Neutralizing Antibodies and Antibody-Dependent Enhancement in COVID-19: A Perspective

Swati Ajmeriya¹, Amit Kumar¹, Subhradip Karmakar², Shweta Rana¹ and Harpreet Singh¹*

Abstract | Antibody-dependent enhancement (ADE) is an alternative route of viral entry in the susceptible host cell. In this process, antiviral antibodies enhance the entry access of virus in the cells via interaction with the complement or Fc receptors leading to the worsening of infection. SARS-CoV-2 variants pose a general concern for the efficacy of neutralizing antibodies that may fail to neutralize infection, raising the possibility of a more severe form of COVID-19. Data from various studies on respiratory viruses raise the speculation that antibodies elicited against SARS-CoV-2 and during COVID-19 recovery could potentially exacerbate the infection through ADE at sub-neutralizing concentrations; this may contribute to disease pathogenesis. It is, therefore, of utmost importance to study the effectiveness of the anti-SARS-CoV-2 antibodies in COVID-19-infected subjects. Theoretically, ADE remains a general concern for the efficacy of antibodies elicited during infection, most notably in convalescent plasma therapy and in response to vaccines where it could be counterproductive.

Keywords: ADE, SARS-CoV-2, Neutralizing antibodies, Enhancement, ARDS, ERD

1 Introduction
With the emergence of the SARS-CoV-2 pandemic in December 2019 in the Wuhan province of China as its epicenter, it brought a wave of morbidity and mortality worldwide, spreading rapidly to more than 190 nations infecting over 180 million people¹⁻⁵. SARS-CoV-2 is a betacoronavirus that is zoonotic in nature, causes pulmonary infection, and infects the upper or lower respiratory tract⁶. This virus shares a sequence similarity of 79% with SARS-CoV and about 50% with MERS-CoV at the whole genome level⁷⁻⁹. A spectrum of clinical signs and symptoms have been observed for COVID-19 patients ranging from mild symptoms like fever, cough, sore throat, loss of taste and smell to severe form of illness¹⁰⁻¹². People with underlying comorbidities and elderly populations seem to be at heightened risk and more susceptible to infection, including other complications¹³,¹⁴.

Coronaviruses gain entry into the cell upon binding to the cellular receptor for angiotensin-converting enzyme 2 in the epithelial cells (ACE2) through the viral spike(S) protein⁸,⁹; this is followed by S protein priming by host cell surface protease, the serine protease TMPRSS²⁸,¹⁵. The S protein of SARS-CoV-2 consists of the S1 subunit, which has a receptor-binding domain (RBD), and the S2 subunit that mediates membrane fusion for viral entry¹. Currently, the vaccines available for SARS-CoV-2 target the RBD region of S protein for preventing its attachment and thus infection via blocking RBD-ACE2 interaction¹⁶⁻²³.

When whole antibodies elicited in viral infection at a suboptimal concentration that is generally expected to be protective, provide an advantage to the virus by giving entry access to the cells that could lead to the enhancement of the infection called antibody-dependent...
enhancement (ADE), then the risk of aggravating the severity of infection increases. SARS-CoV-2 infection leads to the production of neutralizing antibodies, but the extent to which these antibodies would be neutralizing and protective to the subsequent SARS-CoV-2 infection is still not clear. Some reports of SARS-CoV-2 reinfection have been published, elucidating illness with the genetically distinct strain of SARS-CoV-2 with symptomatic reinfection\textsuperscript{24–26}. There is a possibility of severe cases of infection during a secondary infection with SARS-COV-2, similar to DENV serotypes as reported previously, due to the risk of cross-reactive antibodies potentially capable of promoting ADE. This cross-reactivity of antibodies with different strains may give rise to the phenomenon of ADE and make the symptoms more severe; acute respiratory distress syndrome (ARDS) is majorly attributed to the severe cases of illness that have emerged to be the leading cause of death in COVID-19, similar to SARS and MERS\textsuperscript{9}.

