Good practice statement on the use of variant-containing COVID-19 vaccines

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World Health Organization

Background

This Good practice statement has been developed on the basis of advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on 5 October 2022, and was updated on 20 February 2023 based on additional evidence and advice by SAGE.

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 Covid-19 Working Group webpage. This guidance should be considered along with the broader COVID-19 policy advice to WHO member states and in particular the advice on how to reach the COVID-19 vaccination targets.

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

This Good Practice Statement summarizes current evidence on variant-containing vaccines and provides guidance on their use in the context of the continued availability of ancestral virus-only (monovalent) COVID-19 vaccines.

To date, the following variant-containing vaccines have been authorized for the use as booster vaccine: the variant-containing bivalent mRNA vaccines by Pfizer-BioNTech and Moderna, and the monovalent Sanofi-GSK Vidprevtyn Beta (CoV2 preS dTM-AS03 (B.1.351)) vaccine against COVID-19.

Countries that achieved high levels of vaccine uptake in priority groups have seen reductions in rates of COVID-19-related hospitalizations and deaths. Most countries have now relaxed many or all public health and social measures with a consequential rise in community infection rates *(1, 2)*. However, a concomitant rise in rates of severe disease and death has been much less marked, especially among persons who have been vaccinated. The longer-term impacts of post-COVID-19 conditions due to increased infection rates are yet to be fully understood and quantified. Questions remain as to the evolution of the virus, the characteristics of new variants of concern[1], or descendent lineages from current variants, that will shape the trajectory of the pandemic and when SARS-CoV2 will become an endemic virus.

Currently, the Omicron variant (including its descendent lineages BA.1, BA.2, BA.4, BA.5, BQ.1, XBB and others) is the predominant variant globally. It is associated with less severe disease compared to the ancestral strain (also known as the index virus or original strain) and pre-Omicron variants. However, as Omicron is more transmissible and circulates faster, it is associated with large numbers of hospitalizations and deaths due to the resulting high incidence in the community, although wide variations in testing and surveillance practices make causal attribution challenging. However, with increasing population-level immunity due to vaccination, infection-induced immunity or both, cases, hospitalizations and deaths have been declining, and the acute phase of the pandemic is coming to an end, with periodic waves of infections still being observed.

Of the different viral variants that have caused infection waves, Omicron is antigenically the most distant from the ancestral strain and is associated with greater immune evasion than other variants. While vaccine effectiveness is still relatively high and well-maintained over time against severe disease, protection against mild disease and infection declines rapidly with time since the last vaccination. As effectiveness declines, older adults and people with comorbidities continue to be at greatest risk of morbidity and mortality due to the Omicron variant; even a minor decrease in vaccine effectiveness in such vulnerable persons results in increased risk of severe disease and death. Boosting with existing vaccines (which contain the ancestral virus) provides a higher degree of protection against severe disease with variants of concern than primary vaccination schedules alone *(3, 4)*.

In an effort to broaden and further enhance protection against circulating and emerging variants, and consistent with the interim statement issued by the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) *(5, 6)*, a number of manufacturers have developed variant-containing vaccines, including a number of bivalent formulations that retain the ancestral virus.

Four bivalent variant-containing vaccines are currently authorized as booster doses by various stringent regulatory authorities (SRAs). Pfizer-BioNTech and Moderna have each developed two of these variant-containing vaccines – one each containing the ancestral strain of the SARS-CoV-2 virus and the Omicron BA.1 subvariant, and one each containing the ancestral strain of the SARS-CoV-2 virus and the Omicron BA.5 subvariant.

The European Medicine Agency`s (EMA's) Emergency Task Force (ETF) has recently considered that adapted mRNA bivalent vaccines targeting the original/ancestral strain and Omicron BA.5 subvariants of SARS-CoV-2 may be used for primary (initial) vaccination*(7)*.

