Interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19

Interim guidance

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World Health Organization

Background

This interim guidance[1] has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its plenary meeting on 11 August 2022.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

This interim recommendation pertains to the COVID-19 Valneva vaccine (VLA2001), developed by Valneva's research and development teams in France and Austria with the marketing authorization holder, Valneva Austria GmbH. In the subsequent text the vaccine will be referred to as VLA2001.

The guidance is based on the initial evidence summarized in the Background document and the Annexes which include GRADE and evidence-to-recommendations (ETR) tables.

All referenced documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Methods

SAGE applies the principles of evidence-based medicine and has set in place a thorough methodological process for issuing and updating recommendations *(1)*. A detailed description of the methodological processes as they apply to COVID-19 vaccines may be found in the SAGE evidence framework for COVID-19 vaccines *(2)*. This framework

[1] The recommendations contained in this publication are based on the advice of independent experts who have considered the best available evidence, a risk–benefit analysis, and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national, legal, and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.

contains guidance on considering data emerging from clinical trials and post-introduction effectiveness and safety monitoring.

General goal and strategy for the use of VLA2001 against COVID-19

The COVID-19 pandemic has caused significant morbidity and mortality throughout the world, as well as major social, educational and economic disruptions. There remains an urgent global need to make COVID-19 vaccines available and deploy them at scale and equitably across all countries. Countries are recommended to use the WHO Prioritization Roadmap *(3)* and the WHO Values Framework *(4)* as guidance for their prioritization of target groups. The WHO Prioritization Roadmap recommends that priority of vaccine use be given to the highest priority-use groups (health workers, older persons, persons with moderate to severe immunocompromising conditions), and high priority-use groups (persons with comorbidities, teachers, pregnant women etc). Within the capacity of programmes and vaccine availability, additional priority-use groups should be vaccinated as outlined in the WHO Prioritization Roadmap *(4)*, taking into account national epidemiological data and other relevant considerations.

Vaccine performance

The VLA2001 is a purified, inactivated, and adjuvanted whole virus SARS-CoV-2 vaccine. The whole-virion inactivated vaccine is adsorbed to alum with a toll-like receptor 9 agonist adjuvant (CpG 1018 in combination with aluminium hydroxide). Following administration, the spike protein of SARS-CoV-2, and other viral surface antigens, stimulate both neutralizing and other functional binding antibodies, as well as cellular immune responses (Th1) directed against the spike and other surface proteins, which are thought to contribute to protection against COVID-19. Inactivated vaccines platforms have been used in the production of vaccines against diseases such as seasonal influenza, polio, and pertussis, as well as COVID-19. Inactivated vaccines cannot replicate, therefore cannot infect individuals.

There is no vaccine efficacy data available from this trial and the evidence assessment is of the immunogenicity data. There is currently no established correlate of protection. WHO has acknowledged that immunogenicity data may be used in certain situations as agreed under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA) and have updated their guidance to manufacturers accordingly *(5)*. Immunobridging refers to "*a situation where vaccine efficacy can be inferred by demonstrating a non-inferior immune response between an investigational vaccine and an authorized vaccine for which efficacy and/or effectiveness against a specific disease has been estimated" (6)*.

The immunogenicity of VLA2001 has been assessed in a phase 1/2 and a phase 3 trial involving participants aged 18–55 years. In the phase 3 study, COV-COMPARE (NCT04864561; ISRCTN79815558), 2975 participants were randomized (2:1) to receive a two-dose intramuscular vaccination with either VLA2001 or ChAdOx1-S (ChAdOx1-S [recombinant] vaccine against COVID-19, AstraZeneca AZD1222), administered about 28 days apart. A primary statistical analysis was performed after all participants were vaccinated and had completed day 43 with a mean safety follow-up of 151.4 days (standard deviation 19.27 days). Median age was 34 years for VLA2001 and 35 years for ChAdOx1-S, with less than 1% of the populations older than 50 years of age. Both study arms included slightly more

male (57%) than female (43%) participants; 93% were white (Caucasian) and the majority were seronegative for COVID-19 at screening (95% in the VLA2001 arm, and 97% in the ChAdOx1-S arm). A total of 990 participants were analysed in the immunogenicity (IMM) population (*n*=492, VLA2001; *n*=498, ChAdOx1-S), and 987 participants in the per protocol (PP) population *(7, 8)*. For both the comparative populations the age range was ≥30 years.

