Herd immunity and SARS-CoV-2 pandemic

Research project

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SUPERVISOR CERTIFICATE

This is certifying that the article review on “Herd Immunity and SARS-CoV-2 Pandemic” submitted by (Shahen Hamadamin Ebrahim) as partial fulfilment of the requirements for the Degree of B.Sc. work carried out by her under our guidance. It is certified that the work has not been submitted anywhere else for the award of any other diploma or degree of this or any other university.

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Abstract
The SARS-COV-2 pandemic has been a global threat. Through rapid and effective surveillance and control, the newly confirmed patients have been fluctuated at a very low level and imported case explained most of them through March, 2020 to the present, indicating China’s response has achieved a stage victory. By contrast, the epidemic of SARS-COV-2 in other countries out of China is bursting. Different countries are adopting varied response strategy in terms of their public health system to prevent the spread. Herd immunity has been a hot topic since the outbreak of SARS-COV-2 pandemic. Can it be a possible strategy to combat COVID-19? To fully interpret the knowledge regarding the term upon the background of COVID-19-related health crisis, we aim to systematically review the definition, describe the effective measures of acquiring herd immunity, and discuss its feasibility in SARS-COV-2 prevention. Findings from this review would promote and strengthen the international cooperation and joint efforts when confronting with COVID-19.

Keywords: SARS-CoV-2, outbreak, pandemic, herd immunity.
1. Introduction

On March 11st, 2020, the world health organization (WHO) declared Coronavirus Disease 2019 (COVID-19) as a global pandemic. By 10am on August 30th, 217 countries or regions had reported confirmed cases, with a total of more than 25,070,000 cases (World Health Organization, 2020b). In early March, British Prime Minister Boris Johnson unveiled UK’s plan to tackle the SARS-COV-2 outbreak through four phases – Contain, Delay, Research and Mitigate. On March 12nd, the Prime Minister announced that the country had switched from the “Contain” to “Delay” phase. On March 13rd, Sir Patrick Valance, the Government’s chief scientific adviser, mentioned “herd immunity” and pointed out that passively waiting for “herd immunity” would lead to 60% of the population infected with SARS-COV-2. Ever since then, “herd immunity” was top searched through the internet and remains to be a hot issue in debate. Even in April, Sweden’s chief epidemiologist, Dr. Anders Tegnell, said Sweden was tackling the SARS-COV-2 outbreak through “herd immunity.” At approximately the same time, the United States and Australia were also under public scrutiny over whether the two countries were adopting “herd immunity” strategy.

The term “herd immunity” has never been noticed by the general public before and this is unprecedented that it comes into our sight. Here, we choose China, the United Kingdom, Sweden, the United States, and Australia as our settings, illustrating the theoretical basis of “herd immunity,” and discuss its feasibility in the fight of curtaining SARS-COV-2 outbreak. Here, we explain the basic concepts of herd immunity and discuss its implications in the context of SARS-COV-2. In this review, we summarize relevant herd
immunity to SARS-CoV-2 immunization strategies, and recent efforts of SARS-COV-2 vaccine development. We hope this review can provide essential knowledge for any researcher who is interested in herd immunity achievement.

