Immunity

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Primer

Herd Immunity: Understanding COVID-19

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https://doi.org/10.1016/j.immuni.2020.04.012

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated disease, COVID-19, has demonstrated the devastating impact of a novel, infectious pathogen on a susceptible population. Here, we explain the basic concepts of herd immunity and discuss its implications in the context of COVID-19.

Basic Concepts 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 (Box 1) 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 1). 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 (Anderson and May, 1985). Above this level of immunity, herd immunity begins to take effect, and susceptible individuals benefit from indirect protection from infection (Figure 1B).

Under the simplest model, the herd immunity threshold depends on a single parameter known as R_0, or the basic reproduction number (Figure 2A). R_0 refers to the average number of secondary infections caused by a single infectious individual introduced into a completely susceptible population (Anderson and May, 1985). If we consider a hypothetical pathogen with an R_0 of 4, this means that, on average, one infected host will infect four others during the infectious period, assuming no immunity exists in the population. Mathematically, the herd immunity threshold is defined by $1 - 1/R_0$ (e.g., if $R_0 = 4$, the corresponding herd immunity threshold is 0.75) (Anderson and May, 1985). Therefore, the more communicable a pathogen, the greater its associated R_0 and the greater the proportion of the population that must be immune to block sustained transmission (Figure 2B). A similar parameter important for understanding population-level immunity is the effective reproduction number (R_e or R_t). R_e is defined as the average number of secondary cases generated by a single index case over an infectious period in a partially immune population (Delamater et al., 2019). Unlike R_0, R_e does not assume a completely susceptible population and, consequently, will vary depending on a population's current immune state, which will change dynamically as an outbreak event or vaccination campaign unfolds. Ultimately, the goal of vaccination programs is to bring the value of R_e below 1. This occurs when the proportion of the population with immunity exceeds the herd immunity threshold. At this point, pathogen spread cannot be maintained, so there is a decline in the number of infected individuals within the population.

Establishing Herd Immunity within Populations

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

Box 1. Glossary

Herd immunity: the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population
Herd immunity threshold: the point at which the proportion of susceptible individuals in a population falls below the threshold needed for transmission
R_0: the average number of secondary infections caused by a single infectious individual introduced into a completely susceptible population
R_e: the average number of secondary infections generated by a single infectious individual over an infectious period in a partially immune population
Onward transmission: the effective transmission of a pathogen from an infected individual to susceptible host(s)
Case Fatality Rate (CFR): proportion of deaths attributed to a certain disease among all individuals diagnosed with that disease
Infection Fatality Rate (CFR): proportion of deaths attributed to a certain disease among all infected individuals

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.

Herd Immunity and SARS-CoV-2

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. 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 (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 (Li et al., 2020). More recent estimates place the R_0 higher at 5.7, although many estimates fall within this range (Sanche et al., 2020). 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.

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%) (Huang 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; Wu et al., 2020a). 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.

