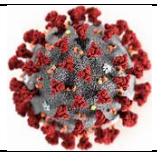
National COVID-19 Science Task Force (NCS-TF)



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Comment on planned updates : new data is regularly provided by various studies, possibly requiring updates of this PB	

Title: SARS-CoV-2 infection-induced immune responses: meaningful immune protection?

Summary of request/problem

There are increasing numbers of reports describing that people with SARS-CoV-2 infection generate immune responses (antibodies, T cells). Here we address the questions whether these immune responses confer protection against re-infection with SARS-CoV-2, and whether they may eventually help reducing pandemic virus spread.

Executive summary:

SARS-CoV-2 infection has been shown to induce both T cell responses and antibodies. Unfortunately, neutralizing antibody responses are often relatively weak and rather short-term, particularly in persons with mild symptoms (*1*, *2*). Preliminary data suggest that that protection induced by natural infection with SARS-CoV-2 may be short-lived. Few patients may have been infected with COVID-19 twice, as demonstrated by a virus free interval in between (*3*-*5*). Although further studies are necessary to determine to which degree natural infection may lead to prolonged immunity, the current evidence argues that it is not justified to let this virus circulate broadly with the aim to induce protective immunity in the population. As can be seen in most countries with such 'open' strategies, high infection rates may also compromise the economy significantly, besides health. Thus, both health and economy may benefit from the measures that keep infection rates low (5b).

Current results show that some vaccines induce stronger immune responses than natural infection. Therefore, it may be possible that vaccines will be superior than natural infection in establishing long-lasting immunity in many people. However, more and robust data are needed to demonstrate vaccine efficacy and very high degree of safety, before one can consider starting broad vaccination campaigns.

Main text

An increasing number of studies shows that SARS-CoV-2 infection may induce robust T cell and B cell (antibody) responses (*6-11*). Such studies represent a good start towards understanding the interaction between the virus and the human body, and particularly the human immune system.

Importantly, however, the demonstration of immune responses does not necessarily indicate immunity. “Immunity” refers to the highly desired protection from (subsequent) infection, or at least a meaningful reduction of disease severity. To know more about immunity, one must perform studies that directly determine whether or not exposed persons are protected from SARS-CoV-2 infection or from developing COVID-19 disease depending on previously acquired immune responses either by natural infection, crossreactivity or vaccination. Such studies are challenging and time-consuming.

Only few laboratory parameters can be used to tentatively predict protective immunity, most prominently the presence of neutralizing antibodies (nAbs) at sufficiently high concentrations. In many viral infections, nAbs are the best laboratory indicators of immunity. However, even presence of nAbs must be interpreted with caution, as we currently lack information about the amounts required for protection (*12*). It thus remains necessary to further test whether certain (concentrations of) nAbs really do confer resistance to infection (*13*). Furthermore, besides nAbs, other parts of the immune system also contribute to immune protection (*14*). Currently, there is no reliable diagnostic test available to indicate immune protection against re-infection with SARS-CoV-2. Therefore, the concept of providing 'immune passports' to people who recovered after a first infection episode cannot be pursued.

It is well known that SARS-CoV-2 undergoes mutations, albeit at low rates (14b). There is currently no major evidence that the virus escapes immunity. It is more likely that waning immunity is the reason for re-infection (14c).

Immune protection after SARS-CoV-2 infection may often be as weak and short-term as those induced by the seasonal common cold Coronaviruses (*14*, *15*). Also for these viruses, protective antibody responses are short-lived, in the range of one year (*16*) or even less (*17*). Consequently, symptomatic infections occur regularly, including re-infections with the same virus (*16*, *18*).

There is hardly any evidence that common cold Coronaviruses induce neutralizing antibodies (nAbs) that would cross-react with SARS-CoV-2 and mediate some level of cross-protection. Common cold Coronaviruses have been shown to induce cross-specific non-neutralizing antibodies and cross-specific T cells (*19*). It is possible that such T cells reduce COVID-19 severity. The same may be the case for the T cells induced by previous infection with SARS-CoV-2 (*20-22*). Presence of SARS-CoV-2-specific memory T cells might indeed reduce the severity of infection, a promising notion that needs further investigation and verification.

Importantly, however, while memory T cells may facilitate virus clearance and reduce severity of the disease, they are inefficient in preventing infection (entry of the virus into target cells) and may therefore not help reducing infection rates, in the absence of nAbs.

After most infections, there is a substantial early decay of antibody titers, because the first antibody wave is based on short-lived plasma cells. In contrast, the second wave of antibodies decays much more slowly (*23*). Therefore, early antibody decay is normal and seen in many types of infections, emphasizing the need to clearly define the precise time points at which antibodies are being measured. By doing so, a recent study showed stable titers of SARS-CoV-2 specific antibodies within the first four months after infection (*11*), questioning whether COVID-19 immunity wanes rapidly. However, this and the majority of the remaining COVID-19 studies focus on non-neutralizing antibodies, often specific for the nucleoprotein which is much more immunogenic than the S protein. Yet, protection from infection is primarily mediated by neutralizing antibodies which are mostly S protein specific (7).

Although infected persons may lose immune protection as early as after a few weeks or months, it is too early to draw definitive conclusions on the efficacy and duration of immunity induced by SARS-CoV-2 infection, because of the lack of long-term follow-up studies.

The worldwide COVID-19 vaccine development is broad and rapidly moving forward (*24-27*). Nevertheless, most developers take great care to ensure the process is done properly, particularly with in depth investigation of efficacy and safety. Without sound data, neither public health experts nor the public itself would accept vaccination. Remarkably, phase 1+2 data show that several vaccines induce stronger immune responses than natural infection, with a good chance that they are lasting longer than after natural SARS-CoV-2 infection. Provided that phase 3 data clearly demonstrate efficacy and safety, vaccination may become possible during the year 2021. However, it remains possible that the first-generation vaccines turn out to be insufficiently protective or safe and that more efforts are needed which would mean further delays.

Conclusions

Keeping SARS-CoV-2 infection rates as low as possible is the most reasonable strategy in the current pandemic. The antibody responses induced by natural infection are often weak and short-lasting, and may therefore provide only limited protection and inefficiently slow down viral spread. However, it is too early for definitive conclusions on these points. Hopefully, future vaccines will induce strong and long-lasting immunity. Broad immunity may be achieved if vaccines are accepted by the population, based on sound data that the approved vaccines are highly safe and efficient.

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