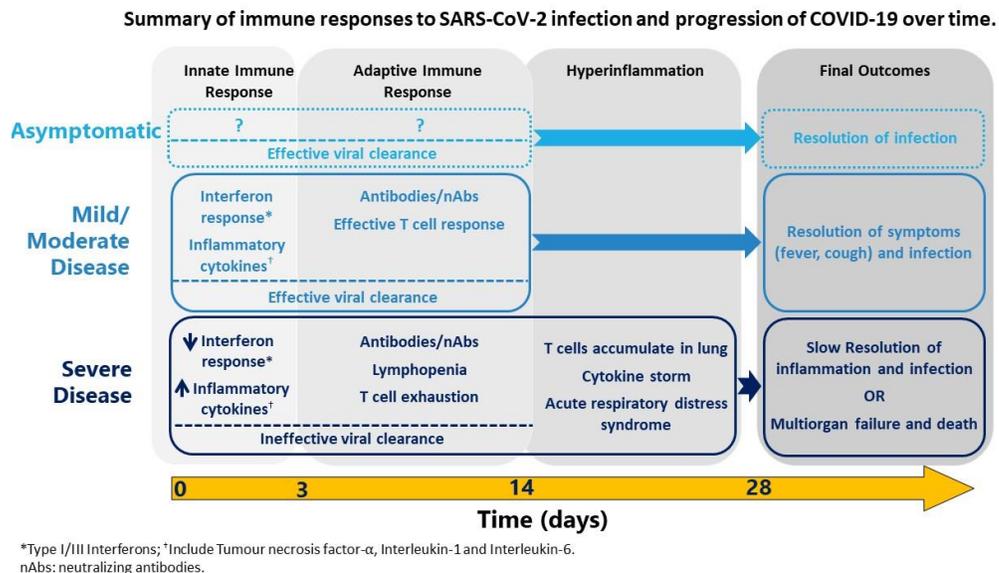


# UNDERSTANDING IMMUNE RESPONSES TO SARS-COV-2

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## Summary

SARS-CoV-2 is a newly emergent coronavirus that is highly infectious and is the cause of COVID-19. The disease caused by the virus is characterized primarily by mild to severe respiratory symptoms that can lead to hospitalization and death in ~1% of cases. Diagnostic tests for detection of the virus in the airways were developed quickly, within weeks of the outbreak, and have played a key role in public health strategy used globally to test, track and isolate cases, likely saving millions of lives worldwide. However, a lot more research is needed to understand this new virus, the disease, and the immune response that could potentially protect, or contribute, to COVID-19. Based on rapidly emerging data, SARS-CoV-2 infection induces differential disease, which is likely the outcome of the interaction between the virus and host immune response (Figure). The most severe disease outcomes are correlated with an over-exuberant immune response. The role of antibodies in immune protection is still not completely understood, making predictions around herd immunity uncertain and utility of “immunity passports” difficult to assess. The final exit strategy from the current pandemic will very likely involve a combination of effective therapeutics to decrease the burden of disease and vaccines to prevent transmission.

### 1. Immune responses to viruses: innate versus adaptive immunity

Viruses are submicroscopic parasites that require host cells to replicate. These tiny organisms are composed of basic genetic information in the form of nucleic acids (RNA or DNA) packaged within a shell made of protein, called the capsid. Many viruses also have an outer shell called envelope, a lipid membrane

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containing viral glycoproteins, that facilitates the entry of the virus into host cells. The main function of this whole viral structure is to infect cells, take over the host cellular machinery to multiply and produce lots of virions, that are subsequently released and repeat the process in other cells. While viruses can infect a wide range of animals and plants, most have a narrow range of hosts, and a few can infect different species. Coronaviruses are among the latter category<sup>1</sup>. Upon infection, the host detects the virus as a “foreign’ entity and mounts a defense through its immune system<sup>2</sup>. The human immune system is a complex network of cells and organs that can detect and defend against harmful organisms through a variety of mechanisms.