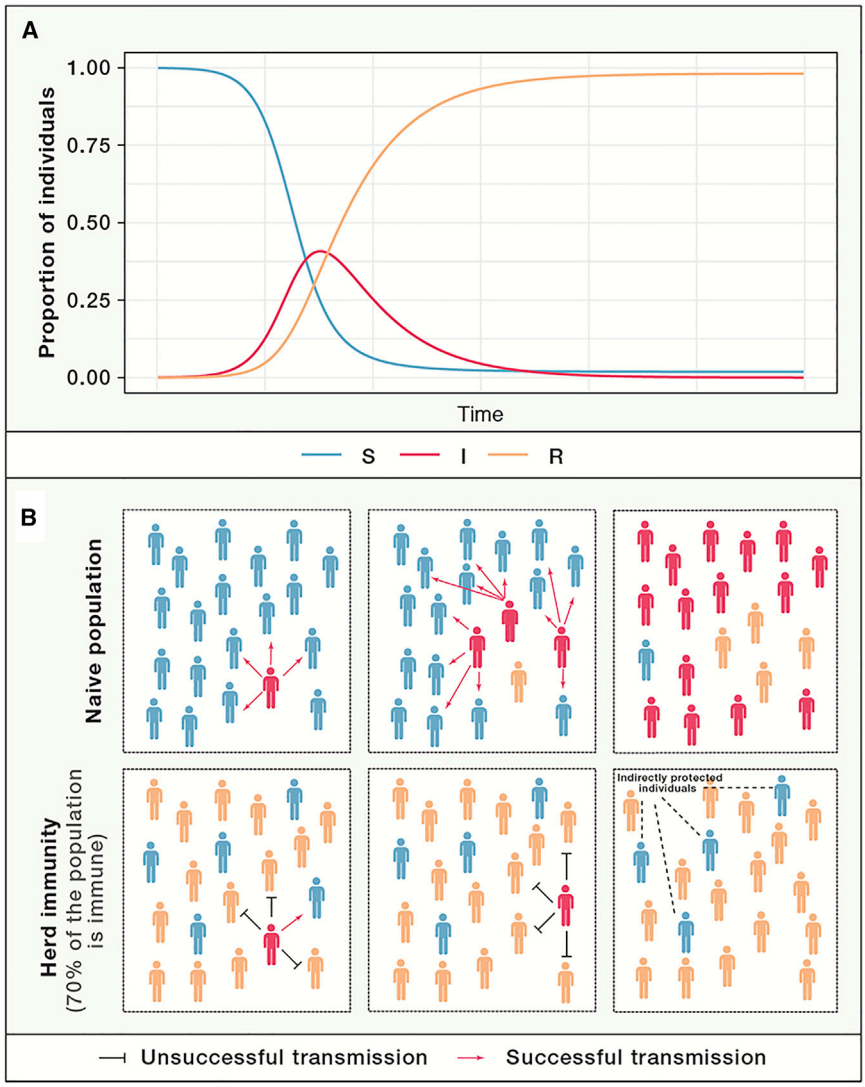

Figure 1. Herd Immunity

(A) SIR (susceptible, infectious, recovered) model for a completely immunizing infection with an $R_0 = 4$. 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).

(B) Schematic depiction of the disease propagation dynamics when one infected individual is introduced into a completely susceptible population (top panel) versus a situation in which an infected individual is introduced into a population that has reached the herd immunity threshold (bottom panel). In the naive population, an outbreak quickly emerges, whereas under the scenario of herd immunity, the virus fails to spread and persist in the population.

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% (Figure 2C). 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 (Figure 2C). 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%; The Centre for Evidence-Based Medicine, 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 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.

