



Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies

Wen Shi Lee ¹, Adam K. Wheatley ^{1,2}, Stephen J. Kent ^{1,2,3} ✉ and Brandon J. DeKosky ^{4,5,6} ✉

Antibody-based drugs and vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being expedited through preclinical and clinical development. Data from the study of SARS-CoV and other respiratory viruses suggest that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through antibody-dependent enhancement (ADE). Previous respiratory syncytial virus and dengue virus vaccine studies revealed human clinical safety risks related to ADE, resulting in failed vaccine trials. Here, we describe key ADE mechanisms and discuss mitigation strategies for SARS-CoV-2 vaccines and therapies in development. We also outline recently published data to evaluate the risks and opportunities for antibody-based protection against SARS-CoV-2.

The emergence and rapid global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has resulted in substantial global morbidity and mortality along with widespread social and economic disruption. SARS-CoV-2 is a betacoronavirus closely related to SARS-CoV (with ~80% sequence identity), which caused the SARS outbreak in 2002. Its next closest human coronavirus relative is Middle East respiratory syndrome-related coronavirus (MERS-CoV; ~54% sequence identity), which caused Middle East respiratory syndrome in 2012 (refs. ^{1,2}). SARS-CoV-2 is also genetically related to other endemic human coronaviruses that cause milder infections: HCoV-HKU1 (~52% sequence identity), HCoV-OC43 (~51%), HCoV-NL63 (~49%) and HCoV-229E (~48%)¹. SARS-CoV-2 is even more closely related to coronaviruses identified in horseshoe bats, suggesting that horseshoe bats are the primary animal reservoir with a possible intermediate transmission event in pangolins³.

Cellular entry of SARS-CoV-2 is mediated by the binding of the viral spike (S) protein to its cellular receptor, angiotensin-converting enzyme 2 (ACE2)^{4,5}. Other host entry factors have been identified, including neuropilin-1 (refs. ^{6,7}) and TMPRSS2, a transmembrane serine protease involved in S protein maturation⁴. The SARS-CoV-2 S protein consists of the S1 subunit, which contains the receptor binding domain (RBD), and the S2 subunit, which mediates membrane fusion for viral entry⁸. A major goal of vaccine and therapeutic development is to generate antibodies that prevent the entry of SARS-CoV-2 into cells by blocking either ACE2–RBD binding interactions or S-mediated membrane fusion.

One potential hurdle for antibody-based vaccines and therapeutics is the risk of exacerbating COVID-19 severity via antibody-dependent enhancement (ADE). ADE can increase the severity of multiple viral infections, including other respiratory viruses such as respiratory syncytial virus (RSV)^{9,10} and measles^{11,12}. ADE in respiratory infections is included in a broader category named enhanced respiratory disease (ERD), which also includes

non-antibody-based mechanisms such as cytokine cascades and cell-mediated immunopathology (Box 1). ADE caused by enhanced viral replication has been observed for other viruses that infect macrophages, including dengue virus^{13,14} and feline infectious peritonitis virus (FIPV)¹⁵. Furthermore, ADE and ERD has been reported for SARS-CoV and MERS-CoV both in vitro and in vivo. The extent to which ADE contributes to COVID-19 immunopathology is being actively investigated.

In this Perspective, we discuss the possible mechanisms of ADE in SARS-CoV-2 and outline several risk mitigation principles for vaccines and therapeutics. We also highlight which types of studies are likely to reveal the relevance of ADE in COVID-19 disease pathology and examine how the emerging data might influence clinical interventions.

Mechanisms of ADE

ADE has been documented to occur through two distinct mechanisms in viral infections: by enhanced antibody-mediated virus uptake into Fc gamma receptor IIa (FcγRIIa)-expressing phagocytic cells leading to increased viral infection and replication, or by excessive antibody Fc-mediated effector functions or immune complex formation causing enhanced inflammation and immunopathology (Fig. 1, Box 1). Both ADE pathways can occur when non-neutralizing antibodies or antibodies at sub-neutralizing levels bind to viral antigens without blocking or clearing infection. ADE can be measured in several ways, including in vitro assays (which are most common for the first mechanism involving FcγRIIa-mediated enhancement of infection in phagocytes), immunopathology or lung pathology. ADE via FcγRIIa-mediated endocytosis into phagocytic cells can be observed in vitro and has been extensively studied for macrophage-tropic viruses, including dengue virus in humans¹⁶ and FIPV in cats¹⁵. In this mechanism, non-neutralizing antibodies bind to the viral surface and traffic virions directly to macrophages, which then internalize the virions and become productively infected. Since many antibodies against different dengue serotypes