2. Herd Immunity and its threshold

“Herd immunity,” as a concept in immunology, is used to describe the resistance to the spread of a contagious disease within a population or herd. The concept was first proposed in Topley and Wilson (1923) in their publication named the spread of bacterial infection: The problem of “herd immunity.” Herd immunity only exists when a sufficiently high proportion of the population generate immunity against the foreign pathogen so that the probability of transmission between infected and susceptible individuals is reduced (Smith, 2019). In other words, it is becoming difficult for contagious disease to spread between individuals if herd immunity exists as the chain of transmission is broken and the susceptible individuals are protected from infection. In 1933, Dr. Arthur W. Hedrich, health official of Chicago, Illinois, observed the phenomenon that the measles outbreak was prevented after 68% of children were infected between 1900 and 1930 in Boston, Massachusetts (Fine, 1993). The number of cases were kept to a low level after the measles vaccine was legalized in 1964 and the second dose was inoculated till the late 1980s (Figure 1) (Measles and Use, 1998, McNabb et al., 2007).
The herd immunity threshold is defined as the proportion of individuals in a population who, having acquired immunity, can no longer participate in the chain of transmission. If the proportion of immune individuals in a population is above this threshold, current outbreak will extinguish and endemic transmission of the pathogen will be interrupted. In the simplest model, the herd immunity threshold depends on the basic reproduction number (R0; the average number of persons infected by an infected person in a fully susceptible population) and is calculated as $1 - 1/R0$ (Figure).2,3
The effective reproduction number incorporates partially immune populations and accounts for dynamic changes in the proportion of susceptible individuals in a population, such as seen during an outbreak or following mass immunizations. A highly communicable pathogen, such as measles, will have a high $R_0$ (12-18) and a high proportion of the population must be immune to decrease sustained transmission. Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, most of the studies estimated the SARS-CoV-2 $R_0$ to be in the range of 2 to 3.2. Assuming no population immunity and that all individuals are equally susceptible and equally infectious, the herd immunity threshold for SARS-CoV-2 would be expected to range between 50% and 67% in the absence of any interventions.

2.1 Achievement of herd immunity
Herd immunity is based on individual immunity which refers to a physiological function that the body’s immune system recognizes and differentiates its own and alien substances and eliminates the antigenic substances (such as bacteria and viruses) through immune response to maintain health. It may be built up by confronting a disease or infection in the
past and recovering from it. Immunity can also be induced by vaccination. Herd immunity is usually achieved by vaccination (e.g., smallpox vaccine) or by lots of people being infected with the contagious disease (e.g., influenza). (Xia et al., 2020)

The above interpretation of $R_0$ and its relation to the herd immunity threshold is the simplest understanding of these terms. It relies on several key assumptions, including homogeneous mixing of individuals within a population and that all individuals develop sterilizing immunity—immunity that confers lifelong protection against reinfection—upon vaccination or natural infection. In real-world situations, these epidemiological and immunological assumptions are often not met, and the magnitude of indirect protection attributed to herd immunity will depend on variations in these assumptions. $R_0$ is defined by both the pathogen and the particular population in which it circulates. Thus, a single pathogen will have multiple $R_0$ values depending on the characteristics and transmission dynamics of the population experiencing the outbreak (Delamater et al., 2019). This inherently implies that the herd immunity threshold will vary between populations, which is a well-documented occurrence (Delamater et al., 2019).

For any infectious disease, communicability depends on many factors that impact transmission dynamics, including population density, population structure, and differences in contact rates across demographic groups, among others (Anderson and May, 1985). All of these factors will directly or indirectly impact $R_0$ and, consequently, the herd immunity threshold. To establish herd immunity, the immunity generated by vaccination or natural infection must prevent onward transmission, not just clinical disease. For certain pathogens, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), clinical manifestations are a poor indicator of transmissibility, as asymptomatic hosts can be highly infectious and contribute to the spread of an epidemic. Once the herd immunity threshold is reached, the efficacy of herd immunity largely depends on the strength and duration of the immunity acquired. For pathogens in which lifelong immunity is induced, as is the case for measles vaccination or infection, herd
immunity is highly effective and can prevent pathogen spread within a population. However, this situation is relatively rare, as immunity for many other infectious diseases, such as pertussis and rotavirus, wanes over time. As a consequence, herd immunity is less effective, and periodic outbreaks can still occur. Finally, if immunity is unevenly distributed within a population, clusters of susceptible hosts that frequently contact one another may remain. Even if the proportion of immunized individuals in the population as a whole surpasses the herd immunity threshold, these pockets of susceptible individuals are still at risk for local outbreaks.