Even though the link between ADE of infection and disease severity is yet to be established, in the past, the severity of infection and cross-reactivity of antibodies to other viral serotypes have been linked and established in vitro for Zika, Dengue, and Influenza A viral infection\textsuperscript{28–30}. These previous and current studies point towards the requirement of proactive research in the immunopathology caused by COVID-19. Because a large and variable group of people are getting infected with severity ranging from mild to severe cases of illness, therefore, the possibility of ADE is worth considering.

### 2 ADE in Related Organism: Dengue

Dengue virus (DENV) is a single positive-stranded RNA virus of the family Flaviviridae and genus Flavivirus. ADE has been well documented in this disease. Dengue fever is caused by four antigenically distinct dengue virus serotypes (DENV 1–4). Live attenuated vaccine (LAV) for Dengue raised a serious concern due to their capacity to elicit an adverse immune response. The concern behind this limited approval is that this vaccine predisposed some of the dengue-naive recipients to severe dengue fever due to their cross-reactivity with other DENV serotypes, thereby contributing to ADE. Therefore, the major bottleneck with whole DENV-based vaccine strategies may be overcome using an antibody response serotype. ADE may be a significant concern in the case of COVID-19, not just due to a suboptimal response to different variant of concern (VoC) but also due to an inadequate viral neutralization.

In this review, we aim to assess the hypothesis that non-neutralizing antibodies or antibodies that are neutralizing but possess a low affinity to critical regions of virus entry points may be associated with the severity of infection in COVID-19 that fails to neutralize the virus. These antibodies may be formed by infection or vaccination with a closely related serotype of SARS-CoV-2, previous exposure to other classes of coronaviruses. In this review, we discuss the phenomenon of ADE, its possible mechanism that may play a significant role in the pathogenesis of COVID-19 by relating the previous and some current findings with the COVID-19 pandemic and highlights the interplay of antibodies that may be neutralizing or non-neutralizing in nature with viral surface receptors that may lead to this condition.

### 3 Antibody-Dependent Enhancement Phenomenon

Virus entry into host cells is a primary obligate process in viral pathogenesis; this is usually mediated by hijacking the cellular mechanism. Neutralizing antibodies aid in inhibiting the attachment of the virus to the host cell receptors by targeting the viral surface proteins or glycoproteins and is considered to be a crucial mechanism to eliminate the virus\textsuperscript{31–36}, and the attachment between viruses and target cells plays an essential role in most cases and may produce different outcomes. However, in some instances, paradoxically, binding of the antibodies at sub-neutralizing concentrations to non-critical sites of the virion can result in non-neutralization of the virion that may lead to virion entry and invasion into certain cell types via antibody Fc region present on the carboxyl-terminal domain of antibody with Fc gamma receptor IIa (FcRIIa)-expressing phagocytic cells like the monocytes, macrophages, or through interaction with complement receptors contributing in the enhancement of infection, a process known as antibody-dependent enhancement\textsuperscript{37–41} during these instances, the binding of antibodies to these non-critical sites leaves the virus with retainment of its infectivity\textsuperscript{37}. Virus possesses various kinds of different antigenic epitopes capable of inducing neutralizing antibodies, but some might induce non-neutralizing antibodies that may enhance the infection\textsuperscript{42}. Despite the presence of multiple critical sites on the virus surface, immunoglobulins, after attaching to this area, may not neutralize the virus completely because the virus
can utilize another site for interacting with the host cell\textsuperscript{37}. Diluting concentrations of antibodies have been shown to increase lung pathology and infiltration of cells into the alveolar air space observed in vivo mouse model during the influenza virus life cycles\textsuperscript{43}. In an experimental study, it was observed that lower levels of IgG could promote the uptake of human parvovirus (B19V) in endothelial cells showing an enhancing effect of lower levels of antibodies at the level of virus internalization\textsuperscript{44}. Seropositive people who may have successfully eliminated one viral serotype may well be at increased risk of infection with other viral serotypes. The neutralizing antibodies preformed for one of these serotypes might often not be neutralizing for different serotypes that may cross-neutralize the epitopes, and these deficient and incompetent neutralizing antibodies may instead allow ADE mechanism to kick in, leading to enhanced infection\textsuperscript{45–47}. Dengue viruses, one of the best studied, representing a classic example of flaviviruses exhibiting ADE cause infection through four distinct serotypes DENV1, DENV2, DENV3, and DENV4; antibodies raised for one Dengue serotype do not protect against other serotypes failing to block the virus entry into cells\textsuperscript{42,48,49}; the humoral response produced against one Dengue serotype provides protective serotype-specific antibodies; however, these antibodies do cross-react with other Dengue viral serotypes but do not neutralize them that may promote the entry of the virus via antibody Fc regions failing in protecting against different viral serotypes (Fig. 1); as a result, a second

