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.

aggressive treatment. The field of prostate cancer had long been accused of overtreatment and the realisation that aggressive treatment was unnecessary for many men led to the concepts of active surveillance for many patients with early prostate cancer and the concept of intermittent ADT for selected patients with advanced prostate cancer. In that vein, the authors are to be congratulated for having limited exposure to abiraterone to only 2 years for the large majority of the patients who entered the study. This new study should inspire additional research to further improve early identification and treatment of potentially lethal prostate cancer.

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Trimeric S protein COVID-19 vaccine needs to find its place

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See **Articles** page 461

When the race towards the development of vaccines against COVID-19 began in early 2020, many of the front-line candidates were based on the spike (S) protein of SARS-CoV-2, coupled with an adjuvant. But it was the mRNA vaccines of BioNTech[1] and Moderna[2] that not only turned out to be highly efficacious but were produced and supplied in large quantities. The second place in the race has been divided between inactivated whole virion vaccines (from China[3] and India[4]) and adenovirus-vectored vaccines.[5] Even now, protein vaccines are not highly prominent. Novavax in December, 2021 received approval for its virus-like particles protein vaccine in the EU. Companies in other countries, such as Cuba, have successfully developed and introduced adjuvanted protein vaccines,[6] but these are far from mainstream.

Against this background, the development and testing of Clover Biopharmaceuticals' trimeric S-protein recombinant vaccine SCB-2019 has been met with anticipation and success. In *The Lancet*, Lulu Bravo and colleagues[7] report the results of their phase 2 and 3 efficacy trial (SPECTRA) of this vaccine in 30 174 participants in four continents, with the greatest contribution (45·4%) from the Philippines. A trial of this size nowadays is challenging because of the widespread roll-out of COVID-19 vaccinations. In this case, the intention was to find and recruit vaccine naive participants but, of the 30 155 with valid baseline serological data, 13 389 (44·4%) participants, including 61·5% (8406 of 13 676) in the Philippines, were seropositive for SARS-CoV-2 at the start. This situation in fact proves useful because information is needed on the performance of COVID-19 vaccines in seropositive individuals.

The SPECTRA trial was conducted at a time when the spectrum of variants was much different from the early studies in 2020, and allowed for establishing the vaccine efficacy against delta (78·7% [95% CI 57·3–90·4]), gamma (91·8% [44·9–99·8]), and mu (58·6% [13·3–81·5]). 30 128 participants (including 14 119 [46·9%] women) received their first dose of the vaccine (n=15 064) or placebo injection (n=15 064), and the per-protocol population consisted of 12 355 participants who were

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baseline SARS-CoV-2 naive (6251 vaccinees and 6104 placebo). Overall, in initially seronegative participants, the vaccine efficacy against any strain was 67·2% (95·7% CI 54·3–76·8) for any severity COVID-19, 83·7% (97·86% CI 55·9–95·4) for moderate-to-severe COVID-19, and 100% (97·86% CI 25·3–100·0) for severe COVID-19. One limitation of the study is that the participants were mostly young (mean age 32·1 years [18–86]). Furthermore, the follow-up time was short (mean 82 days). Thus, efficacy in older participants and the duration of protection are not known, although information on duration will be collected as the follow-up is being continued. Reactogenicity was low. Local reactions were reported in 36% of the vaccine recipients (compared with 10% in the placebo group). Systemic reactions were similar between the vaccine and placebo groups.

The study vaccine was not a final formulation but consisted of the vaccine (30 µg of recombinant trimeric S protein) and adjuvant (1·50 mg of CpG-1018 and 0·75 mg alum) mixed on site. A single vial combination is needed before the vaccine can be launched successfully. CpG-1018 was chosen for an adjuvant because it is already being used in a licensed vaccine, the HEPLISAV-B hepatitis B vaccine by Dynavax.[8] A previous phase 1 trial concluded that 30 µg of trimeric S antigen combined with CpG-1018 was similar to 9 µg of antigen combined with adjuvant system 03.[9] The antigen and adjuvant system combination induced somewhat higher antibody titres but was more reactogenic.[9] The choice of CpG-1018 might be wise, because there have been reports of a potential association of adjuvant system 03 with narcolepsy after H1N1 2009 influenza vaccinations.[10] Although the antigen that caused it was probably influenza nucleoprotein or neuraminidase, the potent adjuvant probably had a role.[11] However, the case of the SARS-CoV-2 S protein vaccine is different.