The human immune response to a virus can be divided into different phases, starting within minutes of a viral infection, and lasting over weeks, months, or sometimes years<sup>3</sup>. The acute phase of the immune response lasts ~72 hours and is dominated by “*innate immunity*”, which consists of cells and processes that can be deployed quickly and act rapidly to contain the virus and stop its replication within the host. Every cell in the human body is equipped to recognize and react to viruses, this is especially true for the cells that line the mucosal surfaces, the moist inner lining of the body that covers the airways, gastrointestinal and urogenital tracts and other organs. When a respiratory virus, such as coronavirus, encounters the epithelial cells that line the airways, it attaches to specific receptors present on the host cell surface with the help of the viral envelope glycoproteins. This facilitates the entry of the virus into the cell, where it can start replicating by hijacking the cellular machinery. At the same time, the host cell has a variety of receptors on its cell surface and in the cytoplasm, called pattern recognition receptors [PRRs], that recognize the virus and initiate innate immune responses. These include the initiation of Type I and III Interferons (IFNs) and cellular factors that have anti-viral effects, as well as inflammatory factors that send alarm signals and bring in immune cells such as macrophages, dendritic cells and natural killer (NK) cells to the area of infection. The anti-viral and inflammatory milieu as well as immune cells that comprise the innate immune response primarily aim to a) destroy the virus or limit its replication, and b) activate the next phase of the immune response within 48-72 hours. The second phase of immune response is *adaptive or acquired immunity* which is maintained from weeks to years and involves special organs and tissues like lymph nodes and specialized immune cells such as B and T cells. The adaptive immune response is slower but can customize the immune responses with high specificity to a large variety of pathogens, such as harmful bacteria and viruses. The adaptive immune response is capable of targeting novel viruses that the host has never encountered, and it is also responsible for the “memory” of the immune system, allowing hosts to respond much more rapidly to re-infections even years later.

Vaccines take advantage of this ability to customize a specific memory response, using weakened viruses or viral parts, such that when the host encounters a fully infectious virus, a rapid secondary immune response is mounted that helps resist the infection. The adaptive immune responses have two main components: 1) cellular immunity comprised of T lymphocytes that can attack and kill the infected cells directly or indirectly and 2) humoral immunity which is mediated by B lymphocytes and antibodies, which are complex proteins secreted by plasma cells (differentiated B lymphocytes). Antibodies are found in blood and body fluids, and perform a range of functions such as inhibiting the virus binding, neutralizing the virus, or activating immune cells to kill the virus or infected cells. The characteristic feature of antibodies lies in the ability to recognize and bind to very specific epitopes of the virus or “antigens”. Although antibodies may only last in blood stream for a few days to a few weeks, the plasma cells can keep replenishing them

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for months. Antibodies belong to five different classes, IgD, IgM, IgA, IgE and IgG, based on the type of protein chains they are made of. They all have slightly different structures, characteristics, and functions. IgM, IgG and IgA antibodies all have anti-viral functions, but IgG antibodies are the longest lasting, are present in high amounts in both blood and body fluids and perform a whole range of anti-viral activity.

In summary, the human immune system responds to viruses in a variety of ways, starting with innate immunity which is composed of rapid and broad responses followed by adaptive immunity that is mediated by specialized immune cells and antibodies and is characterized by specificity, diversity and memory. The outcome of a viral exposure is determined by the sum total of the ability of the virus to subvert and overcome host responses and the ability of the host to mount rapid and potent anti-viral immune responses.

## 2. Immune responses to SARS CoV-2: current state of knowledge

The coronaviruses belong to a large family of RNA viruses that can infect several mammalian species including cats, bats, camels, cows, pigs and humans<sup>4</sup>. There are seven coronavirus species capable of infecting humans, all of which cause respiratory infections. Four of these cause colds (alpha CoV, 229E, NL3 and beta CoV, OC43, HK41) that vary in severity but rarely cause fatality. Three coronaviruses that cause much more serious respiratory infections and high mortality rates<sup>5,6</sup> have crossed from other species into humans in the last two decades: Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2. SARS-CoV-2 causes COVID-19 which is causing widespread morbidity in the current pandemic.