\begin{figure}[h]
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\caption{Antibody-dependent enhancement in DENV. \textbf{a} Primary infection of DENV induces neutralizing antibodies at sufficient concentration that potentially neutralizes and destroys DENV providing protective immunity. \textbf{b} In secondary infection, neutralizing antibodies that are elicited successfully neutralize the virus when the DENV serotype is similar to the primary DENV infection. \textbf{c} Antibody-dependent enhancement of infection in DENV infection occurs when non-neutralizing antibodies formed from primary infection bind with different DENV serotypes during secondary infection, these Ab from a primary infection are unable to neutralize the different DENV serotype that enhances the virus entry and replicate into cells leading to a heightened risk of dengue viral infection severity. Image credit smart.servier.com.}
\end{figure}
Dengue viral infection could arise, being more lethal, leading to dengue hemorrhagic fever and shock syndrome, this similar instance of ADE can happen in COVID-19 in which RBD region of S protein of SARS-CoV-2 may get mutated as found in some studies. Enhancement of disease and more severity has been described in infants who received inactivated respiratory syncytial virus (RSV) vaccine as well as inactivated measles vaccine after they encountered a secondary viral infection.

4 Mechanism of ADE
The virus–antibody complex binds with either Fc or complement receptors expressed on immune cells leading to the internalization of the virus–antibody complex that must follow the destruction of the virus. However, in some instances, the virus escapes the antigen–antibody complex and starts a replication cycle inside immune cells that possibly occurs when the virus is bound to low-affinity antibodies. Although the exact mechanism of ADE remains to be understood, ADE has been reported to take place in two possible ways, first, internalization of virus–antibody immune complexes into phagocytic cells via interaction of the antibody Fc region with the FcγR on myeloid cells such as macrophage, phagocytosis occurs, resulting in an increased number of virus particles. This type of Fc-dependent mechanism has been documented in West Nile virus, dengue virus, and human immunodeficiency virus. Fc receptors have been shown to play a pivotal in promoting antibody-dependent cell enhancement mechanisms. Generally, cells that express Fc receptors lead to phagocytosis of antigen–antibody complexes as well as the direct killing of target cells by a process known as Antibody-dependent cellular cytotoxicity (ADCC). However, type 1 FcγR receptors are expressed by myeloid lineage cells such as monocytes, macrophages, dendritic cells, granulocytes including neutrophils and eosinophils.
B and NK cells, ADE is primarily observed in monocytes, macrophages, and dendritic cells. CD32 (FcγRII) in monomeric form has a low affinity for the Fc region of IgG antibodies but possesses a high affinity for IgG immune complexes. FcγRI (CD64) binds with monomeric IgG with high affinity. The second possible mechanism of ADE is the complement-mediated enhancement of infection by complement protein C1q that is activated in the classical pathway or C3 that is activated in an alternative pathway followed by the binding of the antibody to the viral surface proteins forming the complex of virus-antibody-complement protein (Fig. 3). C1q binds to the Fc region of IgG1 and IgM that are complement-fixing antibodies attached to the viral proteins followed by the interaction between the corresponding receptor and complement protein that increases viral adhesion leading to the formation of the
virus, antibody, and complement complex. ADE mediated by complement protein C1q has been found with Ebola virus in non-monocytic cells by endocytosis or enhancing virus attachment to the target cell; thus, this resulting complex consisting of virus-antibody-C1q binds to C1q cell surface receptors leading to either the binding of the virus to Ebola-specific receptors or endocytosis via C1q receptors. The involvement of complement protein C1q has also been shown to mediate HIV-1 infection by binding to the Fc portion of antibodies that enhanced infection in vitro as immunocomplex as C1q binds with C1q receptors at the cell surface. C3-mediated ADE is found in both the West Nile and HIV virus. Principally, IgG antibodies have been observed to mediate ADE; however, IgM as well as IgA along with Complement have also been shown to be capable of ADE, for instance, IgM-dependent enhancement of West Nile virus mediated by complement protein CR3 has been found in macrophage immune cells.

