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COVID-19: the immune response, inflammation, and vascular disease

This rapid review of the science of the immune response, inflammation, and vascular disease from the Royal Society is provided to assist SAGE in relation to COVID-19.

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KEY POINTS

- The presence of antibody to SARS-CoV-2 does not necessarily indicate protection from re-infection.
- Immunity to a virus, whether elicited by a vaccine or by infection, rarely completely prevents re-infection, but is usually very effective in preventing or attenuating disease.
- The aim of a viral vaccine is to prevent disease and further virus transmission, not necessarily to prevent re-infection.
- The immune response must be distinguished from the inflammatory response. In COVID-19, it is becoming clear that a strong early immune response to the virus protects the host by limiting viral spread, whereas severe disease is caused by inflammation resulting from widespread viral infection.
- Protective immunity to the four endemic human coronaviruses wanes after 1 to 3 years, allowing frequent re-infection. It is not known whether this applies to COVID-19.

This paper provides commentary on:

1. Levels of immunity achieved from mild and asymptomatic infections;
2. The immune response vs other physiological responses e.g. viral toxicity and inflammatory; and
3. Insights on the quantitative aspects of the response in terms of proportions of people that do/don't experience which symptoms and serology.

1. Levels of immunity achieved from mild and asymptomatic infections: immunity to COVID-19

KNOWLEDGE GAPS

To understand immunity to the COVID-19 agent SARS-CoV-2, we first need a comprehensive description of the nature of the innate and acquired immune response to the virus in people from across the clinical spectrum, from asymptomatic infection to severe disease. Data are then required to answer the following specific questions:

1. Can you be symptomatically re-infected with SARS-CoV-2? And if so, are you infectious to others?
2. If so, does prior infection prevent or diminish serious disease and complications?
3. If so, what are the correlates of protective immunity?
4. And how long does protective immunity last?

1.1 Can you be re-infected with SARS-CoV-2?

To quantify the frequency of re-infection, large longitudinal cohort studies are needed stratified by various confounding variables such as age, pre-existing medical conditions etc. The time taken to complete such studies will depend strongly on the prevalence of the virus in the population at the time: if the virus becomes rare in the population, the study will take a long time. Also, if reinfection leads to mild disease it will need blood tests to diagnose accurately. Human infection challenge studies are now being discussed by some; however, such studies, even among younger people (who are less likely to develop severe disease and complications) may carry unacceptable risks before an effective antiviral drug becomes available.

1.2 What is the impact of previous SARS-CoV-2 infection?

It is necessary to distinguish between infection and disease. Natural viral infections and viral vaccines rarely (if ever) completely prevent re-infection, as demonstrated by the rise in virus-specific antibody titre and reactivation of virus-specific T cells following re-exposure. Both natural infection and vaccines can, however, give good protection against disease, by attenuating the infection. **The chief requirement is to prevent serious disease, complications, and onward transmission to susceptible individuals, but not necessarily to prevent re-infection itself.**

1.3 What are the correlates of protective immunity?

- 1.3.1 We need to know the correlates of immunity for several reasons. First, to provide a benchmark against which the immune response of an individual or population can be compared. Second, to devise a pragmatic test to aid in vaccination policy and practice, public health measures, to guide clinical management and prognosis in individual cases, etc. Third, understanding immunity is needed to guide the design and testing of vaccines. Finally, understanding the mechanisms of pathogenesis will hasten effective treatment, which is likely to need combination therapy.
- 1.3.2 Detection of anti-SARS-CoV-2 antibodies can, if the assay is sensitive and specific, reliably indicate past infection, but does not necessarily indicate immunity to reinfection. The presence of antibodies may, however, prevent or diminish both disease and transmission to others. Some infected individuals do not develop detectable COVID-19-specific antibodies until 2 or 3 weeks after the onset of symptoms¹.
- 1.3.3 The data from serological surveys, and the prognostic value of antibody assays, must therefore be incorporated into models and interpreted with caution.

