Immunological characteristics govern the transition of COVID-19 to endemcity

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We are currently faced with the question of how the severity of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may change in the years ahead. Our analysis of immunological and epidemiological data on endemic human coronaviruses (HCoVs) shows that infection-blocking immunity wanes rapidly but that disease-reducing immunity is long-lived. Our model, incorporating these components of immunity, recapitulates both the current severity of SARS-CoV-2 infection and the benign nature of HCoVs, suggesting that once the endemic phase is reached and primary exposure is in childhood, SARS-CoV-2 may be no more virulent than the common cold. We predict a different outcome for an emergent coronavirus that causes severe disease in children. These results reinforce the importance of behavioral containment during pandemic vaccine rollout, while prompting us to evaluate scenarios for continuing vaccination in the endemic phase.

Humans have regularly been threatened by emerging pathogens that kill a substantial fraction of all people born. Recent decades have seen multiple challenges from acute virus infections, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Hendra, Nipah, and Ebola. Fortunately, all were locally contained. When containment is not immediately successful, as is likely for the novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2), we need to understand and plan for the transition to endemcity and continued circulation, with possible changes in disease severity owing to virus evolution and buildup of host immunity and resistance.

SARS-CoV-2 is an emerging virus that causes COVID-19. The virus has a high basic reproductive number (R0) and is transmissible during the asymptomatic phase of infection, both of which make it hard to control (3). However, there are six other coronaviruses with known human chains of transmission, which may provide clues to future scenarios for the current pandemic. There are four human coronaviruses (HCoVs) that circulate endemically around the globe; these cause only mild symptoms and are not a considerable public health burden (4). Two other HCoV strains, SARS-CoV-1 and MERs-CoV, emerged in recent decades and have higher case fatality ratios (CFRs) and higher infection fatality ratios (IFRs) than COVID-19 but were contained and thus never spread widely (5, 6).

We propose a model to explore the potential changes in both transmission and disease severity of emerging HCoVs through the transition to endemcity. We focus on SARS-CoV-2 and discuss how the conclusions would differ for emerging coronaviruses more akin to SARS-CoV-1 and MERS-CoV. Our hypothesis is that all HCoVs elicit immunity with similar characteristics, and the current acute public health problem is a consequence of epidemic emergence into an immunologically naive population in which older age groups with no previous exposure are most vulnerable to severe disease. We use our estimates of immunological and epidemiological parameters for endemic HCoVs to develop a quantitative model for endemic transmission of a virus with SARS-CoV-2-like characteristics, including the age dependence of severity. Our model explicitly considers three separate measures for immune efficacy that wane at different rates (fig. S1).

Building on ideas from the vaccine modeling literature, we suggest that immunity may provide protection in three ways (7). In its most robust form, sterilizing immunity can prevent a pathogen from replicating, thereby rendering the host refractory to reinfection. We term this property immune efficacy with respect to susceptibility (IE5). If immunity does not prevent reinfection, it may still attenuate pathology due to reinfection (IE9) and/or reduce transmissibility or infectiousness (IE1). Indeed, experimental reexposure studies on endemic HCoVs provide evidence that the three immune efficacies do not wane at the same rate (8, 9). Callow et al.’s experimental study (8) shows that reinfection is possible within one year (relatively short IE5); however, upon reinfection, symptoms are mild (high IE9) and the virus is cleared more quickly (moderate IE1). Details on the derivation of the model can be found in section 2 of the supplementary materials (SM).

We reanalyze a detailed dataset that estimates age-specific seroprevalence on the basis of both immunoglobulin M (IgM; acute response) and IgG (long-term memory) against all four circulating HCoVs in children and adults (10) to estimate parameter ranges for transmission and waning of immunity (Fig. 1A). The rapid rise in both IgM and IgG seroprevalence indicates that primary infection with all four endemic HCoV strains happens early in life, and our analysis of these data gives us an estimate for the mean age of primary infection (MAPI) between 3.4 and 5.1 years, with almost everyone infected by age 15 (see SM section 1 for details). The absence of detectable IgM titers in any individual over the age of 15 years suggests that reinfection of adults causes a recall response, indicating that while HCoV-specific immunity may wane, it is not lost. Whether immunity would wane to naïve levels in the absence of high pathogen circulation remains an open question.

