https://doi.org/10.1038/s41591-023-02220-y

When to update COVID-19 vaccine composition

Rebecca Grant, Jilian A. Sacks, Priya Abraham, Supamit Chunsuttiwat, Cheryl Cohen, J. Peter Figueroa, Thomas Fleming, Paul Fine, David Goldblatt, Hideki Hasegawa, C. Raina MacIntrye, Ziad A. Memish, Elizabeth Miller, Sergio Nishioka, Amadou A. Sall, Samba Sow, Oyewale Tomori, Youchun Wang, Maria D. Van Kerkhove, Marie-Ange Wambo, Homa Attar Cohen, Samuel Mesfin, James R. Otieno, Lorenzo Subissi, Sylvie Briand, David E. Wentworth & Kanta Subbarao

Vaccines against different SARS-CoV-2 variants have been approved, but continued surveillance is needed to determine when the antigen composition of vaccines should be updated, together with clinical studies to assess vaccine efficacy.

Entering the fourth year of the COVID-19 pandemic, index virus-based[1] vaccines across several different platforms continue to provide high levels of protection against severe disease caused by all variants of SARS-CoV-2, including Omicron[2]. However, there has been continuous and substantial evolution of SARS-CoV-2 since the virus emerged, posing challenges to the ongoing public health response, including ensuring that vaccines continue to provide protection. In September 2021, the World Health Organization (WHO) established the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC)[3] to assess the public health implications of emerging SARS-CoV-2 variants of concern (VOC) on the performance of COVID-19 vaccines and to issue timely recommendations on proposed modifications to vaccine antigen composition. The TAG-CO-VAC has evaluated evidence to inform its advice on COVID-19 vaccine composition so far, but there remain challenges and evidence gaps that the scientific community needs to address to enable future, timely decisions on modifications to COVID-19 vaccine antigen composition.

The case for Omicron

The TAG-CO-VAC is an independent and multidisciplinary group of 18 experts[3]. As an advisory group, the TAG-CO-VAC recommends if and when updates to vaccine composition are needed so that they continue to safely provide protection against VOCs[4]. The current decision-making process of the advisory group is triggered by the designation of VOCs by the WHO, upon the advice of the Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE)[5], and consists of two steps (Fig. 1). The first step is to decide whether an update to vaccine composition should be considered, based on the nature and location of changes in the spike protein and associated antigenic effect, transmissibility or spread, and clinical severity of the VOC; and the effectiveness of current vaccines. The second step is an assessment of whether an updated vaccine composition is warranted to maintain protection against severe disease and death and elicit a greater breadth in immunological cross-reactivity against circulating and emerging VOCs. The key data considered are cross-neutralization of VOCs in the context of the emerging variant after infection or vaccination with current and alternative antigens in people with varied previous exposure with SARS-CoV-2 antigens.

Omicron was first designated as a VOC by the WHO in November 2021 and has more than 30 mutations in the spike protein compared to the index virus[6]. The first major lineage (B.1.1.529/BA.1) rapidly and relatively synchronously displaced all other circulating variants globally, including Delta VOC lineage variants (Fig. 2), with its transmission advantage largely driven by immune escape properties[7].

