In the Know

Can Herd Immunity Save Us from COVID-19?

Richard Simoneaux

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Since the advent of the novel coronavirus in Wuhan, China in late 2019, there has been a resurgent interest in formerly arcane epidemiologic topics. One concept that has been revisited of late is that of "herd" immunity. In principle, this occurs when a significant enough portion of a population has become immune to an infectious disease; this can occur either by recovery from a prior infection or effective vaccination. When a high enough proportion of a population is immune, then the chances of an individual who is uninfected and susceptible to infection encountering an infectious individual are drastically reduced, thus interrupting the chain of transmission.

Herd immunity is only possible if prior infection and/or vaccination confers immunity from subsequent infection. With only about seven months of data, we simply don't know whether immunity to SARSCoV-2 is durable.

Haseltine Opinion Article

In a recent opinion article sent to CNN, William A. Haseltine, PhD, Chair and President of ACCESS Health International, a global health think tank, discussed the prospects for herd immunity for the current COVID-19 pandemic (asamonitor.pub/2YQjTPj). On this subject, Haseltine is somewhat less than optimistic about our ability to attain herd immunity against this pathogen, stating, "... we waste critical time with this pointless discussion, because the facts are already quite clear: herd immunity will likely never be achieved for COVID-19 or any other coronavirus."

Spanish ENE-COVID Serological Study

One of the initial studies cited by Haseltine in his opinion piece was a Spanish investigation that detailed initial seroprevalence data from the ENE-COVID study, which was a nationwide epidemiological study designed to assess the extent to which SARS-CoV-2 had spread across that country (*Lancet* 2020; 396: 535-544).

Between April 27, 2020 and May 11, 2020, a total of 61,075 participants (75.1% of the contacted individuals within the 35,883 selected households) answered a questionnaire concerning risk factors for and symptoms consistent with those of COVID-19. In addition, these participants also received a point-of-care antibody test, and if they were amenable to doing so, donated a blood sample that was subjected to a chemiluminescent immunoassay.

Using the point-of-care and immunoassay tests yielded figures of 5.0% and 4.6%, respectively, for seroprevalence. Interestingly, no differences were noted by sex for seroprevalence; however, geographic variability was significant. In hotspot areas around Madrid, seroprevalence was greater than 10%, while in coastal areas, the figures were much lower, below 3%. Among 195 patients who tested positive via PCR assays more than 14 days before study participation, the seroprevalence figures ranged from 91.8% (either test positive) to 87.6% (both tests positive). Roughly one-third of participants who were seropositive were also asymptomatic, while only approximately 20% of symptomatic participants by both tests (point-of-care and immunoassay) had a prior PCR assay.

Although Spain has been severely impacted by COVID-19, the seroprevalence estimates are well below the estimates of 60% prevalence necessary for herd immunity for COVID-19, based on its R_0 values. In the view of ENE-COVID researchers, the attainment of herd immunity for COVID-19 cannot be accomplished without unacceptable deaths in susceptible communities and an overwhelmed health care infrastructure. As a result, they speculate that social distancing and epidemiological efforts for identifying and isolating infected individuals and their contacts are crucial for halting this epidemic.

Infection-Based Immunity Model for Herd Immunity Threshold

Although some studies have estimated the herd immunity threshold (i.e., the proportion of immune individuals necessary to attain herd immunity) for COVID-19 as ranging from 60%-80% depending if R_0 values of 2.5-5.0 are used, if some researchers from the U.K. and Portugal are correct, that figure could be significantly lower (medRxiv 2020.07.23.20160762). In their pre-peer-reviewed article, the researchers note that as a population is exposed to an infectious agent, the number of individuals susceptible to infection decreases, thus slowing down the transmission of the disease, an effect that can be enhanced by variation in susceptibility or infection exposure. The herd immunity threshold is reached once the number of susceptible individuals becomes low enough to halt epidemic growth.