2.2 SARS-COV-2 and Herd immunity
There are many examples in human history of blocking or even eliminating infectious diseases through herd immunity (Plotkin et al., 2001). Smallpox is considered to be among the deadliest infectious diseases human are generally prone to be infected. Its spread in populations initiated for thousands of years from ancient times to the recent human history (Xia et al., 2020). In 1979, smallpox was officially declared eradicated based on herd immunity achieved by intensive vaccination campaigns (Lane, 2006). Similarly, rinderpest, a highly contagious disease, was eradicated in 2011 through herd immunity in animals (Tounkara and Nwankpa, 2017). Other ubiquitous diseases such as measles, rubella, pertussis are not eradicated yet, herd immunity is maintained by keeping the proportion immune above some threshold to protect susceptible individuals (Black,1982;Assaad,1983;fine et al , 2011) Up to now the number of cases were kept in a low level (Adams et al., 2017). In 1988, the incidence of measles in the United States fell to 1.3 cases per million following the introduction of measles vaccines by initiating two measles elimination efforts, and reemergence of indigenous transmission in the United States finally disappeared since 2000 (Orenstein et al., 2004, Phadke et al., 2016). After the whole-cell pertussis vaccines were widely used into routine childhood immunization in the mid- 1940s, there was a mark able reduction in the pertussis incidence, from 150,000 to 260,000 cases to a nadir of just 1010 cases in 1976 annually (Xia et al., 2020, Phadke et al., 2016).
The ongoing SARS-CoV-2 pandemic has caused over 3.5 million clinically confirmed cases of SARS-COV-2 and has claimed more than 250,000 lives worldwide (as of May 4, 2020). Numerous clinical trials to evaluate novel vaccine candidates and drug repurposing strategies for the prevention and treatment of SARS-CoV-2 infection are currently ongoing. However, it is unknown whether these trials will produce effective interventions, and it is unclear how long these studies will take to establish efficacy and safety, although an optimistic estimate for any vaccine trial is at least 12–18 months. In the absence of a vaccine, building up SARS-CoV-2 herd immunity through natural infection is theoretically possible. However, there is no straightforward, ethical path to reach this goal, as the societal consequences of achieving it are devastating. Since the onset of SARS-CoV-2 spread, various studies have estimated the basic reproductive number (R0) of the virus to be in the range of 2 to 6. From an initial cohort of 425 confirmed cases in Wuhan, China, an R0 of approximately 2.2 was estimated, meaning that, on average, each infected individual gives rise to 2.2 other infections (Huang et al., 2020).

More recent estimates place the R0 higher at 5.7, although many estimates fall within this range (Sanche et al., 2020). This variation reflects the difficulty of obtaining accurate R0 estimates in an ongoing pandemic, and the current estimated SARS-CoV-2 R0 values likely do not indicate a complete picture of the transmission dynamics across all countries. Assuming an R0 estimate of 3 for SARS-CoV-2, the herd immunity threshold is approximately 67%. This means that the incidence of infection will start to decline once the proportion of individuals with acquired immunity to SARS-CoV-2 in the population exceeds 0.67. As discussed above, this model relies on simplifying assumptions, such as homogeneous population mixing and uniform sterilizing immunity in recovered individuals across demographic groups, which are unlikely to hold true. Nevertheless, this basic model can give us a rough idea of the number of individuals that would need to be infected to achieve herd immunity in the absence of a vaccine given an approximate herd immunity threshold and a country’s population.
2.3 Prognosis after immunity

Since there’s no approved vaccine for SARS-COV-2 yet, the herd immunity cannot be achieved by vaccination. If herd immunity is derived from natural infection, what is the proportion of a population that need to be immunized in order to achieve the effect of protection? We can estimate this ratio based on the basic infection number (R0, the expected average number of additional cases that one case will generate over the course of its infectious period in an otherwise uninfected and generally susceptible population) of COVID-19. The R0s of some common vaccine-preventable contagious diseases are shown in Table 1 (Xia et al., 2020). Based on the formula of herd immunity threshold (threshold = 1−1/R0)(Plotkin et al., 2001), and the R0 of SARS-COV-2 being 2.27 (Zhang et al., 2020), only when about 56% of population get specific immunity to SARS-CoV-2, then transmission-blocking can be achieved with herd immunity.