The study was funded by the Coalition for Epidemic Preparedness Innovations, which is anticipated to add the SCB-2019 vaccine into its COVID-19 arsenal for use in low-income and middle-income countries through the COVAX mechanism.[12] To this end, Gavi, the Vaccine Alliance has already placed a tentative order for 400 million doses pending emergency use listing by WHO.[13] Given that less than 50% of the world's population has received any COVID-19 vaccine, the new protein vaccine will be a welcome addition to the global response to COVID-19.[14]

The trimeric S protein recombinant vaccine used in the SPECTRA trial was based on the original SARS-CoV-2 virus and, therefore, the observed protection against other variants, such as the delta variant, might be called cross-protection. Studies have also shown that immune responses to the adjuvanted SCB-2019 vaccine measured against the alpha variant are similar to those induced by licensed mRNA vaccines.[15] Still, cross-protection against the omicron variant might be lower than against other variants and modification of the vaccine might be required for omicron. This requirement adds to the list of challenges for the SCB-2019 vaccine.

I am the lead investigator of studies on hepatitis B vaccine by VBI Vaccines, unrelated to the topic of this Comment.

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COVID-19 will continue but the end of the pandemic is near

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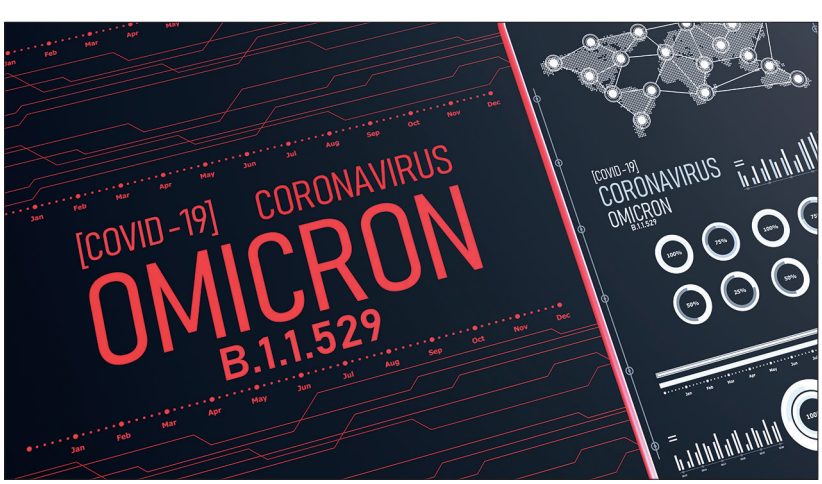
The world is experiencing a huge wave of infection with the omicron variant of SARS-CoV-2. Estimates based on Institute for Health Metrics and Evaluation (IHME) models[1] suggest that on around Jan 17, 2022 there were 125 million omicron infections a day in the world, which is more than ten times the peak of the delta wave in April, 2021.[1] The omicron wave is inexorably reaching every continent with only a few countries in eastern Europe, North Africa, southeast Asia, and Oceania yet to start their wave of this SARS-CoV-2 variant.[1,2] The unprecedented level of infection suggests that more than 50% of the world will have been infected with omicron between the end of November, 2021 and the end of March, 2022.[1] Although IHME models suggest that global daily SARS-CoV-2 infections have increased by more than 30 times from the end of November, 2021 to Jan 17, 2022, reported COVID-19 cases in this period have only increased by six times.[1,2] Because the proportion of cases that are asymptomatic or mild has increased compared with previous SARS-CoV-2 variants,[3,4] the global infection-detection rate has declined globally from 20% to 5%.[1]

Understanding the burden of omicron depends crucially on the proportion of asymptomatic infections. A systematic review based on previous SARS-CoV-2 variants suggested that 40% of infections were asymptomatic.[3] Evidence suggests that the proportion of asymptomatic infections is much higher for omicron, perhaps as high as 80–90%. Garrett and colleagues found that among 230 individuals in South Africa enrolling in a clinical trial, 71 (31%) were PCR positive for SARS-CoV-2 and had the omicron variant and no symptoms.[4] Assuming this prevalence of infection was representative of the population, the implied incidence compared to detected cases suggests that more than 90% of infections were asymptomatic in South Africa. The UK Office for National Statistics (ONS) infection survey estimated a point prevalence of PCR positive SARS-CoV-2 infection of 6·85% for England on Jan 6, 2022.[5] Hospital admission prescreening of individuals without COVID-19 symptoms in the University of Washington Medical Center in Seattle, WA, USA, did not exceed 2% throughout the COVID-19 pandemic but exceeded 10% in the week of Jan 10, 2022 (Murray CJL, unpublished). In addition to the much larger proportion of asymptomatic infections, in the USA the



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