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## Review

## Immune response to SARS-CoV-2 variants: A focus on severity, susceptibility, and preexisting immunity



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## ABSTRACT

The heterogeneous phenotypes among patients with coronavirus disease 2019 (COVID-19) has drawn worldwide attention, especially those with severe symptoms without comorbid conditions. Immune responses to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative virus of COVID-19, occur mainly by the innate immune response via the interferon (IFN)-mediated pathways, and the adaptive immunity via the T lymphocyte and the antibody mediated pathways. The ability of the original Wuhan SARS-CoV-2 strain, and possibly more so with new emerging variants, to antagonize IFN-mediated antiviral responses can be behind the higher early viral load, higher transmissibility, and milder symptoms compared to SARS-CoV and are part of the continued clinical evolution of COVID-19. Since it first emerged, several variants of SARS-CoV-2 have been circulating worldwide. Variants that have the potential to elude natural or vaccine-mediated immunity are variants of concern. This review focuses on the main host factors that may explain the immune responses to SARS-CoV-2 and its variants in the context of susceptibility, severity, and preexisting immunity.

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## Introduction

Since the emergence of coronavirus disease 2019 (COVID-19) in December 2019, it has caused a rapid worldwide emergency [1]. Unlike previous pandemics, the cause of the infection was promptly identified; the International Committee on Taxonomy of Viruses named the causative virus of COVID-19 as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) based on its genetic similarity to SARS-CoV (80%) [2]. The major impact worldwide was mostly due to the high transmission rate and a high number of cases. However, the fatality rate of SARS-CoV-2 (5%) is lower, in comparison to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (10%), and Middle East Respiratory Syndrome Coronavirus (MERS CoV) (30%) [3,4]. However, SARS-CoV-2 transmission has also been reported even among asymptomatic patients [5]. Mutations in the SARS-CoV-2 receptor binding domain which has given rise to new SARS-CoV-2 variants including B.1.1.7, B.1.351, P.1, B.1.526, B.1.427 and B.1.429, has been suggested to have increased the binding affinity of the virus to Angiotensin-converting enzyme 2 (ACE2), and increased virus infectivity as compared to its most genetically related virus, SARS-CoV and earlier variants of SARS-CoV-2 [6]. The clinical manifestations of COVID-19 range from being asymptomatic to critically ill, such as pneumonia, severe acute respiratory distress, multi-organ damage, and, possibly, death [7]. An estimated 15% of all confirmed cases progress to present a severe form of the disease with a higher percentage seen among the elderly [8]. In COVID-19 patients, the dysfunction, dysregulation, over activation, and intertwining of the different mechanisms of innate and adaptive immunity are thought to lead to severe pneumonia [9,10], which suggests that COVID-19 induced pneumonia can be considered as an immune-mediated disease [11,12]. The phenomenon of the cytokine storm is thought to be responsible for the most severe forms of SARS-CoV-2 infection [13–16].

The objective of this review is to explore how specific immune mechanisms play a role in the: (1) severity of COVID-19 phenotype among patients that lack comorbidities of the infection, (2) development of cytokine storm in a subset of patients, (3) clinical predictors of severe COVID-19 phenotype and associated immune components, and (4) immune response to the different emerging SARS-CoV-2 variants of concern (VOC) in relation to evading natural and/or vaccine induced immunity. In this review, to be able to demonstrate the impact of the notable variants on the immune system, we will first present the foundational roles of the major immune components involved in COVID-19 infection and their contribution to the severity of the disease. We will also shed light on different variants of SARS-CoV-2, cross-reactivity and its possible role in the pathogenesis of COVID-19 infection.

## Innate immune response in COVID-19

Innate immunity is the first line response to protect host cells from viral infection. The features of this response elicit nonspecific immune reactions that determine the outcome of the infection and the heterogeneous clinical phenotypes [17]. Innate defense mechanisms were found to be sufficient to control SARS-CoV infection,

in the absence of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells and antibodies [18–20]. In fact, the response to SARS-CoV has been reported to be mainly through the innate inflammatory response, rather than the specific adaptive immune response, due to possibly a lack of cytokine activity [21]. However, viruses have evolved to either evade or inactivate the innate immune responses or lead to a hyperactivated inflammatory response [22]. SARS-CoVs are single-stranded RNA (ssRNA) viruses that stimulates innate immune responses and are excessive when compared to other viruses, such as influenza [23,24].

Regions of the SARS-CoVs genome were shown to work as immunostimulants for several components of innate immunity through the activation of Toll-like receptors, such as TNF- $\alpha$ , IL-6 and IL-12 [25,26]. In comparison to other ssRNA viruses, this immunostimulant activity is two-fold higher [23]. A major factor related to disease outcome is the ability to resolve the initial inflammatory response [27], demonstrating that a strong innate immune response is not necessarily the best response [28]. Several components of the innate immune response have been found to play an important role in the progression and clinical presentation of COVID-19 infection.

### *Pattern recognition receptors, neutrophils, and macrophages*

The innate immune response to SARS-CoV-2 infection is mediated via alveolar macrophages and dendritic cells which express pattern recognition receptors (PRR) which recognize Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) [29]. During this recognition, the NOD-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome is activated [30,31]. This activation of the NLRP3 inflammasome plays a vital role in the early stages of infection to efficiently limit virus replication by subsequent inflammation [32,33]. Limited or dysfunctional NLRP3 inflammasome activation has an essential role in the pathogenesis of severe organ injury [31,33–35]. Although activation of the NLRP3 inflammasome and its mediated inflammation is necessary for the defense against viruses, impaired/excessive activation can also mediate damage and adverse disease outcomes [31,33–35]. In SARS-CoV-2 infection, despite the lack of data regarding any direct association between the NLRP3 inflammasome and COVID-19, several studies suggested the involvement of NLRP3 and cytokine storm and cell apoptosis [30,36–39]. The activation of inflammasome in macrophages, epithelial cells, and endothelial cells results in the releases of pro-inflammatory cytokines, most notably, IL-1 $\beta$  and IL-18, leading to the characteristic feature of neutrophilia and leukopenia seen in severe COVID-19 cases [40,41].