For most people to be infected so early in life—younger even than measles in the pre-vaccine era—the attack rate must exceed transmission from primary infections alone. The model shows that a high attack rate can arise from a combination of high transmissibility from primary infections (i.e., high R0), waning of sterilizing immunity, and substantial transmission from reinfections in older individuals. The rapid waning of sterilizing immunity is also reported in experimental HCoV infections of humans, which showed that reinfection is possible 1 year after an earlier infection, albeit with milder symptoms (IE9) and a shorter duration (IE1) (8). Figure 1B shows the plausible combinations of waning immunity and transmission from reinfeected individuals that are required to produce the MAPI observed in Fig. 1A, based on steady-state infection levels (see SM section 2.1 for details). Table 1 shows the ranges of the parameters used in our simulations.

At the beginning of an outbreak, the age distribution of cases mirrors that of the population (Fig. 2A). However, once the demographics of infection reaches a steady state, our model predicts that primary cases occur almost entirely in babies and young children, who, in the case of COVID-19, experience a low CFR and a concomitantly low IFR. Reinfections in older individuals are predicted to be common during the endemic phase and to contribute to transmission, but in this steady-state population, older individuals, who would be at risk for severe disease from a primary infection, have acquired disease-reducing immunity after infection during childhood. The top panel of Fig. 3B illustrates how the overall IFR for SARS-CoV-2 drops drastically, eventually falling below that of seasonal influenza (~0.001) once the endemic steady-state is reached.

The time it takes to complete the shift in IFR as endemcity develops depends on both transmission (R0) and loss of immunity (waning of sterilizing immunity (w) and transmissibility...
show the dynamics for higher confidence interval (CI); data from (20).

Fig. 1. A low mean age of primary infection suggests that partially transmissible reinfections are common. (A) Mean proportion seropositive for IgG (green, top lines) and IgM (purple, bottom lines) against the four endemic HCoV strains (dots connected by dashed lines; vertical lines represent the 95% confidence interval (CI); data from (20)). The mean age of primary infection (MAPI) based on IgM data with 95% CI is shown in the inset of each panel (see SM for details). (B) MAPI as a function of waning of sterilizing immunity \( \omega \) (y axis) and transmissibility of reinfections \( \rho \) (x axis). The MAPI was calculated from the equilibrium dynamics of the model shown in fig. S1 and supplementary equations 3 to 9 with a plausible basic reproductive number \( R_0 = 5 \), \( 0 < \omega < 2 \), and \( 0 < \rho < 1 \). See SM section 2.1 for details. The inset shows the plausible combinations of values of \( \rho \) and \( \omega \) consistent with the MAPI for HCoVs estimated in (A). F.O.I., force of infection; \( I_2 \), reinfection. [See fig. S1 for parallel figures calculated at extreme plausible values for \( R_0 \) (i.e., \( R_0 = 2 \) and 10).]
**Fig. 2. The time scale of the transition from epidemic to endemic dynamics for emerging coronaviruses depends on $R_0$ and the rate of immune waning.**

Transition from epidemic to endemic dynamics for emerging HCoVs, simulated from an extension of the model presented in fig. S1 that includes age structure. Demographic characteristics (age distribution, birth, and age-specific death rates) are taken from the United States, and seasonality is incorporated via a sinusoidal forcing function (see SM section 2.2). Weak social distancing is approximated by $R_0 = 2$. (See figs. S9 to S11 for strong social distancing results. $R_0 < 1.5$.) (A) Daily number of new infections (black line; calculations in SM section 2.3). An initial peak is followed by a low-incidence endemic state (years 5 to 10 shown in the inset). A higher $R_0$ results in a larger and faster initial epidemic and a more rapid transition to endemic dynamics. The proportion of primary cases in different age groups changes over time (plotted in different colors), and the transition from epidemic to endemic dynamics results in primary cases being restricted to younger age groups. Parameters for simulations: $\omega = 1$ and $\rho = 0.7$. (B) Time for the average IFR (6-month moving average) to fall to $0.001$, which is the IFR associated with seasonal influenza. Gray areas represent continual vaccination will depend on the age-dependence of the IFR. If primary infections of children are mild (as for SARS-CoV-1 and SARS-CoV-2), continued vaccination may not

IE$_p$, and IE$_w$, respectively) and their different rates of waning. In our analysis, we hypothesized that these components of immunity for SARS-CoV-2 are comparable to those of endemic HCoVs, and this needs to be determined. Additionally, during the transition to endemicity, we need to consider how the immune efficacies depend on primary and secondary infections across ages (27) and how responses differ between vaccination and natural infection.

Longitudinal analysis of SARS patients provides an opportunity to measure the durability of immune memory in the absence of reexposure. The only long-term study we know of that follows SARS-CoV-1-specific antibodies suggests that they wane faster than antibodies to other live viruses and vaccines such as measles, mumps, rubella, and smallpox (18) and fall below the threshold of detection in 6 years (19). In contrast to antibody responses, memory T cells persist for much longer periods (19, 20) and confer protection in animal model systems (21).