5 Neutralizing Antibodies and ADE

As the virus utilizes its envelope proteins to attach to the target cell surface receptors or coreceptors, neutralizing antibodies targeted against viral proteins generally hinder this step by targeting critical regions of the viral proteins preventing the binding of the virus (Fig. 4), this, in turn, reduces the infectivity of the virus leading to its neutralization. The production of neutralizing antibodies is the desirable primary goal of vaccination, and therefore, antibodies that are secreted are expected to be neutralizing. Neutralizing antibodies are secreted as part of the humoral response of the active immune system mediated by Ab secreting plasma cells. Pathogens disarmed by these antibodies are generally phagocytosed by macrophages; neutralization of viral infectivity can take place in some ways; they may either interfere with the binding of the virion to the cellular receptors, fusion with the host membrane in case of enveloped viruses, membrane penetration (for non-enveloped viruses), may block uptake into the cells, prevent uncoating of the genomes in the endosomes or cause aggregation of virus particles. Antiviral antibodies lyse the enveloped viruses and serum complement disrupt membranes. The neutralizing effect of antibodies depends on certain factors, for instance, the stoichiometry of antibody(Ab titer), that must exceed a particular threshold; the antibody affinity for viral epitopes regulates the fraction of epitopes on the viral particle occupied by antibodies at any given concentration that is referred to as occupancy that predominantly determines the neutralization potential, as well as the accessibility of epitope, are both obligatory to exceed the threshold requirements as the antibodies possessing poor accessibility to specific epitopes require a higher concentration to exceed the occupancy threshold for neutralization. A similar observation has been made in a study, where the diluted form of antisera against SARS-CoV spike protein has been found to promote ADE and enhanced apoptosis at the same time, while neutralizing antibodies against SARS-CoV neutralized infection; so, it is the avidity that is more important and not merely the affinity. An increasing body of evidence shows that cross-reactive antibodies can have a crucial impact but greatly varied, these cross-reactive antibodies can perform neutralization if they bind viral epitopes with higher affinity, nonetheless, the longevity of neutralizing antibodies is found to be higher than cross-neutralizing antibodies; a study found neutralizing antibody IgG to last longer than cross-reactive antibody that declined over time specific against a dengue virus serotype. Cross-neutralizing antibodies may bind to specific regions of antigen but fail to neutralize it. Similar results have shown that neutralizing antibodies (nAbs) when targeting SARS-CoV, binds to viral RBD epitope of the spike protein, but not the receptor-binding motif that culminated in the failure of cross-neutralization of infection. Kathleen et al. found that S-RBD-specific antibodies exhibited more neutralizing potential than N-proteinspecific antibodies, this in vitro study explains that not all antibodies elicited are neutralizing. In an in vivo study, Syrian hamsters were tested for the efficacy of antibodies isolated from convalescent donors, it was found that despite their efficient binding to S and/or RBD proteins of SARS-CoV-2, antibodies not competitive with ACE2 failed to inhibit the virus from entering host cells. The early presence of IgG subtypes has been observed in some patients, indicative of a possible memory to a cross-reactive antigen in a secondary immune response that might increase disease severity due to ADE. Mutations in the concerned viral proteins may render the immune system to preferentially utilize the immunological memory from a previous
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Evidence of ADE in Coronaviruses

