissibility will determine the pattern of endemicity. Outside the tropics, the incidence of many common respiratory virus infections increases during particular times of the year. This phase-locked behavior is due to accumulated susceptibility to reinfection, which increases over time because of immune escape and waning immunity, and seasonal modulation of virus transmissibility derived from environmental conditions, changing behavior (e.g., mixing indoors in cold weather), or altered immune function. For example, influenza incidence is greatest during winter in temperate regions. Once expelled from an infectious host, the influenza virus appears to be more stable in low-humidity conditions (*11*), which are prevalent both indoors and outdoors during winter. Further, during colder months, people spend more time indoors and school is in session, which may facilitate transmission, and shorter days and less sunlight exposure may suppress immune function.

The endemic HCoVs (OC43, HKU1, NL63, and 229E) all exhibit a seasonality in temperate regions, similar to influenza viruses (*12*). Consequently, numerous studies have sought to determine whether conditions such as temperature, sunlight, humidity, ozone, and pollution affect SARS-CoV-2 viability and transmissibility. The results are not currently conclusive, although it appears that environmental conditions, such as sunlight and humidity, may modulate SARS-CoV-2 transmissibility—not enough to preclude transmission during the first waves of the pandemic when immunity is generally low—but perhaps sufficient to favor seasonal, phase-locked transmission during winter in temperate regions, similar to influenza virus, once immunity increases.

Like the 2009 influenza pandemic, the continued circulation by SARS-CoV-2 following this initial pandemic period will manifest as a function of reinfection rates, vaccine availability and efficacy, and social, immune, and innate factors that modulate virus transmissibility (see the figure). In addition, the cyclic persistence of SARS-CoV-2 in human populations may be affected by ongoing opportunities for interaction with other respiratory pathogens.

Co-circulating respiratory viruses may interfere with one another while competing for the same resources, and their interactions have been studied at population and individual levels, in reconstructed human tissues and in animal models. The outcomes in individuals of serial exposure to different viruses vary and in general appear to depend on the order and timing of exposures. Many studies have documented evidence of negative interference between viruses caused by short-lived (days) protection elicited from the first infection. Host antiviral interferon responses are often regarded as the main mechanism by which interference manifests; that is, as a result of a recent infection, the host cells up-regulate the synthesis of interferons, potentially inhibiting a secondary infection. Even though it is short-lived, this effect can be strong at population scales and temporarily reduce the prevalence of a virus or shift the timing of its circulation. For example, it is hypothesized that a large summer 2009 rhinovirus outbreak delayed pandemic influenza virus emergence in Europe (*13*).

The clinical and population-scale interactions of SARS-CoV-2 with other respiratory viruses, particularly influenza viruses and other HCoVs, need to be monitored in the coming years. To date, some SARS-CoV-2 coinfections have been documented (*14*), including coinfections with influenza and RSV; however, testing for multiple pathogens has not been routinely carried out, and the scarce data that do exist, mostly for older adults with high rates of preexisting medical conditions, do not support a definitive evaluation of coinfection likelihood or severity. Studies prior to the pandemic indicate that simultaneous infections with multiple respiratory viruses are not uncommon but are not associated with increased disease severity.

At the population scale, a possible overlap between influenza and SARS-CoV-2 outbreaks poses a serious threat to

public health systems. Seasonal influenza produces millions of severe infections worldwide every year, and this additional burden could be catastrophic on systems already challenged by the COVID-19 pandemic. Conversely, given similar modes of transmission among different respiratory viruses, the nonpharmaceutical interventions adopted to mitigate SARS-CoV-2 transmission (personal protective equipment, social distancing, increased hygiene, limited indoor gatherings) may reduce the magnitude of seasonal influenza outbreaks. Such increased use of nonpharmaceutical measures, and possible virus interference, could be responsible for the reduced incidence of influenza during the recent winter of the Southern Hemisphere (*15*).