Herd immunity in measles suggests the whole population is protected from emerging infections when 90% or more are immunized, whether by vaccination or recovery from natural infection. However, in the case of COVID-19, there are two outcomes when people get naturally infected – recovery and death. It is unclear whether those who are cured are free of the virus and exempted from the contagious, which indicates that the percentage of infected people would be more than 60–70%. According to an epidemiological analysis of SARS-COV-2 in China, SARS-COV-2 can cause about 15% severe cases and a 2% death rate (Organization, 2020);(Zhang et al., 2020). Particularly, the projections above were based on the existing data in China where the overall isolation and the centralized allocation of medical resources of the whole country are adopted. Without effective medical resources and isolation interventions, natural infection may result in a more severe mortality rate. What will be the cost of the government’s “herd immunity” or “mitigate” strategy? A simulation study about the pandemic trend by epidemiological model found that an estimated number of 510,000 British people will die if nothing is carried out, and about 250,000 British people would also die if mitigation
measures were maximized. The study predicted that the peak in mortality would occur after 3 months and, given the estimated R0 of 2.4, 81% of United Kingdom and United States populations would be infected (Mellan et al., 2020).

**TABLE -1** R0 and threshold value of herd immunity of common vaccine-preventable contagious diseases (Xia et al., 2020).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Route of transmission</th>
<th>R0</th>
<th>Herd immunity threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>Saliva</td>
<td>6–7</td>
<td>83–85%</td>
</tr>
<tr>
<td>Measles</td>
<td>Air borne</td>
<td>12–18</td>
<td>92–94%</td>
</tr>
<tr>
<td>Mumps</td>
<td>Droplet spread</td>
<td>4–7</td>
<td>75–86%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Droplet spread</td>
<td>12–17</td>
<td>80–94%</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Fecal-oral transmission</td>
<td>5–7</td>
<td>50–95%</td>
</tr>
<tr>
<td>Rubella</td>
<td>Droplet spread</td>
<td>5–7</td>
<td>83–85%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Contact transmission</td>
<td>6–7</td>
<td>80–85%</td>
</tr>
</tbody>
</table>

2.4 Herd immunity lessons from other Viruses
The length of duration of herd immunity was challenged by immune senescence, and the breadth of duration was challenged by antigenic diversity of a pathogen (Mallory et al., 2018). Over time, the progressive loss of responsiveness to a pathogen and the decreased antibody titer or cellular responses would result in loss of immunity. In the early 21st century, measles infections peaked in Chinese middle-aged adults after re-introduction of the wild type virus, who had been immunized by early-age vaccination and then boosted with attenuated virus after a time interval (Hull et al., 2013). And this phenomenon also occurred in South Korea (Lazalde et al., 2018). Generally, a viral species especially RNA viruses, consists of multiple antigenically distinct variants resulted from antigenic drift, antigenic shift, and recombination(Pica and Palese, 2013);(Payne, 2017). However, most RNA polymerases lack a proofreading function to solve it. It poses challenging obstacles in eliciting broad immunity through vaccination with a single serotype of attenuated virus, as evidenced by Norovirus(Debbink et al., 2014), dengue (Midgley et al., 2011), and influenza (Karthik et al., 2014). Moreover, vaccination with a single serotype may increase the severity of a secondary infection, which ever occurred in Dengue virus with
four serotypes (Chrisman et al., 2011). Similarly, vaccination with the bivalent HPV vaccine caused decline in the prevalence of HPV types 16 and 18 and cross-protection against non-vaccine types HPV 31, 33, and 45, but increased prevalence of non-vaccine, non–cross-protective HPV types (Brisson et al., 2016, Zhang et al., 2010, Ribeiro et al., 2020).

