

Balancing Expediency and Scientific Rigor in Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Development

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Over the last 5 months, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has precipitated a global health and economic crisis, dramatically altering the daily lives of billions of people. Rapid community transmission of SARS-CoV-2 has been enabled, in part, by its biology and its novelty. Humans have no preexisting immunity to this brand-new human pathogen, and we are all susceptible to infection (though not uniformly likely to develop symptomatic coronavirus disease 2019 [COVID-19]). In the short term, social distancing measures are decreasing community transmission but are exacting enormous costs from individuals and businesses, leading prominent voices to call for lifting restrictive measures. However, as relatively few people are immune to SARS-CoV-2, COVID-19 cases will almost certainly surge if normal activities resume.

The only long-term way to control SARS-CoV-2 is for most people to become immune to the virus, so that herd immunity slows down spread. One way to achieve the needed level of protection is for the virus to sweep through the

population, at the cost of extensive casualties. Far better would be developing and deploying a safe and effective vaccine to generate widespread immunity, with dual goals of protecting individuals and controlling the pandemic.

The COVID-19 pandemic has triggered an explosion of potential vaccine candidates and calls for their rapid and widespread deployment, prompting discussions about the risks of advancing unvetted vaccines into the general population. Fortunately, the process of vaccine licensure is designed to ensure vaccine safety and efficacy, particularly since vaccines are given to healthy people who might never be exposed to SARS-CoV-2 or develop severe disease. The most effective way to identify and deploy efficacious SARS-CoV-2 vaccines with acceptable safety profiles is through carefully designed, scientifically rigorous clinical trials conducted at an accelerated pace.

Recent technological advances in vaccine design and global commitments to addressing epidemic diseases have provided a rich infrastructure to support the necessary response to COVID-19. The Moderna messenger RNA vaccine, currently being studied in the United States, was administered to the first human subject just 63 days after the SARS-CoV-2 genetic sequence was released from China. This achievement was facilitated by the acceptable human safety profiles of similar vaccine constructs targeting other diseases, including Zika and avian

influenza. Seven other vaccine clinical trials have started in the United States, United Kingdom, Germany, and China, and the list of preclinical vaccine candidates now is 100 [1, 2].

It is not yet clear whether SARS-CoV-2 infection results in durable protective immunity, by what mechanism it might do so, and whether vaccine-elicited immune responses will protect without causing harm. Early studies are promising. Up to 95% of mild COVID-19 cases induce some level of neutralizing antibodies against SARS-CoV-2 [3], and nonhuman primates infected with SARS-CoV-2 are protected from reinfection with the virus [4]. Survivors of infections with related coronaviruses, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), developed neutralizing antibodies that persisted for 1–3 years after infection. Phase 1 studies of DNA vaccines for SARS-CoV-1 and MERS-CoV were well tolerated and immunogenic in humans [5, 6]. These reports suggest that SARS-CoV-2 vaccines could safely induce protective immune responses, and it seems likely that 1 or more of the 108 candidate vaccines in development will be ultimately licensed.

Yet, there is reason for caution as the experience in animal models is inconclusive. Some SARS-CoV-1 and MERS-CoV vaccine candidates appear to exacerbate illness in animals after subsequent viral challenge [7]. Such vaccine-enhanced disease harks back to respiratory

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syncytial virus (RSV) and dengue vaccines that caused harm. The mechanisms underlying enhanced disease remain controversial, but certain patterns have emerged. Detrimental responses were more common but not ubiquitous after immunization with whole-inactivated SARS-CoV-1 and MERS-CoV vaccines [8–10], perhaps due to immune responses against the nucleocapsid protein [11] (not present on the viral envelope) or to chemical modifications that alter epitopes or antigen processing [12]. However, a new whole-inactivated SARS-CoV-2 vaccine reportedly induced neutralizing antibodies and protected rhesus macaques from viral challenge without overt safety concerns [13].

