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.

criteria for this diagnosis exist. Patients have a variety of symptoms, involving multiple organ systems. These symptoms have not been attributed to other causes, except for previous COVID-19 disease. Studies in this field are scarce. Almost 90% of COVID-19 survivors have developed sequelae, including not only general symptoms such as fatigue but also severe neurological, cardiac, renal, or respiratory manifestations.[8] SARS-CoV-2 infection has been also associated with long-term changes in brain structure according to a UK Biobank study.[9]

In this context, the study by Jeremy Werner Deuel and colleagues,[10] reported in *The Lancet Infectious Diseases*, explores sequelae after SARS-CoV-2 infection in young adults (median age 21 years [IQR 21–23]). Deuel and colleagues did a longitudinal cohort study of 501 mainly young male adults (464 [93%]) undertaking a comprehensive test battery designed to evaluate physical and psychosocial outcomes after COVID-19. All participants at the time of the study had not received a dose of any COVID-19 vaccine and were members of the Swiss Armed Forces. Increased BMI, dyslipidaemia, and decreased physical endurance 6 months after COVID-19 were suggestive of a higher risk of developing metabolic disorders and possible cardiovascular complications. These findings might support the hypothesis of endothelial dysfunction as a primary driver of COVID-19 sequelae. Obesity, dyslipidaemia, and low physical activity are known risk factors for future cardiovascular complications, characterised by endothelial dysfunction. Cardiovascular risk factors can be modified through lifestyle changes and medications. More importantly, novel vascular and biochemical markers have been discovered over the last decade that can better predict cardiovascular risk.[11]

In conclusion, although no accurate prediction models exist for who will develop severe COVID-19 or sequelae, risk factors of vascular damage have emerged as important predictors. Large and high-quality studies are needed utilising multidisciplinary teams not only from different medical specialties but also from computational scientists that could suggest novel predictive models for the development of COVID-19 sequelae.

We declare no competing interests.

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Evaluating novel COVID-19 vaccines in the current chapter of the pandemic

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The field of vaccine development against COVID-19 has rapidly evolved over the past 2 years. Different vaccine delivery platforms were used in different geographical areas, of which mRNA-based vaccines (BNT162b2 [Pfizer–BioNTech] and mRNA-1273 [Moderna]) and vector-based vaccines (Ad26.COV2.S [Johnson & Johnson] and ChAdOx1-S [Oxford–AstraZeneca]) were initially approved for use in Europe, Australia, and the USA. Later, a subunit S-protein-based vaccine (NVX-CoV2373 [Novavax]) was approved, mainly to be

used as a booster vaccine. The adenovirus-based Gam-COVID-Vac (also known as Sputnik V, Gamaleya National Centre of Epidemiology and Microbiology, Moscow, Russia) was predominantly used in Russia and South America, whereas whole-virus inactivated adjuvanted vaccines (CoronaVac [Sinovac Biotech], BBIBP-CorV [Sinopharm], and Covaxin [Bharat Biotech]) were first approved in Asia and South America, and were used throughout those continents. Whole-virus inactivated vaccines have the advantage that they are relatively easy to produce (without the need for genetic modification) and are stable at refrigerated temperatures.

On June 24, 2022, the European Medicines Agency (EMA) granted full market authorisation to the whole-virus inactivated adjuvanted vaccine VLA2001 (Valneva), which is the first inactivated vaccine to be approved for use in Europe and was additionally approved in the UK, United Arab Emirates, and Bahrain. The approval was based on the interim results (up to day 43) of the randomised, controlled, phase 3 trial by Rajeka Lazarus and colleagues,[1] published in *The Lancet Infectious Diseases*. In this trial, the safety and immunogenicity of primary vaccination with two doses of VLA2001 was assessed in an immunobridging study including 4017 adult participants, with ChAdOx1-S as a comparator. Vaccination with VLA2001 led to significantly fewer solicited local or systemic adverse events than did ChAdOx1-S. Based on seroconversion rates on day 43 in adults aged 30 years and older, VLA2001 was non-inferior to ChAdOx1-S (both led to >95% seroconversion), but VLA2001 induced superior neutralising antibody titres (geometric mean titre [GMT] 803·5 [95% CI 748·5–862·6] in the VLA2001 group *vs* 576·6 [543·6–611·7] in the ChAdOx1-S group; GMT ratio 1·39 [95% CI 1·25–1·56]; p<0·0001).

Because of the geographical differences in the use of mRNA-based or vector-based vaccines compared with inactivated vaccines, clinical trials making direct comparisons between multiple vaccine platforms are extremely rare, making this study by Lazarus and colleagues unique. By contrast with Lazarus and colleagues' study, cross-sectional studies comparing primary regimens of ChAdOx1-S with another inactivated vaccine (Covaxin), or the mRNA-based BNT162b2 with BBIBP-CorV, showed that whole-virus inactivated vaccines were inferior to vector-based or mRNA-based vaccines when assessing antibody levels.[2,3] Interestingly, the difference in binding antibody levels between the two vaccine platforms in the study by Lazarus and colleagues was less pronounced than the difference between neutralising antibody levels, indicating that VLA2001 might induce more functional antibodies than ChAdOx1-S. Clear differences in T-cell responses were not observed, with the exception that whole-virus inactivated vaccines in general, and VLA2001 in the discussed study, induce broader responses than do vaccines that exclusively encode for the S protein, activating T cells that additionally target the nucleocapsid (N) and matrix (M) proteins.