For the IMM population (with no neutralizing antibodies at baseline, considered for the primary immunogenicity analysis) results indicate that the second dose of VLA2001 was necessary to induce robust antibody levels in baseline negative participants *(7, 8)*. On day 43, the geometric mean titre (GMT) was 803.5 (95% confidence interval [CI]: 748.5–862.6) for the VLA2001 group aged ≥30 years, and 576.6 (95% CI: 543.6–611.7) for the ChAdOx1-S group, aged ≥30 years (p<0.0001; 1.39 [95% CI: 1.25–1.56] superiority). For the VLA2001 group aged <30 years, GMT was 1043.4 (95% CI: 926.6–1174.9) and in the three participants aged >50 years, the neutralizing antibody GMT was 611.4 (95% CI: 158.9–2352.0). For participants aged ≥30 years who were seropositive at baseline, GMT for day 1 was 269.2 (95% CI: 226.4–320.0) which had increased to 1478.6 (95% CI: 1245.6–1755.1) by day 43.

At day 43, 98.0% of VLA2001 recipients and 98.9% of ChAdOx1-S recipients in the IMM population had seroconverted (as measured by ELISA [2]); and 97.4% versus 98.9% (respectively) in the PP population (difference: -0.015 [95% CI: -0.033–0.002; p=0.0911; non-inferiority: -3.3%) *(7-9)*. A higher GMT of S-protein binding antibodies (IgG ELISA) was observed at day 43 in the VLA2001 group (GMT: 2361.7 [95% CI: 2171.08–2569.11]) compared to the ChAdOx1-S group (GMT: 2126.4 (95% CI: 1992.42–2269.45) for the IMM population. The results were similar in the PP population. Numbers of participants with ≥2-fold, ≥10-fold and ≥20-fold increase in S-protein binding antibody titre at day 43 were similar for both treatment groups with nearly 100% for ≥2-fold increase and 90% or more for ≥10-fold and ≥20-fold increase *(8)*. For S-protein binding antibodies at day 43 for the younger cohort aged <30 years, GMT was 3121.5 (95% CI: 2699.3–3609.7) with participants with COVID-19 infection excluded compared to the group aged ≥30 years, which was 2385.0 (95% CI: 2159.5–2634.0), p-value of 0.0032. The T-cell response against the spike protein tended to be lower for VLA2001 compared to ChAdOx1-S; that is 74.3% (55/74) participants in the VLA2001 group and 86.5% (64/74) participants in the ChAdOx1-S group had a T-cell response on day 43 for the peripheral blood mononuclear cells (PBMC) subset of the IMM population[3]. For VLA2001, 45.9% (34/74) showed responses to the N-protein, and 20.3% (15/74) to the M-protein), which did not exist for ChAdOx1-S (0/74 for the N-protein, and 1/74 for the M-protein) *(7-9)*. An exploratory analysis, conducted for the number of COVID-19 cases for the entire observation period (mean follow-up 151.4 days), showed no severe COVID-19 infection cases in any study arm. Among participants who received two doses of VLA2001, 87 (8.4%) COVID-19 cases were reported in those aged 18–29 years, and 139 (7%) in those aged ≥30 years. In contrast 60 (6%) COVID-19 cases were reported among participants who received two doses of ChAdOx1-S *(7-9)*.

Children and adolescents: No data are available. Two trials, VLA2001-301a (for adolescents aged 12–17 years, NCT04864561; ISRCTN 79815558), and VLA2001-321 (for children aged 2–12 years, NCT05298644) are underway.

[2] ELISA: enzyme-linked immunosorbent assay.

[3] The number of spot-forming units/number of reactive cells per $2.5x10^5$ peripheral blood mononuclear cells.