Herd immunity threshold calculations are different, depending on whether variation occurs within infection exposure or susceptibility. According to their figures, herd immunity could start to mitigate spread if only 10%-20% of the population has been infected, far lower than the 60%-80% figures obtained in most studies for COVID-19. This variation, the authors argue, is due to the fact that the higher figures obtained are for a model employing randomized vaccination as a means of immunity rather than infection, which does not occur randomly. In their mathematical model, individuals who are more exposed to or susceptible to infection are more likely to derive infection-induced immunity, and thus, they provide greater community protection than random vaccinations.

The underlying concept is that the majority of spread occurs from a small fraction of the population that is highly mobile (and, perhaps, highly irresponsible!). In the researchers' model, these mobile vectors of transmission rapidly become infected, recover, and then become immune. Their immunity is protective of the less mobile fraction of the population. The size of the decline is dependent upon how heterogeneous the population is in terms of virus transmission. The authors note that the downward impetus for the herd immunity threshold remains fairly strong in instances when susceptibility or infection exposure are variable and acquired immunity is sufficient to maintain transmission levels below reinfection threshold. The subject of immunity for SARS-CoV-2, whether obtained by vaccination or by infection, remains a matter that is far from settled, and consequently, is still being thoroughly investigated.

Longitudinal Study of Declining SARS-CoV-2 Neutralizing Antibody Levels

In a longitudinal study performed in the U.K., sequential samples were taken from 65 individuals having PCR-confirmed cases of SARS-CoV-2 and 31 seropositive health care workers up to 94 days post onset of symptoms to assess the kinetics of neutralizing antibody formation as well as the magnitude and duration of the neutralizing antibody response (medRxiv 2020.07.09.20148429).

In this study, the investigators determined that while the magnitude of the neutralizing antibody response was dependent on disease severity, the kinetics of the neutralizing antibody response was not. In that follow-up period, declines in neutralizing antibody titers were observed; some subjects having high peak ID_{50} (serum dilution that inhibits 50% infection) values greater than 10,000 were able to maintain titers at greater than 1,000 for 60 days post onset of symptoms. However, subjects with lower peak ID_{50} values had titers approximating baseline levels during follow-up. An analogous decrease in neutralizing antibodies was noted in a cohort of seropositive health care workers, leading the investigators to speculate that the transient neutralizing antibody levels is a feature common to both those infected with commonly circulating seasonal coronaviruses and those having a SARS-CoV-2 infection with low disease severity.

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The authors speculate that a higher viral load at the time of infection induces more severe disease and a more vigorous antibody response. They raise the possibility that antibodies themselves may play a role in disease severity, acknowledging that antibody-dependent enhancement of COVID-19 has not been documented.

The authors also note that the role played by T cell-based responses (either via vaccination or infection) may be critical in recovery from COVID-19 and subsequent immunity to SARS-CoV02.

Coronavirus Reinfection

One of the primary reasons that Haseltine discounted the possibility of herd immunity is that reinfection occurs with the four endemic human coronaviruses. Although there has not been sufficient time since the onset of the COVID-19 to study reinfection rates for SARS-CoV-2, there are four seasonal coronavirus species, 229E, HKU1, NL63, and OC43 for which there are decades of research data available. Although all four are associated with mild respiratory tract infections, they are biologically distinct, with two being alphacoronaviruses (NL63 and 229E) and two being betacoronaviruses (HKU1 and OC43) (medRxiv 2020.05.11.20086439). In this study, researchers sought to assess the duration of protection from reinfection afforded by an initial coronavirus infection.

Median reinfection times for individual virus species ranged from 27 to 46 months, with a median figure of 30 months for the four coronaviruses included in this study. Reinfections were observed at six months after a prior infection, but the authors found no cases at three months. There was no decrease in antibodies between the first and second infection in those subjects reinfected at six months, suggesting that the presence of antibodies does not ensure immunity.