The coronaviruses have a relatively simple structure: a single stranded RNA genetic core surrounded by a capsid and an outside envelope. Four structural proteins make up the virus: the nucleocapsid (N), the membrane (M), the envelope (E) and the spike protein (S)<sup>7</sup>. The S protein forms trimers which project out from the viral envelope like a crown, hence the name “coronavirus”. The spike protein plays a crucial role in infection, since it contains the *receptor binding domain* (RBD) that facilitates viral attachment to the host cell. The S proteins of both SARS-CoV-1 and SARS-CoV-2, that are closely related to each other, bind to a common protein found on the surface of cells, called Angiotensin converting enzyme 2 (ACE2), to enter host cells<sup>8,9</sup>. ACE2 is commonly expressed in cardiopulmonary (heart and respiratory) tissues, the gastrointestinal tract, immune cells (monocytes, macrophages and dendritic cells) and other tissues, with the main function of regulating blood pressure<sup>10</sup>. The S protein is the immunodominant protein, meaning it gives rise to potent T cell and antibody responses and is an attractive target for vaccine and therapeutics because of its involvement in viral attachment and entry. However T and B cells are capable of targeting the M and N proteins as well<sup>11</sup>.

Although few studies have examined innate immunity to SARS-CoV-2, thus far it appears that like other coronaviruses, it induces a range of innate immune responses, including Type I/III IFNs, the primary anti-viral factors made by cells, and proinflammatory cytokines like TNF- $\alpha$ , IL-1 and IL-6<sup>12</sup>. Early studies indicate that SARS-CoV-2 suppresses Type I/III IFNs to a greater extent than SARS-CoV-1<sup>13</sup>. However, it does induce potent proinflammatory cytokine response<sup>14</sup> and this imbalance between low innate anti-viral response

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and high inflammation may contribute to development of the new coronavirus disease 2019 (COVID-19). Indeed, IFN antagonism correlated with increasing severity of COVID-19<sup>15</sup>.

Information regarding the adaptive immune responses against SARS-CoV-2 is starting to emerge. Although T cell responses against the S and N proteins of the virus have been observed in most clinical studies, patients with more severe disease appear to have significant lymphopenia with drastic decreases in T cell numbers in the blood<sup>16,17</sup>. T cells in patients with severe COVID-19 are activated but show mainly inflammatory responses as well as characteristics of exhaustion<sup>18</sup>, whereas individuals with mild disease show more effective, multifunctional T cells, with CD8 T cells able to kill virus-infected cells and CD4 T cells producing a variety of cytokines that help other aspects of immune responses<sup>19,20</sup>. In general, the T cell responses to the virus are biased towards inflammation which may contribute to the severity of COVID-19. Other studies have shown that in severely sick patients, while T cells are decreased in the blood, large numbers accumulate in the lungs and likely contribute to the acute respiratory distress syndrome (ARDS)<sup>21,22</sup> by inducing a cytokine storm characterized by uncontrolled levels of inflammatory cytokines (cytokine release syndrome)<sup>23</sup> (discussed in Section 7).

The humoral response to SARS-CoV-2 is being studied extensively, given the expected importance of antibodies in protection from re-infection. Several studies have now shown that SARS-CoV-2 infection leads to a robust antibody response within 7-14 days as IgM, IgG and IgA have been detected in almost all infected individuals and that IgG antibodies persist in the weeks following recovery<sup>24</sup>. The antibodies most commonly detected are against the SARS-CoV-2 N and S proteins<sup>25,26</sup>. Antibodies against the RBD of the S protein are of interest because they can prevent the virus from attaching to the entry receptor, ACE2, on host cells. RBD-specific antibodies, which are very effective neutralizing antibodies (nAbs) have been detected in most patients<sup>27,28</sup>. What is less clear is whether all infected individuals make high amounts of these nAbs, how long the antibody response will persist, and whether the nAbs correlate with protection. Studies of other coronavirus infections showed that less severe infections and mild disease led to short-term antibody responses<sup>29,30</sup> whereas SARS-CoV-1 and MERS, which cause more severe disease, led to longer-term responses that lasted for 2-3 years<sup>29,31,32</sup>, with some reports showing even longer memory<sup>33</sup>.

