

## PRIORITY PAPER

# Long-term and herd immunity against SARS-CoV-2: implications from current and past knowledge

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**One sentence summary:** The authors analyze factors regarding COVID-19 and herd immunity, such percentage of immune population, the length and effectiveness of immune response and stability of the viral epitopes.

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## ABSTRACT

Effective herd immunity against SARS-CoV-2 will be determined on many factors: the percentage of the immune population, the length and effectiveness of the immune response and the stability of the viral epitopes. The required percentage of immune individuals has been estimated to be 50–66% of the population which, given the current infection rates, will take long to be achieved. Furthermore, data from SARS-CoV suggest that the duration of immunity may not be sufficiently significant, while the immunity response against SARS-CoV-2 may not be efficiently effective in all patients, as relapses have already been reported. In addition, the development of mutant strains, which has already been documented, can cause the reemergence of the epidemic. In conclusion, the development of an effective vaccine is an urgent necessity, as long-term natural immunity to SARS-CoV-2 may not be sufficient for the control of the current and future outbreaks.

**Keywords:** COVID-19; antibodies; pandemic; outbreak; coronavirus; quarantine

Herd immunity provides an indirect protection from infection, which is conferred by immune to susceptible individuals in a given population, thus limiting the spread of the disease (Syal 2020). It can be achieved either through vaccination or naturally, following recovery from the disease (Kwok et al. 2020). Effective herd immunity relies on the percentage of the immune population, the length and effectiveness of the immune response and the stability of the viral epitopes (Mallory, Lindesmith and Baric 2018). Whether these factors will permit the development of

herd immunity against severe acute respiratory syndrome coronavirus (SARS-CoV)-2 is of significant concern.

Firstly, regarding the percentage of immune individuals, calculations about the current pandemic suggest that the minimum threshold capable of providing herd immunity against SARS-CoV-2 is at least 50–66.66% (Kwok et al. 2020; Syal 2020). It is speculated that the threshold may be even higher, as cases are likely under-reported (Syal 2020). At the time of writing, roughly 1260 000 people are considered recovered from the infection worldwide (Dong, Du and Gardner 2020), which is less than 0.02%

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of the world's population. Even if these numbers are grossly underestimated, it will be long before an adequate percentage of the population of the world or any given region become immune to SARS-CoV-2 to a degree that can confer herd immunity to susceptible individuals.

Furthermore, the proportion of SARS-CoV-2 infected population differs not only between countries but also between regions of the same country. For example, in Italy, which is among the most heavily affected countries, the distribution of spread within the country varies extensively, with a notable gradient from the North to the South of Italy (La Maestra, Abbondandolo and De Flora 2020); at the same time, USA states report markedly different attack rates per 10 000 population, from 4.27 in Montana or 15.38 in California to 169.33 in New York state (Wissel et al. 2020). This implies that, even if the percentage of recovered population in some regions eventually reaches the level needed for herd immunity, the spread of the virus will not necessarily be controlled, and the epidemic may reemerge soon after restriction measures are lifted. In addition, countries which had less infections and therefore a diminished number of immune individuals, will take longer to achieve herd immunity, provided the transmission of COVID-19 chronically continues.

Secondly, the duration of immunity against SARS-CoV-2 is currently unknown. Information from follow-up studies of patients recovered from other coronaviruses may provide a background regarding the possible long-term immune response of SARS-CoV-2 infection. Cohort studies of recovered SARS-CoV patients found that SARS-CoV-specific antibody titers decline over time. Mo et al. reported that, while IgG titers were declining, they were still detectable in all 18 patients at two years, and retained their neutralizing capabilities in 17/18 patients (MO et al. 2006). Tang et al. (2011) reported that antibody titers were undetectable in 21/23 patients at six years post-infection, while SARS-CoV antigen-specific memory B-cell response was undetectable in all 23 patients. However, memory T-cell responses were still detectable in 14/23 patients. Rokni, Ghasemi and Tavakoli (2020) reported that T-cell responses persist for more than ten years in patients recovered from SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV, even though their protective efficacy is unknown. If similar long-term immunity responses are observed in SARS-CoV-2, it is possible that, while IgG titers and memory B-cells may decline, memory T-cells may remain; however, it is uncertain whether they will be able to mount an adequate immune response.

