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Herd immunity: In relation to COVID-19

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Abstract

Herd immunity, also known as indirect protection, community immunity, or community protection, refers to the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population. In other words, herd immunity is the inability of infected individuals to propagate an epidemic outbreak due to lack of contact with sufficient numbers of susceptible individuals. It stems from the individual immunity that may be gained through natural infection or through vaccination. The term herd immunity was initially introduced more than a century ago. In the latter half of the 20th century, the use of the term became more prevalent with the expansion of immunization programs and the need for describing targets for immunization coverage, discussions on disease eradication, and cost-effectiveness analyses of vaccination programs. Eradication of smallpox and sustained reductions in disease incidence in adults and those who are not vaccinated following routine childhood immunization with conjugated Haemophilus influenzae type B and pneumococcal vaccines are successful examples of the effects of vaccine-induced herd immunity.

Keywords: Susceptible Individuals; Vaccination; Natural Infection; Immunization; Herd Immunity

1. Basic concept of herd immunity

Acquired immunity is established at the level of the individual, either through natural infection with a pathogen or through immunization with a vaccine. Herd immunity stems from the effects of individual immunity scaled to the level of the population. It refers to the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population. This population-level effect is often considered in the context of vaccination programs, which aim to establish herd immunity so that those who cannot be vaccinated, including the very young and immunocompromised, are still protected against disease. Depending on the prevalence of existing immunity to a pathogen in a population, the introduction of an infected individual will lead to different outcomes Figure-2. In a completely naive population, a pathogen will propagate through susceptible hosts in an unchecked manner following effective exposure of susceptible hosts to infected individuals. However, if a fraction of the population has immunity to that same pathogen, the likelihood of an effective contact between infected and susceptible hosts is reduced, since many hosts are immune and, therefore, cannot transmit the pathogen. If the fraction of susceptible individuals in a population is too few, then the pathogen cannot successfully spread, and its prevalence will decline. The point at which the proportion of susceptible individuals falls below the threshold needed for transmission is known as the herd immunity threshold. Above this level of immunity, herd immunity begins to take effect, and susceptible individuals benefit from indirect protection from infection. 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

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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.

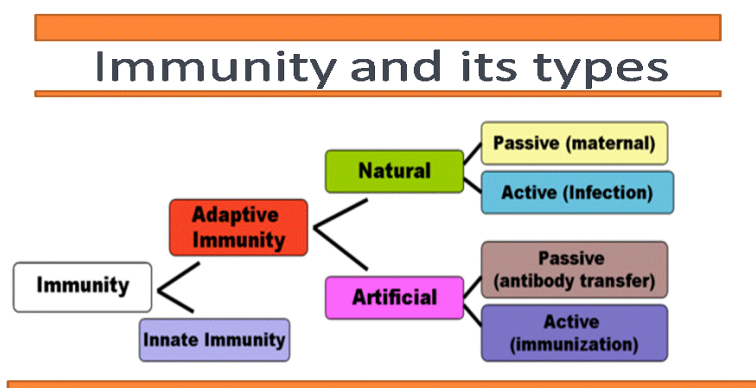


Figure 1 Classification of immunity

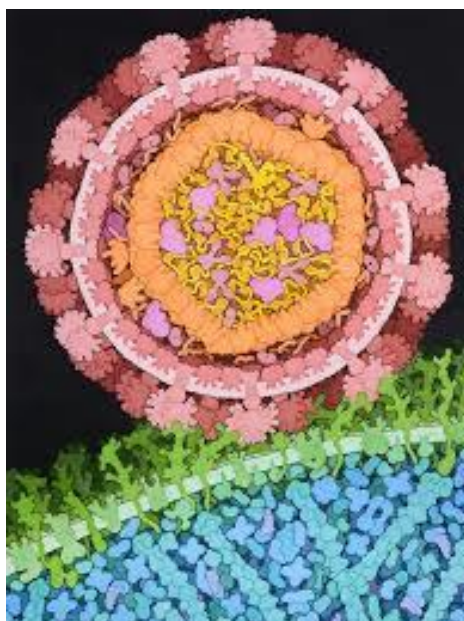


Figure 2 Probable diagrammatic representation of pathogen

2. New corona virus encouraging scientists to find vaccine early

2.1. Herd immunity threshold

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 outbreaks 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 (R_0 ; the average number of persons infected by an infected person in a fully susceptible population) and is calculated as $1 - 1/R_0$. 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.