EMA has given full marketing authorization for the monovalent variant-containing vaccine developed by Sanofi and GSK, the CoV2 preS dTM-AS03 (B.1.351) as a booster vaccine for the use in persons aged 18 years and above. The CoV2 preS dTM-AS03 (B.1.351) is a recombinant protein-based vaccine that consists of stabilised pre-fusion spike protein of the B.1.351 (Beta) strain (trimer of the SARS-CoV-2 B.1.351 Spike protein with deletion of the transmembrane domain and addition of a trimerization motif (T4 foldon)) produced in a baculovirus expression system developed against SARS-CoV-2 (B.1.351 strain) adjuvanted with AS03 (an oil-in-water emulsion containing squalene, α tocopherol and polysorbate 80). It can be used once as a booster in people who have already received an mRNA or adenoviral vector COVID-19 vaccine. For more information on CoV2 preS dTM-AS03 (B.1.351) as a booster vaccine *(8)*.

Methods

Data were identified through various sources and in consultation with the respective compagnies (see below). No systematic search for literature was performed. The available evidence that served as the basis for this guidance is outlined below, and was obtained from scientific publications, preprints, assessment reports from regulatory authorities and materials presented to the US FDA and ACIP, and EMA, and data presented directly by the companies Moderna, Pfizer-BioNTech and Sanofi Pasteur to the SAGE Working Group. The available supportive body of evidence was deemed not to lend itself to formal GRADE-ing of evidence due to the absence of direct clinical and real-world data demonstrating the efficacy or effectiveness of variant-containing vaccines. Risk of bias assessment was deemed not feasible, as only data from immunogenicity studies were available. Nevertheless, SAGE considered the available indirect data from immunogenicity studies to be sufficient to proceed with issuing this Good Practice Statement on variant-containing vaccines. All studies were weighed equally, irrespective of publication status (pre-print or full publication), though potential limitations were taken note of and considered by the SAGE Working Group. This document contains off-label recommendations[a]. This statement will be updated once more data become available.

Evidence synthesis on the immunogenicity of variant-containing mRNA vaccines

Some stringent regulatory authorities and WHO *(9, 10)* have established immunological criteria for authorization of variant-containing vaccines, including non-inferiority (compared to the already authorized vaccine) and superiority (compared to the already authorized vaccine) of the variant-specific response contained in the vaccine. All authorized variant-containing vaccines have met the superiority criteria against Omicron variant and the non-inferiority criteria against the ancestral strain, as provided by the manufacturers.

Bivalent ancestral/Omicron BA.1 developed by Pfizer-BioNTech:

A randomized controlled trial evaluated a fourth dose of Pfizer ancestral (30 mcg) or Pfizer ancestral/Omicron BA.1 (15/15 mcg) in persons who had received their third dose ("monovalent" recipients ranged from 5.3 to 13.1 months previously versus "Bivalent" recipients who ranged from 4.7 to 11.5 months previously*) (11)*. The study was conducted

[a] The recommendations contained in this paper 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 paper 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.

in adults older than 55 years (N=610) who had received three prior doses of the monovalent Pfizer vaccine. The primary objective of the study was to assess superiority with respect to the level of neutralizing antibody titre and noninferiority with respect to the sero-response rate of the anti-Omicron immune response induced by a dose of Pfizer ancestral/Omicron bivalent BA.1 relative to the response elicited by a dose of the monovalent mRNA vaccine.

The interim analysis included sero-response rates and geometric mean ratio (GMR) – defined as the neutralizing antibody titres against Omicron BA.1 elicited by the Original/Omicron BA.1 divided by those elicited by the Original vaccine 1 month (median 1.7 months) after the fourth dose. Sero-response was defined as achieving ≥ 4-fold rise from baseline (before the study vaccination). The difference in percentages of participants who achieved sero-response to the Omicron variant between the Pfizer Original/Omicron BA.1 group (71.6%) and the Pfizer Original group (57%) was 14.6% (2-sided 95% CI: 4.0%, 24.9%). Thus, noninferiority of sero-response was met. Analysing neutralization of BA.1, a GMR of 1.56 (95% CI 1.17, 2.08) was found for the bivalent product compared to the original booster, suggesting superiority of the Pfizer mRNA ancestral/Omicron BA.1 bivalent vaccine over the monovalent vaccine*(11)*.