Mannose-binding lectin (MBL) protein is also a contributor to pattern-recognition molecules and plays a critical role in the first-line host defense against SARS-CoV, before antibody production. MBL deficiency has been linked to an increased susceptibility to SARS-CoV infection [42–44], and correlated with an increased genetic predisposition to SARS-CoV [43]. In COVID-19 patients, MBL pathway-mediated complement activation has been shown to contribute to thrombosis and coagulopathy in patients with severe COVID-19 [45]. In addition, Toll-Like Receptor (TLR) sense viral RNA

that results in the activation of TLR3, TLR7, TLR8, and TLR9, and consequently activates the Nuclear Factor kappa B (NF- $\kappa$ B) pathway. A large number of pro-inflammatory cytokines play a major role in triggering virus-induced inflammation [46]. The increased secretion of the pro-inflammatory cytokines and chemokines recruits mainly monocytes and T lymphocytes, but not neutrophils to the infected site, elucidate the presentation of lymphopenia and the high neutrophil-lymphocyte ratio seen in most COVID-19 patients [47].

### Interferons and cytokines

In most COVID-19 patients, recruited immune cells controls the infection in the pulmonary tissue that terminates the immune response, and leads to recovery from the viral infection. However, in a subset of patients, evasion of innate immunity occurs and a later excessive/dysfunctional immune response is triggered, culminating into a cytokine storm during which an unusual lack of IFN and a massive elevation of Granulocyte Colony-Stimulating Factor (G-CSF), IP-10, MCP-1, Macrophage Inflammatory Protein 1 $\alpha$  (MIP-1 $\alpha$ ) and Tumor Necrosis Factor-alpha (TNF- $\alpha$ ), IL-2, IL-6, IL-7, IL-10 are observed [47,48]. The exact mechanism of how SARS-CoV-2 evades the innate immunity and causes excessive inflammatory response that result in a higher degree of viral load is yet to be determined, but antagonism of the interferon signaling pathway have been highlighted [47]. Another mechanism could be the significantly high N protein expression in SARS-CoV-2-infection [49]. N protein was reported to antagonize IFN $\beta$  response in SARS-CoV infected cells [50]. IFN synthesis and signaling have also been found to be antagonized by SARS-CoV open reading frame (Orf) 3b and Orf6 [51]. Innate immunity is mainly mediated via interferons (IFN), which are the first line of defense against viral infections by activating macrophages and natural killer (NK) cells. This interferes with the production of viral proteins by presenting antigens to cytotoxic T-cells that can directly bind and destroy the virus-infected host cells, hence preventing severe consequences of the disease [4,52].

Crosstalk between macrophages, conventional dendritic cells and plasmacytoid dendritic cells are a major cellular pathway for the control of severe and fatal cytopathic virus infection [53]. All three types of interferons (I, II, and III IFNs) share a common signal transducer and activator of transcription 1 (STAT1) that control the expression of several IFN regulated genes [54]. Deletion of any of the signaling components involved in the STAT1 signaling pathway significantly weakens the innate immune response and increases susceptibility to several pathogens, including viruses [55]. STAT1 has also been reported to play a role in adaptive immune processes, especially those seen in SARS-CoV patients with severe infection [55]. MERS-CoV, SARS-CoV and SARS-CoV-2 have been found to encode proteins that contribute to the suppression of IFN by avoiding interferon-stimulated gene (ISG) effector functions and evading antiviral innate immune pathways [52,56–62]. This occurs in severe outcome patients that showed lower ISG and immunoglobulin gene expression levels, persistent chemokine levels, and deficient anti-SARS spike antibody production [63,64]. However, during SARS-CoV-2 infections, levels of IFN-I and IFN-III have also been shown to be low despite sufficient ISG expression, which resulted in a decrease in the innate antiviral response [65,66]. This low IFN level was accompanied with elevation in proinflammatory cytokines, which culminated in an inadequate antiviral response in a hyperinflammatory setting that can explain the pathogenicity of severe COVID-19 cases [65]. In patients with severe COVID-19 enhanced expression of TNF- $\alpha$ , macrophage inflammatory protein 1- $\alpha$  (MIP-1 $\alpha$ ), GM-CSF, IL-2, IL-6, MCP3, and IP-10 were detected. Excessive levels of chemokines (CXCL1, IP-10, CXCL5, CCL2/MCP1, CXCL10) were also demonstrated among those patients with severe COVID-19 [13,67–70].

The higher the infectiveness of SARS-CoV-2, the lower the levels of IFNs and proinflammatory cytokines/chemokines are, compared to SARS-CoV (52). SARS-CoV-2 reportedly does not trigger any IFN response, and only significantly activates 5 of the 13 proinflammatory mediators, compared to 11 of the 13 that are activated during SARS-CoV infection. The low degree of innate immune activation can also explain the asymptomatic or mild symptoms in more than 80% of COVID-19 patients [71]. The angiotensin converting enzyme 2 (ACE2) receptor, which is utilized by both SARS-CoV and SARS-CoV-2 for cell entry, is also down regulated by IFN- $\gamma$  and interleukin-4 (IL-4) [72]. However, unlike IFN- $\gamma$  that may not be activated, IL-4 acts early during the replication cycle of the virus [72].

### Immune complexes and complement system

Pathogenic levels of immune complexes (ICs) are commonly seen in several disorders, such as serum sickness or viral diseases where IC deposition and excessive inflammatory reactions have been reported [73]. The involvement of ICs in the pathogenesis of severe cases of SARS-CoV-2 infection is supported by the late development of the cytokine storm, especially endotheliitis and disseminated microvascular thrombosis, which affects multiple organs, including the heart, brain, and kidney [74–76]. Complement proteins bind to erythrocytes that then carry ICs to phagocytes in the liver and the spleen. The role and activation of the complement and coagulation pathways in the setting of SARS-CoV-2 infection are controversial; despite most studies confirming an essential role [77–80]. Additionally, to activate the innate type-I interferon and IL-6 dependent inflammatory immune responses, complement function was found to modulate and predict immunity, susceptibility, and clinical outcome associated with SARS-CoV-2 infection [81]. For example, the activation of the complement protein, C3, occurs early and contributes to the prothrombotic and proinflammatory states culminating in end organ damage seen in severe cases of COVID-19 [82]. In severe COVID-19 cases, high inflammatory markers were associated with pathologically low levels of C3 and C4 complement components. These low levels were concluded to be a result of excessive activation of the complement pathway with the consequent lung pathology, which resulted in declining C3 level [80].

