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.

at reducing the risk of severe illness in pregnant people and the risk of COVID-19 hospital admission among their infants younger than 6 months.[6,8] Protection in infants born to people vaccinated during pregnancy is particularly important because while mRNA COVID-19 vaccines were approved by the FDA on June 17, 2022, and recommended by the CDC on June 18, 2022, for children aged between 6 months and 5 years,[9] there are not currently any vaccines available for infants younger than six months.

COVID-19 vaccination among pregnant people continues to be lower than among non-pregnant females of reproductive age.[3] Given the risks of severe illness and adverse pregnancy outcomes, continuing to collect and disseminate data on the safety and effectiveness of COVID-19 vaccination in pregnancy and encouraging health-care providers to promote vaccination during all trimesters of pregnancy is imperative.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. We declare no competing interests.

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Protein-based vaccine as the booster dose for adults: evidence and beyond

Since the pandemic began, there have been more than 500 million COVID-19 cases and 6 million deaths.[1] Despite the large number of previous infections and vaccinations (more than 11 billion doses in total), omicron (B.1.1.529)and its sublineages have caused several waves of infection outbreak globally since the end of 2021.[1] There are many potential reasons that might contribute to the ongoing pandemic, such as the waning of immune protection from vaccine or past infection with time, immune escape of the emerging variants, vaccine hesitancy, and the global inequity of vaccine distribution. Booster dose vaccines have been shown to reinforce the immune reaction and elicit increased protective antibodies.[2,3] The need for one or more booster doses will further increase the demand for vaccines. Given the disparities in economic status, health-care systems, and decision-making processes among different countries or regions, besides vaccines' inherent efficacy and safety profile, global vaccine distribution, accessibility, and uptake as well as vaccine-related policies might be influenced by factors such as costs, manufacturing capacity, and vaccine storage requirements.[4,5] Meanwhile, different vaccine platforms might cater to different settings and have a disparate extent of acceptance in the public. Therefore, it is crucial to explore a diversity of vaccine candidates from different platforms to tackle unpredictable challenges in the pandemic.

Protein-based technology is a traditional vaccine platform, with a promising efficacy and safety profile given the success of many precedent protein-based vaccines (eg, hepatitis B vaccine). NVX-CoV2373 is a protein subunit vaccine containing recombinant ancestral SARS-CoV-2 S protein and an immune-response-enhancing adjuvant. As vaccine-elicited neutralising antibody concentrations decline over time,

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booster campaigns have been conducted worldwide to enhance vaccine protection. Raburn M Mallory and colleagues[6] reported the immunogenicity and safety data for the homologous booster dose of NVX-CoV2373. This ongoing phase 2 trial was a continuation of the prime dose phase 2 trial, and this report focused on participants receiving two doses of placebo or NVX-CoV2373 in the primary stage. In the booster stage (ie, roughly 6 months after the primary vaccination), participants who received two doses of NVX-CoV2373 in the primary series were randomly assigned again to receive a booster dose of NVX-CoV2373 or a dose of placebo. Participants who received two doses of placebo in primary series continued into the placebo group. The immunogenicity data for ancestral SARS-CoV-2 and major variants of concern (VOCs), including alpha (B.1.1.7), beta (B.1.351), delta (B.1.617.2), and omicron BA.1 and BA.2 (assays might differ for specific VOCs), were reported in the per-protocol participants. The safety data, such as solicited local and systemic reactogenicity events and unsolicited adverse events, were provided. Notably, when the booster stage was conducted, other authorised vaccines were already available in the study countries (ie, Australia and the USA), so participants could be unmasked at their request and were able to receive an authorised vaccine or retire from the study at any time.

As seen in other studies, the concentrations of binding and neutralising antibodies gradually declined after two prime doses of NVX-CoV2373. After a booster dose of NVX-CoV2373, IgG and neutralising antibody titres increased dramatically from the prebooster low titres to a record high, much higher than the peak titres in the period after the prime doses. The exact extent of the increase in antibody titres from after prime doses to after booster dose differed by VOCs and specific assays, ranging from roughly 3–15 times increase. Given the small sample of participants, Mallory and colleagues compared the safety events numerically, without performing statistical tests. After receiving the booster, local and systematic reactogenicity events were higher than after receiving prime doses and there were more unsolicited adverse events in NVX-CoV2373 boosted group than the two groups that received placebo booster, most of which were not serious. Overall, this phase 2 trial did not identify any notable safety issues.