2.5 being a threat to the world

We are now living in an era of “the global village” with constant flux of large populations. There will be an “Immunity gap” if the majority of people gain antiviral immunity to SARS-CoV-2 in particular countries by natural infection but not in the other countries. Once the solid growth of economy is restored and traffic controls are lifted, there might be large-scale international transmissions with unsatisfactory outcomes. For example, in the early 16th century, the smallpox virus ever killed 3 million Indians who had never been exposed to it after it was introduced to America by European colonists who had been immunized against the smallpox virus (Eyler, 2003). Besides, taking measles as another example, measles epidemics continues to occur even when the measles vaccine is widespread (Smianov et al., 2019). In 2008, an unvaccinated 7-year-old boy contracted measles and infected 11 children, after returning home from a family vacation in Switzerland to San Diego, a city with a 95% measles vaccination rate (Sugerman et al., 2010). That proportion, by the concept of herd immunity, should be enough to keep measles at bay and protect those unvaccinated. This outbreak is mainly due to failure to vaccinate and importation of cases (Shi et al., 2019).

In fact, although the average vaccination rate may be high across the county, it varied locally. Rates in some neighborhoods may be far below the necessary threshold to achieve herd immunity (Peeples, 2019). Various studies have estimated that 2–10% of individuals vaccinated against measles may not develop immunity, allowing a gradual accumulation of susceptible individuals to infection and subsequently outbreaks (Morrison et al., 1994, Shi et al., 2019, Whitaker and Poland, 2014, Haralambieva et al., 2015). Since the mobility
of individuals with measles across global, it is hard to avoid imported infections. The epidemics above can be addressed by vaccinating and treating patients. But now there’s no approved vaccine for COVID-19, many people will inevitably die once the emergence of an epidemic occurs. The total number of imported cases of SARS-COV-2 in China reached 2482 as that of August 30th, which poses a threat to the country.

2.6 Potential risk of virus mutation
To survive and escape the herd immunity, the virus may fight by gene mutation and then the original immune system won’t recognize the mutated virus and the herd immunity will thus be ineffective. In this case the viruses can be divided into two categories – DNA and RNA viruses. DNA viruses are stable with low possibility of mutation while RNA viruses are unstable and prone to mutate (Gelderblom, 1996). The SARS-CoV-2 is an RNA virus with a high potential risk of mutation (Phan, 2020). Homologous recombination may result in the cross-species transmission of SARS-CoV-2 (Ji et al., 2020). Population genetic analysis of 103 SARS-CoV-2 genomes showed that SARS-CoV-2 could be categorized into two major types: L and S. The S type was relatively an ancestral version while the L type was found to be more prevalent than S type in the early stage of the outbreak in Wuhan. Besides, 149 sites across 103 sequenced strains were identified (Tang et al., 2020). Recently, a phylogenetic analysis based on 377 complete genomic sequences of the SARS-COV-2 suggested that the virus was actively evolving in human hosts from December 2019 to March 2020. The highly frequent mutations resulted in York University and the other is the relative of the student. On March 6th, the number of SARS-CoV-2 cases in the United Kingdom showed a rapid increase, and the number of new cases in a single day broke new record, reaching 36, with a total of 87 confirmed cases. United Kingdom was the first country that mentioned “herd immunity,” but in fact United Kingdom did not adopt “herd immunity” as their strategy against the virus. At present, the total number of confirmed cases in the United Kingdom got stabilized and the outbreak has shown a controllable trend. As of August 30st, 2020, the total number of SARS-COV-
2 infections in the United Kingdom reached 334,915. The total number of deaths is 41585 (Li et al., 2020).