The duration of effective immunity against SARS-CoV-2 will determine at large the pandemic and post-pandemic transmission of the virus. This is more clearly demonstrated using in silico models of transmission: in the case that immunity against SARS-CoV-2 is transient, the virus will likely enter into regular circulation over the next five years with biennial or annual outbreaks; only in the case that the immunity is permanent will regular circulation of the virus be prevented. Therefore, there is an urgent need for longitudinal serological studies in order to determine the extent and duration of immunity against SARS-CoV-2 (Kissler et al. 2020).

Thirdly, the efficacy of the antibody response is in question, as a recent case series demonstrated that seroconversion was not followed by an abrupt decline of the viral load in sputum, while antibody titers did not correlate with the clinical course of patients (Wölfel et al. 2020). Another report also demonstrated that the increase in antibody titers was not always accompanied by clearance of viral RNA from the respiratory tract, especially in critical cases, prompting the authors to suggest that the antibody response may not be sufficient for virus clearance (Zhao

et al. 2020). Furthermore, antibody production appears to vary depending on individual factors, as it has been found to be significantly higher in middle-aged and elderly individuals compared to young populations and is also positively correlated with CRP levels (Wu et al. 2020). This begs the question whether all recovered patients will be able to produce an adequate antibody response.

Furthermore, it may be possible for the virus to re-emerge. A case report described a 41-year old patient that was readmitted with symptoms and radiographical findings compatible with COVID-19, despite being discharged 19 days earlier after being considered 'clinically cured' (Li, Zhang and Zong 2020). Another report described four patients with COVID-19 that, despite having two consecutive negative reverse transcription-polymerase chain reaction (RT-PCR) test results separated by at least one day, became RT-PCR positive when evaluated 5 and 13 days later, suggesting that viral shedding may continue in recovered patients (Lan et al. 2020). However, these cases may simply represent a prolonged course of illness rather than re-emergence of the disease.

Finally, the stability of viral epitopes is of significant concern, as the development of mutant SARS-CoV-2 strains is already being reported (Wang et al. 2020). The lethality of COVID-19 is such that it may permit the development of mutant strains. At the time of writing, reports demonstrate that COVID-19 appears to have an overall fatality rate that approximates that of the seasonal flu, rather than the significantly higher fatality rate of infections by SARS-CoV and MERS-CoV. In contrast to viruses with high fatality rate, which infect the host and rapidly lead to death, infections with low fatality rates enable the host to mount an immune response, leading to selection pressure for mutant viruses. As a consequence, the increasing number of individuals recovered from COVID-19 may not be able to provide effective herd immunity during subsequent post-pandemic waves of infection by mutant variants (Biswas et al. 2020).

In conclusion, the development of effective herd immunity may be difficult in the case of SARS-CoV-2, since the various factors that make up herd immunity may be difficult to be achieved concomitantly in all geographical areas and locations. It will be long before the percentage of immune individuals will reach 50–66% of the population (Kwok et al. 2020; Syal 2020), while the duration of immunity may not be sufficiently significant, if it mirrors that of SARS-CoV (MO et al. 2006; Tang et al. 2011). Furthermore, SARS-CoV-2 immunity may not be efficiently effective in all infected individuals, as it is not always associated with viral clearance (Zhao et al. 2020), and cases of relapse have already been reported (Lan et al. 2020; Li, Zhang and Zong 2020). Finally, the development of mutant strains to which immunity has not yet been developed can lead to the emergence of new epidemics (Biswas et al. 2020; Wang et al. 2020). As long-term natural immunity to SARS-CoV-2 is uncertain, herd immunity may depend on effective vaccination even more. Therefore, the development of an effective vaccine is of paramount importance, not only for the control of the current outbreak, but also for the prevention of future outbreaks.

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**Conflict of interest.** None declared.

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