¹Department of Microbiology and Immunology, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia. ²ARC Centre for Excellence in Convergent Bio-Nano Science and Technology, University of Melbourne, Parkville, Victoria, Australia. ³Melbourne Sexual Health Centre and Department of Infectious Diseases, Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia. ⁴Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS, USA. ⁵Department of Chemical Engineering, The University of Kansas, Lawrence, KS, USA. ⁶Bioengineering Graduate Program, The University of Kansas, Lawrence, KS, USA. ✉e-mail: skent@unimelb.edu.au; dekosky@ku.edu

Box 1 | ADE and ERD**ERD**

ERD describes severe clinical presentations of respiratory viral infections associated with medical interventions (especially vaccines). Similar clinical presentations can occur as a result of natural infections, and so ERD is detected during preclinical and clinical trials by comparing the distribution of disease severities between the intervention and placebo study arms. ERD can be associated with a broad range of molecular mechanisms, including FcR-dependent antibody activity and complement activation (that is, ADE), but also to other antibody-independent mechanisms such as tissue cell death, cytokine release and/or local immune cell activation.

ADE

ADE can be broadly categorized into two different types based on the molecular mechanisms involved:

ADE via enhanced infection. Higher infection rates of target cells occur in an antibody-dependent manner mediated by Fc–FcR interactions. ADE via enhanced infection is commonly measured using in vitro assays detecting the antibody-dependent infection of cells expressing FcγRIIa, such as monocytes and macrophages. The link between in vitro ADE assay results and clinical relevance is often implied, rather than directly observed. Dengue virus represents the best documented example of clinical ADE via enhanced infection.

ADE via enhanced immune activation. Enhanced disease and immunopathology are caused by excessive Fc-mediated effector functions and immune complex formation in an antibody-dependent manner. The antibodies associated with enhanced disease are often non-neutralizing. ADE of this type is usually examined in vivo by detecting exacerbated disease symptoms, including immunopathology and inflammatory markers, and is most clearly associated with respiratory viral infections. RSV and measles are well-documented examples of ADE caused by enhanced immune activation.

ERD and ADE (of the second type described above) are often identified by clinical data, including symptom prevalence and disease severity, rather than by the specific molecular mechanisms that drive severe disease. The presence of complex feedback loops between different arms of the immune system makes it very difficult (although not impossible) to conclusively determine molecular mechanisms of ADE and ERD in human and animal studies, even if the clinical data supporting ADE and ERD are quite clear. Many different measurements and assays are used to track ADE and ERD, which can vary based on the specific virus, preclinical and/or clinical protocols, biological samples collected and in vitro techniques used.

Respiratory ADE is a specific subset of ERD.

are cross-reactive but non-neutralizing, secondary infections with heterologous strains can result in increased viral replication and more severe disease, leading to major safety risks as reported in a recent dengue vaccine trial^{13,14}. In other vaccine studies, cats immunized against the FIPV S protein or passively infused with anti-FIPV antibodies had lower survival rates when challenged with FIPV compared to control groups¹⁷. Non-neutralizing antibodies, or antibodies at sub-neutralizing levels, enhanced entry into alveolar and peritoneal macrophages¹⁸, which were thought to disseminate infection and worsen disease outcome¹⁹.

In the second described ADE mechanism that is best exemplified by respiratory pathogens, Fc-mediated antibody effector functions can enhance respiratory disease by initiating a powerful immune cascade that results in observable lung pathology^{20,21}.