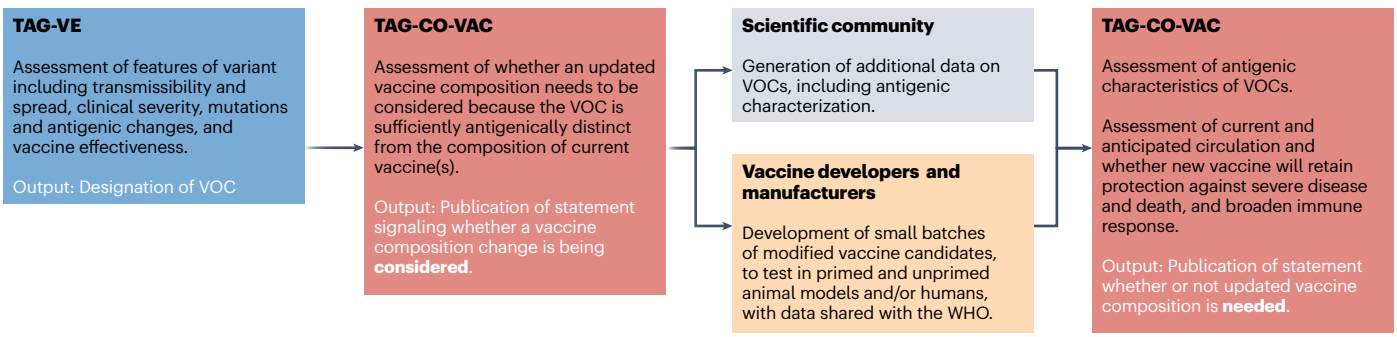

Fig. 1 | Decision-making process for vaccine updates. The current decision-making process of the WHO TAG-CO-VAC is shown.

Both pre-clinical data from animal models and clinical data in humans indicated that several mutations in the spike gene altered the antigenic properties of Omicron, as shown by the substantially lower Omicron-specific neutralizing antibody titers induced by infection or vaccination with the index virus or infection with earlier VOCs, such as Alpha and Delta.

Antigenic maps of data derived from neutralization assays using post-infection or post-vaccination human or animal sera show that of the VOCs so far, Omicron lineages are the most antigenically distant from the index virus[8,9] and the various descendent lineages of Omicron are antigenically more closely related to each other than to the index virus or previous VOCs. Antibody responses to Omicron depend on vaccination and infection status. Sera from previously naive (unprimed) individuals infected with Omicron showed strong antibody responses, but these Omicron-specific responses did not cross-react well with previous variants, including previous VOCs[10]. By contrast, individuals infected with the index SARS-CoV-2 virus, Alpha or Delta, or vaccinated (with a vaccine based on the index virus) and then subsequently infected with Omicron, mounted broadly cross-reactive antibody responses[10–12].

These data demonstrate the effect of Omicron on the performance of currently licensed COVID-19 vaccines and led the TAG-CO-VAC to publish an interim statement in June 2022[13]. The statement highlighted that currently licensed index virus-based vaccines continue to confer high levels of protection against severe disease caused by all VOCs, including Omicron, which is the primary objective of vaccination. However, given the antigenic distance and uncertainties of further viral evolution, it is likely that the effectiveness of the vaccine based on the index virus will reduce over time. The TAG-CO-VAC advised vaccine manufacturers and regulatory authorities to consider an update of vaccine antigen composition by including Omicron, as the most antigenically distinct SARS-CoV-2 VOC so far[8,9]. This updated vaccine would be used in a booster dose for those who have already received a primary series of COVID-19 vaccine to achieve greater breadth in the immune response against circulating and emerging variants[13]. Several vaccine manufacturers are developing updated COVID-19 vaccines and several mRNA-based vaccines containing descendent lineages of Omicron, in addition to the index virus, have been approved for emergency use by regulatory authorities[14–16].

In its advisory role, the TAG-CO-VAC will continue to issue timely recommendations on proposed modifications to vaccine antigen composition as needed. Some of the contextual challenges and evidence requirements that will inform future deliberations are described below and in Table 1.

Continuous virus evolution

There has been continuous and substantial evolution of SARS-CoV-2, especially in the spike protein that is the primary target of vaccines, since SARS-CoV-2 emerged in humans in December 2019. The WHO has classified five major viral lineages as VOCs[1]. There has also been increasing diversity within VOCs. For example, there are many descendent lineages among Omicron viruses, notably BA.1, BA.2, BA.4 and BA.5, which share many of the same spike protein changes. In addition, more recent descendant lineages including XBB and BQ.1, derived primarily from BA.2 and BA.5, respectively, have displaced earlier Omicron variants (Fig. 2), with their subtle fitness advantages driven by further immune escape and/or adaptations in receptor binding[17,18].

Sustained community transmission of SARS-CoV-2 applies selective pressure on the virus, leading to further evolution[5]. The trajectory and timeline of further virus evolution are uncertain, and delays between recommendations to update vaccine antigen composition and roll-out of updated vaccines are inevitable. Although index virus-based vaccines are still highly effective in preventing severe illness and death from Omicron, the rates of Omicron breakthrough infection among vaccinated people have been high, which suggests that although immunity induced by index virus-based vaccines is sufficient to prevent severe disease, it is not sufficient to prevent Omicron infection. The goal of an update in vaccine strain composition for COVID-19 is to broaden immunological cross-reactivity against newly emerged VOCs while preserving reactivity to current and earlier circulating strains, rather than an attempt to match the vaccine composition to what is circulating. This can be achieved as a booster dose and/or through the use of a multivalent vaccine[19,20].