We further consider the effects of strain variation both for natural infection and vaccination. Strain variation and antibody escape may occur in endemic strains (22); however, the fact that symptoms are mild suggests that immunity induced by previously seen strains is nonetheless strong enough to prevent severe disease. Indeed, among HCoVs, frequent reinfections appear to boost immunity against related strains (12). However, the effect of strain variation may differ for vaccine-induced immunity, especially in light of the narrower epitope repertoire of many currently authorized vaccines.

If frequent boosting of immunity by ongoing virus circulation is required to maintain protection from pathology, then it may be best for the vaccine to mimic natural immunity insofar as preventing pathology without blocking ongoing virus circulation. Preliminary results suggest the adenovirus-based vaccine is better at preventing severe than mild or asymptomatic infections (23), and it will be important to collect similar data for the other vaccines. Should the vaccine cause a major reduction in transmission, it might be important to consider strategies that target delivery to older individuals for whom infection can cause higher morbidity and mortality, while allowing natural immunity and transmission to be maintained in younger individuals. During the transition to endemicity, primary SARS-CoV-2 infections will frequently occur in older individuals, and we need to determine whether immunity induced by infection or vaccination in adulthood is similar to that produced by natural infections in childhood. Thus far, there have been few reinfections reported with SARS-CoV-2, and disease severity has varied (24); the only population-level study of reinfection that we are aware of estimates a low rate of re-infection in the first 6 months after primary infection and mild disease upon reinfection (25), but further analysis and monitoring are vital.

The findings presented here suggest that using symptoms as a surveillance tool to curb the spread of SARS-CoV-2 will become more difficult, as milder reinfections increasingly contribute to chains of transmission and population-level attack rates. In addition, infection or vaccination may protect against disease but not provide the type of transmission-blocking immunity that allows for shielding (26) or the generation of long-term herd immunity (2).

The details of the change in overall IFR through the transient period will be affected by a wide array of factors, such as age-specific human contact rates (27) and susceptibility to infection (28) as well as improvement in treatment protocols, hospital capacity, and virus evolution. The qualitative result of mild disease in the endemic phase is robust to these complexities, but quantitative predictions for the transient phase will depend on a careful consideration of these realities and how they interact with the dynamics of infection and components of immunity (29).

The changes in the IFR over time predicted by the model have implications for vaccination strategy against current and future emerging HCoVs. Social distancing and an effective vaccine are critical for control during a virgin epidemic and the transition out of it, but once we enter the endemic phase, mass vaccination may no longer be necessary. The necessity for continual vaccination will depend on the age-dependence of the IFR. If primary infections of children are mild (as for SARS-CoV-1 and SARS-CoV-2), continued vaccination may not
be needed as primary cases recede to mild childhood sniffles. If, on the other hand, primary infection in children is severe (as for MERS), then vaccination of children will need to be continued.

From an ecological and evolutionary perspective, our study opens the door to questions regarding the within-host and between-host dynamics of human immune immunity and pathogen populations in the face of immune efficacies with different kinetics. It also opens the question of how these immune efficacies interplay with strain cross-immunity, which is likely relevant within the alpha- and betacoronavirus. Considering data and model predictions from emergence through endemcity of HCoVs revealed a framework for understanding immunity and vaccination that may apply to a variety of infections, such as respiratory syncytial virus and seasonal influenza, which share similar age distributions and immune responses.

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Methodology, Writing, Visualization, Supervision, and Funding acquisition. O.N.B.: Conceptualization, Methodology, and Writing – review and editing. Competing interests: The authors declare no competing interests. Data and materials availability: The scripts and data used to perform the analysis and generate the figures in this paper are available on GitHub (https://github.com/JennieLavine/covid-immunity-endemicity) and archived in Zenodo (35). This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

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Supplementary Text

Figs. S1 to S13
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Taming a pandemic
One year after its emergence, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become so widespread that there is little hope of elimination. There are, however, several other human coronaviruses that are endemic and cause multiple reinfections that engender sufficient immunity to protect against severe adult disease. By making assumptions about acquired immunity from its already endemic relatives, Lavine et al. developed a model with which to analyze the trajectory of SARS-CoV-2 into endemicity. The model accounts for SARS-CoV-2's age-structured disease profile and assesses the impact of vaccination. The transition from epidemic to endemic dynamics is associated with a shift in the age distribution of primary infections to younger age groups, which in turn depends on how fast the virus spreads. Longer-lasting sterilizing immunity will slow the transition to endemicity. Depending on the type of immune response it engenders, a vaccine could accelerate establishment of a state of mild disease endemicity.

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