16 February 2024
EMA/46094/2024
Emergency Task Force

# ETF statement on use of recently updated COVID-19 vaccines

Since the declaration of the COVID-19 pandemic in early 2020, multiple vaccines have been approved in the European Union and elsewhere for the prevention of COVID-19. Early deployment of the first of these vaccines, which were based on the ancestral strain of SARS-CoV-2, played a significant role in curbing the pandemic's effects.[1]

As SARS-CoV-2 circulates and evolves, new SARS-CoV-2 variants continue to emerge with the ability to evade immunity induced by prior infection or vaccination. Consequently, COVID-19 vaccines require regular strain updates, a situation very similar to the regularly updated influenza vaccines.[2]

**SARS-CoV-2 evolution**

After a lag phase during which the D614G substitution was the most significant change, SARS-CoV-2 evolved further in the human population. Many variants of concern (VOCs) emerged and replaced prior VOCs.[3,4] Some of the new VOCs harboured more than 30 amino acid mutations in the spike protein, with 15 mutations in the receptor-binding domain alone.[5] These changes affected virus transmission (ACE2 receptor binding) and resulted in reduced virus neutralization by pre-existing antibodies,[6] allowing new global waves of infections to occur. The ancestral virus as well as the first variant lineages are no longer circulating in the human population to any meaningful extent.

**Immune response to SARS-CoV-2 variants**

Updated vaccines expand the breadth of the neutralizing antibody response, targeting emerging variants and boosting the immune response to the ancestral variant.[7] Furthermore preferential re-direction of the neutralizing antibody response towards currently circulating variants could be achieved by repeated exposure to the variants in the absence of simultaneous boosting with the ancestral virus.[8]

T-cell immunity appears to be directed mostly to conserved epitopes still present in the most recent VOCs.[9] To what extent boosting of T-cell immunity by the recently updated or previous versions of the COVID vaccines contributes to protection from the currently circulating strains is not established.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

**Updated vaccines and vaccine effectiveness**

In a population largely exposed to the virus and/or vaccines, the main focus of vaccination programmes is on single dose re-vaccination. Initially immune responses were boosted by re-vaccination with the ancestral virus vaccine but subsequent campaigns in Europe have used updated vaccines. The first of these updated vaccines were bivalent vaccines targeting a newly emerged Omicron VOC in addition to the ancestral virus. The latest updated vaccines are monovalent vaccines targeting only a more recent VOC, i.e. XBB1.5.

Vaccine effectiveness data have shown that updated vaccines are effective in preventing disease caused by contemporary viral strains. In a head-to-head comparison of ancestral virus vaccines and bivalent ancestral plus Omicron vaccines, recipients of bivalent vaccines had a 12 to 39% additional protection (depending on age) against SARS-CoV-2 Omicron disease.[10] In the same study, extended to include over 2 million participants, the relative vaccine effectiveness of a booster dose of the bivalent vaccines versus a booster dose of ancestral virus vaccines was 42.4% against SARS-CoV-2 infection and 81 to 85% against severe disease or death.[11] Emerging effectiveness data also show evidence of the protection against COVID-19 with the updated XBB.1.5 vaccines.[12,13,14]

**In conclusion**

EU Member States are recommending that people in the EU/EEA at increased risk for severe COVID-19 disease should be offered vaccination. To provide optimal protection against circulating strains, ETF recommends that the most recently updated COVID-19 vaccines should be used.

The ETF recognizes that, in the future, new COVID-19 vaccines may initially be authorised with a composition that does not match circulating VOCs but reflects the composition of the vaccines used in pre-licensure clinical trials. Whenever this occurs, similarly to influenza, the vaccines are expected to be updated before deployment to reflect recent and/or circulating SARS-CoV-2 variants.

The ETF will continue to evaluate SARS-CoV-2 epidemiological data and provide updated vaccine composition recommendations as appropriate.