### 3. Testing for immune responses versus testing for virus

Given that SARS-CoV-2 is a newly emerged coronavirus that spread at an unprecedented speed across the world, it has been a race against time to develop diagnostic tests. Within the first few weeks of the infection spreading in Wuhan, it became increasingly clear that controlling the spread of this new virus was going to be very challenging, because it is highly infectious, not everyone who gets infected develops full blown disease, and the virus can be transmitted by people with very mild symptoms or no symptoms. In the last few months, epidemiological data has shown that the average number of people infected by one person, if no control measures are in place (known as  $R_0$  [R naught]) for SARS-CoV-2 is around 2.2-2.6<sup>34-37</sup>. This means that the virus is more infectious than flu ( $R_0$ , 1.8<sup>38</sup>) and less than measles ( $R_0$ , 15<sup>39</sup>). Although asymptomatic transmission rate varies significantly depending on geographical locations and the public health measures in place in different countries, some estimates have put the contribution of asymptomatic transmission to overall number of cases as high as 40-45%<sup>40</sup>.

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**Molecular Tests:** Within weeks of COVID-19 emergence, the first diagnostic tests to be developed were molecular tests based on nucleic acid amplification. These are PCR (polymerase chain reaction)-based tests that rely on detecting viral genetic material isolated from throat or nasal swabs. Sputum or bronchoalveolar lavage (BAL) samples can also be used, if infection has spread to the lungs<sup>41</sup>. The basic process involves isolating viral RNA from the biologic samples, converting it into DNA using reverse transcriptase enzyme and then amplifying the DNA by PCR, using SARS-CoV-2-specific primers. The methods for these assays were quickly shared and published, and have become widely used around the world<sup>42,43</sup>. While this type of testing is labour intensive, it can detect active infection with high sensitivity<sup>44</sup>. In the absence of vaccine and therapies, this test has played a key role in the global public health strategy to keep SARS-CoV-2 infections in check, using rapid testing, tracing and isolation. The limitation of this assay is that it is typically used for diagnosing active infection in symptomatic individuals. Given that the virus can be transmitted asymptotically, it is challenging to be able to trace every infected person using this test.

**Serologic Testing:** This type of testing detects the presence of antibodies against SARS-CoV-2 in the blood of individuals<sup>45</sup>. Antibodies develop almost universally following infection with the virus, in all individuals who are not immunocompromised, within 1-2 weeks after infection<sup>24</sup>. Therefore, it can not only confirm viral infection in people who developed symptoms, but also those with asymptomatic infection. Because the antibodies are likely present in blood for weeks to months after infection, these tests can be performed long after recovery to identify individuals who have previously been infected with SARS-CoV-2. However, there is a lag between the start of infection and the appearance of antibodies in the blood, therefore serology tests cannot be used reliably diagnose active infection. Many of the commercially approved serology tests are called *lateral flow assays (LFA)*, based on immunochromatography technique, which involves running the fluid containing antibodies (patient blood) over a solid substrate containing SARS-CoV-2 antigens. If the antibodies are present in the blood, they will bind the viral protein and cause a color change indicating a positive test. This type of test, based on simple positive or negative detection of antibodies, is useful for large scale surveillance, but does not provide any information regarding the amount, type, or function of the antibodies. A better test for accurately detecting antibodies against SARS-CoV-2 is the enzyme-linked immunosorbent assay (ELISA), a common laboratory test that can measure not only the presence but also the titer (amount) and type (IgG, IgM, IgA) of antibody. This test allows for a better measure of the strength of the humoral response<sup>46</sup>. In general, the higher the antibody titer the better the protection. The ELISA assays are more complex and can only be performed in a laboratory setting, while the LFA assays are being promoted as easy to perform, inexpensive, point of care tests. However, many of the LFA assays are currently being examined more carefully to ascertain their sensitivity (how frequently they miss positive samples) and specificity (how often they incorrectly diagnose negative samples as positive), both of which have important public health consequences. If the presence of antibody is indeed confirmed to protect against re-infection, then performing serological testing in large populations (sero-surveillance) can play an important role in determining the level of population-based immunity (herd immunity) and validate the concept of an “immunity passport”<sup>47</sup>.

