Understanding Individual Immunity and Herd Immunity Against SARS-CoV-2: A Brief Primer for Public Health Professionals

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Running Head: COVID-19 Herd Immunity Primer
SUMMARY

The emergence of coronavirus disease 2019 (COVID-19) has resulted in an unprecedented public health challenge. Federal, state, and local officials have begun weighing public safety with the economic consequences of prolonged stay-at-home orders. In the absence of an approved vaccine or effective treatment options, the concept of herd immunity has become increasingly prominent in international discussions and popular press articles regarding COVID-19. A core understanding of how individual and population level immunity may develop is essential for public health professionals, who are often the public face of the pandemic response and are called upon to help make key decisions regarding public safety using the available evidence. In this primer, we provide a brief overview of the concept of herd immunity with relation to what is known about COVID-19, distilling key information about viral and host immunological factors that may influence the eventual development of herd immunity at a population level.

**Keywords:** COVID-19; SARS-CoV-2; herd immunity; public health
INTRODUCTION

The coronavirus disease 2019 (COVID-19; virus: SARS-CoV-2) pandemic started in Hubei Province, China in December 2019 and has since spread rapidly to almost all countries worldwide in just over four months [1]. Thus far, the global case-fatality rate has been relatively lower compared to recent epidemics caused by related viruses—namely, the severe acute respiratory syndrome (SARS) epidemic that emerged in 2002 and was caused by SARS-CoV-1 and the Middle East respiratory syndrome (MERS) epidemic that emerged in 2012 caused by MERS-CoV [2, 3]. Overall, the severe negative economic impacts accompanied by the high morbidity and mortality rates associated with the COVID-19 pandemic will significantly impact our daily lives for the foreseeable future [4].

Various epidemiological models have been developed to project COVID-19 prevalence and mortality rates and to serve as a tool for estimating whether the supply of hospital beds, ventilators, and personal protective equipment (PPE) in respective cities would be sufficient as the pandemic evolves [5, 6]. Many major assumptions must be made about key factors when developing these models, partly because they attempt to project the disease trajectory in populations without sufficient data regarding the total number of individuals (detected and undetected) affected by COVID-19. Depending on the model, assumptions may include the effectiveness of public health responses, continual changes in the basic reproduction number (defined as the number of others infected by one case) due to potential seasonality or other reasons, the rate at which immunity develops in asymptomatic/exposed individuals, and the possibility that some degree of protective immunity exists in a subset of individuals as a consequence of exposure to related coronaviruses. These assumptions have been made in the
absence of significant amounts of data, and their accuracy will remain unknown until more data is generated over the coming months and years.

The concept of herd immunity, along with its possible impact on the COVID-19 pandemic, has been widely debated by epidemiologists, scientists, and medical professionals in the popular press, especially as public discussion about re-opening the economy intensifies in various regions [7-9]. Public health professionals need a core understanding of the individual-level immune response to SARS-CoV-2 and should be aware of what other factors may be at play in achieving herd immunity against COVID-19. The purpose of this primer is to provide a brief overview of the concept of herd immunity with relation to what is known about COVID-19, distilling key information about viral and host immunological factors that may influence the eventual development of herd immunity at a population level.

**HERD IMMUNITY OVERVIEW**

Herd immunity is usually used to describe adequate vaccination coverage critical to the prevention of outbreaks [8]. ( Typically, 85% vaccine coverage against a specific pathogen will prevent pathogen transmission throughout a community.) In recent years, herd immunity has been used to refer to slightly different, though related, concepts. For example, it has been utilized to describe the proportion of a population immune to an infection or what immunologic pattern may be needed to protect a population from infection. While this term describes population or community level immunity, individual-level immunity is prerequisite to attaining herd immunity. In this primer, we define herd immunity as the vaccine coverage or the population level of
immunity resulting from natural infection and recovery, if conferred and maintained, that would be needed to achieve substantial reduction in incidence.