2.7 Consequences of Reaching the SARS-CoV-2 Herd Immunity Threshold in the Absence of a Vaccine

One important measure to evaluate the impact of SARS-CoV-2 spread is the overall case fatality rate (CFR). The CFR is the proportion of deaths attributed to a certain disease among all individuals diagnosed with that disease (i.e., cases) over a specified period of time. It is worth noting that there is still significant uncertainty in the CFR for SARS-CoV-2 due to variation in the testing capacity per country, selection bias for which individuals receive testing, and differences in how deaths are officially attributed to COVID-19. Further, CFR is also sensitive to variation in the underlying age structure and distribution of comorbidities among populations. Consequently, CFRs may differ considerably over time and between countries. In the case of COVID-19, the initial estimate of the CFR in a small cohort of 41 individuals with laboratory-confirmed SARS-CoV-2 infection was high (15%) (Wu et al., 2020). However, this number has markedly decreased as more data have become available. Using data from all laboratory-confirmed and clinically diagnosed cases from mainland China, Verity et al. obtained an estimated overall CFR of 1.38%, adjusted for censoring, under-ascertainment, and the underlying demography in China, and similar estimates have been obtained from other groups (Verity et al., 2020, Lu et al., 2020). Like many other infectious diseases, a non-uniform SARS-CoV-2 CFR has been reported across age groups, with the vast majority of deaths occurring among individuals 60 years old or greater.
Figure 3: Herd Immunity (A) SIR (susceptible, infectious, recovered) model for a completely immunizing infection with an R0 = 4. The model assumes a closed population in which no people leave and no new cases are introduced. Following the introduction of a single infected individual, the proportion of infected individuals (red line) increases rapidly until reaching its peak, which corresponds to the herd immunity threshold. After this point, newly infected individuals infect fewer than one susceptible individual, as a sufficient proportion of the population has become resistant, preventing further spread of the pathogen (orange line) (Randolph and Barreiro, 2020).

The most relevant measure to evaluate the societal cost of achieving global SARS-CoV-2 herd immunity is the overall infection fatality rate (IFR). The IFR is defined as the proportion of deaths caused by a certain disease among all infected individuals. Because some cases will not be reported, especially among asymptomatic hosts or individuals with mild symptoms, the IFR will inherently be lower than the CFR. If we combine infection fatality data with an estimate of the number of individuals that need to develop immunity
to reach the herd immunity threshold, we can project the expected number of deaths as a consequence of meeting this threshold. Because of the uncertainty in the SARS-COV-2 IFR, we use three different point estimates in our analysis: (1) an IFR of 0.2%, (2) an IFR of 0.6% that is in line with the IFR determined by Verity et al., and (3) an IFR of 1% (Figure 3C). Assuming a uniform herd immunity threshold of 67% (R0 = 3) and an IFR of 0.6%, the absolute number of expected deaths across the globe would exceed 30 million people (Figure 3C).

![Figure 4: The Potential Health Burden of SARS-COV-2 if Herd Immunity Is Achieved in the Absence of Vaccination](image)

(A) Relationship between R0—the basic reproduction number (Box 1)—and the herd immunity threshold, which corresponds to the proportion of individuals in the population that would need be become immune for herd immunity to be established (y axis). As R0 increases, the proportion of the population that must be immune to generate herd immunity increases (1 – 1/R0) (Randolph and Barreiro, 2020).

(B) Notably, this analysis assumes that IFRs do not vary across countries, and it does not consider factors that lead to heterogeneity in IFRs, including differences in access to healthcare resources and variation in the prevalence of comorbidities. In reality, CFRs and IFRs vary dramatically across countries, as highlighted by the current estimates of
unadjusted CFRs across the globe (Italy, 13.7%; United States, 5.77%; South Korea, 2.33%; (Van Hecke and Lee, 2020). Although testing biases and differences in age demographics across countries account in part for these elevated regional CFRs, additional factors likely play a role, most notably a strain on local healthcare systems. In Italy, a sudden influx of COVID-19 patients in March led to a shortage of intensive care unit beds and other essential medical resources, causing a substantial burden on hospitals.