### Adaptive immune response in COVID-19

#### Lymphocytes

T lymphocytes are of high importance for clearing an infectious process that has begun, as their plasma levels correlate with higher survival [83,84]. Activated killer T cells in response to SARS-CoV-2 have the ability to prevent the spread of the virus from the upper respiratory tract. Hence, the efficiency of this response will determine the fate of the symptom severity, host viral load and transmission rates into the community. Leukopenia and lymphocytopenia have been proposed as a way the virus evade the host immune response [85–87]. At the time of SARS-CoV infection, CD8<sup>+</sup> T cell depletion did not affect viral clearance or replication, whereas CD4<sup>+</sup> T cell depletion resulted in pathologic consequences represented by interstitial pneumonitis and delayed clearance of infection from the lungs [18]. This CD4<sup>+</sup> T cell depletion and delay in viral clearance was found to be associated with a reduction in the production of cytokines, neutralizing antibodies, and the recruitment of lymphocytes to lung tissue [18], highlighting the impact of COVID-19 on CD4<sup>+</sup> T lymphocyte [79,88].

Severity, mortality, and dysregulated immunological response towards SARS-CoV-2 induces lymphopenic community-acquired pneumonia (L-CAP), and the presence of lymphopenia and hypercytokinemia indicates poor control of the pathogen [7,48,89,90]. This has also been seen in patients with severe SARS-CoV infections

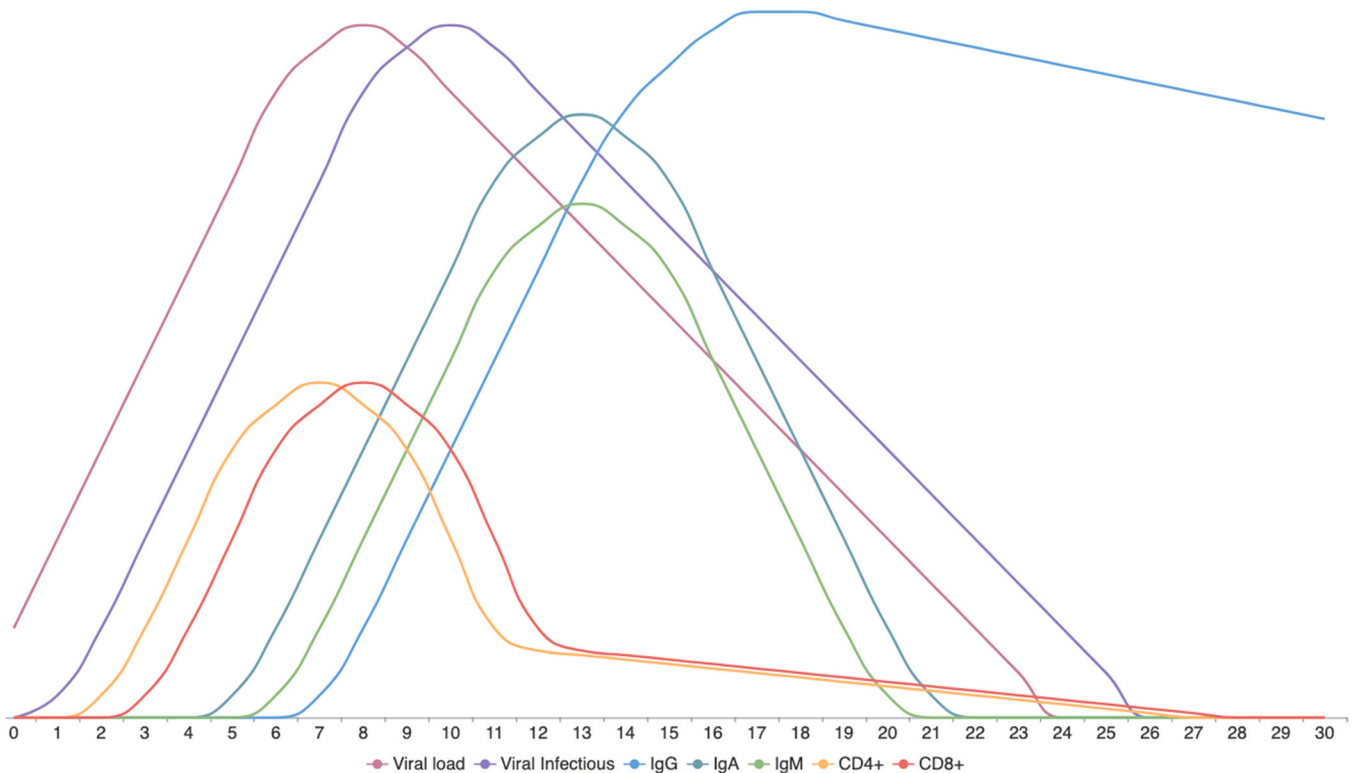


Fig. 1. The time relationship between viral load, viral infection, IgG, IGA, IgM, CD4 +, and CD8 +.