There are many factors that determine whether (or when) herd immunity is attained [10, 11]. Here, we focus on three key points. First, individual infection or vaccination with the pathogen must result in a host response that establishes immunologic memory. Second, enough individuals would have to become infected and develop immunologic memory so that the number of immune individuals reaches a threshold that can prevent the spread of the pathogen should a new case arise. Third, the antigens expressed by the pathogen that are the targets of the host’s immune response and critical to the establishment of a memory response against that organism must not change significantly over time. In the case of COVID-19, if the viral epitopes targeted by the immune response change substantially over time, the ability of the host’s immune system to recognize the virus could be impaired and an immune response to these novel epitopes would have start anew. Such changes to immunologic targets would preclude the development of herd immunity and allow for reinfections of previously immune individuals. These three points are discussed separately in the sections below.

INDIVIDUAL-LEVEL IMMUNE RESPONSE TO SARS-CoV-2

Since the emergence of COVID-19, researchers have tried to better understand host immune responses to the virus in the hopes of expediting the development of a vaccine and effective therapeutics. Much remains unknown regarding the nature of immune responses associated with either protection or disease following exposure to this virus, although preliminary data provide some information about the nature of the immune signature that develops during the early stages of the disease [12-16].
Briefly, in an immunocompetent host, immune responses to most pathogens involve both innate and adaptive immune responses [17]. The innate immune system plays a role during the early stages of infection and occurs rapidly in response to pathogen exposure. Innate immune cells (e.g., macrophages, dendritic cells) are able to recognize, using innate receptors, specific pathogen-associated patterns that are absent on human cells or tissues. Failure of innate immune responses to clear a pathogen leads to the activation of the adaptive immune system. Adaptive immunity involves the development of an antigen-specific immune response (per T-cells and B-cells) that, in most cases, effectively clear the pathogen. An important function of B-cells is their ability to secrete antigen-specific antibodies of varying specificities. Immunoglobulin M (IgM) antibodies are produced first, having a lower binding affinity to respective antigens, and are markers of an early exposure to an infectious agent. Over time, B-cells switch production from IgM to IgG, an antibody with higher affinity to the antigen and a marker of past exposure to the antigen/pathogen or of an immune response that is further developed. An additional hallmark of adaptive immune responses is the establishment of immunological memory that allows memory T-cells and B-cells to respond in a seemingly instantaneous manner to protect the host against subsequent infections with the same pathogen.

It has been hypothesized that if the host is unable to mount an appropriate and timely adaptive immune response following a COVID-19 infection, the innate immune response continues to produce a persistent hyperinflammatory state that could lead to a “cytokine storm” and the development of the acute respiratory distress syndrome that is observed in a subset of patients [18]. For this reason, the initial inflammatory response to COVID-19 has been of particular interest in the context of disease progression or amelioration [19]. In some studies, patients with more severe illness have presented with higher levels of certain pro-inflammatory
cytokines, such as TNF-α and IL-6, compared to those with milder illness [12, 14]. Interestingly, patients with severe illness have been found to have higher neutrophil-to-lymphocyte ratios (a well-established marker of inflammation) in some studies [12, 20]. Although inflammation is associated with clinical severity as a result of infections that can cause sepsis, the mechanisms by which hyperinflammation and immune dysregulation occur following COVID-19 infection and the reason why some patients are more susceptible to such reactions is not well understood yet [19].

An effective adaptive (also called acquired) immune response to the virus, either through vaccination or infection, is prerequisite for establishing immunologic memory, and depending on the degree of population exposure, the development of herd immunity [17]. Recent studies have explored the role of adaptive immunity against COVID-19, although data available to date are limited [13]. A small case series that examined serum samples (n=16) collected at least 2 weeks post onset of illness demonstrated that 88% (14/16) and 94% (15/16) of patients developed IgM antibodies specific to the viral nucleoprotein (NP) and the spike protein receptor binding domain (SRBD), respectively [13]. In addition, these individuals also developed anti-NP (94%; 15/16) and anti-SRBD specific IgG responses (100%; 16/16) [13]. IgG levels correlated with viral neutralizing activity. In a different study, yet to be peer-reviewed (preprint only), the proportion of patients that seroconverted was 94% (75/80) for anti-SARS-CoV-2 IgM and 94% (75/80) for IgG [21]. Using information from contact tracing, the authors estimated that median seroconversion time was 18 days post exposure for IgM and 20 days for IgG. Furthermore, increasing levels of anti-COVID-19 specific antibody levels were correlated with decreasing viral loads. Other case series have also reported relatively high rates of seroconversion [15, 22], and the available literature on this topic is expanding rapidly. For now, given the recent
emergence of SARS-CoV-2, detailed long-term longitudinal data are not available on humoral (antibody-based) and cell-mediated responses to the virus.