- 1.3.4 Reports of antibody assays frequently refer to neutralizing antibodies, i.e. antibodies that neutralizes viruses in an *in vitro* assay. Although neutralizing antibodies are usually beneficial, their presence is not sufficient for protective immunity in some viral infections. The reason is that *in vitro* neutralization assays capture only certain methods of antibody-mediated killing of viruses, and do not quantify complement fixation or ADCC (antibody-dependent, cell-mediated cytotoxicity), which contribute significantly to protective immunity in some virus infections. Total antibody titre can be a stronger correlate of protection than the titre of neutralizing antibodies. Also, antibodies on mucosal surfaces might be most protective, and the quantity of mucosal antibody is not necessarily correlated with the concentration of antibody in the blood.
- 1.3.5 Recovery from MERS is associated with both antibody responses and T cell responses².
- 1.3.6 Airway memory CD4+ T cells mediate protective immunity against emerging respiratory coronaviruses in mice³. This protection may be effected either directly by the CD4+ cells⁴ or via the cytotoxic (CD8+) T lymphocytes (CTLs), which require help from the CD4+ T cells; probably both are necessary. Virus-specific CTLs protect mice from lethal infection with SARS-CoV-1⁵. Activated SARS-CoV-2-specific CD8+ T cells were found only in patients with mild disease⁶, consistent with the expected protective role of these cells.
- 1.3.7 Memory T cell responses to SARS-CoV-1 persist up to 11 years after infection⁷.
- 1.3.8 CD4+ T cell responses have also been detected to three major SARS-CoV-2 proteins – S, M and N^{8,9}, and CD8+ cells recognise at least 8 antigens, including M and S.
- 1.3.9 If immunity to COVID-19 wanes over time (see section 1.4), vaccination may need to be repeated periodically, perhaps every one to three years, as is required for influenza. If so, live viral vaccines may become less effective with repeated inoculation, and vaccines based on viral proteins or RNA may be necessary.
- 1.3.10 T cell depletion (both CD4+ and CD8+ T cells) in the blood is a prominent feature of severe COVID-19¹⁰. It is not specific to this disease: lymphopenia was observed in 61% of patients with pneumonia caused by influenza A virus H1N1¹¹. This is likely to contribute significantly to the failure to limit the virus replication, with consequent widespread viral dissemination and secondary inflammatory consequences. The causes of this T cell depletion from the blood are not understood: likely factors include direct viral toxicity, as seen in SARS¹² and sequestration in the tissues.
- 1.4 How long does any immunity to SARS-CoV-2 last?**
- Although the antiviral immune response is often long-lasting, the duration of protection varies widely between different virus infections, from lifelong (e.g. measles virus) to about two years (e.g. Respiratory Syncytial Virus (RSV)). The duration of protection is typically related to the antigenic diversity of the viral infection: both measles and rubella show little antigenic diversity, while RSV has great diversity as do coronaviruses. The titre of anti-coronavirus antibodies wanes over time, and frequent reinfection of normal adults with the four endemic coronaviruses indicates that natural infection with these agents does not induce lasting immunity^{13,14,15}. However, the highly pathogenic human coronaviruses that cause MERS and SARS respectively may confer more durable immunity. It is not yet known whether SARS-CoV-2 elicits short-term or long-term immunity, if either. CD4+ T cells that recognize SARS-CoV-2 antigens were detected in ~50% of people unexposed to the virus, suggesting that T cells elicited to the widespread endemic coronaviruses might cross-react with SARS-CoV-2¹⁶. If so, such cross-reactive T cells could give a degree of cross-protection against COVID-19¹⁷.

2. The immune response vs other physiological responses e.g. viral toxicity and inflammatory: pathogenesis of COVID-19

For a description of clinical features of COVID-19, see Huang *et al* 2020¹⁸ and Wang *et al* 2020¹⁹. A recent review of the immunology and inflammation in COVID-19 has been written by Tay *et al* 2020²⁰.