[63,64]. The low lymphocyte counts have been suggested to be due to the direct cytotoxic action of the virus by preventing cytokine storm and dampening the innate immune responses [90–92]. Multiple genes involved in apoptosis and P53 signaling were found to be upregulated in patients with COVID-19, which may help explain the development of lymphopenia in these patients [70]. In addition, host factors have also been reported to contribute to the lymphopenic state in severe SARS-CoV-2 infections, as patients requiring intensive care generally have comorbidities such as hypertension, diabetes, cardiovascular and cerebrovascular disease and are commonly older than those with mild disease presentation [7]. Both older age and comorbidities are associated with endothelial dysfunction, which increases the risk of enhanced leukocyte adhesion and extravasation and contributes to lymphopenia seen in severe SARS-CoV-2 infections [93,94]. During severe SARS-CoV infection, an unusual conversion of B lymphocytes to macrophage-like cells leads to inability of the humoral and cellular component of the immune system to respond in time to neutralize viral infection [95,96]. This is thought to be driven by the spike protein of SARS virus, and the local hypoxia seen in patients with severe SARS-CoV infection [96]. COVID-19 has led to an exhaustion of effector T cells, negatively affecting their defense against SARS-CoV-2 [97,98]. This loss of effector T cell function is either due to the increased expression of inhibitory receptors on the surface of T cells due to cytokine activity or a reduction in regulatory T cells [79,99].

#### T cells and pre-existing immunity

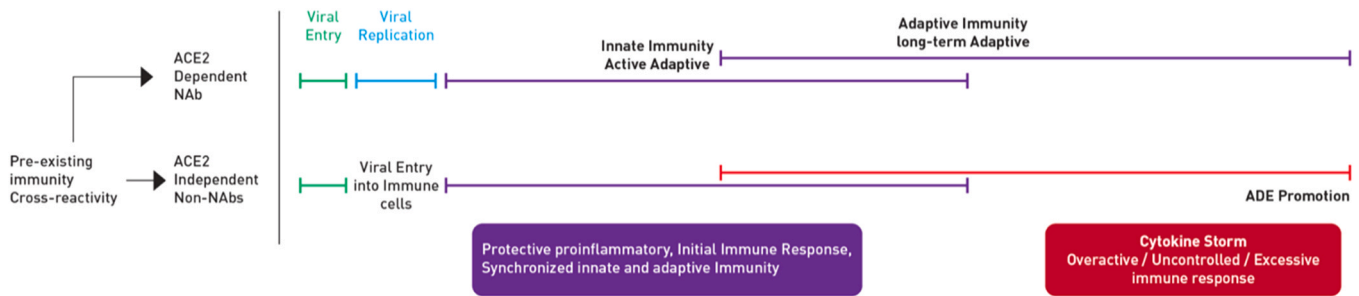
The membrane (M), spike (S), nucleocapsid (N), open reading frame (ORF), mainly ORF3a, and ORF8 proteins, and non-structural proteins (NSP), specifically NSP3 and NSP4, are all proteins targeted by SARS-CoV-2-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells. The presence of S-reactive CD4<sup>+</sup> T cells was reported in 83% of patients with SARS-CoV-2 infection. Interestingly, the detection of SARS-CoV-2-reactive CD4<sup>+</sup> T cells in healthy controls highlighted possible cross-reactive T cell

recognition between circulating CoV and SARS-CoV-2 [100]. Studies have demonstrated the presence of SARS-CoV-2-reactive CD4<sup>+</sup> T cells in 20% of SARS-CoV-2 seronegative healthy donors in the Netherlands [88], 34–81% in Germany [101,102], 40–60% in the United States of America [100], 51% in Singapore [103], and 30% in the United Kingdom [104]. However, a study from the UK did not detect any SARS-CoV-2-reactive T cell responses in unexposed healthy volunteers [105], and a study from Wuhan failed to detect any spike-specific T cell responses before vaccination on 108 volunteers without pre-exposure to COVID-19 [106].

#### Antibodies

Humoral response against SARS-CoV-2 has been found to be comparable to other CoVs, SARS-CoV in particular [107–111]. During SARS-CoV-2 infections, SARS-specific immunoglobulin M (IgM) antibodies were found to appear two weeks (can be as early as 3–6 days) after the onset of the infection, last one month before they gradually start to disappear until the end of week 12 [107,109–111] (Fig. 1). Immunoglobulin G (IgG) was produced 16–18 days after the onset of infection [107,109] (Fig. 1) and to last for a longer but limited time in COVID-19 patients [107]. Overall, the antibody responses for SARS-CoVs do not last for a very long time [112–114]. SARS-CoV antibodies were not detectable in 91% of tested samples when measured six years after SARS-CoV infection [115]. In SARS-CoV-2 infected patients, detection of both IgM and IgG antibodies are used to identify the stage of the infection. While it is still unclear on how long antibodies to SARS-CoV-2 will be present in the system, a recent study reported the level of anti-SARS-CoV-2 antibodies reduced by half-life during week 4–12 following the start of infection [116]. However, studies have shown that patients can recover from SARS-CoV-2 infection without functional B cells, highlighting that despite the importance of the antibody response, it is not essential [117,118].

While CoV infections were shown to trigger an antibody response, this usually results in the formation of neutralizing or



**Fig. 2.** The possible roles of preexisting immunity in the protective and excessive immune response (cytokine storm) against SARS-CoV-2.

enhancing antibodies as seen in SARS-CoV and MERS-CoV [119–121]. Enhancing antibodies and neutralizing antibodies can counteract each other’s function [122]. Neutralizing antibodies exert their action via blocking the entry, egress, or the fusion of the virus into the host cell; for example, recognition of spike protein RBD by neutralizing antibodies blocks viral entry [123]. Even though virus-specific antibodies are considered to have antiviral effects and aid in viral clearance, the presence of specific antibodies can enhance viral infections through antibody-dependent enhancement (ADE) [124]. ADE was correlated with an increase in the level of proinflammatory mediators and a decrease in anti-inflammatory mediators [125]. In SARS-CoV infection, ADE was facilitated by the engagement of Fc receptors on different immune cells, which facilitated viral entry [126–130]. Whether the triggered antibodies will have enhancing or neutralizing properties, is proposed to be a function of antibody quality and quantity. Antibodies produced with higher concentrations, and those with higher affinity are less likely to result in ADE [131]. In the setting of ADE, engagement of Fc receptors of immune cells is proposed as an ACE2 independent path of viral entry into host cells [130] (Figs. 2,3).