In the first report of ADE in 1964, enhancement of the infectivity of arboviruses such as Murray Valley encephalitis virus, West Nile virus, and Japanese encephalitis virus was observed during their neutralization in the presence of chicken antisera, all of which belong to the family Flaviviridae. It was found afterwards that the IgG antibodies in the sera were responsible for this enhancement; however, no biological explanation was being given for this process of enhancement. Since then, flaviviruses have been intensively studied to elucidate ADE’s mechanisms and clinical implications.

Figure 4: Secretion of neutralizing antibodies and its mechanism of blocking of viral infection. 

a. Non-neutralizing antibodies binding to non-critical sites in SARS-CoV-2 spike proteins.

b. Neutralizing antibodies binding to critical sites on viral spike proteins.

e. Blockading viral attachment to host cell receptor ACE2 preventing fusion between.

Facilitation of virus entry in cell

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significance in viral pathogenesis. Among flaviviruses, Dengue was the first virus in which ADE was clearly established in 1977, and the relationship between the secondary infection associated with antibody response and severe illness was recognized in Dengue viruses; studies showed that low concentrations of IgG Abs were able to enhance infection. A probable role of ADE was speculated by a mathematical model that related the disease severity with enhancing effect of cross-reactive antibody to different DENV serotypes during secondary infection. In vitro studies of ADE have been observed for Flaviviruses such as Dengue virus, yellow fever virus, and zika virus; Coronaviruses including alpha and beta coronaviruses, orthomyxoviruses such as influenza viruses, retroviruses such as HIV and feline infectious peritonitis virus (FIPV), other viruses such as Coxsackievirus B, respiratory syncytial virus, Ebola virus, alphaviruses and rabies virus. The in vitro and in vivo studies done to demonstrate ADE in different viruses is summarised in Table 1.

In vivo studies done in rhesus monkeys reflecting the relationship between antibody response and increased Dengue viremia have added further evidence to ADE phenomenon. Complement-mediated ADE has been extensively studied in HIV and West Nile virus. In vitro studies have shown that sera from convalescent patients from Ebola virus disease contain antibodies capable of promoting ADE. In vivo studies done in rhesus monkeys reflecting the relationship between antibody response and increased viremia to different DENV serotypes has been added to further evidence to the phenomenon of ADE. Similarly, in an experimental finding, enhanced yellow fever immunogenicity upon yellow fever vaccination was observed in subjects with a specific range of cross-reactive antibody titers from a previous inactivated Japanese encephalitis vaccination; similar observations have been made when antibodies elicited after vaccination against Japanese encephalitis virus were found to enhance dengue virus infection; a study in COVID-19-affected patients reported that the higher antibody titers against SARS-CoV-2 were associated with more severe disease that raises the possibility of antibody-dependent disease enhancement effect.

