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PERSPECTIVE

The Concept of Classical Herd Immunity May Not Apply to COVID-19

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There has been speculation about when in the coronavirus disease 2019 (COVID-19) pandemic we will be able to live with the virus in a manner that does not disrupt most peoples' lives. Much of this discussion has focused on herd immunity thresholds (Box 1). As commonly understood [1–7], herd immunity thresholds are reached when a sufficient proportion of the population is vaccinated or has recovered from natural infection with a pathogen such that its community circulation is reduced below the level of significant public health threat. For example, this threshold has been met with polio and measles circulation in the United States.

However, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is so different from polio and measles that classical herd immunity may not readily apply to it. Important differences include the phenotypic stability of polio and measles viruses, and their ability to elicit long-term protective immunity, compared to SARS-CoV-2. For these and other reasons, controlling COVID-19 by increasing herd immunity may be an elusive goal.

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HISTORICAL UNDERSTANDING OF HERD IMMUNITY

Conceptualizations of herd immunity thresholds evolved gradually before the microbiology era. By about 1700, a few diseases such as smallpox and measles had been distinguished based on pathognomonic signs and symptoms. The 1720 European and colonial introduction of smallpox inoculation [8] clarified that both natural infection and inoculation protected against infection and reinfection. At the population level, widespread use of smallpox inoculation in human cohorts prevented or limited epidemics, including inoculation of soldiers during the American Revolutionary War [9] and of enslaved people on US plantations. Such early observations of "herd protection" led scientists of the late 19th century to propose that smallpox could be eradicated, a goal finally realized in 1978.

Around 1807, a crucial observation—seemingly unrelated to immune protection—was made. In cities and large towns, childhood measles was documented to occur in regular cycles. Comparing one city to another, cycle intervals varied from as short as 2 to 3 years, to as long as 6 to 7 years, with different cities having their own characteristic intervals. Longer cycles were seen in towns and smaller cities, whereas shorter cycles were more common in large, crowded cities with high birthrates. Contemporary data, such as those in Britain's mortality registry or from comparative examination of early 19th century measles cyclicity in 20 international cities, could not explain this phenomenon [10, 11].

After 1876, the new sciences of microbiology, immunology, and epidemiology began to clear up the mystery: measles and some other epidemic infections of early childhood elicited long-term protective immunity that reduced or prevented epidemics, until such time as cumulative births resulted in sufficiently large cohorts of susceptible children to support new waves of transmission. Among the first direct observational studies of this phenomenon was a 1904–1907 report of measles outbreaks in British primary schools. Classroom measles epidemics occurred when fewer than 70% of children were immune, and tended to end or be prevented when classroom immunity reached 85% [12]. In short, measurable rules about epidemic disease transmission were related to population cohort immune status.

Such rules initially had no name. The terms "herd immunity" and "herd immunity threshold" emerged when American veterinary researchers began using them during World War I [13]. The terminology was soon adopted by British statistician-epidemiologists studying herd immunity in laboratory animals, hoping to identify human disease-control variables [14–20]. But as experimental and human observational research progressed, such hopes were soon dashed. Numerous variables greatly affected herd immunity thresholds, including differences among diseases and hosts, transmission modes (eg, respiratory, enteric),

Box 1. Herd Immunity Threshold

A herd immunity threshold is the proportion of a population with immunity against a communicable disease agent (resulting from innate immunity, natural infection, or vaccination) above which transmission of the agent is largely prevented, except for sporadic outbreaks in undervaccinated or otherwise incompletely protected subsets of individuals.

duration and completeness of immunity, crowding and population movement, and small pockets of nonimmune persons (religious groups or other unvaccinated groups), among other factors. These variables interacted in complex ways to result in herd immunity thresholds that were situation specific and often significantly altered by small changes in key variables. For example, in mathematical studies, even small changes in population density had large effects on herd immunity thresholds. Herd immunity theory seemed useful as a general concept but was inadequate in important real-world situations.

HERD IMMUNITY THRESHOLDS IN 2022

Over the past 70 years, herd immunity threshold concepts have been repeatedly questioned amid attempts to control, to geographically eliminate, or to eradicate infectious diseases [3, 6]. With influenza, for example, the inadequacy or limited durability of immunity after vaccination or infection, and the continual antigenic drifting and occasional pandemic-producing antigenic shifting, has foiled attainment of strong herd immunity threshold effects. Moreover, small numbers of unvaccinated individuals make completely protective herd immunity difficult even for the most phenotypically stable disease agents [21]. For example, long after the 1960s to 1970s, when measles and polio in the United States seemingly had been controlled by mass vaccination and school-exclusion policies, disease importations from abroad continued to cause localized outbreaks [22]. These outbreaks occurred even with nationwide immunity levels above ostensible herd immunity thresholds, as enclaves of undervaccinated populations provided vulnerable targets for pathogen reemergences [21, 22]. Time and again, human movement and other human behaviors have circumvented physical barriers between the infectious and the susceptible. Even global smallpox eradication had to contend with repeated outbreaks and cases among unvaccinated individuals [3] throughout the decade leading to the very last natural case in 1978.