This outbreak underscores the importance of taking into account the limits of local healthcare infrastructure and how exceeding these limits can exacerbate negative outcomes of COVID-19. Particularly in the context of attaining herd immunity to SARS-CoV-2, a regard for finite healthcare resources cannot be overstated, as this policy inherently relies on allowing a large fraction of the population to become infected. Unchecked, the spread of SARS-CoV-2 will rapidly overwhelm healthcare systems. A depletion in healthcare resources will lead not only to elevated SARS-COV-2 mortality but also to increased all-cause mortality. This effect will be especially devastating for countries in which hospitals have limited surge capacity, where minimal public health infrastructure exists, and among vulnerable communities, including prison and homeless populations.

2.8 Epidemiological Considerations for SARS-CoV-2 Herd Immunity

Because SARS-CoV-2 is a novel pathogen, many features of its transmission and infection dynamics are not well characterized. Thus, our above analysis provides only a sense of the potential ramifications given a scenario in which we attain herd immunity via natural infection. We do not consider numerous complexities of viral spread and infectivity, including variation in R0 across time and populations, heterogeneity in the attack and contact rates across demographic groups, and inter-individual variation in communicability and disease severity, although these aspects are essential to understand the full picture of SARS-CoV-2 community spread. While these epidemiological factors have important implications in the context of herd immunity, currently, they are difficult
to estimate given the limited data available. Differences in population density, cultural behaviors, population age structure, underlying comorbidity rates, and contact rates across groups influence transmission dynamics within communities, so the assumption of a uniform R0 across populations is not realistic.

Further, variation in transmissibility between individuals may play a major role in SARS-CoV-2 spread. Super spreading events occur when circumstances favorable for high rates of transmission arise. These events involve a single index case infecting a large number of secondary contacts and are known to be important in driving outbreaks of infectious diseases, including SARS, Middle East respiratory syndrome (MERS), and measles (Lloyd-Smith et al., 2005). Reports of SARS-CoV-2 super spreading events have been documented, suggesting that heterogeneity in infectivity may significantly impact the dynamics of its (Wang et al., 2020). Finally, the factors that influence inter-individual heterogeneity in SARS-COV-2 susceptibility, clinical pathology, and disease outcome are not well understood. Reported differences in sex- and ethnicity-specific CFRs suggest that genetic, environmental, and social determinants likely underlie variation in susceptibility to SARS-COV-2 and the severity of SARS-COV-2 complications, although future studies are needed to explore this further (Maghbooli et al., 2020).

2.9 Immunological Considerations for SARS-CoV-2 Herd Immunity
The ability to establish herd immunity against SARS-CoV-2 hinges on the assumption that infection with the virus generates sufficient, protective immunity. At present, the extent to which humans are able to generate sterilizing immunity to SARSCoV-2 is unclear. A recent study assessing the possibility of SARS-CoV-2 reinfection in a small cohort of rhesus macaques found that reinfection was not able to occur 1 month after the first viral challenge, suggesting at least short-term sterilizing immunity in these animals (Zandifar and Badrfam, 2020). In a cohort of 175 recovered SARS-COV-2 patients, SARS-CoV-2-specific serum neutralizing antibodies (NAbs) were detected at considerable, albeit variable, titers in most (n = 165) individuals (Zhao et al., 2020),
indicating that the production of NAb against SARS-CoV-2 is relatively common. Whereas these findings are promising, other important questions to consider are whether NAb titers will wane over time and how long acquired immunity will last. Previous studies in confirmed SARS patients have demonstrated that NAb responses against SARS-CoV persisted for several months to 2 years, although all individuals displayed low titers after about 15 months (Mo et al., 2008). Further, elevated concentrations of specific antibodies to coronavirus 229E, one of the viruses responsible for the common cold, were found 1 year after infection, although these titers were not sufficient to prevent reinfection in all individuals (Callow et al., 1990). Together, these studies suggest that protection against reinfection with coronavirus species tends to diminish given sufficient time, although longitudinal serological studies are needed to assess the duration of SARS-CoV-2 immunity. If this proves to also be true for SARS-CoV-2, persistent herd immunity may never be attained in the absence of recurrent vaccination. Indeed, modeling of the transmission dynamics of SARS-CoV-2 predicts that short-term immunity (10 months) would give rise to annual outbreaks, while longer-term immunity (2 years) would lead to biennial outbreaks (Kissler et al., 2020).

