EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Criteria and requirement for the licensing of new vaccines with special emphasis on COVID-19 the view of EMA

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Correlate of protection

- **Immune correlate of protection**: an immune parameter that has been demonstrated to correlate with protection at defined values
- May differ based on vaccine type, population, endpoint and timing
- Different methodologies to establish ICP.

Approval of new vaccines without ICP

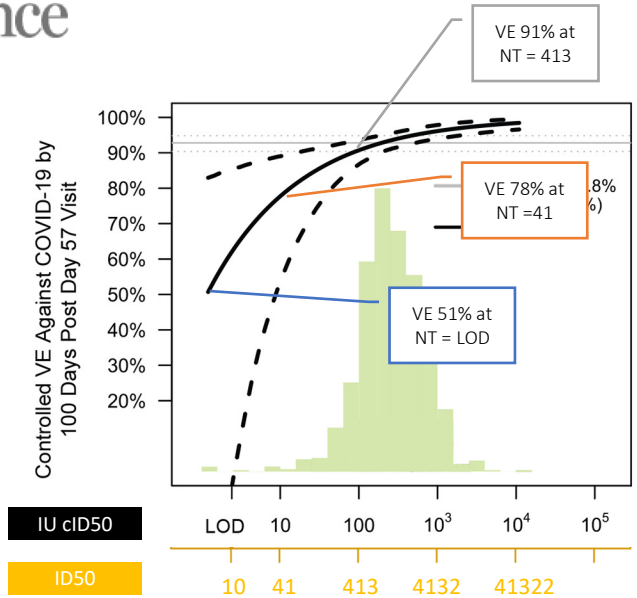
If no Correlate of protection or threshold for benchmarking immunogenicity of vaccines is available, and clinical efficacy studies not feasible, it could still be possible to use an immune marker that best represent response to a vaccine that showed efficacy, e.g. aP vaccines

Approval of new vaccines based on an immune marker suitable to infer protection

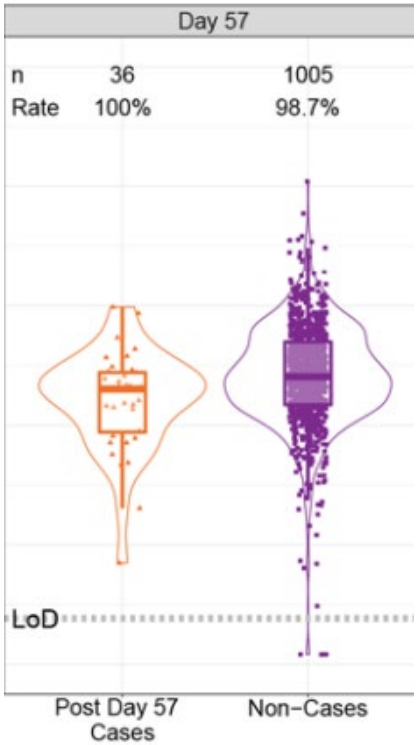
- Comparison of immune response between candidate vaccine and a licensed vaccine for which efficacy and /or effectiveness has been shown
- If no threshold value available, primary endpoint is usually the seroconversion rate, i.e. pre-defined increment in antibodies from pre to post-vaccination, and in some instances also the Geometric Mean Titres of the antibodies
- Functional antibodies generally preferred to binding antibodies – full assay validation expected
- T cells responses difficult to use as part of the inferential testing but exploratory analyses would be additional valuable evidence

COVID-19 vaccines:
Correlation of neutralizing antibodies with protection from disease