### Table 1: List of viruses in which the phenomenon of ADE has been documented.

| Virus name | Type of study |
|------------|---------------|
| Severe acute respiratory syndrome coronavirus (SARS-CoV) | In vivo, in vitro |
| Middle East respiratory syndrome coronavirus (MERS-CoV) | In vitro |
| Japanese encephalitis virus | In vivo |
| Yellow fever virus | In vitro |
| Dengue virus | In vitro |
| Human immunodeficiency virus type 1 (HIV-1) | In vivo, in vitro |
| Respiratory syncytial virus (RSV) | In vitro |
| Hantavirus | In vitro |
| Ebola virus | In vitro |
| Getah virus | In vitro |
| Sindbis virus | In vitro |
| Bunyamwera virus | In vitro |
| Influenza virus | In vivo |
| West Nile virus (WNV) | In vivo |
| Rabbitpox virus | In vivo |
| Feline infectious peritonitis virus (FIPV) | In vivo |
| Rabies virus | In vitro |
| Murine cytomegalovirus | In vitro |
| Foot-and-mouth disease virus | In vitro |
| Coxsackievirus B3 | In vitro |
of COVID-19 reinfection has been observed in a patient with two different COVID-19 infection who was found to be infected with two genetically different SARS-CoV-2 variants. ADE of SARS-CoV-2 spike protein-specific antibodies via FcγRII cellular receptor; a similar kind of result was obtained when ADE was shown to be mediated by S(spike) protein-specific antibodies in SARS-CoV-2. Furthermore, a study of SARS-CoV-2 spike protein-specific antibodies in SARS-CoV-2 has been detected from severely affected elderly patients plasma with high titers of SARS-CoV-2 spike protein-specific antibodies via FcγRIIa both in vitro and in vivo. Also, the researchers have developed non-fucosylated antibodies that, at lower concentrations, were shown to exhibit strong ADCC deploying this glycosylation feature of antibodies. Such a low level of fucosylation has been shown in S, and RBD-specific IgG antibodies in COVID affected symptomatic patients as compared to either asymptomatic or mildly infected patients.  

7 ADE Risk Factors in COVID-19
Antibody-dependent enhancement (ADE) might be one of the causes behind worsening in the severity of symptoms, and this process might have implications for Convalescent therapy used for patients. Due to epitope heterogeneity, there may be a chance that prior exposure to SARS-CoV-2 or other coronaviruses may trigger ADE. One such observation has been made in the study, which indicated the cross-reactivity of antibodies for previous coronavirus endemic among the human population, and recent studies have shown the presence of IgG serum positivity for OC43 and NL63 in individuals who have not been exposed to SARS-CoV-2 forming immune responses against SARS-CoV-2. Thus, prior exposure to other coronaviruses may be a risk factor for ADE. Glycosylation of antibodies, particularly in the Fc region of IgG, has been extensively studied in health and disease. The Fc region of IgG1 antibodies binds with the FcγRIII receptor through interaction with the hinge region and the CH2 domain. The interaction of Fc with FcγRIII receptor is significantly influenced by the presence of glycans at the N-glycosylation site in each of the CH2 domains. It has been widely studied that the absence of core fucose from N-glycans of antibodies leads to an enhanced ADCC activity that subsequently increases affinity for FcγRIIIa both in vitro and in vivo. Also, the researchers have studied increased lung pathology and infiltration of cells into the alveolar air space on challenging with neutralizing antibodies for Influenza A virus demonstrating increased lung pathology and infiltration of cells into the alveolar air space on challenging with neutralizing antibodies. SARS-CoV-2 may escape the antibody–virus complex at sub-neutralizing concentrations of antibodies progressing towards replication process that may be abortive without producing viable virus particles or non-abortive, in either case, massive death of immune cells into the alveolar air space on challenging with neutralizing antibodies.