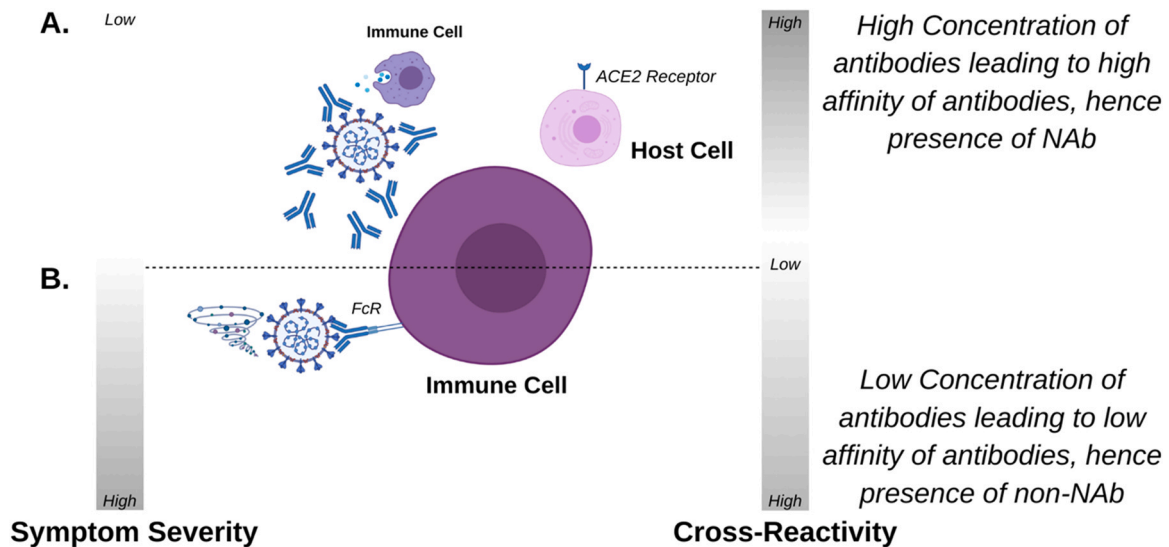
**Autoimmunity**

SARS-COV-2 antigenic mimicry with human tissue has received attention recently. It was found that several host tissue antigens had

strong reactions with the SARS-CoV-2 antibodies; this highlighted that not only pulmonary tissue antigens, but several other tissue antigens cross-reacted with SARS-CoV-2 proteins [132,133]. Specifically, the relationship between SARS-CoV-2 spike, nuclear proteins and autoimmune target proteins highlighted the possibility of an autoimmune reaction against human tissues resulting in the extensive organ, tissue, and cellular damage seen in severe SARS-COV-2 infections, this significant reaction can potentially result in an autoimmune reaction against host proteins and tissues such as pulmonary surfactant proteins, connective tissue, the respiratory, digestive, cardiovascular, and nervous systems [132–135]. It is worth mentioning that a recent study demonstrated that the risk of developing severe COVID-19 phenotype among patients with autoimmune diseases concluded no difference compared to controls [136]. This can be due to their concomitant use of immune suppressant, which can play a role in modulating cytokines storm in severe COVID-19 cases.

**Antibodies and pre-existing immunity**

The cross-reactivity between CoVs, SARS-CoV, MERS-CoV, and SARS-CoV-2 is unclear. A study of COVID-19 specific humoral immune response has shown that the patient’s produced IgM and IgG antibodies, cross-reacted with SARS-CoV, but not with other human CoVs (HCoVs) [137]. If cross-reactivity exists between pre-existing



**Fig. 3.** The relationship between symptom severity, cross-reactivity, neutralizing antibodies, and antibody dependent enhancement. A. Neutralizing antibodies (NAb) bind to SARS-CoV-2, neutralize it, and prevent its binding to ACE2 on host cells, the NAb-virus complex is engulfed and degraded by phagocytes. B. A demonstration of antibody-dependent enhancement (ADE) where non- neutralizing antibodies (non-NAB) bind to SARS-CoV-2 but lack the ability to neutralize it, the NAb-virus complex binds to immune cells via the Fc receptors (FcR) on their surface, this results in marked increase in the release of inflammatory cytokines (cytokine storm) and suppression of anti-inflammatory cytokines. If cross-reactivity with other human coronaviruses (hCoV) exists and triggers high concentration of antibodies with strong affinity this results in an efficient immune response and subside SARS-CoV-2. If cross-reactivity with other hCoV exists but rather triggers low concentration of antibodies with low affinity this results ADE where non-NAB mediate massive increase in inflammatory cytokines which results in severe SARS-CoV-2 infection with cytokine storm as a hallmark. Created with BioRender.com.

antibodies against other CoVs, then cross-reactive ADE is possible where infection with the new SARS-CoV-2 can be enhanced, resulting in a more severe illness or a faster adaptive immune response (Figs. 2,3). The higher prevalence of common CoVs in previous years in some regions in the world, might explain the higher pathogenicity of SARS-CoV-2 infection in these affected regions based on the assumption of ADE with pre-existing enhancing antibodies against those common CoVs. For example, the link between early response with higher titers and older age may indicate a priming effect from existing antibodies against other endemic strains [128]. The HCoV circulate continuously, therefore, it is sensible to assume that CoVs antibodies are higher in older people compared to children, including enhancing antibodies [138]. Children infected by SARS-CoV-2 usually have milder presentation of the disease [139]. However, we do not have enough evidence to conclude such role of ADE.