While the development of COVID-19-specific IgG responses are an important indicator of possible humoral immunity to the virus, additional serological studies incorporating longer-term follow-up data on convalescent cases are warranted to help assess the extent to which adaptive responses and subsequent memory responses can help prevent re-infections. Some insights may be gained from previous studies examining the nature of infections with related coronaviruses, such as SARS-CoV-1 and MERS-CoV [23-27]. A small study of nine MERS survivors found that asymptomatic patients did not mount a detectable antibody response, whereas patients who developed severe pneumonia still had detectable antibodies to MERS-CoV 18 months later [25]. In a longitudinal study of 176 convalescent SARS patients, IgG levels peaked 3-4 months after symptom onset and were substantially reduced 2 to 3 years later [23]. A smaller study indicated that only 2 out of 23 recovered SARS patients still had detectable anti-SARS-CoV-1 IgG levels approximately 6 years post infection [28].

Similarly, little is currently known about potential long-term cell-mediated immunity against SARS-CoV-2, but again some information from related human coronaviruses is available [24, 27]. Overall, previous studies have indicated that infection with SARS-CoV-1 induces a robust and lasting memory T cell response to viral structural proteins [24]. For example, a few studies have reported that patients who recovered from SARS still retained cytotoxic T cells responsive to the spike and nucleocapsid proteins of SARS-CoV in their peripheral blood mononuclear cells from 1 to more than 10 years after infection.[27]

With regard to current knowledge about potential re-infection with COVID-19 specifically, preliminary reports on viral clearance and repeat reverse transcription polymerase
chain reaction (RT-PCR)-based testing provide conflicting evidence on this topic and are complicated by issues related to test accuracy and the potential for human error in the collection or processing of test specimens [29, 30]. Additionally, there have been some unconfirmed media reports of individuals testing positive for the virus months after initially becoming infected [31]. However, there is insufficient evidence to suggest that these individuals represent instances of actual re-infection, rather than persistent mild infection or inaccurate serial test results. For example, a few case series have described convalescing patients who tested positive for SARS-CoV-2 following more than one negative test, suggesting that the virus may persist for some time following clinical recovery [13, 30]. It is also possible that some individuals, such as those who are older or may be immunosuppressed, are unable to mount a sufficiently robust immune response to completely clear the virus. Future longitudinal studies will shed additional light on the nature of the adaptive immune response during illness and after recovery from COVID-19 and may also elucidate whether asymptomatic and mild SARS-CoV-2 infections result in long-lasting immunity.

**FROM INDIVIDUAL-LEVEL IMMUNITY TO HERD IMMUNITY**

In the absence of an available COVID-19 vaccine, a natural development of adaptive immune responses resulting in effective COVID-19-specific immunological memory would need to develop before herd immunity can be established. Discussions aimed at determining the rate at which infections would have to progress without overburdening the healthcare system (and the resultant morbidity and mortality of such widespread infection) before herd immunity could be established are beyond the scope of this primer. However, estimating the basic reproduction number from existing data, Kwok et al. provided a crude calculation, suggesting that, at
minimum, almost 70% of the U.S. population would need to develop immunity (either through vaccination or infection/recovery) to achieve herd immunity, assuming the absence of cross-reactivity or partial immunity from the four endemic human coronavirus strains (229E, NL63, HKU1, and OC43) [32].