Fc-mediated activation of local and circulating innate immune cells such as monocytes, macrophages, neutrophils, dendritic cells and natural killer cells can lead to dysregulated immune activation despite their potential effectiveness at clearing virus-infected cells and debris. For non-macrophage tropic respiratory viruses such as RSV and measles, non-neutralizing antibodies have been shown to induce ADE and ERD by forming immune complexes that deposit into airway tissues and activate cytokine and complement pathways, resulting in inflammation, airway obstruction and, in severe cases, leading to acute respiratory distress syndrome^{10,11,22,23}. These prior observations of ADE with RSV and measles have many similarities to known COVID-19 clinical presentations. For example, over-activation of the complement cascade has been shown to contribute to inflammatory lung injury in COVID-19 and SARS^{24,25}. Two recent studies found that S- and RBD-specific immunoglobulin G (IgG) antibodies in patients with COVID-19 have lower levels of fucosylation within their Fc domains^{26,27}—a phenotype linked to higher affinity for FcγRIIIa, an activating Fc receptor (FcR) that mediates antibody-dependent cellular cytotoxicity. While this higher affinity can be beneficial in some cases via more vigorous FcγRIIIa-mediated effector functions^{28,29}, non-neutralizing IgG antibodies against dengue virus that were afucosylated were associated with more severe disease outcomes³⁰. Larsen et al. further show that S-specific IgG in patients with both COVID-19 and acute respiratory distress syndrome had lower levels of fucosylation compared to patients who had asymptomatic or mild infections²⁶. Whether the lower levels of fucosylation of SARS-CoV-2-specific antibodies directly contributed to COVID-19 immunopathology remains to be determined.

Importantly, SARS-CoV-2 has not been shown to productively infect macrophages^{31,32}. Thus, available data suggest that the most probable ADE mechanism relevant to COVID-19 pathology is the formation of antibody–antigen immune complexes that leads to excessive activation of the immune cascade in lung tissue (Fig. 1).

Evidence of ADE in coronavirus infections in vitro

While ADE has been well documented in vitro for a number of viruses, including human immunodeficiency virus (HIV)^{33,34}, Ebola^{35,36}, influenza³⁷ and flaviviruses³⁸, the relevance of in vitro ADE for human coronaviruses remains less clear. Several studies have shown increased uptake of SARS-CoV and MERS-CoV virions into FcR-expressing monocytes or macrophages in vitro^{32,39–42}. Yip et al. found enhanced uptake of SARS-CoV and S-expressing pseudoviruses into monocyte-derived macrophages mediated by FcγRIIa and anti-S serum antibodies³². Similarly, Wan et al. showed that a neutralizing monoclonal antibody (mAb) against the RBD of MERS-CoV increased the uptake of virions into macrophages and various cell lines transfected with FcγRIIa³⁹. However, the fact that antigen-specific antibodies drive phagocytic uptake is unsurprising, as monocytes and macrophages can mediate antibody-dependent phagocytosis via FcγRIIa for viral clearance, including for influenza⁴³. Importantly, macrophages in infected mice contributed to antibody-mediated clearance of SARS-CoV⁴⁴. While MERS-CoV has been found to productively infect macrophages⁴⁵, SARS-CoV infection of macrophages is abortive and does not alter the pro-inflammatory cytokine gene expression profile after antibody-dependent uptake^{41,42}. Findings to date argue against macrophages as productive hosts of SARS-CoV-2 infection^{31,32}.

ADE in human coronavirus infections

No definitive role for ADE in human coronavirus diseases has been established. Concerns were first raised for ADE in patients with SARS when seroconversion and neutralizing antibody responses were found to correlate with clinical severity and mortality⁴⁶. A similar finding in patients with COVID-19 was reported, with higher antibody titres against SARS-CoV-2 being associated with