This trial presents a timely message that a homologous booster dose of protein-based vaccine could elicit strong immune responses for ancestral SARS-CoV-2 and major VOCs and might actively supplement vaccination schemes worldwide. The interpretation of this study should consider population, variants, and prime vaccination. Vulnerable populations are of high priority in vaccination schemes. About 45% participants in the trial were aged between 60–84 years, and valuable immunogenicity data were provided for the ancestral strain and beta variant, divided by age group. The antibody titres in the 60–84 years age group were lower than in the 18–59 years age group, whereas the booster dose provided a similar trend of antibody increase in both groups, indicating the immune benefits of the booster dose in not only younger but also older populations. However, as the trial excluded many other vulnerable individuals (eg, people with some chronic diseases, taking immunosuppressing drugs, etc), the immunogenicity of the booster vaccine in these populations awaits further study.

Emerging VOCs also pose great challenges. The trial evaluated functional ACE2 receptor binding inhibition titres and anti-recombinant spike IgG titres for ancestral, alpha, beta, delta, and omicron BA.1 and BA.2 strains, and tested microneutralisation titres for ancestral, delta, and omicron BA.1 strains. After a booster dose of NVX-CoV2373, the titres showed a similar trend of increase across all variants. However, the titres in these assays for omicron lineages were markedly lower than for other strains. The circulating BA.4 and BA.5 sublineages were shown to have even stronger immune evasion from three-dose vaccination of other vaccines than other sublineages, and might even escape from neutralising antibodies elicited by past omicron BA.1 infection.[7,8] Although vaccine-elicited antibody titres for different variants might have distinct clinical implications, some evidence suggested that antibody titres were closely correlated with clinical efficacy of vaccines.[9,10] Thus, careful monitoring of vaccine immunogenicity against these emerging variants should be performed, and immunisation strategy should be dynamically adjusted on the basis of the relevant data.

At the time of writing, NVX-CoV2373 is authorised for use in more than 40 countries or regions, mostly for

primary doses, although some administrative agencies have also authorised booster use of the vaccine.[11] Data from this trial indicated the potential of a homologous NVX-CoV2373 booster vaccination. As several vaccines have been authorised and widely distributed before the authorisation of NVX-CoV2373, in places with high prime vaccination rate, NVX-CoV2373 will probably be used as a heterologous booster, and COV-BOOST and Com-CoV2 trials have provided relevant immunogenicity data.[3,12] Further large-scale trials are required to evaluate the clinical efficacy of NVX-CoV2373 as either homologous or heterologous boosters.

The two phase 3 trials of prime doses,[13,14] and several phase 2 trials for booster doses of NVX-CoV2373,[3,6,12] did not identify worrying adverse effects. However, some rare adverse events can be observed only in large population studies after wide use of a vaccine, such as the rare thrombosis with some adenoviral vector-based vaccines (ChAdOx1 nCoV-19 [AstraZeneca] and Ad26.COV2.S [Janssen])[15] and rare myocarditis or pericarditis with mRNA vaccines (BNT162b2 [Pfizer–BioNTech) and mRNA-1273 [Moderna]).[16] With increasing clinical use of NVX-CoV2373 in vaccination schemes, further close surveillance of the postvaccine population is essential.

The journey of vaccine development is an excellent example of how randomised trials and real-world observational studies can complement each other, leading to optimal, individualised vaccination strategies. Preauthorisation trials lay the foundation for vaccines' efficacy and safety profile, and postauthorisation large-scale observational studies can provide additional data on real-world efficacy in different subgroup populations and identify rare side effects. Immune protection induced by current vaccines will inevitably wane over time and might not be strong enough to face the challenges of new SARS-CoV-2 variants. Entering the third year of the COVID-19 pandemic, improved vaccines are needed for future booster doses, which can induce strong and durable immune protection and are easy to store and distribute. Additionally, due to the threat of multiple variants and pathogens that are cocirculating, multivalent vaccines for SARS-CoV-2 or combined vaccines for different pathogens (eg, SARS-CoV-2 and influenza) are also under investigation. While waiting for these vaccines, available vaccines should be used to boost the population's immunity and prevent COVID-19-related hospitalisation and death, especially in vulnerable individuals.

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