This possibility of ADE makes it doubtful that the use of convalescent plasma to treat SARS-CoV-2 infection is of benefit, as theoretically, it can potentially lead to transmission of enhancing antibodies from individuals who recovered from SARS-CoV-2 infection, hence worsening of the disease in recipients. Some studies reported a lack of effectiveness of convalescent plasma and induction of endothelial damage, while clinical studies did not reveal any deleterious effects of using convalescent plasma to treat SARS-CoV-2 infection which makes the possibility of transmission of enhancing antibodies unlikely [122,140]. The mutations present at the spike level of SARS-CoV-2 variants are of concern and have been categorized as immune escapes. It is possible that these mutations influence ADE antibody elicitation, thus making the human host more or less susceptible to infection and reinfection irrespective of possible cross-reactivity of antibodies. Nevertheless, the issue of enhancing antibodies is of great importance for the development of a vaccine against SARS-CoV-2, which ideally should not aim to induce enhancing antibodies in healthy individuals [130]. To date, studies on currently available vaccines excluded the possibility of vaccine triggering enhancing antibodies. Nevertheless, identifying the SARS-CoV-2 neutralizing, cross-neutralizing, and enhancing epitopes is essential for any vaccine design to minimize the risk of ADE. Epitopes of T cell should also be recognized to outline protective immunity [122,141].

### Cross-reactivity and COVID-19 susceptibility and severity

The potential cross-reactivity between seasonal HCoVs, SARS-CoV and MERS-CoV and the pandemic SARS-CoV-2 can have implications on the course of COVID-19 natural infection. While the immunity to some HCoVs such as HCoVOC43 and HCoVHKU1 has been shown to fade within one-year [25,142], SARS-CoV and MERS-CoV infections can potentially induce longer-lasting immunity [143,144]. Memory T-cell responses specific for SARS-CoV have been detected two years after recovery [64]. In general, betacoronaviruses have the potential to trigger immune responses against one another by sharing antigen epitopes for presentation to the immune system via major histocompatibility (MHC) class I receptors [145]. This is why significant titers of cross-reactive antibodies against other betacoronaviruses were detected in sera of SARS-CoV patients [143,145,146]. SARS-CoV and HCoV-OC43 infections have been shown to result in cross-reactive antibodies against MERS-CoV and SARS-CoV, respectively [143,146]. However, some studies reported that antibodies induced by SARS-CoV are unable to cross-neutralize MERS-CoV [147]. The strongest cross-reactivity was detected between SARS-CoV-2 and MERS-CoV/SARS-CoV antibodies due to genetic sequence identity [148]. Nevertheless, cross-reactivity of antibodies against SARS-CoV-2 with MERS-CoV, SARS-CoV, HCoV-OC43, and HCoV-HKU1 is controversial [109,144,148,149]. While some studies demonstrated that the sera of SARS-CoV patients concluded no cross-neutralization against SARS-CoV-2 implicating the lack of

cross-protection, others have reported that SARS-CoV-2 antibodies cross-reacted with SARS-CoV [109,144,146,148,150].

It is unknown whether cross-reactive memory T cells may exacerbate COVID-19 disease or reduce its severity [151]. Increased severity of COVID-19 due to cross reactivity can be due to poor avidities of T cell receptors or abnormal T cell polarization. The concept of cross-reactivity is of great importance however, since taking measures to contain COVID-19 will mean less spread of SARS-CoV-2, it also means less spread of herd immunity to HCoV [152,153]. The consequence of this is the presence of low levels of cross-immunity between other betacoronaviruses and SARS-CoV-2. Ultimately, the result could be that SARS-CoV-2 will start to fade before a resurgence after some time [145].

It is important to note that cross-reactivity does not necessarily mean cross-protection. Cross-reactivity has also been reported between Dengue virus (DENV) and Zika virus (ZIKV) as their immunological cross-reactivity is expected due to the similarity in their geographic distributions and high sequence homology. While T cell responses may help explain the cross-protection against Zika virus from a previous Dengue virus infection, cross-reactive antibody responses may increase the risk of severe secondary Dengue virus infections [154]. Similarly, it was shown that ADE triggered by a previous CoV infection could increase susceptibility to and the severity of SARS-CoV-2 infection [155,156]. Thus, the development of cross-reactive T cell responses and cross-reactive antibodies may prevent or promote severe disease, depending on their precise balance upon the secondary infection with a different serotype (Fig. 3). Subset alteration of lymphocytes were found to be associated with both clinical characteristics and treatment efficacy of COVID-19 [157]. Specifically, cytotoxic T lymphocytes have been reported to be an independent predictor for COVID-19 severity and treatment efficacy [157]. Cross-reactivity may explain the vital involvement of humoral immune response in vaccine-mediated protection against and recovery from SARS-CoV infection, which should be accompanied by the development of a neutralizing antibody response [158–161]. These SARS-CoV-specific neutralizing antibodies developed during convalescence were found to prevent the reinfection with the virus in animal models [162]. A study from the United States reported reinfection in a patient with two distinct strains of the SARS-CoV-2 virus, and suggested that previous exposure to the virus would not result in total immunity [163].

Susceptibility to SARS-CoV-2 can be difficult to define due to largely unknown pre-existing cross-protective immunity in individuals exposed to antigenically related pathogens, including viruses [164]. Reduction in symptom severity and transmission rates of homologous and heterologous HCoVs have been reported in the setting of prior immunity by previous exposure to one HCoV [25,165,166]. However, cross-protective immunity with HCoV is not thought to be long-lasting [167], as repeated infections have been reported in all age groups with both homologous and heterologous HCoVs [25,26]. This might explain the age-related susceptibility to and increased severity of COVID-19 among the elderly as higher HCoV infection rates are seen in children [166,168,169] and reported to be associated with relative protection from SARS-CoV-2 [170]. Despite the scarcity of data regarding the relationship between aging and the host response to virus infection, few studies provided a potential explanation for the increased susceptibility and more severe lung pathology following SARS-CoV infection. Baas et al. reported an age-dependent innate immune response to SARS-CoV in mice. Innate immune response to SARS-CoV was found to differ with the age of the host; older mice respond with a faster and exacerbated innate immune response than younger mice but had a delay in the virus clearance [18,55,171,172]. Animal and human studies are yet to confirm these findings in SARS-CoV-2 infection. Most importantly, a second wave of a biphasic response in aged mice was found to trigger a subset of genes that is responsible for the

activation of T lymphocytes leading to severe histopathologic changes in the lungs [18,55,171–173].