Heterogeneity of immunological profiles

Immunological profiles are increasingly heterogeneous, and so the performance of an updated vaccine will vary depending on the nature and magnitude of previously acquired immunity in each person. There are now individuals who have been previously infected, or previously vaccinated with a primary series and/or booster doses(s) on different platforms, with various spike protein antigens (derived from the index virus, BA.1 or BA.5); as well as individuals who have been infected and then vaccinated, and individuals who have been vaccinated and then infected. Therefore, future vaccine composition decisions will need to be made in the face of increasingly complex and heterogeneous data.

mRNA platform bias

Index virus-based vaccines are available across different platforms, including mRNA-based, viral vectored and inactivated, and they elicit robust systemic immunity that protects against severe disease caused by all variants, including Omicron. However, a preponderance of vaccine effectiveness data is derived from mRNA-based vaccines[2]. So far, available vaccines with an updated composition are predominantly mRNA-based, although others are likely to follow. The paucity of data from vaccines other than those based on mRNA technology is problematic, given the diversity in vaccines in use globally.

Genomic and phenotypic assessment

Since January 2022, there has been a substantial reduction in SARS-CoV-2 diagnostic testing and sequencing globally, as well as in the number of SARS-CoV-2 genome sequences submitted to open access databases, such as GISAID EpiCov. This probably reflects myriad factors, including changes in testing strategies that result in fewer and less representative samples available for genomic sequencing, and cost sustainability challenges. Sustained global virological surveillance that includes quality, geographically diverse and timely genetic sequencing (with sequence availability 3–4 weeks from specimen collection) is needed to understand the evolution of the virus, particularly the spike gene, and to inform future decisions on vaccine antigen composition[21].

The reduction in availability of genetic sequence data will delay the identification and phenotypic assessment of new variants needed to understand the effect of variants on vaccine effectiveness[5] and therapeutic agents. Therefore, efforts to sustain SARS-CoV-2 genetic surveillance capacity must be accompanied by phenotypic analysis of the variants.

Decisions on vaccine antigen composition require extensive evaluation of the neutralizing capacity of well-characterized human convalescent sera, which are obtained from naive and previously vaccinated individuals, including after infection with VOCs and descendent