Persistence of immune response and booster doses

Homologous booster: Preliminary results from a continuation of the phase 1/2 study (NCT04671017; ISRCTN 82411169), where a third dose of VLA2001 was administered as a homologous booster 7–8 months after the second dose of primary vaccination, showed that VLA2001 elicited an anamnestic response, with similar antibody levels observed regardless of whether participants had been initially vaccinated with a low, medium or high dose (GMT: 9699.3 [95% CI: 8497.76–11070.71]). This represents a 42-fold to 106-fold increase, depending on the pre-boosting levels of antibodies (*press release, (10)*).

Heterologous booster: Participants aged >30 years, and who were at least 70 days post receipt of two doses of ChAdOx1nCov-19 (ChAdOx1-S), or at least 84 days post receipt of two doses of BNT162b2 (Pfizer–BioNtech, BNT162b2) as their primary vaccination series, were enrolled in the COV-BOOST study (ISRCTN 73765130) in one of three groups (A, B or C). Group A received (in a 1:1:1:1 ratio), NVX-CoV2373 (Novavax, NVX-CoV2373), *or* a half dose of NVX-CoV2373, *or* ChAdOx1-S, *or* a quadrivalent meningococcal conjugate vaccine (MenACWY) control. Group B received (in a 1:1:1:1:1 ratio), BNT162b2, *or* VLA2001, *or* a half dose of VLA2001, *or* Ad26.COV2.S (Janssen, Ad26.COV2.S), *or* MenACWY. Group C received (in a 1:1:1:1 ratio), mRNA1273 (Moderna, mRNA1273), *or* CVnCov (CureVac; CVnCov), *or* a half dose of BNT162b2, *or* MenACWY.

Immunogenicity of heterologous booster: For participants primed with ChAdOx1-S/ChAdOx1-S, all COVID-19 vaccines given as a booster dose induced significantly higher anti-spike IgG at 28 days post boost, compared with their corresponding controls, and the geometric mean ratios (GMRs) for pseudotype virus neutralizing antibodies against wild-type were consistent with those of anti-spike IgG. Overall, the response with the VLA2001 booster was higher than with the control, and equivalent to that of ChAdOx1-S, but lower than all other options. For participants primed with BNT162b2/BNT162b2 as their primary schedule, significant GMRs were also observed in all study vaccine groups compared with controls for anti-spike IgG at 28 days post boost. However, the upper limit of the 99% CI for VLA2001 and half-dose VLA2001 did not reach the pre-established minimum clinically important difference of 1.75. For the BNT162b2/BNT162b2 participants, the GMRs for pseudotype virus neutralizing antibodies and anti-spike IgG antibodies were also consistent, and overall, the response with VLA2001 was marginally higher (B-cell) or equivalent (T-cell) to that of the control *(11)*.

Safety

In total, 3017 participants from the COV-COMPARE phase 3 study received at least one VLA2001 vaccination, and 995 received ChAdOx1-S. The incidence of adverse events (AEs) until day 43, was 93% in the VLA2001 <30 years age group, 89% in the VLA2001 ≥30 years age group, and 98% in the ChAdOx1-S cohort, with most events reported as mild. Of participants in the VLA2001 ≥30 years age cohort, 73% reported local injection site reactions compared with 91% of the ChAdOx1-S cohort (p<0.0001). Of participants in the VLA2001 ≥30 years age cohort, 70% reported systemic reactions up to 7 days after the first vaccination compared with 91% of the ChAdOx1-S group (p<0.0001). The most frequently reported adverse reactions were tenderness at injection site (>60%), pain (>40%), fatigue (>50%), headache (>30%), muscle pain (>30%) and nausea/vomiting (>10%). Most of the adverse reactions were mild and

resolved within two days of vaccination. The incidence and severity of adverse reactions were similar after the first and second doses and tended to decrease in relation to participants' age. The incidence of unsolicited AEs with VLA2001 was 29% in the <30 years age group, and 29% in the ≥30 years age group, compared with 35% in ChAdOx1-S group (p=0.0003). The incidence of serious AEs overall was similar across all treatment groups (0.7% in the VLA2001 groups and 1.0% in the ChAdOx1-S group) *(7-9)*.