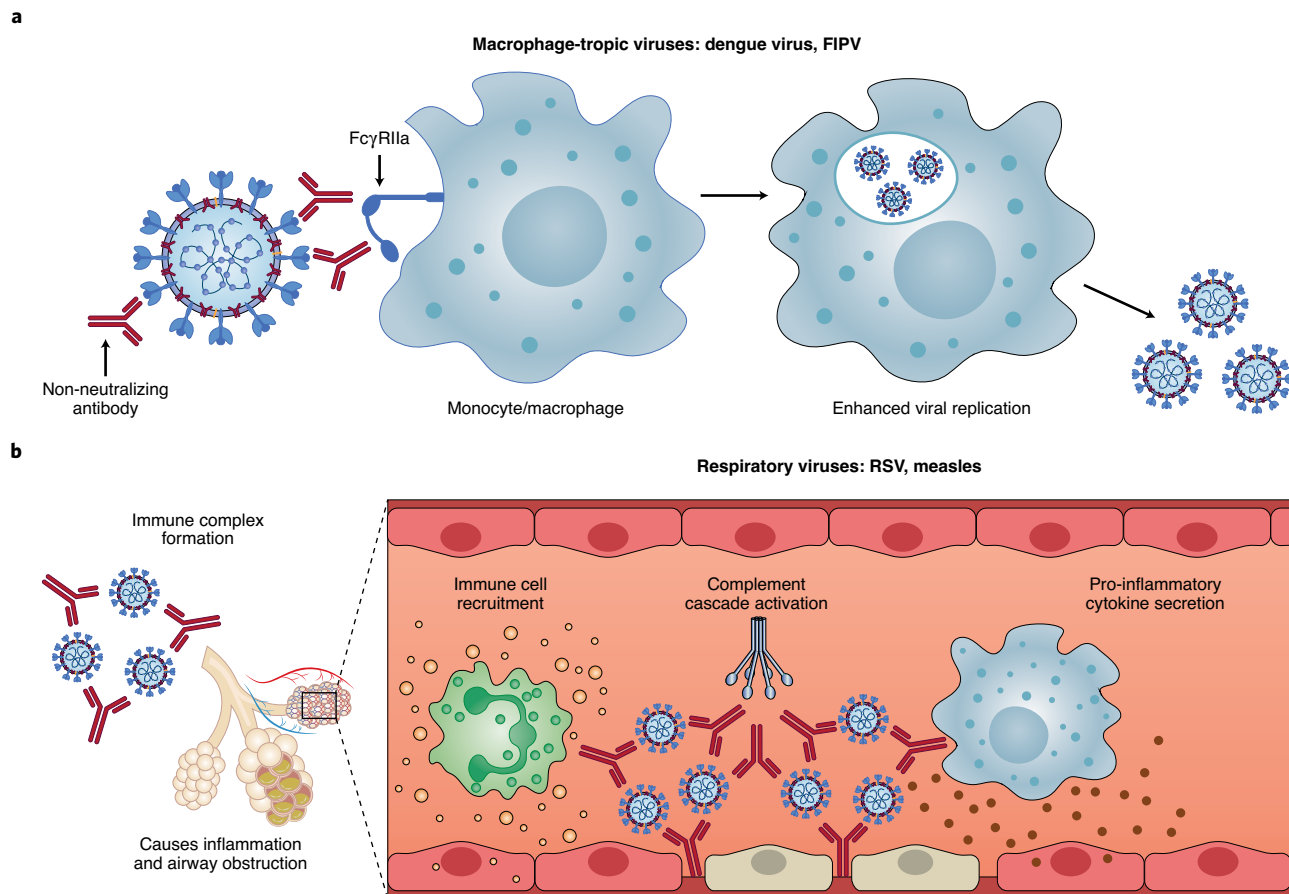


Fig. 1 | Two main ADE mechanisms in viral disease. a, For macrophage-tropic viruses such as dengue virus and FIPV, non-neutralizing or sub-neutralizing antibodies cause increased viral infection of monocytes or macrophages via FcγRIIIa-mediated endocytosis, resulting in more severe disease. **b**, For non-macrophage-tropic respiratory viruses such as RSV and measles, non-neutralizing antibodies can form immune complexes with viral antigens inside airway tissues, resulting in the secretion of pro-inflammatory cytokines, immune cell recruitment and activation of the complement cascade within lung tissue. The ensuing inflammation can lead to airway obstruction and can cause acute respiratory distress syndrome in severe cases. COVID-19 immunopathology studies are still ongoing and the latest available data suggest that human macrophage infection by SARS-CoV-2 is unproductive. Existing evidence suggests that immune complex formation, complement deposition and local immune activation present the most likely ADE mechanisms in COVID-19 immunopathology. Figure created using [BioRender.com](https://www.biorender.com).

more severe disease⁴⁷. One simple hypothesis is that greater antibody titres in severe COVID-19 cases result from higher and more prolonged antigen exposure due to higher viral loads^{48,49}. However, a recent study showed that viral shedding in the upper respiratory tract was indistinguishable between patients with asymptomatic and symptomatic COVID-19 (ref. ⁵⁰). Symptomatic patients showed higher anti-SARS-CoV-2 antibody titres and cleared the virus from the upper respiratory tract more quickly, contradicting a simpler hypothesis that antibody titres are simply caused by higher viral loads. Other studies showed that anti-SARS-CoV-2 T-cell responses could be found at high levels in mild and asymptomatic infections^{51,52}. Taken together, the data suggest that strong T-cell responses can be found in patients with a broad range of clinical presentations, whereas strong antibody titres are more closely linked to severe COVID-19. One important caveat is that viral shedding was measured in the upper respiratory tract rather than in the lower respiratory tract⁵⁰. The lower respiratory tract is likely more important for severe COVID-19 lung pathology, and it is unclear how closely SARS-CoV-2 viral shedding in the upper and lower respiratory tracts correlate throughout the disease course.