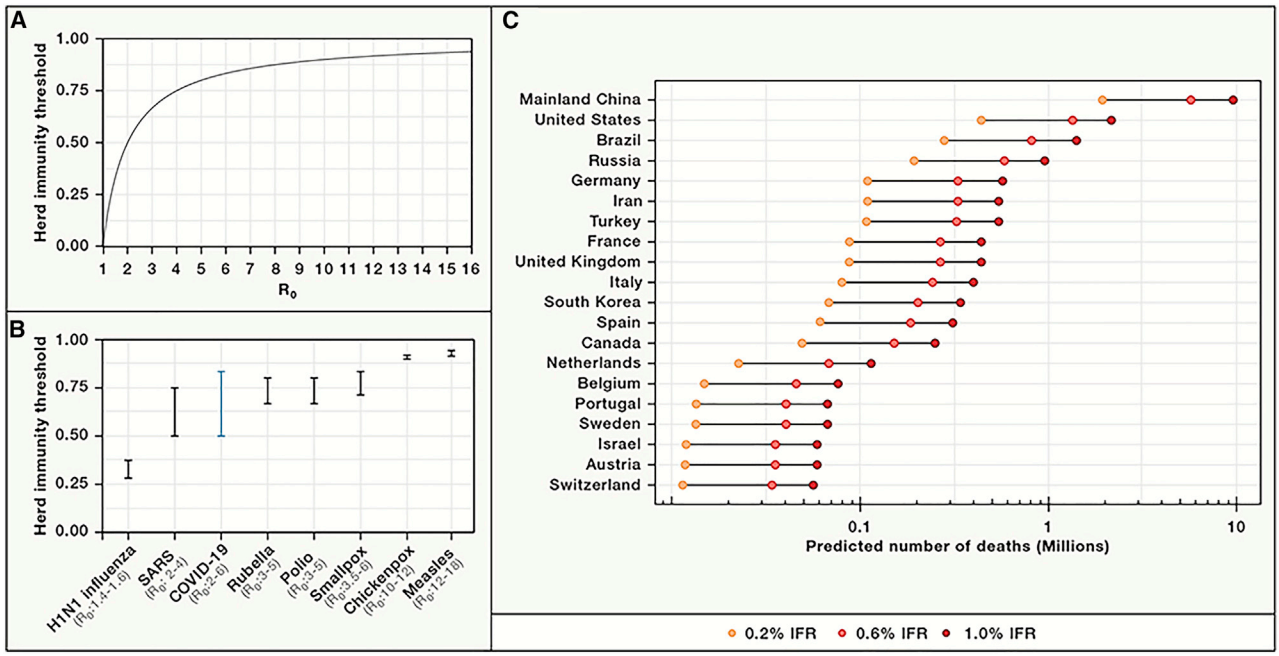

Figure 2. The Potential Health Burden of COVID-19 if Herd Immunity Is Achieved in the Absence of Vaccination

(A) Relationship between R_0—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 R_0 increases, the proportion of the population that must be immune to generate herd immunity increases ($1 - 1/R_0$).

(B) Basic reproduction numbers (R_0) and the corresponding herd immunity thresholds for various infectious diseases. R_0 estimates represent the commonly accepted R_0 range for each of the pathogens reported.

(C) Expected number of absolute deaths for the top 20 countries with the highest incidence of COVID-19 as of April 10, 2020, assuming herd immunity is established at a uniform threshold of 67% ($R_0 = 3$) in each country. Overall COVID-19 infection fatality rates (IFR) of 0.2%, 0.6%, and 1.0% are considered. We note that these numbers are necessarily underestimates given that, even after the herd immunity threshold is reached, it will take a long time until there are no more new cases, and therefore, no new deaths.

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 R_0 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 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 (Lloyd-Smith et al., 2005). Reports of SARS-CoV-2 superspreading events have been documented, suggesting that heterogeneity in infectivity may significantly impact the dynamics of its transmission (Liu et al., 2020). 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 (Nasiri et al., 2020).

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 SARS-CoV-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 (Bao et al., 2020). In a cohort of 175 recovered COVID-19 patients, SARS-CoV-2-specific serum neutralizing antibodies (NAbs) were detected at considerable, albeit variable, titers in most (n = 165) individuals (Wu et al., 2020b),

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., 2006). 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.

Recap

In a sufficiently immune population, herd immunity provides indirect protection to susceptible individuals by minimizing the probability of an effective contact between a susceptible individual and an infected host. In its simplest form, herd immunity will begin to take effect when a population reaches the herd immunity threshold, namely when the proportion of individuals who are immune to the pathogen crosses $1 - 1/R_0$. At this point, sustained transmission cannot occur, so the outbreak will decline. However, in real-world populations, the situation is often much more complex. Epidemiological and immunological factors, such as population structure, variation in transmission dynamics between populations, and waning immunity, will lead to variation in the extent of indirect protection conferred by herd immunity. Consequently, these aspects must be taken into account when discussing the establishment of herd immunity within populations. There are two possible approaches to build widespread SARS-CoV-2 immunity: (1) a mass vaccination campaign, which requires the development of an effective and safe vaccine, or (2) natural immunization of global populations with the virus over time. However, the consequences of the latter are serious and far-reaching—a large fraction of the human population would need to become infected with the virus, and millions would succumb to it. Thus, in the absence of a vaccination program, establishing herd immunity should not be the ultimate goal. Instead, an emphasis should be placed on policies that protect the most vulnerable groups in the hopes that herd immunity will eventually be achieved as a byproduct of such measures, although not the primary objective itself.