For many common respiratory viruses such as influenza and respiratory syncytial virus, the barriers to achieving herd immunity are even greater than with measles, polio, and smallpox. These barriers include asymptomatic transmission, incomplete or short-duration protective immunity, and viral immune escape [23]. Indeed, for many such respiratory viruses, including SARS-CoV-2, immunity is itself a fluid concept, ranging from complete and durable (long-lasting) immunity that fully protects against infections, to immunity that protects against severe disease but does not prevent reinfection and onward transmission.

HERD IMMUNITY AND COVID-19

There are significant obstacles to achieving complete herd immunity with COVID-19. Classical herd immunity, leading to disease eradication or elimination, almost certainly is an unattainable goal. As noted, mass vaccination and aggressive public health approaches have struggled to control other (seemingly more controllable) respiratory infectious diseases, such as smallpox, measles, and rubella, all caused by viruses with limited phenotypic evolution. Controlling SARS-CoV-2 and its cycles of new variants presents a much more formidable challenge [23]. Like influenza, SARS-CoV-2 mutates continually into new variants that can escape immunity derived from infections and vaccines. It also can be transmitted asymptomatically and without pathognomonic signs, impeding public health control. SARS-CoV-2 appears not to substantially engage the systemic immune system, as do viruses such as smallpox, measles, and rubella that consistently have a pronounced viremic phase. Moreover, neither infection nor vaccination appears to induce prolonged protection against SARS-CoV-2 in many or most people. Finally, the public health community has encountered substantial resistance to efforts to control the spread of SARS-CoV-2 by vaccination, mask wearing, and other interventions.

If vaccine- or infection-induced immunity to SARS-CoV-2 indeed proves to be short-lived, or if escape mutants continue to emerge, viral spread may continue indefinitely, albeit hopefully at a low endemic level. This notably has occurred with the 1918 pandemic influenza virus, whose viral descendants still are causing seasonal outbreaks and occasional pandemics 104 years later (pandemic H2N2 in 1957, H3N2 in 1968, and H1N1 in 2009) [24], and which we have been unable, after more than 80 years of trying, to fully control with vaccines. Such factors probably make SARS-CoV-2 impossible to eradicate (only one human virus—smallpox—has ever been eradicated), difficult to eliminate over long periods within large geographic areas, and difficult to satisfactorily control even with good vaccines.

Thus, COVID-19 is likely to be with us, even if at a very low level of endemic community spread and with lower severity, for the foreseeable future. Like influenza, any level of herd protection against SARS-CoV-2 potentially can be overcome by ever-changing levels of immunity among countless subpopulations, by human movement, crowding, changes

in social or prevention behaviors, by demographics, by vaccination levels, by variations in durability of infection- or vaccine-induced immunity, and by evolution of viral variants, among many other variables.

But encouragingly, after more than 2 years of viral circulation, and more than a year of vaccines with boosters, we now have a high degree of background population immunity to SARS-CoV-2, as well as medical countermeasures such as antiviral drugs and monoclonal antibodies to prevent progression of disease, and widely available diagnostic tests. With these interventions we can aspire to, and very likely will succeed in achieving, substantial control of community spread without the disruptions of society caused by COVID-19 over the past 2 years. We no longer need the elusive concept of herd immunity as an aspirational goal: COVID-19 control is already within our grasp.

Looking forward, more broadly protective vaccines could play important roles in controlling SARS-CoV-2 and its inevitable variants. Developing "universal" coronavirus vaccines (or at least universal SARS-CoV-2 vaccines that elicit durable and broadly protective immunity against multiple SARS-CoV-2 variants) is an important goal for the immediate future [23]. Meanwhile, optimal COVID-19 control will require both classic, nonpharmacologic public health approaches and vaccination of many more people globally with the SARS-CoV-2–specific vaccines we already have, with booster shots, and with updates to vaccine antigens if needed.

Living with COVID-19 is best considered not as reaching a numerical threshold of immunity, but as optimizing population protection without prohibitive restrictions on our daily lives. Effective tools for prevention and control of COVID-19 (vaccines, prevention measures) are available; if utilized, the road back to normality is achievable even without achieving classical herd immunity.

Notes

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