Given the association of whole-inactivated vaccines with enhanced disease, one might expect that vaccine platforms delivering isolated spike protein (present on the viral envelope) could elicit protective immunity without provoking immunopathology. Indeed, protein and DNA vaccines can induce strong neutralizing antibody responses against SARS-CoV-1 and MERS-CoV [14, 15]. Accordingly, many SARS-CoV-2 vaccine candidates are designed to elicit neutralizing antibodies against the SARS-CoV-2 spike [1]. However, anti-SARS-CoV-1 spike antibodies elicited by a vaccinia vector were shown to worsen lung injury in Chinese macaques postchallenge, potentially through infection and proinflammatory reprogramming of macrophages [16]. This study, along with several other reports, suggests a role for antibody-dependent enhancement (ADE) through cell-surface Fc receptors [16–19]. The probability of ADE varies with antibody concentration [17, 19], suggesting that its effects might appear late after vaccination and highlighting the need for long-term follow-up in clinical studies.

Many of the harmful immune responses to prior coronavirus vaccine candidates appear to hinge on the balance between the type of helper T-cell response. In general, Th1 responses are

thought to promote protective immunity, while Th2 responses, stimulated by adjuvants such as alum, are associated with eosinophils in the lungs of experimental animals [7]. Pulmonary eosinophilia was a prominent feature of enhanced disease associated with an RSV vaccine [12], but Th2-like responses to SARS-CoV-1 can be protective despite eosinophilic histopathology [9]. Th1- and Th2-type inflammatory responses also influence antibody isotype repertoire and subsequent interactions with Fc receptors [20], potentially modifying the risk of antibody-induced immunopathology. Manipulating the balance of Th1 and Th2 responses through adjuvants, such as Toll-like receptor agonists and delta inulin, may reduce the risk of vaccine-enhanced disease [8, 20].

Overall, the mechanisms underlying the immunopathology of coronavirus vaccines and the differences among vaccine candidates and animal models remain poorly understood. Potential factors include the vaccine itself, the viral strain used for challenge, the animal model, and the timing and dose of both vaccine and challenge. Identifying the basis for immunopathology will be important for optimizing vaccine candidates.

Ordinarily, unresolved questions about coronavirus immunology might have been answered before human clinical trials. Now, however, delays in developing a safe and effective vaccine will cost lives. We thus need to carefully weigh decisions about study duration, follow-up, and clinical and biological monitoring to comprehensively obtain the information needed to assess the safety of SARS-CoV-2 vaccines. Early studies should be performed in healthy adults who are fully informed about areas of uncertainty regarding risks, and human challenge studies are an intriguing but controversial approach to assessing efficacy and safety [21]. These considerations are especially important since many candidate vaccine platforms are novel and have not yet yielded licensed vaccines.

Standardized metrics of immunogenicity, efficacy, and safety should be

coordinated at an international level to ensure that vaccine studies can be directly compared and to promote accountability among research teams and private developers. The World Health Organization has an important role in this process. Experts convened by the Brighton Collaboration working with the Center for Epidemic Preparedness Innovations supported the conduct of ongoing vaccine studies and advocated for standardized safety assessments of local and systemic reactions. They also recommended measuring potential biomarkers of vaccine-enhanced disease, which may include the ratios of neutralizing and nonneutralizing antibodies, antibody isotypes and affinities, proinflammatory cytokine levels, and the polarity of T-cell responses [7]. Ongoing therapeutic trials using convalescent sera should examine the conditions under which infection-derived antibodies are protective. In addition, animal studies should continue concurrently to resolve unanswered questions about immunogenicity and immunopathology. Concerning results in any experimental system should prompt rapid reconsideration of related clinical trials.

The research community is making unprecedented advances toward rapidly developing SARS-CoV-2 vaccines. This is a laudable goal, and scientists, regulators, and clinicians must remain steadfast against pressure to bypass the established scientific, ethical, and regulatory standards in an attempt to accelerate vaccine availability. Our community must push forward in generating high-quality, reliable data while we strive to save lives.

Notes

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