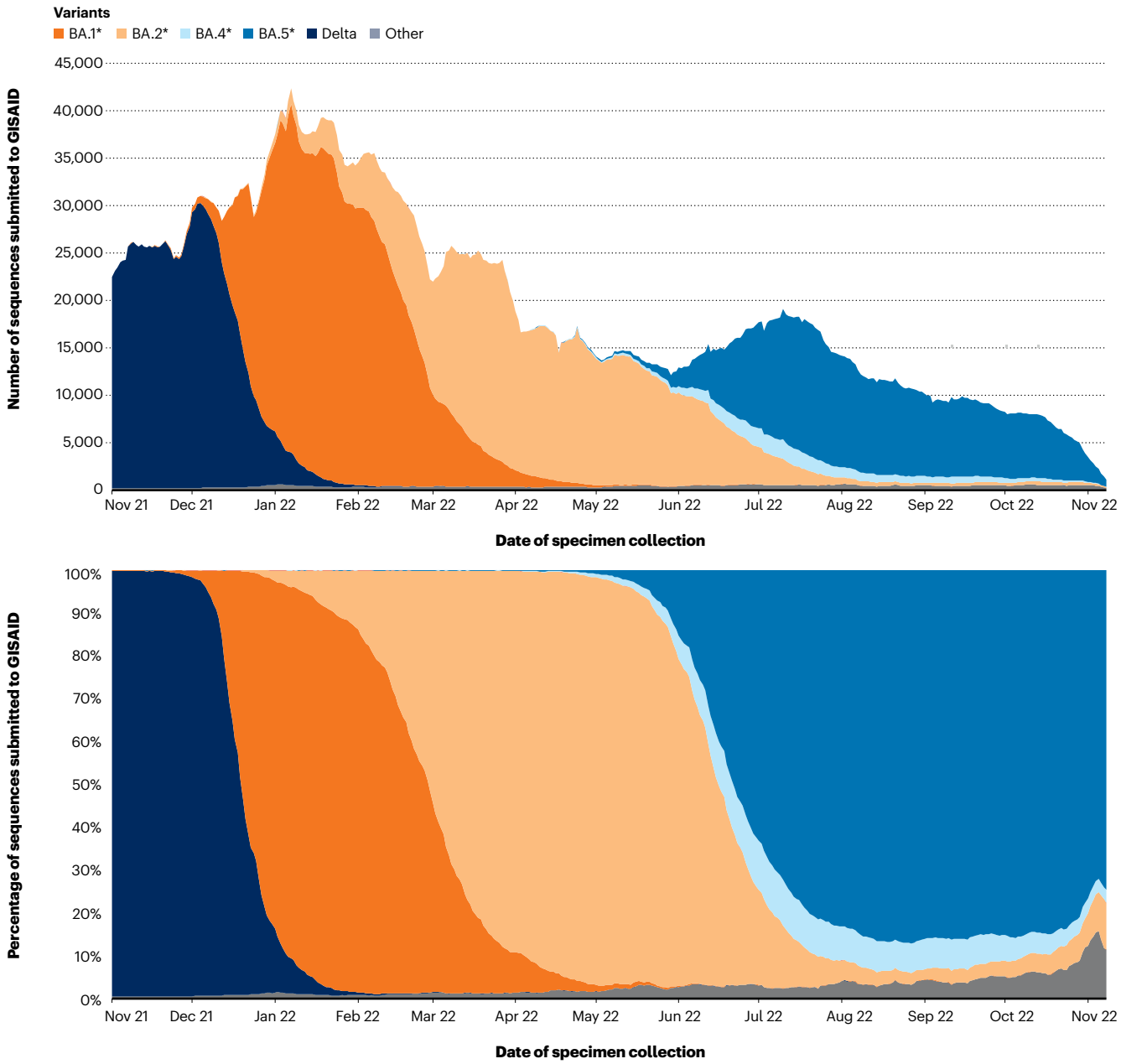

Fig. 2 | Evolution of SARS-CoV-2 lineages. Number (top) and proportion (bottom) of Omicron descendent lineages, Delta descendant lineages or other lineages submitted to GISAID from November 2021 to November 2022. 'Other' is inclusive of unassigned lineages, recombinants, non-Omicron and non-Delta lineages.

lineages, well-characterized panels of human monoclonal antibodies, and sera from naive, infected and vaccinated animal models. Neutralizing antibodies are generally studied because they are a strong predictor of protection, and because the assays are amenable to harmonization. However, T cells and other aspects of the immune response also warrant attention. In addition, assessments of viral fitness and pathogenicity, as well as the performance of candidate vaccines in animal models are also important. Such data should be generated from samples that are geographically representative, given the increasing heterogeneity of the human immune landscape and the use of different vaccines globally. Continued investment in these crucial studies, with harmonized methods and data analyses, is needed to enable comprehensive and timely decision-making.

Clinical outcome data

The rollout of variant-containing vaccines should be accompanied by systematic collection of data and samples to assess the breadth and magnitude of the elicited immune responses to estimate vaccine

Table 1 | Public health evidence priorities to inform vaccine antigen composition

Objective	Priority actions
Sustain global genetic surveillance and timely data submission	Timely sequencing of geographically diverse samples submitted to open access databases.
Strengthen antigenic analyses of variants	Evaluation of VOCs (including relevant descendent lineages) in neutralization assays using harmonized methods with: well-characterized human convalescent sera from naive, previously vaccinated and previously infected individuals; well-characterized panels of human monoclonal antibodies; and well-characterized sera from infected and previously vaccinated animal models. Reactivity in methodologically harmonized T-cell based assays should be done, where feasible.
Sustain in vitro virological assessments of variants	Continued assessments of viral fitness and pathogenicity of emerging variants.
Assess immunogenicity of variant-containing vaccine candidates	Evaluation of immunogenicity of variant-containing vaccine candidates and vaccines using harmonized methods: in animal models (naive and primed); in sera from recipients of variant-containing vaccines with different antigen composition (such as Omicron BA.1 versus BA.4/BA.5) as a booster[a] across different vaccine formulations (including bivalent and monovalent) and platforms; and in sera from recipients of a variant-containing vaccine administered as a primary series, where possible.
Evaluate vaccine effectiveness of variant-containing vaccines	Standardized generation of clinical data to estimate absolute and relative vaccine effectiveness for different outcomes, such as infection, symptomatic disease, severe disease and death across different vaccine platforms and composition (if applicable).
Support further research and development for COVID-19 vaccines	Development of vaccines that elicit greater mucosal immunity.