In the current phase of the COVID-19 pandemic with many vaccine options now available, defining required endpoints in upcoming clinical trials that assess novel vaccines will be crucial. In our opinion, depending on the intended use of the vaccine, it is important to study the following factors: (1) immunogenicity in populations with pre-existing immunity, either induced by previous vaccination, natural infection, or a combination of both; (2) cross-reactivity of induced (neutralising) antibodies with novel, antigenically distinct SARS-CoV-2 variants; and (3) the breadth of the virus-specific T-cell response after (booster) vaccination. Notably, polyclonal T-cell responses do not seem to be affected by the mutations detected to date in the S protein, whereas these mutations do lead to at least partial escape from neutralising antibodies, making standardised T-cell assessments even more important.[4,5]

Unfortunately, to date, clinical trials addressing the crucial endpoints we propose have not been performed for whole-virus inactivated vaccines. For example, the report of a phase 2 trial in which a third dose of CoronaVac was administered to CoronaVac-primed individuals clearly showed immunological recall responses but did not include an analysis of variant-specific antibodies or virus-specific T cells.[6] In a direct comparison between BNT162b2 and CoronaVac booster vaccination in CoronaVac-primed individuals, restoration of omicron (B.1.1.529) BA.1 neutralisation was observed after BNT162b2 booster immunisation but not after a third dose of CoronaVac; again, virus-specific T-cell responses were not measured.[7]

Taken together, VLA2001 can be regarded a promising addition to the arsenal of COVID-19 vaccines. However, despite the positive findings of Lazarus and colleagues, it is important to note that the bridging with ChAdOx1-S

might not be an optimal choice. ChAdOx1-S was shown to induce less virus-specific immune responses than the mRNA-based vaccines.[4] Additionally, the usefulness of VLA2001 in the current phase of the pandemic remains to be determined through critical studies with VLA2001 in the intended target populations, thereby defining its position in the landscape of available vaccines.

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Time to redefine a primary vaccination series?

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In the third year of the COVID-19 pandemic, it is getting harder to define what a full-dose COVID-19 vaccination series is, especially in the era of emerging variants such as omicron (B.1.1.529). The definition might differ depending on the dominant variant in circulation, the availability of vaccines, the risk factors of vaccine recipients, and the availability of surveillance and COVID-19 vaccine safety and effectiveness data. Inequitable vaccine availability adds to the problem as on one hand, in many high-income countries, a fourth dose of an mRNA vaccine is offered and gives well tolerated boosting of cellular and humoral immunity,[1] and on the other hand, only 19·7% of people in low-income countries have received at least one dose of any COVID-19 vaccine.[2] These facts all make it difficult to comment on what a primary COVID-19 vaccination series should consist of and how we should boost protective immunity in the face of emerging variants in a world with marked inequalities.

In *The Lancet Infectious Diseases*, Karin Hardt and colleagues[3] report on the efficacy, safety, and immunogenicity of a second dose of Ad26.COV2.S vaccine against COVID-19 given as part of the ENSEMBLE2 trial, wherein participants were randomly assigned from the first visit either to get two doses of the vaccine or two doses of placebo 2 months apart. The two-dose regimen provided 75·2% (adjusted 95% CI 54·6–87·3) efficacy against moderate to severe–critical COVID-19 and 100% (32·6–100·0) efficacy against severe–critical COVID-19. Meanwhile, the final analysis of the double-blind phase of the ENSEMBLE vaccine trial showed that primary vaccination with a single dose of Ad26.COV2.S had 56·3% (95% CI 51·3–60·8) efficacy against moderate to severe–critical COVID-19, 74·6% (64·7–82·1) efficacy against severe–critical COVID-19, and 82·8% (40·5–96·8) efficacy against COVID-19 related death.[4] The data collection for the primary analyses of one-dose and two-dose regimens was completed before the global dominance of delta (B.1.617.2) and the emergence of omicron.

The follow-on, single-arm, open-label, phase 3b, Sisonke study in health-care workers in South Africa showed that after two doses of Ad26.COV2.S vaccine, effectiveness against severe disease during the omicron surge was equal to that of two doses of BNT162b2.[5] Moreover, a longer interval (4 months) between the two doses of Ad26.COV2.S led to lesser omicron immune escape than other two-dose vaccine regimens (given 3–4 weeks apart).[6] However, vaccinees receiving two doses of Ad26.COV2.S had greater omicron immune escape than vaccinees receiving three doses of mRNA vaccines or three doses of different heterologous regimens. These findings suggest that a third dose of either Ad26.COV2.S or another vaccine