Herd Immunity to COVID-19

Alluring and Elusive

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is so far the largest infectious disease catastrophe of the 21st century. Its unprecedented political, public health, medical, and research impacts have generated a lot of questions, resurrecting some fundamental dogmas in infectious diseases and immunology. The most highly cited of those is the concept of herd immunity (also known as population/community immunity) that has made its way into the scientific and lay spotlights. Social media and other online platforms are causing public panic and disinformation. For these reasons, one has to ask for a definition and attainability of herd immunity. In simple terms, herd immunity works through achieving a threshold immunity at the population level that is able to theoretically cut the transmission chain of a given infectious disease, be it obtained through natural infection or vaccination.[1] This may not mean that a given individual is fully protected at all times or situations. It is the threshold immunity that, when high enough, can protect most if not all in a population in a given geographical area for a certain time interval. The latter notion, indubitably, however, would very much depend on the duration of individual-level natural or vaccine-induced immunity.

Do we really need a vaccine before a population can achieve herd immunity against COVID-19? The cautious answer is yes, but we need to be cognizant that even with the vaccine, we probably will never reach herd immunity. Here is the explanation: estimated basic reproduction number (R_0) for COVID-19 is 2.5 to 3.5. R_0 is defined as the expected or estimated number of infected individuals when an infected (and infectious) individual enters a population that is immunologically naive to the infectious agent in question, whereas the effective reproduction number (R) is the expected or estimated number of infected individuals when an infected (and infectious) individual enters a population that is not immunologically naive to the infectious agent in question and in fact the population is indeed a mix of immunologically naive and immunologically experienced individuals.[2] The latter is directly influenced by the moving percentage of susceptible individuals and is determined by the following formula: $R = sR_0$, where s is the fraction of "susceptible" individuals in a population. As more people become infected with SARS-CoV-2 and survive, R dwindles. Therefore, one would need to bring R below 1 to prevent transmission. Even with a R as low as 0.99, we will need at least 60% to 72% herd immunity to "just" cut the transmission chain. This is all based on the wishful premises that (1) vaccine efficacy is 100%, and (2) it confers lifelong or long-term immunity. For a vaccine with a claimed 95% efficacy, the required herd immunity level would be 63% to 76% (R divided by the vaccine efficacy). The latter range would be 84% to 90% if we want a decent safety margin with an R of 0.5. According to the current number of diagnosed cases, if we even inflate it by several orders of magnitude to include undertesting or possible infected asymptomatic cases, our numbers would still be far below the above-mentioned required threshold even by using R = 0.99. Not to mention, SARS-CoV-2 antibody levels wane over time, and we now have documented peer-reviewed publications on reinfected cases.[3,4]

Let's take a pause here and highlight the fact that the correlate of protection for COVID-19 is not known yet, and we only use antibody to SARS-CoV-2

targets as a convenient surrogate (or even desirably a co-correlate). In fact, antibody levels are much higher in severe cases compared with mild and asymptomatic ones.[5] Correlate of protection is the defined immune response that prevents infection or disease (depending on the purpose) and is only *inferred* from prospective large vaccine efficacy trials.[6] Our definition of herd immunity for COVID-19 remains tentative at this point. If the vaccine efficacy trials, in their vaccinated arms, include volunteers who wore masks, this would at least partially *mask* the actual vaccine efficacy. Therefore, if the bona fide vaccine efficacy proves to be less than 60% (similar to influenza vaccines),[7] then the entire population needs to be vaccinated. That being said, in trials in which protocols are fully observed (per protocol) vs those in which modified approaches are opted by the designers and/or participants, the ideal conditions based on which "efficacy" is calculated would not be reflective of the real-world situation, for the latter "vaccine effectiveness" is typically estimated. Here are a few caveats regarding COVID-19 vaccination: (1) two doses are required per individual; (2) COVID-19 is a pandemic and world travel is inevitable; and (3) revaccination over multiple seasons due to possible waning immunity may be needed.[8] Therefore, it would be wise not to view the vaccine as a panacea but instead as a helper to pave the way (in addition to other control measures) to eliminate COVID-19. We cannot afford putting all of our eggs in one basket at this juncture. Social distancing, mask wearing, and frequent handwashing are important infection prevention measures that we must continue to adhere to in order to limit the spread of disease while vaccination occurs.

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