Safety of heterologous booster: For the ChAdOx1-S/ChAdOx1-S-primed group, the frequencies of severe local and systemic reactions were less than 5% for all vaccine groups, the exception being severe fatigue which was reported in 12% of the 112 mRNA1273 recipients. For the BNT162b2/BNT162b2-primed group, rates for the following reactions were above 5%: malaise (6%) in each of the ChAdOx1-S, mRNA1273, and CVnCov boosted groups; and chills (6%) and fatigue (8%) in the 103 participants boosted with Ad26.COV2.S. A total of 21 participants reported a PCR test result positive for SARS-CoV-2 with no hospitalization. Of these, 8 cases (38%) were within the VLA2001 arms (4 with full dose and 4 with half dose); 5 cases (24%) occurred within other vaccine arms (1 case (5%) each for ChAdOx1-S and Ad26.COV2.S, and 3 (14%) within NVX-CoV2373 arms; 2 of which were with the half dose); the remaining 8 cases (38%) were in control arms *(11)*.

An open-label, single-arm trial (EudraCT 2022-000035-23; VLA2001-307) is planned using VLA2001 as a heterologous booster vaccination 6–12 months after primary series with an mRNA COVID-19 vaccine; or 6–12 months after PCR confirmation of natural SARS-CoV-2 infection. The study will be conducted in the Netherlands and is expected to recruit about 150 participants with first preliminary results expected in the third quarter of 2022 (*press release, (12)*).

Variants of concern

Studies are ongoing to evaluate the ability of VLA2001 to neutralize variants of the SARS-CoV-2 virus. Initial results from 30 participants in the phase 1/2 trial of VLA2001, used in a pseudovirus assay to analyse neutralization of the ancestral SARS-CoV-2 virus as well as the Delta and Omicron variants, showed that all 30 samples (100%) presented neutralizing antibodies against the ancestral virus and Delta variant, and 26 samples (87%) presented neutralizing antibodies against the Omicron variant with a mean fold reduction of neutralization relative to the ancestral virus of 2.7-fold for Delta and 16.7-fold for Omicron (*press release, (13)* and from data on file).

Intended use

Persons aged 18–50 years (for prioritization of subpopulations by age and other considerations, see the WHO Prioritization Roadmap *(3)*).

Administration

The recommended primary vaccine series is two doses (0.5 ml each dose) given intramuscularly. The second dose is recommended to be administered at least 28 days after the first dose.

Booster doses

In accordance with the WHO Prioritization Roadmap *(3)*, a booster dose of VLA2001 is recommended, administered 4–6 months after completion of the primary series. If more than 6 months have elapsed since completion of the primary series, the booster dose should be given at the earliest opportunity. No data on the need and timing of second homologous boosters are currently available. Inferring from other COVID-19 vaccines, it is likely that second boosters will be necessary in due course (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-good-practice-statement-second-booster).

Interchangeability with other COVID-19 vaccines (heterologous schedules)

VLA2001 given as a heterologous booster after primary vaccination series with BNT162b2 (Pfizer BioNTech) vaccine showed limited or no difference with the placebo, therefore its use as a heterologous booster post primary vaccination with an mRNA vaccine is not recommended.

VLA2001 given as a heterologous booster after primary vaccination series with ChAdOx1-S showed equivalent results to a ChAdOx1-S booster, therefore its use as a heterologous booster post primary vaccination with ChAdOx1-S can be considered.

There are no data for the use of VLA2001 given as a heterologous booster after primary vaccination series with inactivated and protein-based vaccines; until such data become available, use of VLA2001 as a heterologous booster post primary vaccination with inactivated and protein-based vaccines is currently not recommended.

Heterologous boosters should take into account current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Co-administration with other vaccines

There are no data on the use of VLA2001 provided concomitantly with other vaccines. For adults, based on several co-administration studies of COVID-19 vaccines and inferred from co-administration studies of other adult vaccines, COVID-19 vaccines may be given concomitantly with, or at any time before or after, other adult vaccines, including live attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines *(14)*. When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended.

Contraindications

A history of anaphylaxis to any component of the vaccine is a contraindication to vaccination. People who have an anaphylactic reaction following the first dose of VLA2001 should not receive any further doses of the same vaccine.