From their data, the authors conclude that reinfections of seasonal coronaviruses occur in nature. Although reinfections typically occurred within three years, the investigators were careful to note that the duration between infections doesn't necessarily correlate to the time for protective immunity, as it is likely dependent upon the re-exposure time. They also speculate that the protective immunity afforded may last as little as six to 12 months, based on observed antibody-decreasing dynamics and minimum infection intervals.

It is of particular interest to note that three subjects included in the study displayed antibodies that recognized the N protein of SARS-CoV-2. Given when those infections occurred in 1985, 1992, and 2006, it is highly unlikely that recognition was due to SARS-CoV-2 infection. These cross-reactive antibodies may have been the result of coinciding infections of HKU1 and NL63, an alpha- and betacoronavirus, respectively. The authors raise the possibility that conserved epitopes in the HKU1 and NL63 N-proteins give rise to a broadly-acting antibody response.

Cross-Reactive CD4+ T Cells

The presence of SARS-CoV-2-reactive $CD4^+$ T cells have been observed in previously unexposed individuals, which suggests that pre-existing cross-reactive T cell memory may exist in anywhere from 20%-50% of individuals. In a recent study, 142 T cell epitopes across the SARS-CoV-2 genome were mapped, using blood samples obtained before the discovery of SARS-CoV-2 in 2019, to precisely interrogate the repertoire of $CD4^+$ T cells that target SARS-CoV-2. (*Science* August 4, 2020). The investigators found that certain populations of pre-existing memory $CD4^+$ T cells displayed cross-reactivity with similar affinities for SARS CoV-2 as well as common cold-causing human coronaviruses (OC43, HKU1, NL63 and 229E). The authors note that these observed T cell-based cross-reactivities for human coronaviruses run in direct contrast to the neutralizing antibody responses observed for those viruses, which are typically very species-specific. Based on the data obtained in their study, the authors speculate that pre-existing, cross-reactive human coronavirus $CD4^+$ T cell memory in some individuals could be a contributing factor to the widely varying patient outcomes noted with SARS-CoV-2.

Will Herd Immunity End the Pandemic?

Given the uncertainty among seemingly conflicting data from in both peer-reviewed and, increasingly, pre-peer reviewed articles surrounding SARS-CoV-2, one has to ask what one can make of this morass. With additional months of evidence, we will learn more about the durability of immunity to SARS-CoV-2. For now, the most important science describes the actions we can take, as citizens, to help stop the transmission of this virus. As succinctly summarized by Dr. Haseltine: "Every American also has a role to play and an opportunity to stamp out this disease. By wearing masks, practicing safe social distancing, and choosing the inconvenience of self-isolation when we fear we've been exposed to infection, we can stop this outbreak dead in its tracks."

This is clearly the most prudent course of action while the body of research around SARS-CoV-2 immunity continues to unfold in the months ahead. ■

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FEATURED ARTICLE

Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury

Single-center observational cohort study of 1,710 patients aged 60 yr or more after intermediate- or high-risk noncardiac surgery

Hypotension:
- Defined as mean arterial pressure (MAP) below absolute thresholds (50 to 75 mmHg)
- Characterized by cumulative duration, area, and time-weighted average less than MAP

Primary Outcome:
- Myocardial injury based on troponin T test (≥50 ng/l) during first 3 postoperative days

Postoperative Hypotension was common:
- 144 (8%) patients had 2 cumulative h MAP under 60 mmHg
- 824 (48%) patients had 4 h MAP under 75 mmHg

Patients with myocardial injury had more prolonged postoperative hypotension
- Adjusted odd ratios ranged from 2.2 to 3.3 based on severity and duration of hypotension
- Intraoperative hypotension had no effect on myocardial injury

- **Postoperative hypotension was common and was independently associated with myocardial injury**

Anesthesiology 2020;133(3):510-522. doi.org/10.1097/ALN.0000000000003368