Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Out of the frying pan and into the fire? Due diligence warranted for ADE in COVID-19

A B S T R A C T

Antibody-dependent enhancement (ADE) is an atypical immunological paradox commonly associated with dengue virus re-infection. However, various research models have demonstrated this phenomenon with other viral families, including *Coronaviridae*. Recently, ADE in SARS-CoV-2 has emerged as one hypothesis to explain severe clinical manifestations. Whether SARS-CoV-2 is augmented by ADE remains undetermined and has therefore garnered criticism for the improper attribution of the phenomenon to the pandemic. Thus, critical evaluation of ADE in SARS-CoV-2 vaccine development will be indispensable to avoid a global setback and the erosion of public trust.

Antibody-dependent enhancement (ADE) of SARS-CoV-2 infection has recently emerged as one hypothesis to explain the severe clinical manifestations associated with COVID-19 [1–4]. Simply put, ADE is an immunological phenomenon whereby a previous immune response to a virus can render an individual more susceptible to a subsequent analogous infection [5]. Rather than viral recognition and clearance, the prior development of virus-specific antibodies at a non-neutralizing level can *facilitate* viral uptake, enhancing replication; a possible immune evasion strategy avoiding intracellular innate immune sensors, or pattern recognition receptors [6,7]. Contributing to pathology, ADE can be driven by antibody-dependent complement activation resulting in exacerbation of the virus-mediated disease in the presence [8] and absence of significantly enhanced viral replication [9,10]. ADE has been extensively studied in flaviviruses and is associated with 90% of Dengue virus (DENV) hemorrhagic fever and DENV shock syndrome cases [11]. ADE is thought to have contributed to the severity of the Latin American Zika virus (ZIKV) epidemic via DENV serocross reactivity [12,13]. Furthermore, *in vivo* ADE of Murray Valley encephalitis virus has been demonstrated in mice that have been passively immunized with Japanese encephalitis virus serum [14].

However, suggestions of ADE of COVID-19 have garnered justifiable criticism due to little evidence and the lack of a robust demonstration in animal models, as *in vitro* evidence for coronaviruses are not indicative of disease pathology in the absence of ongoing and comprehensive innate and adaptive immunity in the dish [15]. This is of course a rational and appropriate concern that spans all *in vitro* research. However, *in vitro* research is a fundamental prerequisite for animal models and an ethical checkpoint. In fact, without cell culture experiments exploring ADE in arboviruses, we would lack a critical understanding of the fundamental molecular interactions contributing to ADE. Additionally, *in vivo* evidence for ADE is not limited to flaviviruses and has been demonstrated in coronavirus animal models as well. New Zealand white rabbits exposed to a primary single intranasal MERS-CoV infection lacked neutralizing antibodies, were not protected from re-infection, and showed enhanced pulmonary inflammation [16]. The investigators concluded that people exposed to MERS-CoV who fail to develop neutralizing antibodies may be at an increased risk for severe lung disease. Feline infectious peritonitis, a disease caused by coronaviruses, has also been enhanced by vaccines that fail to induce a robust level of protective antibodies [17–19]. ADE of SARS-CoV has also been described through a novel FcγRII-dependent and ACE2-independent cell entry mechanism [20]. The authors state that this warrants concern in the safety evaluation of any candidate human vaccines against SARS-CoV, though their intervention did offer protection. This also illustrates that ADE is not always indicative of disease pathology but raises concern for the immunocompromised. It should also raise concern for the improper attribution of ADE in the absence of robust demonstration in animal models, as clearly articulated by Sharma recently in, “It is too soon to attribute ADE to COVID-19” [15], which could certainly hinder the development and/or uptake of any SARS vaccine. However, a double-inactivated SARS-CoV vaccine has also been shown to provide incomplete protection in aged mice and induce an increased eosinophilic pro-inflammatory pulmonary response [21]. A clear demonstration of the importance for critically evaluating safety across demographics.

Immunization is arguably the greatest medical advance in the history of civilization. In the face of the COVID-19 pandemic, a vaccine that elicits robust SARS-CoV-2-specific neutralizing antibodies will be the most effective way to produce herd immunity, minimizing COVID-19-related deaths. We agree with Sharma [15] that improper attribution of ADE in the absence of a robust

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demonstration in animal models would undoubtedly slow progress in the development and implementation of effective vaccines against SARS-CoV-2. However, we caution that fundamental cellular and molecular mechanisms are ascertained through *in vitro* research and should not be considered extraneous to our understanding of COVID-19, but rather leveraged appropriately and in context. If there is any reason to suspect ADE from a COVID-19 vaccine, it should be met with a critical eye rather than irrational exuberance for a fast-tracked vaccine rollout. Dengvaxia, the first live-attenuated vaccine for DENV, was shown to protect previously infected DENV children, but put DENV-naïve individuals at risk for disease [22,23]. This later resulted in vaccine hesitancy and a lack of trust in public health in the region where Dengvaxia was administered [24–26]. Clearly, vaccine administration without time to fully understand resultant health implications would cause an even greater global setback to the current pandemic [27]. As the entire world sits on the edge of a knife watching the scientific community race toward a solution, delivery of a suboptimal COVID-19 vaccine would significantly contribute to erosion of public trust in scientific pursuit and public health [24,25,27], and jeopardize the integrity and success of immunization programs around the world, especially in this era of mis/disinformation. As others have suggested [28,29], ADE should be given full consideration when evaluating the safety of any candidate SARS-CoV-2 vaccine.

Declaration of Competing Interest

The authors declare no competing interests.

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