The phases and magnitudes of different outbreaks in a multipathogen system are dictated by the interaction dynamics between those pathogens: from large overlapping phases when pathogens enhance one another's transmission, to complete inhibition of a strain by the neutralizing cross-reactivity of a more transmissible one (*9*). Several postpandemic scenarios for SARS-CoV-2 have been modeled (*10*), depending on the duration of immunity and cross-immunity between SARS-CoV-2 and the other betacoronaviruses (OC43 and HKU1). A duration of immunity similar to that of the other betacoronaviruses (~40 weeks) could lead to yearly outbreaks of SARS-CoV-2, whereas a longer immunity profile, coupled with a small degree of protective cross-immunity from other betacoronaviruses, could lead to apparent elimination of the virus followed by resurgence after a few years. Other scenarios are, of course, possible, because there are many processes at play and much that remains unresolved.

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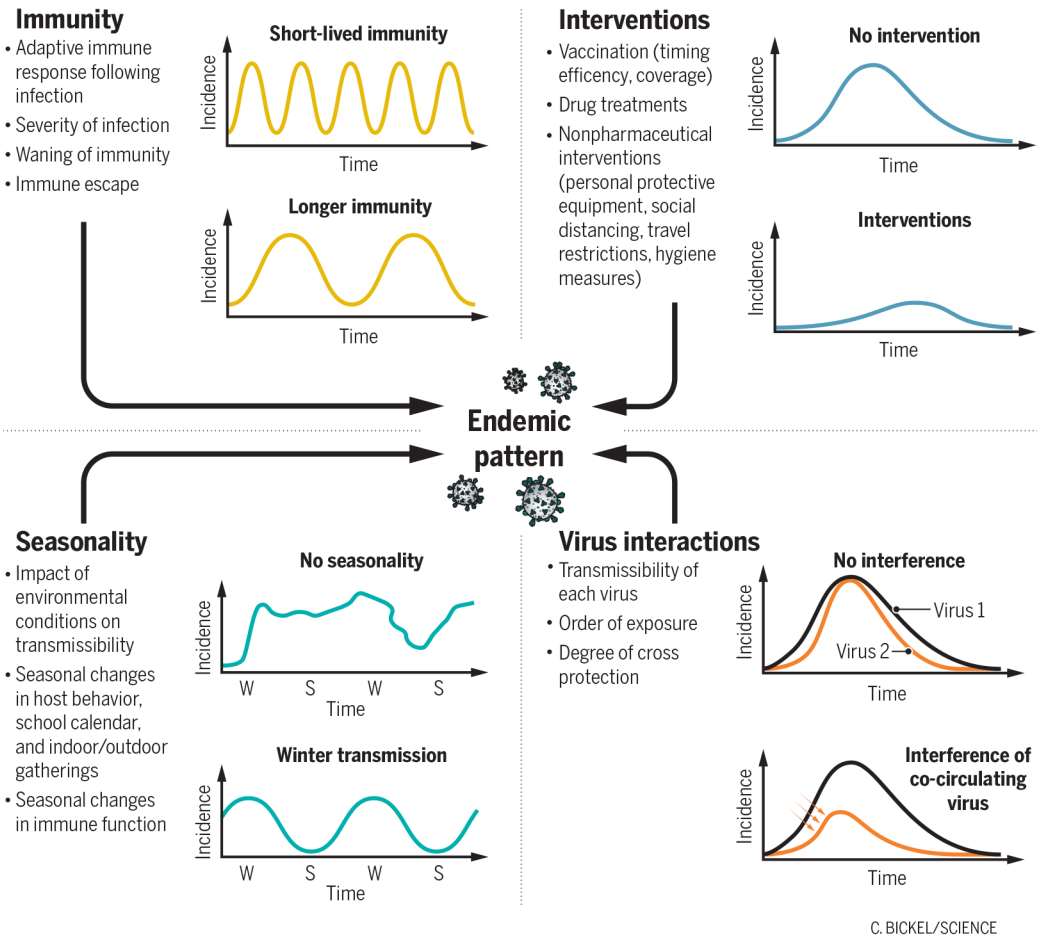
Factors influencing postpandemic transmission of SARS-CoV-2

Rates of repeat infection, factors modulating seasonality, competition with other circulating respiratory viruses, and control measures will influence the endemic pattern of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission.



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