Great Expectations of COVID-19 Herd Immunity

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ABSTRACT There is a common preconception that reaching an estimated herd immunity threshold through vaccination will end the COVID-19 pandemic. However, the mathematical models underpinning this estimate make numerous assumptions that may not be met in the real world. The protection afforded by vaccines is imperfect, particularly against asymptomatic infection, which can still result in transmission and propagate pandemic viral spread. Immune responses wane and SARS-COV-2 has the capacity to mutate over time to become more infectious and resistant to vaccine elicited immunity. Human behavior and public health restrictions also vary over time and among different populations, impacting the transmissibility of infection. These ever-changing factors modify the number of secondary cases produced by an infected individual, thereby necessitating constant revision of the herd immunity threshold. Even so, vaccination remains a powerful strategy to slow down the pandemic, save lives, and alleviate the burden on limited health care resources.

KEYWORDS coronavirus, epidemiology, herd immunity, immunity, respiratory viruses

The COVID-19 pandemic has had a massive impact on all facets of human life. Despite major public health interventions and development of effective vaccines with unparalleled rapidity, over 290 million cases and 5.4 million deaths have been documented as of January 4th, 2021 (1). As the pandemic continues to abate and resurge globally, individual countries have raced to vaccinate their populations in order to save lives and to relieve strained health care systems, stifled economies, and fatigued populations yearning for return to normalcy. Indeed, immunity elicited by COVID-19 vaccination with BNT162b2, ChAdOx1 nCoV-19, mRNA-1273, Gam-COVID-Vac, Ad26.COV2.S, and CoronaVac vaccines has greatly reduced the incidence of symptomatic disease in individuals (2–8). It is assumed based on public health experience with other infectious diseases that as population immunity rises, as a result of vaccination and natural infection, infections in those who remain susceptible should inevitably decrease.

One approach to disease control has been to immunize populations to reach a (theoretical) "herd immunity threshold," estimated by some to be approximately 67% (9, 10). The herd immunity threshold is here defined as "the proportion of a population immune to a communicable disease, either from innate immunity, natural infection, or vaccination, that prevents or significantly reduces serial transmission of its infectious agent." Such thresholds have been predicted mathematically using a transmissibility estimate called the reproductive number (or R_0) in the equation $h = 1 - 1/R_0$ (9, 11). The R_0 is the critical variable in this equation, representing the average number of secondary cases produced by an infected individual in an immunologically susceptible population (11). Initial R_0 estimates varied for COVID-19 within different populations, with most estimates generally ranging from 1.66 to 3.58 (12–15). Social and demographic factors including population density, public health measures, and cultural attitudes and behaviors impact R_0, inevitably resulting in marked variation of estimates of herd

immunity thresholds. Moreover, the herd immunity threshold formula relies on additional assumptions that are unlikely to hold in the case of COVID-19 due to its capacity to mutate, and to the nature of immune responses against nonsystemic respiratory viruses in general, which tend to be incomplete and transient (16–18). Thus, herd immunity threshold estimates should be considered moving targets rather than biologically determined values.

SARS-COV-2, like influenza, is an RNA virus with a high degree of plasticity in its spike protein (S) surface antigen (which elicits protective immune responses) and consequently a potential to rapidly mutate. Host adaptive mutations have been documented in viral variants of concern, including Alpha and Delta (19, 20), which result in higher affinity binding of spike to the human angiotensin-converting enzyme 2 (ACE2) receptor, leading to higher mucosal viral loads and enhanced transmissibility (21, 22). Updated estimates of the reproductive number for variants such as Alpha, Beta, and Gamma have been around 4.7–4.9 (21), and around 5 for the Delta variant (22, 23). Early estimates of Omicron's reproductive number are 4.2 times greater than estimates for Delta (24). Hence, as variants with increasing R_0 values emerge, estimates for the herd immunity threshold will inevitably increase as well.