[a]It will be increasingly rare for individuals to be unvaccinated or naive to SARS-CoV-2 so it is acknowledged that vaccines with updated composition will most readily be administered as booster doses.

effectiveness. Real-world studies are unlikely to inform the initial decisions of TAG-CO-VAC, owing to the time they take. However, specific analyses will enable retrospective reviews of the impact of vaccine composition recommendations made by the TAG-CO-VAC. For example, a comparison of the cross-reactivity of antibodies in panels of sera from recipients of a booster dose of bivalent index plus Omicron BA.1, bivalent index plus Omicron BA.4/5, or monovalent index virus-based vaccine, should be undertaken by several reference labs using a range of antibody assays. Ideally, this would fall within a public health research framework using standardized design methods and data collection tools for clinical and immunological outcome data, enabling the evaluation of the comparative performance of variant-containing vaccines, as well as assessing the public health benefit of such vaccines. Such clinical evaluations will provide valuable data to inform vaccination policy decisions on variant-containing vaccines, including those issued by the WHO Strategic Advisory Group of Experts on Immunization (SAGE).

Further vaccine platforms

The current approach to vaccine antigen composition may not be sustainable in the long term, given the length of time for vaccine development, the paucity of surveillance data globally and the regulatory requirements in different countries. Enhanced mucosal immunity may improve protection against infection and transmission of SARS-CoV-2 (refs. [22,23]), and the TAG-CO-VAC encourages vaccine development in this area[24]. In addition, novel vaccine platforms that elicit broader protection against antigenically diverse viruses are needed to address the challenges of the continuous evolution of SARS-CoV-2, but also the risk of other emerging coronaviruses with pandemic potential. Future development of vaccines that protect against all SARS-CoV-2 variants, pan SARS, and all sarbecoviruses will be technically challenging, but could offer protection from diverse coronaviruses, including those that are enzootic in many animal species[25].

Rebecca Grant[1,24], Jilian A. Sacks[1,24], Priya Abraham[2], Supamit Chunsuttiwat[3], Cheryl Cohen[4,5], J. Peter Figueroa[6], Thomas Fleming[7], Paul Fine[8], David Goldblatt[9], Hideki Hasegawa[10], C. Raina MacIntrye[11], Ziad A. Memish[12,13], Elizabeth Miller[14], Sergio Nishioka[15], Amadou A. Sall[16], Samba Sow[17], Oyewale Tomori[18], Youchun Wang[19], Maria D. Van Kerkhove[1], Marie-Ange Wambo[1], Homa Attar Cohen[20], Samuel Mesfin[20], James R. Otieno[1], Lorenzo Subissi[1], Sylvie Briand[1] ✉, David E. Wentworth[21,25] & Kanta Subbarao[22,23,25]