Interestingly, some very preliminary data are available on the latter assumption [33]. Specifically, Okba et al. observed some cross-reactivity between antibodies against the COVID-19 virus (SARS-CoV-2) and SARS-CoV-1, and to a lesser extent with MERS-CoV and an endemic human coronavirus strain, HCoV-OC43. This was likely due to similarities between these coronaviruses in their epitopes, specifically the amino acid sequences of certain segments of the spike protein that are well conserved between these related viruses. However, this study was based on a very small number of serum samples from COVID-19 patients and was conducted for the purpose of testing different antigens to inform the development of a serological test (enzyme linked immunosorbent assay; ELISA). By contrast, another recent study that used sera from recovered SARS and COVID-19 patients found limited cross-reactivity, suggesting that substantial cross-protection is unlikely against infections with these related viruses [34]. Forthcoming studies will continue to clarify whether a subset of the population may potentially have some protection through antibodies that are cross-reactive to COVID-19. The findings of these studies could have implications about what proportion of the population would need to develop an adaptive immune response to the novel virus before reaching herd immunity.

VIRAL FACTORS IN HERD IMMUNITY

In general, the mutation rate of a virus can influence the development of herd immunity— particularly, if mutations occur in antigens that are the targets of adaptive immune
responses associated with protection against infection. Antigenic drift is a term used to describe gradual changes in the viral antigens stemming from mutations representative of minor errors in the viral replication process (or resulting from host-imposed selection pressures) [35]. In general, antigenic drift could result in changes that would allow viruses to evade the host’s immune response, depending on the nature of the respective mutations. Higher mutation rates are generally associated with an increased probability that viral epitopes targeted by antigen-specific antibodies can no longer be recognized. Therefore, mutations in genes encoding SARS-CoV-2 structural surface proteins, such as the spike protein, could have an impact on both individual and population immunity, although this potential impact is difficult to predict and quantify at this time.

Overall, coronaviruses tend to have lower mutation rates compared to other RNA viruses [26, 36]. Other RNA viruses are well known for undergoing antigenic drift over time, which is partly why the influenza vaccine needs annual modifications. Unlike the influenza virus, human coronaviruses have a proofreading mechanism (an exoribonuclease) that helps reduce errors resulting from viral replication [26, 36]. It has, therefore, been hypothesized that the COVID-19 virus may be more stable over time relative to other RNA viruses (e.g., the influenza virus) [26]. Interestingly, while the SARS virus appears to have a mutation rate somewhat similar to HIV, preliminary evidence to date suggests that the COVID-19 and MERS viruses may both be more genetically stable than SARS-CoV-1, but current knowledge remains limited [26].

Significant efforts are underway to investigate the mutation rate of the COVID-19 virus, and data on over 3200 viral genome sequences are already available through the Global Initiative on Sharing All Influenza Data (https://www.gisaid.org/) [37]. Recently, Wang et al. compared 95 published full-length SARS-CoV-2 genomic sequences, and found a 99.99% homology both at
the nucleotide and amino acid levels [38]. However, 12 regions of the viral genome had mutations in at least 3 of the 95 full-length sequences examined. These regions included the spike and nucleoprotein genes, although the significance of these findings is currently unclear outside of the context of designing primers and probes for PCR tests. Regardless, viral evolution is complex, and whether or how new mutations will affect vaccine development or natural development of herd immunity cannot be readily predicted at this time [39].

**SUMMARY & CONCLUSIONS**

New information on COVID-19 is emerging daily and continues to shape our understanding of the three key points discussed in this primer. Whether infections with COVID-19 result in protective memory responses and whether prior exposures to related coronaviruses play any role in the establishment of herd immunity remains unknown at this point. It is also unclear at this juncture what the degree of protection against re-infections may be. Regardless, the number of COVID-19 immune individuals in any given populations will need to be high to establish herd immunity. While preliminary information indicates that the SARS-CoV-2 genome may be more stable compared to other RNA viruses, some emerging data might suggest otherwise, and therefore, it is too premature to draw conclusions about this [37]. If the SARS-CoV-2 genome proves to be relatively stable over time, then it would be more probable that antigens critical to the establishment of immunological memory remain viable targets over time, facilitating the development of herd immunity. This information could be useful for epidemiological inference about the future trajectory of the pandemic. Overall, despite rapidly advancing scientific information, much remains enigmatic about COVID-19, and caution is warranted in popular discussions about the possibility of re-opening society using approaches
based on serostatus or putative immunity until more research is available on the development of immunological memory against COVID-19.

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