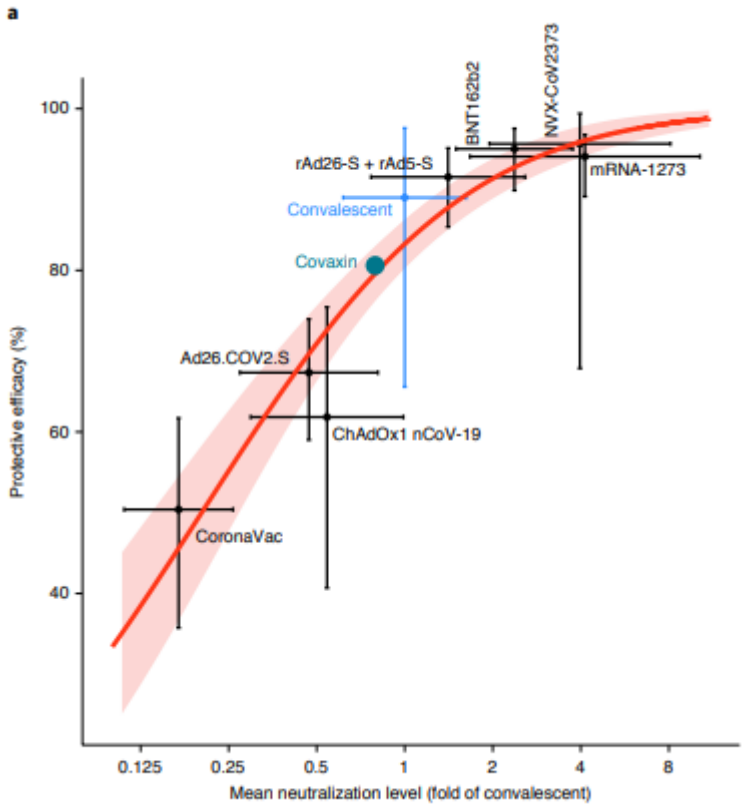
Science



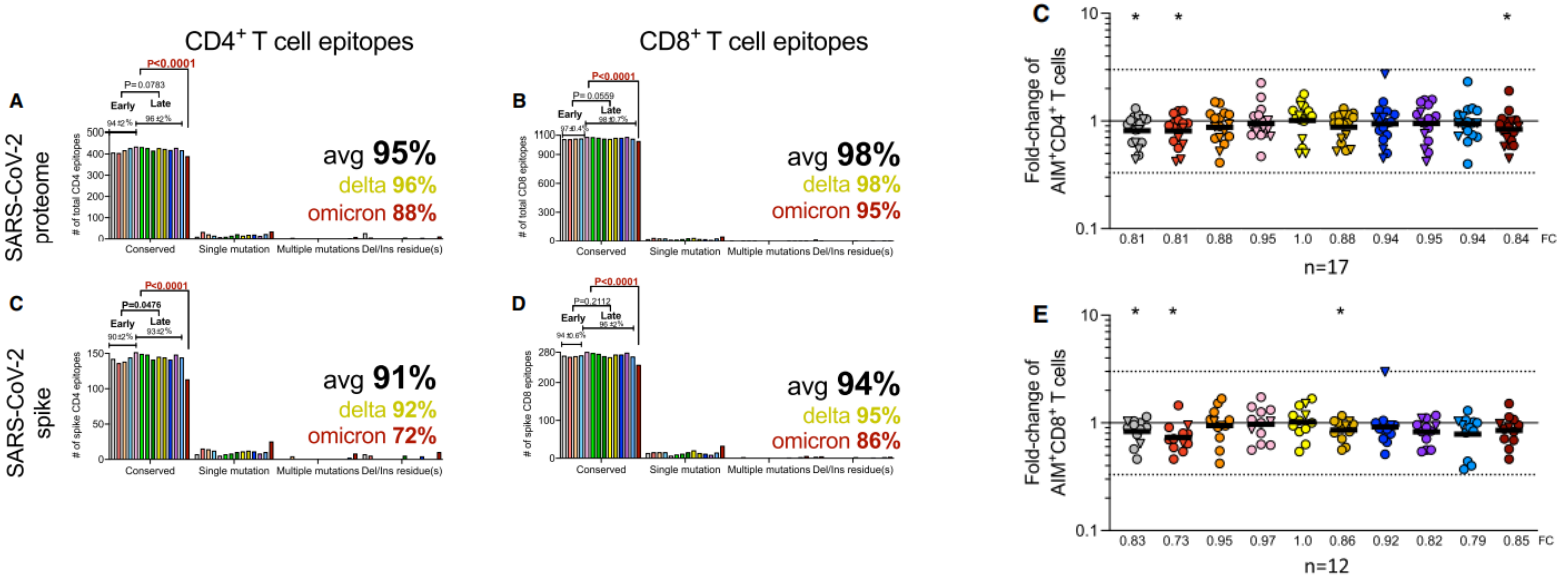
Gilbert et al, *Science,* 2021. https://www.science.org/doi/10.1126/science.abm3425



[Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection | Nature Medicine]



SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron



- T cells responses contribute to protection and are relevant in the long term and against VOCs, BUT difficult to measure and to reliably correlate with protection:
- Different assays used
- Standardisation challenging
- Difficult to disentangle contribution to protection from humoral response