[1]Department of Epidemic and Pandemic Preparedness and Prevention, World Health Organization, Geneva, Switzerland. [2]Indian Council of Medical Research - National Institute of Virology, Pune, India. [3]Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand. [4]Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa. [5]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. [6]University of West Indies, Mona, Jamaica. [7]Department of Biostatistics, University of Washington, Seattle, WA, USA. [8]London School of Hygiene and Tropical Medicine, London, UK. [9]Great Ormond Street Institute of Child Health, University College London, London, UK. [10]Center for Influenza and Respiratory Virus Research, National Institute of Infectious Diseases, Tokyo, Japan. [11]Biosecurity Program, The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia. [12]Research and Innovation Centre, King Saud Medical City, Ministry of Health and College of Medicine, Alfaisal University, Riyadh, Saudi Arabia. [13]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA. [14]Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK. [15]Independent Consultant, Brasilia, Brazil. [16]Institut Pasteur de Dakar, Dakar, Senegal. [17]Centre for Vaccine Development, Ministry of Health, Bamako, Mali. [18]African Centre of Excellence for Genomics of Infectious Diseases, Redeemer's University, Ede, Nigeria. [19]Institute for Biological Product Control, National Institutes for Food and Drug Control, Beijing, China. [20]Department of Acute Response Coordination, World Health Organization, Geneva, Switzerland. [21]Influenza Division, US Centers for Disease Control and Prevention, Atlanta, GA, USA. [22]WHO Collaborating Centre for Reference and Research on Influenza, The Peter Doherty Institute for Infection and Immunity, Melbourne, Victoria, Australia. [23]Department of Microbiology and Immunology, The University of Melbourne, Melbourne, Victoria, Australia. [24]These authors contributed equally: Rebecca Grant, Jilian A. Sacks.

[25]These authors jointly supervised this work: David E. Wentworth, Kanta Subbarao.

✉e-mail: briands@who.int

Published online: 20 February 2023

References

1. World Health Organization. https://www.who.int/activities/tracking-SARS-CoV-2-variants (accessed August 2022).
2. Higdon, M. M. et al. *Lancet Infect. Dis.* **22**, 1114–1116 (2022).
3. World Health Organization. https://www.who.int/groups/technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac) (accessed August 2022).
4. World Health Organization. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines (accessed August 2022).
5. Subissi, L. et al. *Nat. Med.* **28**, 1110–1115 (2022).
6. Viana, R. et al. *Nature* **603**, 679–686 (2022).
7. Iketani, S. et al. *Nature* **604**, 553–556 (2022).
8. Wilks, S. H. et al. Preprint to bioRxiv. https://doi.org/10.1101/2022.01.28.477987 (2022).
9. Rössler, A. et al. *Nat. Comm.* **13**, 7701 (2022).
10. Walls, A. C. et al. *Cell* **185**, 872–880.e3 (2022).
11. Mykytyn, A. Z. et al. *Sci Immunol.* **7**, eabq4450 (2022).
12. Richardson, S. I. et al. *Cell Host Microbe* **30**, 880–886 (2022).
13. World Health Organization. https://www.who.int/news/item/17–06–2022-interim-statement-on–the-composition-of-current-COVID-19-vaccines (accessed August 2022).
14. US Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use (accessed September 2022).
15. Medicines and Healthcare products Regulatory Agency. https://www.gov.uk/government/news/pfizerbiontech-bivalent-covid-19-booster-approved-by-uk-medicines-regulator (accessed November 2022).
16. European Medicines Agency. https://www.ema.europa.eu/en/news/adapted-vaccine-targeting-ba4-ba5-omicron-variants-original-sars-cov-2-recommended-approval (accessed October 2022).
17. Khan, K. et al. *Nat. Commun.* **13**, 4686 (2022).
18. Cao, Y. et al. *Nature* **608**, 593–602 (2022).
19. Chalkias, S. et al. *Nat. Med.* **28**, 2388–2397 (2022).
20. Chalkias, S. et al. *N. Engl. J. Med.* **387**, 1279–1291 (2022).
21. Han, A. et al. *Nat Genet.* **55**, 26–33 (2023).
22. Tang, J. et al. *Sci. Immunol.* **7**, eadd4853 (2022).
23. Topol, E. J. et al. *Sci. Immunol.* **7**, eadd9947 (2022).
24. World Health Organization. https://www.who.int/news/item/08–03–2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition-(tag-co-vac)-08-march-2022 (accessed August 2022).
25. Morens, D. M. et al. *N. Engl. J. Med.* **386**, 297–299 (2022).

Competing interests

The findings and conclusions in this report are those of the authors and do not necessarily represent the views and official policies of their affiliated institutions, including the US CDC and the US government. As per the requirements of WHO advisory groups, all members of the TAG-CO-VAC have disclosed to the WHO any interests of a personal, professional, financial, intellectual or commercial nature that may give rise to a perceived or direct conflict of interest. No conflicts of interest have been identified.