**Viral neutralization assay:** The mere presence of antibodies in blood, measured by LFA or ELISA tests, does not show they can effectively block viral infection. The gold standard of testing the ability of an antibody to

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block or neutralize the virus is viral plaque reduction neutralization assay<sup>48</sup>. When viruses replicate inside cells grown in cultures, they are subsequently released when the cells are lysed or killed. This results in holes known as “plaques” that can be easily counted under the microscope or quantified using automated end points. If the antibody blocks the ability of the virus to infect the cells, there will be fewer or no plaques that form after a mixture of antibodies and virus are layered on the cells – indicating that the antibody can “neutralize” the virus. This assay measures not only the titer of the antibody but also its ability to protect against viral infection. However, these assays are very labour intensive and, because they involve the use of live infectious virus, must be performed in biosafety level 3 (BSL3) labs<sup>48</sup>. Alternate tests that use substitute viruses (pseudovirus neutralization assays) have been developed but are currently only being used in research laboratories.

In summary, a number of tests have been developed quickly and adapted from current tests to provide a variety of ways to test SARS-CoV-2 infection as well as host antibody responses. The diagnostic tests that detect presence of virus are complementary to tests that measure host immunity because together they can diagnose current as well as asymptomatic infections. Although not all tests are completely optimized at this point, they have played a critical role in the current public health strategy of testing, tracing, and isolating which has effectively saved millions of lives across the world.

#### **4. The antibody response to SARS-CoV-2 and population seroprevalence**

While most studies examining antibody responses have found that almost all individuals infected by SARS-CoV-2 develop antibodies to the virus, it is still unknown how long these antibody responses last and whether the antibodies protect from re-infection. While some individuals developed an antibody response as early as 8 days after infection, in most studies, it peaked around 14 days, with significant variation among patients<sup>24</sup>. IgM was the first antibody to be detected within the first week, but its levels decreased after 30 days while IgG levels increased slowly but remained high up to 25 weeks post-infection. The antibody titers correlated with the severity of the infection, with higher antibody levels in individuals who developed more severe symptoms. The majority of the antibodies detected were found to be against the N and S proteins of SARS-CoV-2. In particular, antibodies against the RBD of the S protein, which is highly immunogenic, have the potential to be highly neutralizing<sup>27,28</sup>. Studies found that while in early phase of the immune response, the antibody titer correlated with neutralization, the neutralizing antibodies declined rapidly following recovery<sup>49</sup>. Previous studies have shown that coronaviruses such as SARS-CoV-1 and MERS that cause more severe infections lead to longer and more potent antibody responses compared to coronaviruses that cause milder ones<sup>29,31,32</sup>. Thus far there are few reports of re-infection among individuals recovered from COVID-19, but longitudinal studies need to be done to examine how long the protection will last and whether individuals who had mild symptoms will have shorter-term protection compared to those who developed severe disease.

It has been estimated that 60-70% of the population would need to develop antibody responses before herd immunity could develop against SARS-CoV-2<sup>50</sup>. Sero-epidemiological studies of EU/EEA member states show low levels of seropositivity ranging from ~1% (Finland<sup>51</sup>, Scotland<sup>52</sup>) to 5% in Spain<sup>53</sup> and 8.5% in UK<sup>54</sup>. This is consistent with seroprevalence studies done in other countries as well<sup>55-57</sup> indicating that overall,

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less than 10% of the population in most countries has been exposed to the virus. Global efforts are ongoing to determine an accurate seroprevalence of SARS-CoV-2 antibodies. However, current estimates suggest that it is highly unlikely that herd immunity will be reached anytime soon in any country around the world.