Beyond the host response to new SARS-CoV-2 infections, the potential of pre-existing antibodies against other human coronavirus

strains to mediate ADE in patients with COVID-19 is another possible concern⁵³. Antibodies elicited by coronavirus strains endemic in human populations (such as HKU1, OC43, NL63 and 229E) could theoretically mediate ADE by facilitating cross-reactive recognition of SARS-CoV-2 in the absence of viral neutralization. Preliminary data show that antibodies from SARS-CoV-2-naïve donors who had high reactivity to seasonal human coronavirus strains were found to have low levels of cross-reactivity against the nucleocapsid and S2 subunit of SARS-CoV-2 (ref. ⁵⁴). Whether such cross-reactive antibodies can contribute to clinical ADE of SARS-CoV-2 remains to be addressed.

Risk of ERD for SARS-CoV-2 vaccines

Safety concerns for SARS-CoV-2 vaccines were initially fuelled by mouse studies that showed enhanced immunopathology, or ERD, in animals vaccinated with SARS-CoV following viral challenge^{55–58}. The observed immunopathology was associated with Th2-cell-biased responses⁵⁵ and was largely against the nucleocapsid protein^{56,58}. Importantly, immunopathology was not observed in challenged mice following the passive transfer of nucleocapsid-specific immune serum⁵⁶, confirming that the enhanced disease could not be replicated using the serum volumes transferred. Similar studies

using inactivated whole-virus or viral-vector-based vaccines for SARS-CoV or MERS-CoV resulted in immunopathology following viral challenge^{59–61}, which were linked to Th2-cytokine-biased responses⁵⁵ and/or excessive lung eosinophilic infiltration⁵⁷. Rational adjuvant selection ensures that Th1-cell-biased responses can markedly reduce these vaccine-associated ERD risks. Candidate SARS-CoV vaccines formulated with either alum, CpG or Advax (a delta inulin-based adjuvant) found that while the Th2-biased responses associated with alum drove lung eosinophilic immunopathology in mice, protection without immunopathology and a more balanced Th1/Th2 response were induced by Advax⁶². Hashem et al. showed that mice vaccinated with an adenovirus 5 viral vector expressing MERS-CoV S1 exhibited pulmonary pathology following viral challenge, despite conferring protection. Importantly, the inclusion of CD40L as a molecular adjuvant boosted Th1 responses and prevented the vaccine-related immunopathology⁶³.

Should it occur, ERD caused by human vaccines will first be observed in larger phase II and/or phase III efficacy trials that have sufficient infection events for statistical comparisons between the immunized and placebo control study arms. Safety profiles of COVID-19 vaccines should be closely monitored in real time during human efficacy trials, especially for vaccine modalities that may have a higher theoretical potential to cause immunopathology (such as inactivated whole-virus formulations or viral vectors)^{64,65}.

Risk of ADE for SARS-CoV-2 vaccines

Evidence for vaccine-induced ADE in animal models of SARS-CoV is conflicting, and raises potential safety concerns. Liu et al. found that while macaques immunized with a modified vaccinia Ankara viral vector expressing the SARS-CoV S protein had reduced viral replication after challenge, anti-S IgG also enhanced pulmonary infiltration of inflammatory macrophages and resulted in more severe lung injury compared to unvaccinated animals⁶⁶. They further showed that the presence of anti-S IgG prior to viral clearance skewed the wound-healing response of macrophages into a pro-inflammatory response. In another study, Wang et al. immunized macaques with four B-cell peptide epitopes of the SARS-CoV S protein and demonstrated that while three peptides elicited antibodies that protected macaques from viral challenge, one of the peptide vaccines induced antibodies that enhanced infection *in vitro* and resulted in more severe lung pathology *in vivo*⁶⁷.