2.2. Herd immunity and COVID/SARS

The ongoing SARS-CoV-2 pandemic has caused over 3.5 million clinically confirmed cases of COVID-19 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 Figure-3. However, there is no straightforward, ethical path to reach this goal, as the societal consequences of achieving it are devastating.

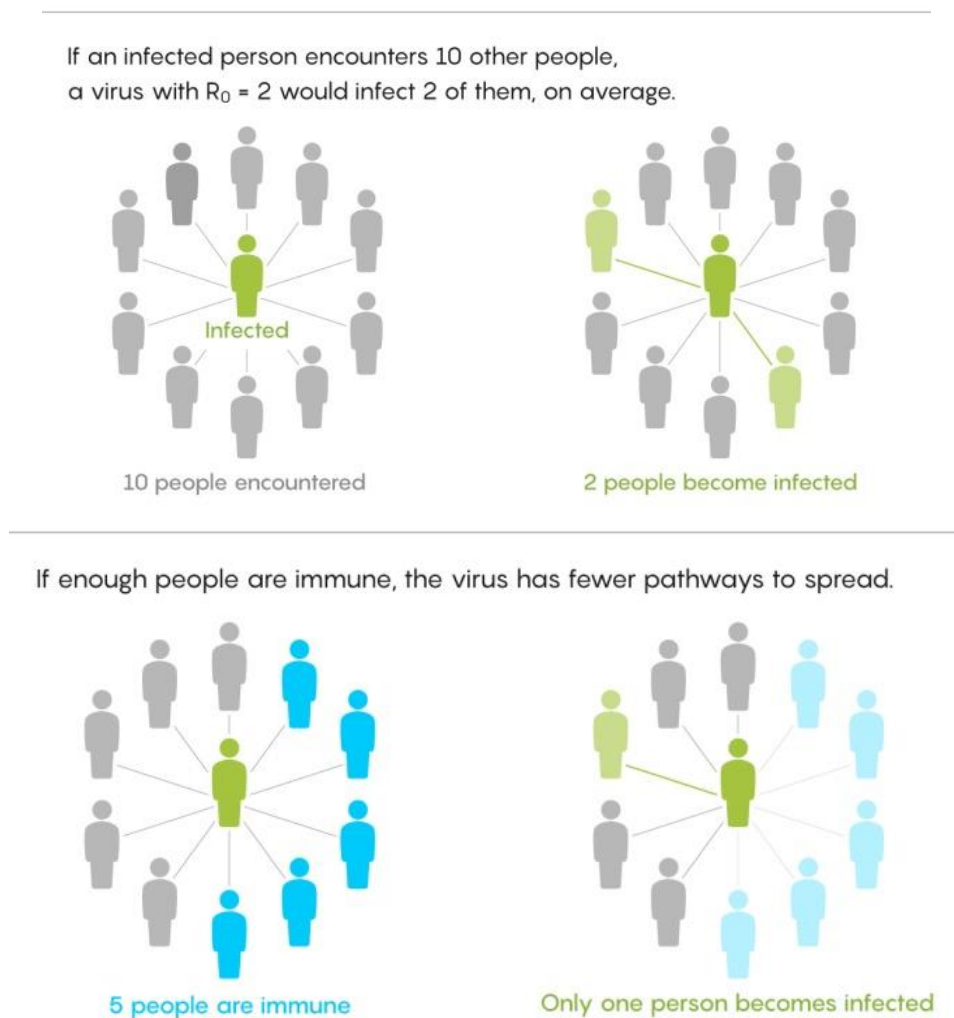


Figure 3 Herd immunity threshold

Since the onset of SARS-CoV-2 spread, various studies have estimated the basic reproductive number (R_0) of the virus to be in the range of 2 to 6. From an initial cohort of 425 confirmed cases in Wuhan, China, an R_0 of approximately 2.2 was estimated, meaning that, on average, each infected individual gives rise to 2.2 other infections. More recent estimates place the R_0 higher at 5.7, although many estimates fall within this range. This variation reflects the difficulty of obtaining accurate R_0 estimates in an ongoing pandemic, and the current estimated SARS-CoV-2 R_0 values likely do not indicate a complete picture of the transmission dynamics across all countries. Assuming an R_0 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.