Mass serological testing is now needed to determine how many individuals have been infected, how many individuals are immune, and how far we are from reaching the herd immunity threshold. That said, even if reinfection can occur after sterilizing immunity wanes, enduring memory cells of the adaptive immune system would likely facilitate immune control of the virus and limit disease pathology, which would hopefully decrease the clinical severity of subsequent infections.

T-Cell Cross-reactivity T-cells are important mediators of immunity. Recent reports have suggested that cross-reactivity with other coronaviruses may confer relative protection of the population from coronavirus disease 2019 (COVID-19). It is less clear that T-cell cross-reactivity could provide sterilizing immunity (ie, that the host could not carry nor transmit infection) as opposed to reducing the severity of illness).
2.10 Infection-Based Herd Immunity as Policy

An infection-based herd immunity approach (ie, letting the low-risk groups become infected while “sequestering” the susceptible groups) has been proposed to slow the spread of SARS-CoV-2. However, such a strategy is fraught with risks. For example, even with modest infection fatality ratios, a new pathogen will result in substantial mortality because most, if not all, of the population would not have immunity to the pathogen. Sequestering the high-risk populations is impractical because infections that initially transmit in low mortality populations can spread to high-mortality populations. Moreover, so far, there is no example of a large-scale successful intentional infection-based herd immunity strategy. There are only rare instances of seemingly sustained herd immunity being achieved through infection. The most recent and well documented example relates to Zika in Salvador, Brazil. Early in the SARS-COV-2 pandemic, as other countries in Europe were locking down in late February and early March of 2020, Sweden made a decision against lockdown. Initially, some local authorities and journalists described this as the herd immunity strategy: Sweden would do its best to protect the most vulnerable, but otherwise aim to see sufficient numbers of citizens become infected with the goal of achieving true infection-based herd immunity.

By late March 2020, Sweden abandoned this strategy in favor of active interventions; most universities sand high schools were closed to students, travel restrictions were put in place, work from home was encouraged, and bans on groups of more than 50 individuals were enacted. Far from achieving herd immunity, the seroprevalence in Stockholm, Sweden, was reported to be less than 8% in April 2020,7 which is comparable to several other cities (ie, Geneva, Switzerland,8 and Barcelona, Spain9). The population of the United States is about 330 million. Based on World Health Organization estimates of an infection fatality rate of 0.5% about 198 million individuals in the United State are needed to be immune to reach a herd immunity threshold of approximately 60%, which would lead to several hundred thousand additional deaths. Assuming that less than 10% of the population has been infected so far,10 with an infection-induced immunity lasting 2 to 3 years (duration
unknown), infection-induced herd immunity is not realistic at this point to control the pandemic. SARS-CoV-2 vaccines will help to reach the herd immunity threshold, but the effectiveness of the vaccine(s) and the vaccine coverage are to be seen (Randolph and Barreiro 2020).

3. Conclusions
Herd immunity is an important defense against outbreaks and has shown success in regions with satisfactory vaccination rates. Importantly, even small deviations from protective levels can allow for significant outbreaks due to local clusters of susceptible individuals, as has been seen with measles over the past few years. Therefore, vaccines must not only be effective, but vaccination programs must be efficient and broadly adopted to ensure that those who cannot be directly protected (Children, too young to be vaccinated, Immunosuppressed patients who cannot be vaccinated, To elderly who cannot mount optimal immunoresponse to vaccine, to people who have independent access to immunization and to people who remain unvaccinated by choice) will nonetheless derive relative protections.
References