In addition to host adaptational mutations, viruses have also developed numerous mutations that may allow them to evade host immune responses. Decreased binding of neutralizing antibodies (which are presumed to be correlates of protection) (25) from both convalescent COVID-19 patients and vaccinated individuals, to the Beta, Gamma, and Delta variants has been described (26, 27), and vaccine efficacy has been lower in countries where the Beta and Gamma variants were more prevalent (3, 6). This phenomenon is further exemplified with Omicron, which contains 32 S protein changes contributing to a 27- to 127-fold reduction in neutralization titers relative to wild-type SARS-COV-2. Not surprisingly, it has been spreading explosively in populations with high levels of vaccine- and natural infection-induced immunity (28). While herd immunity threshold formulae assume robust and durable immunity, variants that evade population immunity can change estimates dramatically. Furthermore, waning of detectable anti-S, anti-receptor binding domain (RBD), and neutralizing antibody titers against COVID-19 over time, has occurred in the setting of natural and vaccine-induced immunity, with some half-life estimates ranging from 58 to 106 days (25, 29–31). This is in contrast to immunity against other systemically-infecting respiratory viruses like measles. After recovery from infection, measles immunity is usually lifelong, associated with an estimated antibody half-life as high as 3,014 years (32). Similarly, vaccination with a licensed live measles vaccine provides robust and durable immunity, lasting decades. However, this is not the case with COVID-19, where susceptibility to infection increases with increasing time since vaccination (33–35). Therefore, estimates of herd immunity thresholds must account not only for partial vaccine efficacy but also changes in key parameters associated with a dynamic, mutating virus and with continuously waning immunity.

Asymptomatic infection, which occurs in nearly one third of all COVID-19 cases (36), further complicates the ability to estimate vaccine efficacy and herd immunity thresholds because it perpetuates occult transmission. While an effective vaccine would protect against symptomatic disease, an ideal vaccine would prevent infection entirely, whether symptomatic or not. The effectiveness of COVID-19 vaccines in preventing asymptomatic infection, which may still be associated with transmission, is often lower and not well estimated (37, 38). A retrospective study of health care workers who received the BNT162b2 vaccine determined that its effectiveness in preventing symptomatic disease was 97%, but only 86% in preventing asymptomatic infection (39). Estimates from randomized trials are less optimistic: efficacy against asymptomatic disease of the mRNA-1273 vaccine was only 63% (compared to 93.2% against symptomatic illness), while the efficacy of the ChAdOx1 nCoV-19 vaccine was only 3.8% with the original dosing regimen (3, 40). If the public health goal is to eradicate COVID-19 entirely, the effectiveness of vaccines in preventing both symptomatic and

asymptomatic disease must be considered, since asymptomatic transmission in a pandemic setting can continue indefinitely.

Finally, population heterogeneity must be considered: despite high overall theoretical population immunity, pockets of susceptible individuals can sustain viral circulation, as has been demonstrated with many other viruses including smallpox virus and polioviruses. Although more sophisticated mathematical models have attempted to address imperfect immunity and population heterogeneity (at least from the perspective of social interactions) (41), it is important to consider that persistent circulation of virus in pockets of susceptible hosts can facilitate further mutation and eventually spark additional outbreaks after immunity wanes in the population at large, as seen with vaccine-derived polioviruses (42). In short, mathematical estimates of R_0 and herd immunity thresholds may help guide public health responses but are likely to be poor predictors of epidemic reality and should not replace effective and adaptive public health responses against the evolving pandemic.

Such conclusions are not surprising considering experience with other respiratory viruses. Serologic studies have demonstrated that the vast majority of the human population has been exposed to seasonal coronaviruses, endemic influenza virus strains, and other respiratory viruses like respiratory syncytial virus, but despite eliciting some degree of protective immunity, the viruses continue to circulate (43, 44) and reinfect individuals months or years after initial infection (17, 18, 45). Vaccine approaches that induce more durable immunity and provide broader protection against future variants, so-called "universal vaccines" (46), may alleviate some of the issues associated with herd immunity against respiratory viruses, but such vaccines are still under development.

SARS-COV-2, like the descendants of the 1918 influenza pandemic, is undoubtedly here to stay. Indeed, all influenza pandemic strains since 1918 have established endemicity after their initial explosive spread. Fortunately, the presence of some degree of immunity against SARS-COV-2, even immunity that has waned over time or diminished in the face of viral escape mutations, may still provide protection against severe disease and save lives (47, 48). Current vaccine strategies may be able to slow down SARS-CoV-2 spread and are likely to alleviate the burden that waves of severe cases can inflict on limited health care resources, but they are unlikely to lead to SARS-COV-2 eradication.

Although herd immunity thresholds should not be thought of as precise biological parameters that can predict SARS-CoV-2 control, they may nevertheless have value in setting public health goals and in reminding us that our current pandemic control tools, when used aggressively, can reduce viral circulation, thereby saving lives and reducing illnesses and social–economic disruption.

ACKNOWLEDGMENTS

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