Bivalent ancestral/Omicron BA.1 vaccine developed by Moderna:

One clinical trial (N=814) conducted in adults over the age of 18 years who had received three doses of mRNA-1273 vaccine provides clinical data on a booster dose of the original vaccine (mRNA-1273) versus the mRNA-1273 bivalent Original/Omicron BA.1 (50 mcg), termed mRNA-1273.214. The median time interval between the third and the fourth doses was 4.4 months (range 3.0–10.2 months) in the group that received a fourth dose of the original vaccine, and 4.5 months (range 2.9–13.4) in the group that received the bivalent vaccine. A non-inferior sero-response rate was elicited against the ancestral strain with a difference in sero-response rate of 1.5 (-1.1, 4.0) and a superior neutralizing antibody response against the Omicron subvariant BA.1 compared with a booster dose of the original mRNA-1273 vaccine with a GMR of 1.78 (97.5% CI 1.56, 2.04) 28 days after vaccination *(12)*.

Further testing using other variants of concern (Alpha, Beta, Delta, Gamma and Omicron BA.4/5) was also investigated to determine the breadth of the immune response elicited by the novel bivalent vaccine. Binding antibody titres at day 29 after the second booster (i.e. dose four) resulted in GMR as follows: Alpha 1.17 (95% CI 1.09, 1.24), Beta 1.14 (95% CI 1.07, 1.22), Delta 1.10 (1.03, 1.16) and Gamma 1.16 (1.09, 1.24). Higher neutralizing antibodies were also found against BA.4/5 with an elicited GMR of 1.68 (95% CI 1.52-1.84). These data indicate statistically higher binding antibody titres elicited by the bivalent booster compared to the ancestral virus-containing booster. This trend was also seen with the neutralization antibody titres in persons over the age of 65 years.

Bivalent ancestral/Omicron BA.5 developed by Pfizer-BioNTech:

Data derived from immunogenicity studies in mice, where the mice were boosted (third dose) using either the ancestral virus-containing vaccine or the bivalent BA.5-containing vaccine, met superiority criteria (approximately a 2.6-fold increase, neutralization titres of 2075 compared to 800) *(13)*. Further human immunogenicity data on Pfizer Original/Omicron BA.5 are being generated but are not yet available.

Bivalent ancestral/Omicron BA.5 developed by Moderna:

Data derived from immunogenicity studies in mice, where the mice were boosted (third dose) using either the ancestral virus-containing vaccine or the bivalent Original/Omicron BA.5 vaccine met superiority criteria (approximately 4.5-fold increase, with titres of 267 compared to 73 *(14)*. Further human immunogenicity data are being generated.

Benefit of bivalent versus monovalent mRNA COVID-19 vaccines as booster doses

Neutralization levels have been shown to be predictive of immune protection *(15, 16)*. Modelling based on neutralization levels shows that the largest proportion of the benefit comes from receiving any booster at all (including an ancestral-based booster) *(16)*. It is inferred from these neutralization data that the use of a variant-containing vaccine may provide a modest additional increase in protection against symptomatic illness and severe disease, especially if the vaccine matches the strains in circulation. Analysing data from various reports that included a direct comparison of immunogenicity of an ancestral-based vaccine with a variant-modified vaccine, an ancestral-based vaccine increased neutralisation titres by a mean of 11-fold from pre-booster titres (95%CI 8-15.2) *(17)*. Variant-modified vaccines on average produced 1.51-fold [95% CI 1.4-1.6] higher titres than the equivalent ancestral-based vaccine ($p<0.0001$). Boosting was higher against homologous antigens (1.75 vs. 1.31-fold, $p=0.00032$) *(18)*.

Data indicate that the immune responses induced by such Omicron subvariant-containing vaccines covers other Omicron subvariants beyond the vaccine-specific strains *(17)*.

Observational population-based data show that bivalent booster doses provide additional protection against symptomatic SARS-CoV-2 infection during a period when Omicron variant BA.5 lineages and their sub-lineages predominated, although the studies did not conduct a head-to-head comparison with the ancestral-virus monovalent vaccine *(19)*.

To date, there are no head-to-head comparisons between mRNA bivalent boosters and boosters with other platforms or heterologous schedules.

Benefit of the BA.5 versus BA.1 mRNA vaccines

In a period of BA.5 subvariants predominance, the comparative vaccine effectiveness of the bivalent Pfizer and Moderna BA.5 was compared with the BA.1 mRNA-booster vaccines given as a fourth dose in Denmark, Finland, Norway, and Sweden. Bivalent BA.5 boosters conferred moderately greater vaccine effectiveness against Covid-19 hospitalization compared with bivalent BA.1 boosters, which can be explained by the fact that the BA.5 variant was circulating at the time of vaccine roll-out(https://www.medrxiv.org/content/10.1101/2023.01.19.23284764v1).