ICMRA COVID-19 Vaccine development: Future steps Workshop

Thursday 24 June 2021

There was consensus that immunogenicity bridging studies may be needed if an assessment of effectiveness of 2nd generation COVID-19 vaccines in clinical endpoint efficacy studies are no longer feasible. These could be designed as non-inferiority immunogenicity studies if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or superiority designs if the comparator vaccine has demonstrated modest efficacy. The selection of immune markers to predict effectiveness (e.g. neutralizing antibody titre using WHO certified reference standard), identification of meaningful endpoints and statistical criteria, choice of appropriate vaccine comparators (e.g. platform) and population comparator groups (e.g. matched by age, gender, prior vaccination status) were also highlighted as critical factors to agree upon.

COVID-19 vaccines: immunogenicity studies to support approval

- Comparator should be an authorised vaccine, belonging to the same type of platform technology and based on the same antigen, e.g. Spike protein
- If comparison with vaccine from the same vaccine platform is not possible, NI vs. a vaccine with same antigen that demonstrated high level of efficacy and high level of neutralising antibodies is expected
- Alternatively, BUT much less preferred, superiority in terms of GMTs to vaccines that demonstrated efficacy but with lower humoral immune response and efficacy
- Non-inferiority in terms of seroresponse should be formally tested
- The immune response should be fully characterised, i.e. binding antibodies and cellular mediated immunity

COVID-19 vaccines: immunogenicity studies to support approval

- The SARS-COV2 strain to be tested for neutralisation in the primary analysis should be a strain for which the comparator vaccine has shown clinical efficacy or vaccine effectiveness
- comparison of neutralisation of VOCs should be performed either as secondary or exploratory analyses
- assays should be fully validated for primary analysis (at least)
- For booster vaccines, it is recommended that clinical trials are conducted after priming with a single selected type of vaccine

COVID-19 vaccines: when immunobridging studies would not be suitable

- A new vaccine that includes different antigens than the ones approved and for which it would be not possible to bridge immune response
- A new vaccine that is specifically directed at eliciting T cells responses and not antibodies
- A new vaccine that is delivered via mucosal administration and would not be able to reach the same level of systemic neutralising antibodies as the currently approved vaccine
- *In all these cases, clinical efficacy needs in principle to be shown*

COVID-19 Vaccine (inactivated, adjuvanted) Valneva

AUTHORISED
This medicine is authorised for use in the European Union.

COVID-19 vaccine (inactivated, adjuvanted, adsorbed)

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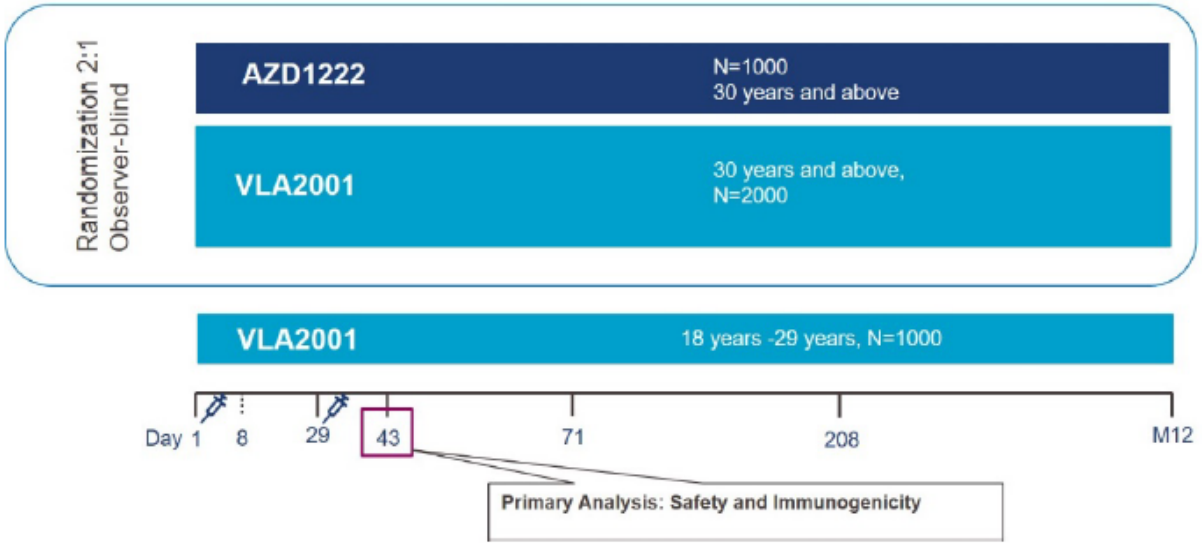
Valneva COVID-19 clinical immunogenicity pivotal trial