Similarly, higher levels of PGD<sub>2</sub> seen in the lungs of older patients with severe respiratory infections have been found to negatively affect the initial innate immune and the later adaptive immune responses [174]. Studies in macaques using SARS-CoV also concluded a more robust innate immune response in older macaques, while IFN-β expression as an anti-inflammatory cytokine was found to be low in older macaques [175]. Despite rare deaths and better prognosis in children younger than 15 years, among the rare severe cases, they were found to have more severe symptoms than those displayed by older children [139]. Higher ACE2 activity in younger children [25,26,145,146,165–170], compared to those older than 13, have been noticed and suggested to explain the more severe symptoms among the younger children [176]. This higher ACE2 activity is not believed to result in severe complications in children as in adults [177]. In addition, SARS-CoV-2 has been shown to be associated with a decreased count of CD4 cells; children have been found to have higher numbers of CD4 cells compared to adults, this may explain their better prognosis [178,179]. Although rare, severe cases of COVID-19 among children have been reported, SARS-CoV-2 in these cases has been associated with triggering Kawasaki disease and toxic shock syndrome [141,180].

### Notable variants of SARS-CoV-2

Over the past 18 months, the SARS-CoV-2 virus has started to acquire mutations, approximately two single-letter mutations per month in its genome, resulting in new variants. Several significant, more fit to survive, variants have emerged. As SARS-CoV-2 began to spread rapidly, the number of immune individuals was insignificant, so the variant with more efficient transmission prevailed and gained an advantage over other circulating strains. With the greater spread of infection, and as the number of immune individuals increased, the virus started to gain benefits from evading naturally induced immunity where it can potentially reinfect the same individual, so variants with better ability to evade naturally induced immunity have better chances for survival in the new host. Those variants have been labeled by the World Health Organization as variants of concern (VoC). With the initiation of a global vaccination program, those VoCs can potentially threaten to elude vaccine-induced immunity, which may jeopardize vaccination efficacy. Eventually, when much of the susceptible population is vaccinated with effective vaccines, the variant better suited for survival in the new host will be the one with a better ability to evade the vaccine-induced immunity. However, variants that are able to evade vaccine-induced immunity have not yet been reported and may not necessarily emerge [181].

One of the first identified variants includes the D614G mutation in the Spike (S) protein modification [182,183]. This mutation targets amino acid 614, which is located outside the receptor binding domain (RBD) and is known to enhance viral infectivity by shifting the S protein conformation towards ACE-2 binding fusion state to allow viral entry and replication [182,184,185]. Another variant that emerged in North Jutland, Denmark but with very limited spread is the Cluster 5 SARS-CoV-2 variant which was related to infection spread in mink farms and was transmitted to humans. This variant has been shown to have a combination of mutations that have not been observed before. To date, following extensive investigation and surveillance, Danish authorities have identified only 12 human cases of the Cluster 5 variant up to September 2020, and it does not appear to have spread widely.

More recently, a combination of mutations and deletions have appeared in the RBD region, which contains a N-terminal domain of S protein and a receptor-binding motif (RBM). The B.1.1.7 variant or the Alpha VOC of SARS-CoV-2 emerged in the United Kingdom, (also previously known as S gene negative, 20I/501Y.V1, or VOC 202012/

01), has notable mutations that include N501Y, where asparagine (N) has been replaced with tyrosine (Y) at position 501 of the RBD of the S protein. This variant has a 69/70 deletion, which can result in conformational changes in the spike protein, and a mutation in P681H, which occurs in a highly variable region in coronaviruses, near the S1/S2 furin cleavage site. This S gene negative variant is now replaced by the Delta VOC (also known as the B.1.617.2) [186].

The B.1.351 variant of SARS-CoV-2 has emerged independently in South Africa (also termed 20H/501Y.V2). B.1.351 variant contains several mutations in the spike protein, which include E484K, K417N, and N501Y. A resurgence of the COVID-19 in Manaus, Brazil, is also associated with a new variant (known as P.1 lineage). The P.1 lineage began circulating in Manaus and has seventeen unique mutations detected; three of these mutations were identical to the B.1.351 variant and were reported in the RBD of the spike protein: K417T, E484K, and N501Y. Variant B.1.17, B.1.351, P.1 have been declared as variants of concern (VoC) by the WHO, as these variants share common characteristics, including escape mutations and impact neutralization efficacy. While variant B.1.1.7 has been shown to be more sensitive to neutralization, it does not appear to evade the immune system [187,188]. Mutations present in the B.1.351 and P.1 variant (K417T, E484K, and N501Y) are highly concerning, since they have shown to compromise neutralization that was generated by a previous infection or vaccination and may increase viral infectivity and fitness [189–191]. Two other SARS-CoV-2 sequences belonging to the B.1.1.207 lineage have been reported recently in Nigeria. These sequences have been shown to share one non-synonymous mutation in the spike protein (P681H) in common with the UK B.1.1.7 variant; none of the other 22 unique mutations of the B.1.1.7 lineage was detected in these sequences. The P681H mutation occurred at the highly variable region near the S1/S2 furin cleavage site [192].