ACKNOWLEDGMENTS

We thank members of the Barreiro lab, Valerie Abadie, Sarah Cobey, Maziar Divangahi, Bana Jabri, William Koval, Joaquin Sanz, and Patrick Wilson for the constructive comments and feedback. This work was supported by grant R01-GM134376 from the National Institute of General Medical Sciences to L.B.B. H.E.R is supported by a National Science Foundation Graduate Research Fellowship (DGE-1746045).

REFERENCES

Anderson, R.M., and May, R.M. (1985). Vaccination and herd immunity to infectious diseases. Nature *318*, 323–329.

Bao, L., Deng, W., Gao, H., Xiao, C., Liu, J., Xue, J., Lv, Q., Liu, J., Yu, P., Xu, Y., et al. (2020). Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. bioRxiv. https://doi.org/10.1101/2020.03.13.990226.

Callow, K.A., Parry, H.F., Sergeant, M., and Tyrrell, D.A. (1990). The time course of the immune response to experimental coronavirus infection of man. Epidemiol. Infect. *105*, 435–446.

Delamater, P.L., Street, E.J., Leslie, T.F., Yang, Y.T., and Jacobsen, K.H. (2019). Complexity of the basic reproduction number (R_0). Emerg. Infect. Dis. *25*, 1–4.

The Centre for Evidence-Based Medicine (2020). Global COVID-19 case fatality rates. https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet *395*, 497–506.

Kissler, S.M., Tedijanto, C., Goldstein, E., Grad, Y.H., and Lipsitch, M. (2020). Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science, eabb5793.

Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Ren, R., Leung, K.S.M., Lau, E.H.Y., Wong, J.Y., et al. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N. Engl. J. Med. *382*, 1199–1207.

Liu, Y., Eggo, R.M., and Kucharski, A.J. (2020). Secondary attack rate and superspreading events for SARS-CoV-2. Lancet *395*, e47.

Lloyd-Smith, J.O., Schreiber, S.J., Kopp, P.E., and Getz, W.M. (2005). Superspreading and the effect of individual variation on disease emergence. Nature *438*, 355–359.

Mo, H., Zeng, G., Ren, X., Li, H., Ke, C., Tan, Y., Cai, C., Lai, K., Chen, R., Chan-Yeung, M., and Zhong, N. (2006). Longitudinal profile of antibodies against SARS-coronavirus in SARS patients and their clinical significance. Respirology *11*, 49–53.

Nasiri, M.J., Haddadi, S., Tahvildari, A., Farsi, Y., Arbabi, M., Hasanzadeh, S., Jamshidi, P., Murthi, M., and Mirsaeidi, M. (2020). COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic Review and Meta-analysis. medRxiv. https://doi.org/10.1101/2020.03.24.20042903.

Sanche, S., Lin, Y.T., Xu, C., Romero-Severson, E., Hengartner, N., and Ke, R. (2020). High contagiousness and rapid spread of severe acute respiratory syndrome coronavirus 2. Emerg. Infect. Dis. *26*, https://doi.org/10.3201/eid2607.200282.

Verity, R., Okell, L.C., Dorigatti, I., Winskill, P., Whittaker, C., Imai, N., Cuomo-Dannenburg, G., Thompson, H., Walker, P.G.T., Fu, H., et al. (2020). Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect. Dis. Published online March 30, 2020. https://doi.org/10.1016/S1473-3099(20)30243-7.

Wu, J.T., Leung, K., Bushman, M., Kishore, N., Niehus, R., de Salazar, P.M., Cowling, B.J., Lipsitch, M., and Leung, G.M. (2020a). Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nat. Med. *26*, 506–510.

Wu, F., Wang, A., Liu, M., Wang, Q., Chen, J., Xia, S., Ling, Y., Zhang, Y., Xun, J., Lu, L., et al. (2020b). Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv. https://doi.org/10.1101/2020.03.30.20047365.