2.1.1 Like SARS²¹, COVID-19 often follows a biphasic course: the severe complications reach a peak incidence at ~two weeks after the onset of symptoms, i.e. ~one week after the peak of virus replication (for example, see Zhou *et al* 2020²²). Further precise data are needed on the course of infection and its relation to viraemia. SARS-CoV-2 infects mainly epithelial cells and macrophages²³, and may also infect dendritic cells.

2.1.2 It is critical to distinguish between the virus-specific (acquired) immune response and the inflammatory response. It is frequently stated that severe disease in COVID-19 is caused by an ‘excessive’ or ‘overactivated’ immune response. However, although there is abundant evidence for a ‘cytokine storm’²⁴, with high levels of IL-1 β , IL-6, IL-8, TNF α , IP-10, MCP-3 etc (for example, see Yang *et al* 2020²⁵), the antibody response and the T cell response do not appear to contribute to the tissue damage. On the contrary, the CD8+ T cell response appears to protect against severe disease²⁶. There is emerging evidence (T Hussell, Manchester, personal communication) of a profound mobilization from the bone marrow of activated (Ki-67+) monocytes and neutrophils in severe COVID-19. Inflammatory chemokine genes are strongly expressed in monocyte-derived macrophages²⁷. The importance of lymphopenia and viral sepsis²⁸ suggests that tissue damage in COVID-19 is due primarily to direct viral toxicity and a consequent strong inflammatory response. See also points 2.3, 2.4 and 2.5 below for further evidence of the importance of inflammation. The importance of viral toxicity itself (damage to the cell by the virus) is not yet clear.

The distinction is important because it directly affects the strategy of both treatment and vaccination. The term ‘immune response’ is now applied widely to host defences, from the sensing of virus infection by pathogen recognition receptors to downstream signalling, inflammation and adaptive immunity. This can lead to significant confusion, with potentially important consequences. At worst, it might discourage vaccination. Inflammation is caused chiefly by the innate immune response in SARS²⁹. SARS-CoV-2 suppresses the interferon response³⁰, allowing efficient viral spread in early infection³¹; the resulting widespread infection generates the exuberant inflammatory response³². The cytokine responses in COVID-19 are very long-lasting, and levels of many mediators correlate with poor prognosis: in particular, IL-6 and TNF α remain independent prognostic factors of disease severity and survival, after adjusting for covariates (M Merad, Mt Sinai Hospital, personal communication).

A strong acquired immune response to the virus early in infection – in the first week – is likely to protect against severe disease, by minimizing virus spread. By contrast, a weak or delayed response, which reaches a peak after the virus has already spread widely, may cause net harm, through excessive inflammatory cytokine production and lysis of infected cells. This is consistent with the observation that severe COVID-19 disease often occurs in the second week of symptomatic illness, often as the cough is receding. That is, the relative timing of the peak of virus replication and the acquired response might determine the balance of good and harm done by the immune response. If true, then accelerating and enhancing the immune response early in infection, by vaccination, would be beneficial. There is a theoretical possibility that a vaccine that elicits a response to SARS-CoV-2 antigens in the absence of the viral products that suppress the innate response³³ might generate immunity that is more efficient and durable than that elicited by natural infection.