8 Health Issues Associated with ADE
ADE has been observed to potentially escalate multiple viral infections, such as in the case of respiratory syncytial virus (RSV) and measles. The outcome of ADE has been shown to affect lungs, causing lung injury and cause enhancement of respiratory disease after a respiratory virus infection takes place with symptoms of monocytic infiltration and profusion of eosinophils in the respiratory tract; the other outcome observed is a vaccine-associated enhanced respiratory disease (VAERD). ADE has been found to be associated with a wider category of infections known as enhanced respiratory disease (ERD), including antibody-based mechanisms such as cytokine cascades and cell-mediated immunopathology. In non-macrophage tropic respiratory viruses, for instance, RSV and measles, non-neutralizing antibodies have been shown to induce ADE and ERD by the formation of immune complexes that get deposited in the airway tissues and activate cytokine and complement pathways that cause inflammation, airway obstruction, and acute respiratory distress syndrome leading to severe cases of illness; and these are some clinical observations of SARS-CoV-2 similar to RSV and measles in severe cases of COVID-19; inflammatory lung injury by activation of hyperactivation of the complement cascade has been observed prevailing in COVID-19 patients. These results collectively indicate that complement pathways can be aggressively activated in the lungs of COVID-19 patients, which may attribute to SARS-CoV-2N protein. In vivo studies in BALB/c mice challenged with non-neutralizing antibodies for Influenza A virus demonstrated increased lung pathology and infiltration of cells into the alveolar air space on challenging with neutralizing antibodies. SARS-CoV-2 may escape the antibody–virus complex at sub-neutralizing concentrations of antibodies progressing towards replication process that may be abortive without producing viable virus particles or non-abortive, in either case, massive death of immune cells.
cells can happen that can result in inflammation cascade and a cytokine storm. As the surge in COVID-19 cases took place, children and adults have been observed to be infected with SARS-CoV-2 more than those observed in the early phase of the COVID-19 pandemic back in 2019. Children who were thought to be largely spared from SARS-CoV-2 had become more prone to multisystem inflammatory syndrome (MIS-C), a post-COVID-19 disorder, which was first recognized in the UK when children were found to be negative for SARS-CoV-2 but were seropositive, indicates the possibility of past infection; multisystem inflammatory syndrome in infants (MIS-C) and adults (MIS-A) associated with COVID-19 has certain implications such as multiple organ failure and shock, in this context, more further research is required to confirm the basis of ADE in MIS-C.

9 Conclusion and Future Anticipation
According to some previous and present studies, cross-reactive non-neutralizing antibodies appear to hamper virus neutralization. However, extensive research on ADE remains to be done to prove its existence; in vitro and in vivo studies done so far underscore the chances of ADE in Flaviviruses infection. Future studies are required to study the immune system physiology of people before and after vaccination as pre-existing antibodies may provide some correlation with recovery as opposed to worsening of disease that may enlighten the type of antibodies to assess in vaccine studies and differences in the severity of COVID-19 illness and how it manifests in old versus young people. Whether the immune system is producing antibodies to the original viral strain from prior exposure or to the currently infecting viral strain needs to be studied. Thus, uncovering these facts and findings could help explain the largely varying response amongst COVID-19 patients with the disease ranging from mild and symptomless to severe infections requiring hospitalization in some cases that often result in death. ADE could be a potentially new avenue to explore in COVID-related fatality.

10 Suggested Recommendations
Globally, new variants of SARS-CoV-2 have emerged that could potentially give rise to the phenomenon of ADE. It is a combination of several factors that may determine its resurgence but nevertheless could trigger reinfection with an enhanced severity and need for healthcare support. The other members of the beta coronavirus lineage, including SARS-CoV and the Middle East respiratory syndrome (MERS) virus, are already known to infect humans. Hence, it is conceivable that protective antibodies against them could initiate ADE in individuals infected with SARS-CoV-2. Maternally acquired SARS-CoV-2 antibodies bound to mast cells could also trigger ADE in children along with the development of MIS (multisystem inflammatory syndrome) via placental transport of these antibodies. However, in contrast to DENV, SARS, and MERS, CoVs infect predominantly the respiratory epithelium, not macrophages which actually expresses the FcγR receptors. Therefore, the chances of ADE are low in COVID cases, and no ADE has been observed in COVID-19 infection. But not just the virus variants; even vaccines against COVID-19 could initiate ADE response. However, the new vaccine technologies consider these facts at the vaccine design stages for any risk of ADE. These are as listed below:

- Targeting a SARS-CoV-2 protein epitope for vaccine development that was the least likely to cause ADE, as evident from in silico studies.
- Evaluating animal-based studies in pre-clinical and phase 1 trials for ADE post-vaccination studies. Further to do the same in human clinical trials.
- Epidemiological surveillances to register cases of ADE in a population

It is, therefore, in the best of everyone’s interest to ramp up the vaccination drive keeping a tab on the vaccinated populations for adverse response and hospitalization. Unvaccinated individuals are the breeding grounds for the emergence of variants of interest (VOI) and variants of concern (VOC), which are more harmful than ADE in terms of the rate of occurrence; this needs coordination between the government and the residents with a public awareness program describing the benefits of vaccines in containing the disease spread in the population. We need to understand that if not facilitating the virus entry, even antibody-mediated elevated effector functions or immune complex formation can also lead to ADE and inflammation. With more innovative algorithms, a vaccine against SARS-CoV-2 generated high neutralizing antibody titers and minimal risk of ADE. With many more vaccines coming up in the market against SARS-CoV-2, the government and regulatory bodies must verify the safety and efficacy of these vaccines for their own population. These necessities the requirement for vaccine bridging trials for the
foreign-made vaccines to look for ADE in the native population. Even if rare for COVID-19, the possibilities for ADE poses a theoretical risk and need to be addressed with utmost care.

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Conflict of interest
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Swati Ajmeriya received her B.Sc. in Life Sciences from the University of Delhi and her M.Sc. in Biotechnology from Kumaun University, Nainital, India. She joined as RA in the ICMR Computational Genomics Centre, New Delhi, in 2018, where her work has centered around handling and analyzing next-generation sequencing data. Her research interests include genome analysis, virology, and immunology.

Amit Kumar received his PhD degree from Jawaharlal Nehru University, New Delhi, in computational biology and bioinformatics in the year 2014. He subsequently joined as Scientist at National Institute of Cancer Prevention & Research, where he worked for 4 years. Currently, he is working as a Scientist at the ICMR Computational Genomics Center, New Delhi. He has worked extensively in the area of structural bioinformatics and next-generation sequencing data analysis.

Dr. Subhradip Karmakar is currently an Additional Professor in Biochemistry at AIIMS, New Delhi. After completing PhD, Dr Karmakar did his postdoctoral training at Yale Medical School, New Haven, USA, and then at the University of Chicago, Illinois, USA. Dr Karmakar worked on human ENCODE project as well as in the molecular pathogenesis of hematopoietic malignancies. His research lab at AIIMS, New Delhi, uses system biology-based computation approaches to understand cancer.

Shweta Rana is working as Public Health Researcher at the Indian Council of Medical Research (ICMR). She is involved in many programs at the Division of Biomedical Informatics Centre; her primary responsibility includes design and development of data collection portal and analysis of collected data. Recently, she is involving in this developing national burn registry and TB reduction survey in Tribal Saharia. She has extensive experience in statistical data analysis.

Dr. Harpreet Singh has 19 years of experience in developing and managing accessible data systems. Dr. Singh obtained his PhD in Bioinformatics from Jawaharlal Nehru University and Postdoctoral training at Cornell University. Presently, Dr. Singh is working as Scientist at the Indian Council of Medical Research (ICMR), New Delhi, and heading Division of Biomedical Informatics, ICMR-AIIMS Computational Genomics Centre and Data Management Laboratory. At ICMR, Dr. Singh is actively working on rationalizing data systems and integrated data platform. Dr. Singh has led teams developing data portals for many programs of ICMR such as ICMR Antimicrobial Resistance Surveillance Network, Nikush for National Leprosy Eradication Program (NLEP), i-Mann for implementation research in mental health, etc. Recently, Dr. Singh's team has developed and maintaining National COVID-19 testing database. Singh has 89 peer-reviewed publications and 14 copyrights for developed tools.