## 5. Antibodies as therapies

Neutralizing antibodies that block viral entry have the potential to be used both for therapy and prophylactic application. Transfer of convalescent plasma, which involves transfusion of the liquid portion of blood from individuals who have recovered from an infection into people who are infected, has been tried as a life-saving therapy for many infectious diseases with varying degrees of success. The plasma of recovered individuals contains a variety of antibodies, including nAbs, against the pathogen, which can block infection of new cells in the recipients, allowing for recovery, although the immunity conferred by this type of treatment is short term. The few studies looking at the effectiveness of convalescent plasma transfusion for individuals with severe COVID-19, show varying results<sup>58-62</sup>, probably because the success of this approach depends on the presence of high titers of nAbs and the timing of the treatment. There are also additional considerations when using convalescent plasma transfusions, including screening for other infectious agents, matching the blood types and potential concerns about the presence of antibodies that could exacerbate disease due to their ability to induce inflammation via antibody dependent enhancement (ADE). Administration of monoclonal antibodies (mAbs), derived from a single plasma cell which produces one type of antibody and results in greater reproducibility and efficiency in biological activity, is an alternative to the use of convalescent plasma, which overcomes most of these limitations<sup>63,64</sup>. Significant advances have been made in rapidly identifying and producing mAbs which can neutralize viruses. Newer approaches involve isolation of single antibody producing cells from recovered patients, immortalization of the cell followed by rapid scale up of antibody production and testing. This method was successfully used to develop mAb114, which comprised a single antibody, and RGEN-EB3, which contained a cocktail of three-antibodies, against the Ebola virus. Both treatments were shown to be effective reducing mortality in randomized trials<sup>65</sup>. There are several reports of successful isolation of nAbs from COVID-19 convalescent donors that have been shown to decrease viral RNA in the lungs of animal models<sup>66,67</sup>. These and other mAb treatments should be entering clinical trials soon and are one of the most promising treatments against COVID-19 that have the potential to be highly efficacious and can be scaled up rapidly.

## 6. Correlates of protection against COVID-19

The term “correlates of protection” was originally coined in the context of vaccines to refer to “an immune responses that is responsible for and statistically interrelated with protection” against a pathogen<sup>68</sup>. Since most current vaccines induce serum antibodies, it commonly refers to levels of antibodies generated after vaccination that lead to protection from infection. For many vaccines, these levels have been determined empirically, either by challenging vaccinated individuals with the pathogen or by large scale studies following vaccination to determine the actual titer of antibody that confers protection. For example, 0.01-0.1IU/ml and 0.5IU/ml serum antibody are considered correlates of protection against diphtheria<sup>69</sup> and rabies<sup>70</sup>, respectively. For the seasonal flu vaccine an antibody titer of 1:40 in the hemagglutinin inhibition assay is considered protective<sup>71</sup>. In the case of vaccines against some pathogens such as varicella zoster

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and *Mycobacterium tuberculosis*, the correlates of protection are known to be CD4+ T cells<sup>72</sup> and interferon levels<sup>73</sup> respectively, but the actual amounts that confer protection has not been deduced.

Outside of vaccines, natural infections also lead to protection against subsequent exposures, therefore correlates of protection are relevant in this context as well. In the current COVID-19 pandemic, the notion of an “immunity passport” has been a popular topic of discussion, referring to the concept that by scaling up antibody testing, it may be possible to determine who is immune to COVID-19, which would provide estimates of a) herd immunity and b) who can re-enter the workforce without fear of being infected<sup>47</sup>. However, this discussion is premature as the correlates of protection against COVID-19 are currently not known, although studies examining antibody levels and functions are starting to provide more information<sup>74</sup>. While almost all individuals infected with SARS-CoV-2 develop antibodies, majority (80-90%) of them had low overall antibody levels and neutralizing antibody titers<sup>49</sup>. The antibody response also appears to be correlated with severity of the disease, which implies that in individuals who had a mild infection, the immune response may have been weak, and the antibody response may not be strong enough to confer protection<sup>29,30</sup>. Furthermore, recent studies have shown that most people who develop the disease develop neutralizing antibodies, but the nAb levels start decreasing within 8 weeks<sup>49,75</sup>.

The contribution of T cells to protection against COVID-19 re-infection is still not known and it is possible that they also contribute to protection. Another concern with coronaviruses is that many of them induce inflammatory immune responses that may exacerbate the disease and both T cells and antibodies can contribute to this<sup>12</sup>. Therefore, much more detailed studies are needed to measure immune responses from individuals across the disease spectrum. Preliminary data show that rhesus macaque monkeys who were re-challenged after recovering from primary SARS-CoV-2 infection were protected. This is promising since the protection correlated with a strong nAb response in the monkeys<sup>74</sup>. Longitudinal studies that follow individuals who have recovered from COVID-19 for subsequent re-infections need to be conducted and levels of antibodies will need to be correlated with re-infections. With these studies we will be able to determine if indeed antibodies are sufficient and if so, what levels are needed to confer protection.