**References**

[1] Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study [published correction appears in Lancet Infect Dis. 2023 Oct;23(10):e400]. Lancet Infect Dis. 2022;22(9):1293-1302. doi:10.1016/S1473-3099(22)00320-6

[2] ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants. The European Centre for Disease Prevention and Control. Published June 7, 2023. Accessed January 28, 2024. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-vaccines-composition-variants-statement-ECDC-EMA_0.pdf

[3] Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. Nat Rev Microbiol. 2023;21(6):361-379. doi:10.1038/s41579-023-00878-2

[4] Nextstrain. Genomic epidemiology of SARS-CoV-2 with subsampling focused globally over the past 6 months. Nextstrain. Updated January 28, 2024. Accessed January 28, 2024. https://nextstrain.org/ncov/gisaid/global/6m

[5] Martin DP, Lytras S, Lucaci AG, et al. Selection analysis identifies unusual clustered mutational changes in Omicron lineage BA.1 that likely impact Spike function. Preprint. bioRxiv. 2022;2022.01.14.476382. Published 2022 Jan 18. doi:10.1101/2022.01.14.476382

[6] Cele S, Jackson L, Khoury DS, et al. Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature*. 2022;602(7898):654-656. doi:10.1038/s41586-021-04387-1

[7] Winokur P, Gayed J, Fitz-Patrick D, et al. Bivalent Omicron BA.1-Adapted BNT162b2 Booster in Adults Older than 55 Years. *N Engl J Med*. 2023;388(3):214-227. doi:10.1056/NEJMoa2213082

[8] Yisimayi A, Song W, Wang J, et al. Repeated Omicron exposures override ancestral SARS-CoV-2 immune imprinting. *Nature*. 2024;625(7993):148-156. doi:10.1038/s41586-023-06753-7

[9] Müller TR, Gao Y, Wu J, et al. Memory T cells effectively recognize the SARS-CoV-2 hypermutated BA.2.86 variant. *Cell Host Microbe*. Published online January 3, 2024. doi:10.1016/j.chom.2023.12.010

[10] Chae C, Kim RK, Jang EJ, et al. Comparing the effectiveness of bivalent and monovalent COVID-19 vaccines against COVID-19 infection during the winter season of 2022-2023: A real-world retrospective observational matched cohort study in the Republic of Korea. *Int J Infect Dis*. 2023;135:95-100. doi:10.1016/j.ijid.2023.08.010

[11] Kim RK, Choe YJ, Jang EJ, et al. Comparative Effectiveness of COVID-19 Bivalent Versus Monovalent mRNA Vaccines in the Early Stage of Bivalent Vaccination in Korea: October 2022 to January 2023. *J Korean Med Sci*. 2023;38(46):e396. Published 2023 Nov 27. doi:10.3346/jkms.2023.38.e396

[12] Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness of BNT162b2 BA.4/5 bivalent mRNA vaccine against a range of COVID-19 outcomes in a large health system in the USA: a test-negative case-control study [published correction appears in *Lancet Respir Med*. 2023 Dec;11(12):e98]. *Lancet Respir Med.* 2023;11(12):1089-1100. doi:10.1016/S2213-2600(23)00306-5

[13] Hansen CH, Moustsen-Helms IR, Rasmussen M, Søborg B, Ullum H, Valentiner-Branth P. Short-term effectiveness of the XBB.1.5 updated COVID-19 vaccine against hospitalisation in Denmark: a national cohort study. *Lancet Infect Dis*. 2024;24(2):e73-e74. doi:10.1016/S1473-3099(23)00746-6

[14] van Werkhoven CH, Valk AW, Smagge B, et al. Early COVID-19 vaccine effectiveness of XBB.1.5 vaccine against hospitalisation and admission to intensive care, the Netherlands, 9 October to 5 December 2023. *Euro Surveill*. 2024;29(1):10.2807/1560-7917.ES.2024.29.1.2300703. doi:10.2807/1560-7917.ES.2024.29.1.2300703