Precautions

A history of anaphylaxis to any other vaccine or injectable therapy (i.e. intramuscular, intravenous, or subcutaneous vaccines or therapies) is not a contraindication to vaccination with COVID-19 vaccines. For such persons, a risk assessment should be conducted by a health professional. It is uncertain if there is an increased risk of anaphylaxis with VLA2001, but counselling should be given about the potential risk of anaphylaxis and the risks should be weighed against the benefits of vaccination. Such persons should be observed for 30 minutes after vaccination in health-care settings where anaphylaxis can be immediately treated.

In general, persons with an immediate non-anaphylactic allergic reaction to the first vaccine dose (e.g. urticaria, angioedema without respiratory signs or symptoms that occur within 4 hours of administration) should not receive additional doses, unless recommended after review by a health professional with specialist expertise. Subject to individual risk–benefit assessment, VLA2001 could be provided under close medical supervision if it is the only available vaccine for persons at high risk of severe COVID-19. If a booster dose is offered, the patient should be observed closely for 30 minutes after vaccination in a health-care setting where severe allergic reactions can be immediately treated.

As for all vaccines, VLA2001 should be given under health-care supervision, with the appropriate medical treatment available in case of allergic reactions. As for any other vaccine, an observation period of 15 minutes after vaccination should be ensured. Anyone with an acute febrile illness (i.e. with a body temperature >38.5 ºC) should postpone vaccination until they are afebrile.

Vaccination of specific populations

Older persons

The risk of severe COVID-19 and death increases steeply with age. There are currently limited data on the immunogenicity of VLA2001 in persons aged 50 years and older; however, a phase 3, open label, multicentre, single arm study (NCT04956224. VLA2001-304) to assess the safety, tolerability, and immunogenicity of VLA2001 in volunteers aged 56 years and older is ongoing, with results expected in the third quarter of 2022. Until such data are available, VLA2001 is not recommended in persons aged over 50 years.

Persons with comorbidities

There are limited data on persons with comorbidities. For people with obesity (body mass index (BMI) >30) at day 43, the ND_{50} GMT was 689.3 (95% CI: 591.0–803.9) for the VLA2001 group (*n*=119) compared to 640.1 (95% CI: 565.3–724.8) for the ChAdOx1-S group (*n*=125), *p*-value 0.534; the seroconversion rates were 94.4% (95% CI: 88.3–97.9), *n*=119, and 99.1% (95% CI: 95.2–100.0), *n*=126 respectively, *p*-value 0.049 (from data on file). Certain comorbidities and health states – such as diabetes mellitus, cardiovascular and respiratory disease, neurodegenerative disease, and obesity – have been identified as increasing the risk of severe COVID-19 and death. WHO generally recommends vaccination of persons with comorbidities.

Children and adolescents below the age of 18 years

There are no data on efficacy or safety for persons below the age of 18 years for VLA2001. Vaccination of individuals in this age group with VLA2001 is therefore currently not recommended.

Pregnant persons

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care; it may also be associated with an increased risk of maternal mortality *(15, 16)*. Pregnant women are at particular risk of serious outcomes from COVID-19 if they are aged 35 years and older, have a high body mass index, or have an existing comorbidity such as diabetes or hypertension.

Developmental and reproductive toxicology (DART) studies have not shown harmful effects of the vaccine in pregnant animals and their foetuses. Available data from clinical trials are insufficient to assess vaccine safety or efficacy of VLA2001 in pregnancy. Aluminium containing adjuvants have been widely used in vaccines since the 1930s; however CpG 1018 has only recently been developed. CpG 1018 is used as an adjuvant in the HepB-CpG (Heplisav-B) vaccine and in pre-licensure clinical trials; adverse events after HepB-CpG were comparable to those observed after another licensed, non-adjuvanted hepatitis B vaccine *(17)*. A retrospective chart review comparing the identified 40 documented pregnancies in the HepB-CpG arm, with the identified 19 documented pregnancies in the HepB-alum arm, showed similar pregnancy safety outcomes for both arms and higher seroprotection rates for the HepB-CpG arm *(18)*. Based on previous experience with other inactivated vaccines during pregnancy, the effectiveness and safety of VLA2001 in pregnant women is expected to be comparable to those observed for non-pregnant women in similar age groups.

WHO has identified pregnant women as a priority-use group for COVID-19 vaccination, given their increased risk of severe outcomes. WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Breastfeeding persons