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.

Is there space for a three-dose vaccine to fight the spread of SARS-CoV-2?

The ongoing responses to the COVID-19 pandemic have resulted in diverse vaccine-based solutions that are advancing our understanding of medical science.[1] Randomised, placebo-controlled clinical trials are providing a unique opportunity to compare the safety and immunogenicity of several different vaccine platforms, including vectored, DNA, inactivated virus, mRNA, and protein subunit vaccines. Strategic differences within each vaccine platform, such as dimer versus trimer protein subunits or modifications in protein design based on dynamic structural modelling, are providing deeper insights into the optimal vaccines of the future—a silver lining to the dark cloud of the COVID-19 pandemic.

In *The Lancet Infectious Diseases*, Shilong Yang and colleagues[2] report the results of two randomised, double-blind, placebo-controlled, phase 1 and 2 trials of ZF2001, a protein subunit vaccine combined with alum as an adjuvant. The key findings from these two trials are that this receptor-binding domain (RBD)-protein subunit vaccine is safe and immunogenic in healthy adults. The use of a dimeric protein rather than native trimer RBD reveals novel insights into the immunogenicity requirements for a COVID-19 vaccine. The combination of a protein subunit and alum adjuvant is expected to generate limited efficacy, which might explain the three-dose regimen and relatively high dose of protein subunit. However, is a COVID-19 vaccine that requires three doses feasible and practical during the ongoing pandemic? The 25 µg and 50 µg doses are relatively high when compared to other protein subunit vaccines, and some immune markers of efficacy such as the IgG titre to the RBD target and the 50% neutralisation titre were lower with the 50 µg dose than with the 25 µg dose. Hence, the dose selection is not compelling and more studies are required to investigate the optimal dose and time regimen for the ZF2001 vaccine. The immunological correlates of protection are not well defined for SARS-CoV-2. Hence, limited measures of IgG and neutralisation titres offer only a glimpse and little guidance for the selection of a sufficiently effective vaccine. Protection from SARS-CoV-2 infection appears to be elicited as early as 9–11 days after the initial vaccination.[3,4] This protection is offered when neutralising antibodies are barely detectable or in limited supply. We recommend more measures of immune response that might provide insights into functional antibody immune responses, such as Fab and Fc-effector functions.[5] A deeper understanding of how various vaccines and adjuvants can broaden these effector functions could clarify ways to extend vaccine efficacy. Finally, at present there is no evidence to suggest that the design and use of a dimer protein will retain protection against the emerging SARS CoV-2 variants. Overall, the silver lining of scientific insight into optimal vaccines for COVID-19 could be substantially brighter.

A recent phase 1 clinical study using the spike-Trimer (SCB-2019) vaccine in combination with various adjuvants demonstrated that the spike-Trimer vaccine elicits high neutralising activity at a dose as low as 3 µg per injection of vaccine, quickly after the second vaccine dose.[6] These data suggest that the use of trimerised spike protein as a vaccine might have some advantages over other forms of spike proteins, but side-by-side clinical studies are required to determine the best vaccine protein and adjuvants.

The state of the current vaccine landscape continues to raise the bar for vaccine candidates. At present, it is unclear whether the use of a three-dose regimen (prime, boost, boost) in a limited timespan for the ZF2001 protein subunit vaccine will offset the benefits of the less demanding storage conditions that limit RNA vaccines. As new SARS-CoV-2 variants emerge, the optimal COVID-19 vaccine should provide broad-spectrum coverage, which might be possible with an engineered spike-protein subunit vaccine comprising a more robust adjuvant. At some point, despite the good intentions to develop a COVID-19 vaccine suitable for global use, less effective vaccines could face ethical scrutiny. If future studies of ZF2001 fall short of the high efficacy milestones seen with the other vaccines developed so far, will people be satisfied with the reduced efficacy?

We declare no competing interests.

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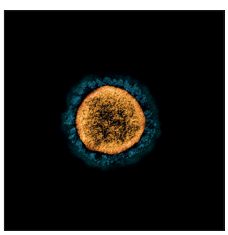

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***Lancet Infect Dis* 2021**
Published **Online**
March 24, 2021
https://doi.org/10.1016/S1473-3099(21)00149-3
See **Online/Articles**
https://doi.org/10.1016/S1473-3099(21)00127-4

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