- 2.1.3 There is growing evidence that two strong correlates of tissue damage in severe cases are lymphopenia³⁴ and the degree of viral dissemination³⁵. Thus the severe phase of the disease may be caused by direct viral tissue damage – viral sepsis – rather than by the (acquired) immune response to the virus. See also section 1.3.9.
- 2.1.4 A machine-learning study identified three predictors of mortality in COVID-19 patients: lactic dehydrogenase (LDH) activity, lymphopenia, and C-reactive protein (CRP)³⁶. LDH and CRP are markers of inflammation and tissue damage.
- 2.1.5 What is the nature of the vascular response in COVID-19? Intravascular clotting is a major complication of COVID-19, and presages a bad outcome. Levels of D-dimers produced by cleavage of fibrin and levels of fibrinogen correlate with poor outcome^{37, 38, 39, 40}. Inflammation is a key driver of intravascular clotting, due to raised fibrinogen, raised platelets and importantly the increased exposure of tissue factor among other factors. Vessels express the receptor for SARS-CoV-2, ACE2 and so virus infection directly as well as inflammation indirectly, via cytokines and activated T cells⁴¹, could lead to endothelial damage and consequent clotting triggered by tissue factor (CD142), potentially blocking vessels locally and sending thrombi. Treatment of inflammation with anti-TNF can reduce clotting in rheumatoid arthritis patients by reducing platelets and fibrinogen production⁴², and so treating inflammation earlier may reduce clotting tendency. There are complicated feedback loops, however: for example, fibrinogen can amplify inflammation⁴³, and hypoxia activates pathways such as VEGF (also known as vascular permeability factor) which might aggravate the local inflammation.
- 2.1.6 Although young children are in general rarely affected by severe COVID-19, in a small minority a severe multiorgan inflammatory syndrome resembling Kawasaki disease has followed COVID-19 infection, typically 1 to 4 weeks after the end of symptomatic infection⁴⁴.
- 2.1.7 Clinical evidence does not support the use of corticosteroids in COVID-19 lung injury⁴⁵.
- 2.1.8 An inactivated SARS vaccine caused an eosinophilic lung inflammation in mice⁴⁶. Live viral vaccines are typically more efficient in protection, because they elicit all arms of the immune response: antibodies, helper T cells and cytotoxic T cells as well as the innate immune response. However, immunity against a live viral vector can limit the effectiveness in repeated vaccination (see section 1.3.9).

3. Insights on the quantitative aspects of the response in terms of proportions of people that do/don't experience which symptoms and serology

- 3.1.1 The titre of IgA antibodies early during acute primary COVID-19 infection correlates with a mild disease outcome⁴⁷, whereas a delayed strong antibody response is positively correlated with disease severity in both MERS⁴⁸ and COVID-19^{49, 50}. The likely reason for the latter observation is simple: severe disease is caused by abundant viral replication, and the resulting high viral antigen load elicits a high titre of antibodies.
- 3.1.2 The possible protective value of either mucosal or systemic anti-SARS-CoV-2 antibodies resulting from either natural infection or vaccination is not yet known.
- 3.1.3 There is a theoretical risk of antibody-dependent enhancement (ADE) of disease in COVID-19⁵¹. ADE can occur in coronaviruses^{52, 53}. ADE causes the severe disease in infection with feline infectious peritonitis virus, a coronavirus⁵⁴. Whereas some anti-SARS spike antibodies neutralize, others enhance infection of macrophages and lymphoblasts by SARS-CoV pseudotype particles⁵⁵ and replication-competent virus⁵⁶, and may contribute to pathogenesis in SARS⁵⁷. The classical mechanism of ADE is Fc receptor-mediated uptake of antibody-bound viruses. In MERS, antibody to the spike protein can also alter its conformation and so enhance infectivity⁵⁸. ADE remains a possibility in SARS-CoV-2 infection; it should be borne in mind in studies on serology and vaccination.
- 3.1.4 In a report on the epidemiology of endemic coronaviruses in Scotland⁵⁹, where they account for ~10% of upper respiratory tract infections, the authors suggested that the relatively high incidence in children of CoV OC43, a betacoronavirus (like SARS-CoV-2) might explain the low incidence of serious COVID-19 in children, because of a degree of cross-reactive immunity.

DISCLAIMER

This paper has drawn on the most recent evidence up to 19 May 2020 and has not been subject to formal peer-review. Further evidence on this topic is constantly published and the Royal Society may return to this topic in the future. This independent overview of the science has been provided in good faith by subject experts and the Royal Society and paper authors accept no legal liability for decisions made based on this evidence.

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