### Immune response and VoC

Among the many concerns of the emergence of new variants, the ability to evade natural or vaccine-induced immunity is of most concern. To be able to evade natural or vaccine-induced immunity, the virus will need to accumulate several mutations in the spike protein to be able to overcome the polyclonal immune response to several parts of the spike protein triggered by vaccines or natural infection with SARS-CoV-2. The most dominant mutation worldwide is presented as SARS-CoV-2 with the D614G variant. *In vitro* studies indicate that this mutation confers greater infectivity, while molecular epidemiology correlates it with an increase in transmissibility with no evidence to date for increased virulence. This variant was shown to be highly sensitive to natural or vaccine-derived neutralizing antibodies, which can be due to the effect of this mutation on the S protein [184,193], so this variant is unexpected to threaten the antibody-mediated immunity produced in response to the original D614 S protein. The Denmark cluster 5 variant has been suggested to have the potential to reduce virus neutralization in humans and consequently decrease the duration of immunity triggered after natural infection or vaccination. Mutations that target regions located outside the RBD have not been associated with increased severity; however, they have been reported to result in increased infectivity and transmissibility [194]. Several studies concluded that SARS-CoV-2 with the D614G variant is highly sensitive to neutralizing antibodies, natural or vaccine-derived, which can be due to the effect of this mutation on the S protein [184,193]. The RBD is immunodominant and accounts for 90% of serum neutralizing activity [195]. Mutations in the RBD have been reportedly associated with a higher potential of evading the immune system. The RBD variant N439K has been found to result in enhanced RBD affinity for ACE2 and higher viral load, it also was concluded to be able to evade antibody-dependent immunity, but no change in disease severity was associated with this variant. B.1.1.7 variant (Alpha variant) that



**Table 1**

The change in transmissibility, virulence and antigenicity in SARS-CoV-2 emerging variants compared to the original Wuhan SARS-CoV-2 strain.

Lineage	Country of first detection	Notable mutations	Transmissibility	Virulence	Antigenicity
B.1.1.7 (Alpha Variant)	United Kingdom	N501Y, 60–70del, P681H	Severe Change	Moderate Change	No Change
B.1.351 (Beta Variant)	South Africa	N501Y, K417N, E484K	Moderate Change	No Change	Severe Change
P.1 (Gamma Variant)	Brazil	N501Y, K417N, E484K	Severe Change	Severe Change	Moderate Change
Cluster 5	Denmark	Y453F, 69–70del	No Information	No Information	Moderate Change
B.1.1.207	Nigeria	P681H	No Change	No Change	No Change
B.1429/B.427	United States	I4205V, D1183Y, S13I, W152C, L452R	Slight Change	Moderate Change	Severe Change
B.1.525	United Kingdom	E484K, F888L	No Information	No Information	Slight Change
B.1.617.2 (Delta Variant)	India	E484Q, L452R, P681R	No Information	No Information	Slight Change

first emerged in the UK before it spreads to several other countries has been shown to be associated with an increased fatality compared with other variants [192]. For the B.1.351 variant (Beta variant) of SARS-CoV-2 that has emerged in South Africa, there is no evidence of any impact on disease severity. There is some evidence though, that linked E484K, one of the spike protein mutations, with an effect on neutralization by some polyclonal and monoclonal antibodies [196,197].

At the time of P.1 variant (Gamma variant) emergence, Manaus, Brazil was expected to have surpassed the theoretical herd immunity threshold (67%) [198]. It was reported that this variant might influence the transmissibility and antigenic profile of SARS-CoV-2, which may affect the ability of antibodies generated through previous natural infection or through vaccination to recognize and neutralize the virus; a study reported that this variant might have the ability to elude the human immune response that was triggered by the previous variant. Although sequencing of the variants that emerged in Nigeria (B.1.1.207) has shown no signs of increased virulence, it is still unknown whether these variants have any impact on the transmission or disease severity of SARS-CoV-2 in Nigeria [192]. Table 1 displays the main variants of SARS-CoV-2 and the consequent change in transmissibility, virulence, and antigenicity. Further studies must investigate the impact of the new variants of concern on reinfection, resurgence, cross-reactivity, and ADE. In-vitro evidence demonstrates that the presence of the E484K mutation reduces the neutralization of monoclonal antibodies in convalescent sera [190]. It is noteworthy to mention that lack of neutralization does not essentially mean lack of protection from disease antibodies; although important, they are not the only immune component in the fight against SARS-CoV-2. The marginal amount of antibodies can still protect from SARS-CoV-2, in fact, the possibility of reinfection can also provide an immunity boost that has been seen in other viral infections such as rubella, where reinfection was shown to be clinically insignificant, patients were noninfectious and boosted immunity against the virus [199].

It is also of high importance to take T cell responses into consideration when talking about immunity towards these new variants. A recent study has shown that, compared to antibodies [200], T cells can be more resilient to threats from emerging variants. This proposed resilience is reportedly due to the fact T cells generated in response to SARS-CoV-2 were found to target at least 15–20 different fragments of coronavirus proteins which hinders the virus's ability to escape cell recognition. In fact, a recent study reported that most T-cell responses are unlikely to be altered by the mutations in emerging variants [201].

## Conclusion

Understanding the mechanisms associated to the innate immunity provides us a better understanding of the pathogenesis of the disease and a promising therapeutic treatment. Despite the increasing number of studies on the immunologic aspects of SARS-CoV-2 infection, more studies are still needed to adequately help predict the progression of the infection into asymptomatic or critical

phenotypes. An early inadequate IFN antiviral response, and a later overproduction of proinflammatory cytokines, ADE, infection of innate immune cells, recruitment of uninfected cells from the circulation to the primary site of infection, and/or the consequent massive immune reactions induce hyperinflammation, may play a vital role in the progression to life-threatening complications seen in severe COVID-19 cases. The roles which SARS-CoV-2-specific T cell phenotypes, autophagy, ADE, and cross-reactivity may play against SARS-CoV-2 needs to be further investigated. Currently, there is also a lack of details of the roles of the hyperactivation of the immune system to the lung and the systemic damage that can lead to patients' death [142,202].

The increased virus infections provide the basis for SARS-CoV-2 to mutate and better evade host immunity, which has led to new variants showing higher transmissibility rates. Any future global immunization program will need to cover immunity against new coronavirus variants to ensure the effectiveness of these vaccination programs. Further research must be conducted to investigate the transmission, virulence, and antigenicity of the VoC's, and its association to the COVID-19 heterogeneous phenotypes.

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## Author Contributions

EA, HJ, MM, GT, HS contributed to conception and design of the study. EA took the lead in writing the manuscript. A comprehensive search using Ovid software on Global Health, Medline, PubMed, Zoological Record was performed by MM. GT and HS supervised the project. All authors contributed to manuscript revision, read, and approved the submitted version.

## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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