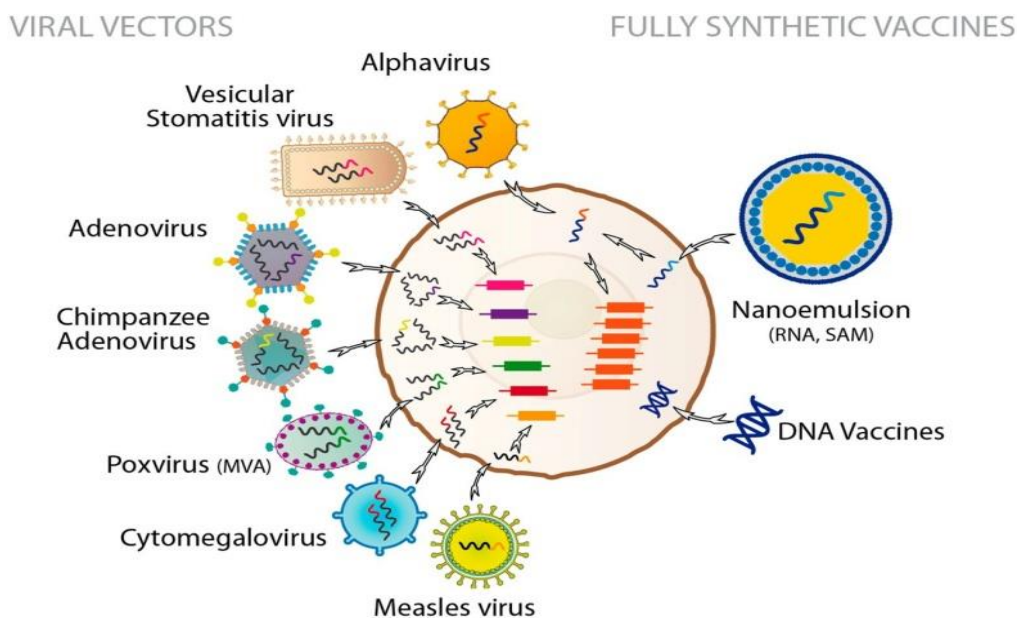


Figure 4 How the viral vectors lead to vaccine

3. Emerging infections

3.1. 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 Figure-. 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.

3.2. 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 COVID-19 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%). 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. Like many other infectious diseases, a non-uniform COVID-19 CFR has been reported across age groups, with the vast majority of deaths occurring among individuals 60 years old or greater. 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 COVID-19 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%. Assuming a uniform herd immunity threshold of 67% ($R_0 = 3$) and an IFR of 0.6%, the absolute number of expected deaths across the globe would exceed 30 million people. 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%). 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 COVID-19 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.

3.3. Epidemiological considerations for SARS-CoV-2 herd immunity

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 R_0 across populations is not realistic. Further, variation in transmissibility between individuals may play a major role in SARS-CoV-2 spread. Superspreading 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. Reports of SARS-CoV-2 superspreading events have been documented, suggesting that heterogeneity in infectivity may significantly impact the dynamics of its transmission. Finally, the factors that influence inter-individual heterogeneity in COVID-19 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 COVID-19 and the severity of COVID-19 complications, although future studies are needed to explore this further. 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 emphasized and 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.

3.4. Coronavirus reinfection

One of the primary reasons that 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.

4. Conclusion

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 will nonetheless derive relative protections.

Compliance with ethical standards

Acknowledgments

The article has been acknowledged by the faculty.

Disclosure of conflict of interest

There is no conflict of address.

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