Figure 2 Study design and flow chart for clinical Phase 3 trial VLA2001-301



Valneva COVID-19 clinical immunogenicity pivotal trial

Table 1: SARS-CoV-2 neutralising antibodies (ND50) on Day 1 and Day 43; co-primary analysis (IMM population)

Treatment group		VLA2001 (n=492)	COVID-19 Vaccine (ChAdOx1-S [recombinant]) (n=498)	Overall (n=990)
Day 43	n	492	493	985
	GMT (95% CI)	803.5 (748.48, 862.59)	576.6 (543.59, 611.66)	680.6 (649.40, 713.22)
	GMT Ratio (95% CI)			**1.39 (1.25, 1.56)**
	Median	867.0	553.0	659.0
	Min, Max	31, 12800	66, 12800	31, 12800
	p-value [1]			**<0.0001**

GMT: Geometric mean titre, GMT ratio: GMT VLA2001/GMT COVID-19 Vaccine (ChAdOx1-S [recombinant]), CI: Confidence interval

[1] p-value and CI calculated using a two-sided t-test applied to log10 transformed data

Table 2: Proportion of participants with seroconversion in terms of neutralising antibodies on Day 43 (PP population)

Treatment group	VLA2001 (N=492)	COVID-19 Vaccine (ChAdOx1-S [recombinant]) (N=498)	Overall (N=990)
Number of patients with eligible samples at visit	456	449	905
Participants with seroconversion at Day 43			
n (%)	444 (97.4)	444 (98.9)	888 (98.1)
95% CI[1]	(0.954,0.986)	(0.974,0.996)	(0.970,0.989)
p-value[2]			0.0911
95% CI for Difference[2]			(-.033,0.002)

Note: Seroconversion is defined as ≥ 4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between Day 1 and post-vaccination sample collection timepoints (for first interim analysis: Day 1 and Day 43). Displayed are only rates at Day 43 (all values at Day 1 are "0").

CI: Confidence Interval

[1] Exact 95% Clopper-Pearson confidence interval for proportion.

[2] P value or two-sided CI is for the difference in proportions (VLA2001-COVID-19 Vaccine (ChAdOx1-S [recombinant])) of participants with seroconversion at each particular visit.

COVID-19 vaccines - Immunobridging across age groups

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.*

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

* Results are for the subset of participants in the dose 2 immunogenicity population that could be evaluated (i.e., participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window, had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations) who had no evidence of previous SARS-CoV-2 infection. Participants without evidence of previous infection were those who had no serologic or virologic evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit up to 1 month after dose 2.

† Geometric mean titers and two-sided 95% confidence intervals were calculated by exponentiating the mean logarithm of the titers and the corresponding confidence intervals (based on the Student's t distribution). Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation.

‡ The geometric mean ratio and two-sided 95% confidence intervals were calculated by exponentiating the mean difference of the logarithms of the titers (the 12-to-15-year-old cohort minus the 16-to-25-year-old cohort) and the corresponding confidence intervals (based on the Student's t distribution). The noninferiority criterion was met, since the lower boundary of the two-sided confidence interval for the geometric mean ratio was greater than 0.67.

Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents (nejm.org)

Vaccine Effectiveness (VE) studies

- from a regulatory perspective, need to generate **vaccine-specific** data to contribute with important information to the overall clinical evidence available for each vaccine, especially new vaccines

- Studies to be conducted in line with Good Epidemiological Practice (GEP) guidelines and with ENCePP guidelines. Companies should liaise with organisations/institutions/public health authorities who have experience in VE and infrastructure to conduct multicentre studies

New mandate and Vaccine Monitoring Platform

Conclusions

- If an ICP is available, clinical immunogenicity data will suffice for licensure
- In case no ICP and field efficacy trial not feasible, but an immune marker applicable, comparison of immune response to a vaccine that showed efficacy/effectiveness (or bridged to one that showed efficacy) is acceptable, e.g. COVID vaccines
- In case no ICP or possibility to bridge immune response, agencies open to discuss use of alternative strategies
- Plans for effectiveness measurement post-approval to be discussed early with regulators to gain good understanding of what can be achieved post-approval