In contrast, to determine whether low titres of neutralizing antibodies could enhance infection *in vivo*, Luo et al. challenged rhesus macaques with SARS-CoV nine weeks post-immunization with an inactivated vaccine, when neutralizing antibody titres had waned below protective levels⁶⁸. While most immunized macaques became infected following viral challenge, they had lower viral titres compared to placebo controls and did not show higher levels of lung pathology. Similarly, Qin et al. showed that an inactivated SARS-CoV vaccine protected cynomolgus macaques from viral challenge and did not result in enhanced lung immunopathology, even in macaques with low neutralizing antibody titres⁶⁹. A study in hamsters demonstrated that despite enhanced *in vitro* viral entry into B cells via FcγRII, animals vaccinated with the recombinant SARS-CoV S protein were protected and did not show enhanced lung pathology following viral challenge⁷⁰.

SARS-CoV immunization studies in animal models have thus produced results that vary greatly in terms of protective efficacy, immunopathology and potential ADE, depending on the vaccine strategy employed. Despite this, vaccines that elicit neutralizing antibodies against the S protein reliably protect animals from SARS-CoV challenge without evidence of enhancement of infection or disease^{71–73}. These data suggest that human immunization strategies for SARS-CoV-2 that elicit high neutralizing antibody titres have a high chance of success with minimal risk of ADE. For example, subunit vaccines that can elicit S-specific neutralizing

antibodies should present lower ADE risks (especially against S stabilized in the prefusion conformation, to reduce the presentation of non-neutralizing epitopes⁸). These modern immunogen design approaches should reduce potential immunopathology associated with non-neutralizing antibodies.

Vaccines with a high theoretical risk of inducing pathologic ADE or ERD include inactivated viral vaccines, which may contain non-neutralizing antigen targets and/or the S protein in non-neutralizing conformations, providing a multitude of non-protective targets for antibodies that could drive additional inflammation via the well-described mechanisms observed for other respiratory pathogens. However, it is encouraging that a recent assessment of an inactivated SARS-CoV-2 vaccine elicited strong neutralizing antibodies in mice, rats and rhesus macaques, and provided dose-dependent protection without evidence of enhanced pathology in rhesus macaques⁷⁴. Going forward, increased vaccine studies in the Syrian hamster model may provide critical preclinical data, as the Syrian hamster appears to replicate human COVID-19 immunopathology more closely than rhesus macaque models⁷⁵.

ADE and recombinant antibody interventions

The discovery of mAbs against the SARS-CoV-2 S protein is progressing rapidly. Recent advances in B-cell screening and antibody discovery have enabled the rapid isolation of potent SARS-CoV-2 neutralizing antibodies from convalescent human donors^{76,77} and immunized animal models⁷⁸, and through re-engineering previously identified SARS-CoV antibodies⁷⁹. Many more potentially neutralizing antibodies will be identified in the coming weeks and months, and several human clinical trials are ongoing in July 2020. Human trials will comprise both prophylactic and therapeutic uses, both for single mAbs and cocktails. Some human clinical trials are also incorporating FcR knockout mutations to further reduce ADE risks⁸⁰. Preclinical data suggest a low risk of ADE for potentially neutralizing mAbs at doses substantially above the threshold for neutralization, which protected mice and Syrian hamsters against SARS-CoV-2 challenge without enhancement of infection or disease^{81,82}. ADE risks could increase in the time period where mAb concentrations have waned below a threshold for protection (which is analogous to the historical mother–infant data that provided important clinical evidence for ADE in dengue⁸³). The sub-protective concentration range will likely occur several weeks or months following mAb administration, when much of the initial drug dose has cleared the body. Notably, Syrian hamsters given low doses of an RBD-specific neutralizing mAb prior to challenge with SARS-CoV-2 showed a trend for greater weight loss than control animals⁸², though differences were not statistically significant and the low-dose animals had lower viral loads in the lung compared to control animals. Non-neutralizing mAbs against SARS-CoV-2 could also be administered before or after infection in a hamster model to determine whether non-neutralizing antibodies enhance disease. Passive transfer of mAbs at various time points after infection (for example, in the presence of high viral loads during peak infection) could also address the question of whether immune complex formation and deposition results in the enhancement of disease and lung immunopathology. If ADE of neutralizing or non-neutralizing mAbs is a concern, the Fc portion of these antibodies could be engineered with mutations that abrogate FcR binding⁸⁰. Animal studies can help to inform whether Fc-mediated effector functions are crucial in preventing, treating or worsening SARS-CoV-2 infection, in a similar way to previous studies of influenza A and B infection in mice^{84,85} and simian-HIV infection in macaques^{86,87}. An important caveat for testing human mAbs in animal models is that human antibody Fc regions may not interact with animal FcRs in the same way as human FcRs⁸⁸. Whenever possible, antibodies used for pre-clinical ADE studies will require species-matched Fc regions to appropriately model Fc effector function.

