PERSPECTIVES

CORONAVIRUS

Herd immunity by infection is not an option

Difficult lessons are learned from a largely uncontrolled COVID-19 epidemic in Manaus, Brazil

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Herd immunity is expected to arise when a virus cannot spread readily, because it encounters a population that has a level of immunity that reduces the number of individuals susceptible to infection. On page 288 of this issue, Buss *et al.* (*1*) describe the extent of the largely uncontrolled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic in Manaus, the capital of Amazonas state in Brazil. Their data show the impact on mortality rates of a largely unmitigated outbreak where even with an estimated 76% of the population being infected, herd immunity was not achieved. Manaus provides a cautionary example of unmitigated spread across a population, showing that herd immunity is likely not achieved even at high levels of infection and that it comes with unacceptably high costs.

Buss *et al.* used data on the occurrence of SARS-CoV-2–specific antibodies (seroprevalence) in blood donors, adjusted for waning antibody responses over time, to calculate an estimated attack rate for COVID-19 of 66% in June, rising to 76% in October, in Manaus. The attack rate is the proportion of at-risk people who develop infection after exposure in a period of time. This attack rate resulted in a factor of 4.5 excess mortality in 2020 relative to previous years. The infection fatality rate was estimated to be between 0.17% and 0.28%, consistent with the population being predominantly young and at reduced risk of death from COVID-19. Manaus recorded 2642 [1193/million inhabitants (mil)] confirmed deaths from COVID-19 and 3789 (1710/mil) deaths from severe acute respiratory syndrome likely to have been caused by SARS-CoV-2 infection. These figures are starkly different from the fatality rates during the same period (until 1 October) in the United Kingdom (620/mil), France (490/mil), and the United States (625/mil), and orders of magnitude higher than in Australia (36/mil), Taiwan (0.3/mil), and New Zealand (5/mil). Despite such a high proportion of the population being infected, transmission in Manaus has continued, even in the presence of nonpharmaceutical interventions (NPIs), with the effective reproduction rate (R) near 1.

These data have numerous implications. In particular, the herd immunity threshold (HIT), the proportion of the population that needs to be immune to reduce the number of susceptible individuals sufficiently to reverse epidemic growth, is likely to be high for SARS-CoV-2. If the basic reproduction

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Gravediggers bury a deceased COVID-19 patient at the Parque Taruma cemetery, Manaus, Brazil, where the disease has caused a huge number of deaths.

number (R_0)—that is, the average number of secondary infections resulting from an index case in a fully susceptible population—is 2.5 to 3, as estimated within Manaus, the expected attack rate would be 89 to 94% and the HIT is expected to be 60 to 70% for a homogeneous population (*2*). Although the epidemic was largely unmitigated in Manaus at the outset, the subsequent introduction of behavioral change (such as social distancing) and NPIs (such as masks), together with nonhomogeneous population mixing, may explain the lower than expected attack rate. However, even with an estimated 76% of the population being infected, it appears the HIT was not reached. It is unclear whether this is due to waning immunity after infection, to a higher HIT than previously anticipated, or possibly a lower attack rate than estimated. Accruing data on reinfection with SARS-CoV-2 suggests that primary infection may not consistently confer long-term immunity to all infected, although the frequency of reinfection and the correlates of an effective immune response remain poorly understood. If immunity wanes over time, exposed individuals may revert to becoming susceptible, providing a new susceptible population that may then contribute to transmission.

These findings also suggest that the majority of people who are unexposed are susceptible to this virus. Although some have suggested that there may be a degree of preexisting cross-reactive T cell and humoral (antibody-related) immunity against SARS-CoV-2 (*3*, *4*) and that a lower proportion of infection of only 10 to 40% of the population could achieve herd immunity (*5*), the study of Buss *et al.* shows that there is no meaningful level of any such immunity.

Additionally, given that seroprevalence is under 20% in most countries (*6*), these data suggest that without strict control measures, the epidemic would continue to accelerate for many months ahead, with an unacceptably high cost. The deaths that would accrue in pursuit of naturally acquired herd immunity would be catastrophic. Manaus has a particularly young population. In populations with a higher proportion of older people, the overall infection fatality rates would be higher, between 0.46% and 0.72% as seen in São Paulo (*1*). Applying age-specific infection fatality rates estimated from the Manaus data, a 76% attack rate would mean 350,000, 386,000, and 1.58 million deaths in the United Kingdom, France, and the United States, respectively.

Buss *et al.* reported similar seroprevalence estimates across the age groups studied, which suggests that spread appears to have occurred relatively uniformly across the population and was not limited to specific subsets of people who may have been more exposed. This is consistent with other global evidence suggesting that it is practically impossible to "shield" the vulnerable or to carry out "focused protection" given the difficulty of identifying and separating the healthy from the vulnerable (*7*). Inevitably, with unmitigated transmission, infection will spread to vulnerable populations, with attendant costs (*8*).

Even in a younger population, SARS-CoV-2 is harmful and deadly. The growing evidence of long COVID and its long-lasting multisystem effects indicates that there may be substantial morbidity after infection (*9*, *10*). Although the risk of long COVID seems to increase with age, recent reports of multisystem disease and long COVID among children suggest that the risk in younger age groups cannot be overlooked (*11*). This highlights the risks associated with exposing large swaths of the population to a virus that is still not fully understood. Strategies for suppression of COVID-19 should not focus only on older people or those with comorbidities, but rather on the entire population, given the substantial impact of unmitigated infection on the health of all groups and the economic impacts of poor health among these groups on society as a whole.

There remain major unknowns about how long immunity to SARS-CoV-2 lasts and the risk of reinfection (*12*). Seasonal coronaviruses, which cause common colds, are known to induce short immunity, and reinfections occur commonly within 12 months of infection (*13*), although immunity to SARS-CoV and MERS-CoV, which cause more severe disease, can last several years (*14*). T cell immunity might be longer-lasting, but it is unclear whether this would fade within 1 to 2 years (*3*). If immunity does fade, this would mean that recurrent epidemic cycles are likely, especially if new strains that can escape immune detection emerge.

What the findings of Buss *et al.* definitively show is that pursuing herd immunity through naturally acquired infection is not a strategy that can be considered. Achieving herd immunity through infection will be very costly in terms of mortality and morbidity, with little guarantee of success. Although the duration and effectiveness of immunity in reducing transmission with vaccination is unclear, experience across several infectious diseases suggests that immunity can be boosted safely through vaccination, if required. Even a mitigation strategy whereby the virus is allowed to spread through the population with the objective of keeping admissions just below health care capacity, as is done for influenza virus, is clearly misguided for SARS-CoV-2. Like SARS-CoV and MERS-CoV, this virus is optimally addressed with an aggressive suppression strategy (*15*). Governments need to focus on more precise NPIs, robust test/trace/isolate systems, border control measures, mass testing, better treatments, and development and delivery of vaccines (*15*). This is the most sustainable path for countries out of this pandemic. ■

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