## **7. Deleterious effects of immune responses to coronaviruses**

Although immune responses to viruses play a critical role in clearing the infection and protecting from re-infection, pro-inflammatory immune responses can also be associated with disease and severe outcomes, especially following respiratory viral infections. Respiratory syncytial virus (RSV), Influenza virus, and adenovirus can all lead to pneumonia associated with host pro-inflammatory immune responses<sup>76</sup>. SARS-CoV-1 and MERS-CoV have also been associated with overexuberant immune responses that can lead to severe disease with symptoms of fever and pneumonia followed by acute respiratory distress syndrome (ARDS), thought to be due to cytokine release syndrome (CRS)<sup>77</sup>. About 20% of SARS-CoV-2 infected patients develop severe symptoms and about 5% develop acute respiratory distress<sup>14,78-81</sup>. In patients with co-morbidities such as cardiovascular disease the proportion of patients with morbidity is higher<sup>82</sup>. Like other coronavirus diseases, the severe disease in SARS-CoV-2 develops 7-10 days after symptoms develop, a timing associated with uncontrolled overexuberant host responses, rather than a direct effect of viremia<sup>83</sup>. Although the symptoms associated with SARS-CoV-2 acute respiratory distress are similar to CRS,

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the underlying mechanism leading to this condition is still being studied. We now know that SARS-CoV-2 infects a variety of host cells including those in the airways, cardiovascular tissue as well as immune cells, including monocytes, macrophages and possibly dendritic cells. Patients with severe disease have elevated levels of C-reactive protein (CRP), IL-6 and other inflammatory cytokines in their serum and these are associated with worse clinical outcomes<sup>84,85</sup>. Lymphopenia characterized by decreased levels of CD4, CD8 and NK cells correlated with severity of COVID-19<sup>86</sup>. T cell markers consistent with exhaustion and presence of inflammatory monocytes have also been reported<sup>18</sup>.

In addition to T cell associated inflammation, there are also concerns that antibody response to SARS-CoV-2 may also contribute to respiratory pathology due to ADE. Other coronaviruses like SARS-CoV-1 were also associated with ADE, where higher antibody titers were associated with worse morbidity and death<sup>87,88</sup>. ADE is a phenomenon associated with presence of non-neutralizing IgG antibodies that bind to the virus and then to cells that express a specific antibody receptor (Fc-receptor). This leads to activation of some cells, like monocytes and macrophages, which express Fc-receptor, production of inflammatory cytokines, and the accumulation of these cells in the lungs leading to injury<sup>89</sup>. Studies are ongoing to determine if ADE is observed in patients with severe outcomes of COVID-19.

In summary, COVID-19 patients with severe disease exhibit acute respiratory distress related to CRS, possibly caused by uncontrolled inflammation. The underlying cause maybe the activation of a number of immune cells including monocytes, macrophages, dendritic cells and T cells and the absence or inability of normal mechanisms that shut off the immune responses. Recent studies showing benefit from the use of dexamethasone, a corticosteroid which is immunosuppressive, in patients with severe disease supports the conclusion that uncontrolled inflammation underlies morbidity in COVID-19<sup>90</sup>.

## 8. Summary

SARS-CoV-2 is a newly emergent coronavirus that is highly infectious and is the cause of COVID-19. The disease caused by the virus is characterized primarily by mild to severe respiratory symptoms that can lead to hospitalization and death in ~1% of cases. Diagnostic tests for detection of the virus in the airways were developed quickly, within weeks of the outbreak, and have played a key role in public health strategy used globally to test, track and isolate cases, likely saving millions of lives worldwide. However, a lot more research is needed to understand this new virus, the disease, and the immune response that could potentially protect, or contribute, to COVID-19. Based on rapidly emerging data, SARS-CoV-2 infection induces differential disease, which is likely the outcome of the interaction between the virus and host immune response (Figure). The most severe disease outcomes are correlated with an over-exuberant immune response. The role of antibodies in immune protection is still not completely understood, making predictions around herd immunity uncertain and utility of “immunity passports” difficult to assess. The final exit strategy from the current pandemic will very likely involve a combination of effective therapeutics to decrease the burden of disease and vaccines to prevent transmission.

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