ADE and convalescent plasma interventions

Convalescent plasma (CP) therapy has been used to treat patients with severe disease during many viral outbreaks in the absence of effective antiviral therapeutics. It can offer a rapid solution for therapies until molecularly defined drug products can be discovered, evaluated and produced at scale. While there is a theoretical risk that CP antibodies could enhance disease via ADE, case reports in SARS-CoV and MERS-CoV outbreaks showed that CP therapy was safe and was associated with improved clinical outcomes^{89,90}. One of the largest studies during the SARS outbreak reported the treatment of 80 patients with SARS in Hong Kong⁹¹. While there was no placebo control group, no CP-associated adverse effects were detected and there was a higher discharge rate among patients treated earlier in infection. Several small studies of individuals with severe COVID-19 disease and a study of 5,000 patients with COVID-19 have shown that CP therapy appears safe and may improve disease outcomes^{92–96}, although the benefits appear to be mild⁹⁷. However, it is difficult to determine whether CP therapy contributed to recovery as most studies to date were uncontrolled and many patients were also treated with other drugs, including antivirals and corticosteroids. The potential benefits of CP therapy in patients with severe COVID-19 is also unclear, as patients with severe disease may have already developed high antibody titres against SARS-CoV-2 (refs. ^{47,98}). CP has been suggested for prophylactic use in high-risk populations, including people with underlying risk factors, frontline healthcare workers and people with exposure to confirmed COVID-19 cases⁹⁹. CP for prophylactic use may pose an even lower ADE risk compared to its therapeutic use, as there is a lower antigenic load associated with early viral transmission compared to established respiratory infection. As we highlighted above with recombinant mAbs, and as shown in historical dengue virus mother–infant data, the theoretical risk of ADE in CP prophylaxis is highest in the weeks following transfusion, when antibody serum neutralization titres fall to sub-protective levels. ADE risks in CP studies will be more difficult to quantify than in recombinant mAb studies because the precise CP composition varies widely across treated patients and treatment protocols, especially in CP studies that are performed as one-to-one patient–recipient protocols without plasma pooling.

To mitigate potential ADE risks in CP therapy and prophylaxis, plasma donors could be pre-screened for high neutralization titres. Anti-S or anti-RBD antibodies could also be purified from donated CP to enrich for neutralizing antibodies and to avoid the risks of ADE caused by non-neutralizing antibodies against other SARS-CoV-2 antigens. Passive infusion studies in animal models are helping to clarify CP risks in a well-controlled environment, both for prophylactic and therapeutic use. Key animal studies (especially in Syrian hamsters, and ideally with hamster-derived CP for matched antibody Fc regions) and human clinical safety and efficacy results for CP are now emerging contemporaneously. These preclinical and clinical data will be helpful to deconvolute the risk profiles for ADE versus other known severe adverse events that can occur with human CP, including transfusion-related acute lung injury^{96,100}.

Conclusion

ADE has been observed in SARS, MERS and other human respiratory virus infections including RSV and measles, which suggests a real risk of ADE for SARS-CoV-2 vaccines and antibody-based interventions. However, clinical data has not yet fully established a role for ADE in human COVID-19 pathology. Steps to reduce the risks of ADE from immunotherapies include the induction or delivery of high doses of potent neutralizing antibodies, rather than lower concentrations of non-neutralizing antibodies that would be more likely to cause ADE.

Going forwards, it will be crucial to evaluate animal and clinical datasets for signs of ADE, and to balance ADE-related safety risks against intervention efficacy if clinical ADE is observed. Ongoing

animal and human clinical studies will provide important insights into the mechanisms of ADE in COVID-19. Such evidence is sorely needed to ensure product safety in the large-scale medical interventions that are likely required to reduce the global burden of COVID-19.

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Competing interests

The authors declare no competing interests.

Additional information

Correspondence should be addressed to S.J.K. or B.J.D.

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