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

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 
tended 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
Time to redefine a primary vaccination series?

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, 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. 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 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. 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. 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). 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 might not be an optimal choice. ChAdOx1-S was shown to induce less virus-specific immune responses than the mRNA-based vaccines. 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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Corine H GeurtsvanKessel, *Rory D de Vries
r.d.devries@erasmusmc.nl
Department of Viroscience, Erasmus Medical Center, 3015 CN Rotterdam, Netherlands

1 Lazarus R, Querton B, Corbic Ramljak I, et al. Immunogenicity and safety of an inactivated whole-virus COVID-19 vaccine (VLA2001) compared with the adenoviral vector vaccine ChAdOx1-S in adults in the UK (COV-COMPARE): interim analysis of a randomised, controlled, phase 3, immunobridging trial. Lancet Infect Dis 2022; published online Sept 5. https://doi.org/10.1016/S1473-3099(22)00502-3.

2 Petrović V, Vuković V, Patić A, Marković M, Ristić M. Immunogenicity of BNT162b2, BBIBP-CorV and Gam-COVID-Vac vaccines and immunity after natural SARS-CoV-2 infection—a comparative study from Novi Sad, Serbia. PLoS One 2022; 17: e0263468.

3 Singh AK, Phatak SR, Singh R, et al. Antibody response after first and second-dose of ChAdOx1-S (Covshield™) and BBV-152 (Covaxin™) among health care workers in India: the final results of cross-sectional coronavirus vaccine-induced antibody titre (COVAT) study. Vaccine 2021; 39: 6492–509.

4 GeurtsvanKessel CH, Geers D, Schmitz KS, et al. Divergent SARS-CoV-2 omicron-reactive T and B cell responses in COVID-19 vaccine recipients. Sci Immunol 2022; 7: eabo2202.

5 Mylékyn AZ, Rissmann M, Kok A, et al. Antigenic cartography of SARS-CoV-2 reveals that omicron BA.1 and BA.2 are antigenically distinct. Sci Immunol 2022; published online June 23. https://doi.org/10.1126/sciimmunol.abq4450.

6 Zeng G, Wu Q, Pan H, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis 2022; 22: 483–95.

7 Cheng SMS, Mok CKP, Leung YWY, et al. Neutralizing antibodies against the SARS-CoV-2 omicron variant BA.1 following homologous and heterologous CoronaVac or BNT162b2 vaccination. Nat Med 2022; 28: 486–89.