Bivalent ancestral/Omicron mRNA vaccines in unvaccinated persons (primary series)

Mouse vaccination-challenge models have been used to study the immune responses induced by bivalent COVID-19 vaccines as a primary series. Robust serum immunoglobulin binding was observed against Wuhan, BA.1 and BA.5 spike proteins at 2 weeks post priming with 2 doses of Moderna bivalent Omicron BA.1 or BA.5 vaccines *(7)*. Bivalent vaccines induced a broader neutralising antibody response compared to administration of each of the mRNA constituents when given alone. Immunisation of SARS-CoV-2 naïve mice with the Pfizer/BioNTech bivalent mRNA vaccine encoding both the Wuhan and the Omicron BA.5 spike proteins induced neutralising activity against Omicron subvariants (BA.1, BA.2, BA.2.12.1, and BA.5) as well as previous variants of concern (Wuhan, Alpha, Delta). These non-clinical data suggest that a primary series with bivalent vaccines could induce broad immune responses in SARS-CoV-2 naïve humans.

The paucity of seronegative persons (i.e. with no serological evidence of prior natural infection and no history of vaccination) poses challenges to generating clinical data to support rapid updating of strains in vaccines indicated for use as a primary series. Preliminary data in humans suggest that SARS-COV-2 Omicron BA.5 infection in unvaccinated subjects induces a broader serum neutralisation capacity (i.e. against D614G, Beta, Delta, BA.1, BA.2 and BA.4) compared to Omicron BA.1 infection as measured by a pseudovirus neutralisation assay*(17)*. In contrast, preliminary clinical data with a monovalent Omicron BA.1 mRNA vaccine suggest that it elicited a very limited cross-neutralisation immune response.

Taken together, these non-clinical and clinical data suggest that a primary series with bivalent ancestral/Omicron BA.4/5 vaccine induce broad immune responses in SARS-CoV-2 naïve humans.

On 26 January, 2023, the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) unanimously voted to recommend replacing the previously authorized COVID-19 vaccination regimen with the bivalent version of the vaccine for those who are receiving a primary COVID-19 vaccine*(20)*. EMA`s Emergency Task Force considers it acceptable that the bivalent original/Omicron BA.5 mRNA vaccines currently authorised in the European Union/European Economic Area for boosting may also be used to deliver a primary series should this become necessary to support vaccination campaigns *(7)*. For the time being, the use of the BA.5 bivalent vaccine is considered off-label use.

Monovalent VidPrevtyn Beta (CoV2 preS dTM-AS03 (B.1.351)) vaccines in vaccinated persons (use as a booster)

The CoV2 preS dTM-AS03 (B.1.351), a monovalent recombinant protein-based vaccine with the Spike Protein of the B.1.351 strain, showed geometric mean titers (GMT) ratio of neutralizing antibodies of 2.53 (95% CI: 1.80–3.57) for CoV2 preS dTM-AS03 (B.1.351) (n=54) versus BNT162b2 (n=60) against the Omicron BA.1 strain and a GMT ratio of 1.43 (95% CI: 1.06–1.94) against the ancestral strain at day 28, as a heterologous booster in persons primed with BNT162b2 *(8)*. The seroconversion at 28 day was 100% (95% CI: 92.9–100) for the CoV2 preS dTM-AS03 (B.1.351) group and 96.2% (95% CI: 87.0–99.5) for the BNT162b2 group, against the Omicron BA.1 strain; (difference 3.8; (95% CI: -3.9–12.8) and was 96.2% (95% CI: 87.0–99.5) for the CoV2 preS dTM-AS03 (B.1.351) group and 93.2% (95% CI: 83.5–98.1) for the BNT162b2 group, against the ancestral strain (difference 3.0; (95% CI: -6.9–12.8).

European Medicine Agency authorized Vidprevtyn Beta as a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 18 years and older. It can be used once as a booster in people who have already received an mRNA or adenoviral vector COVID-19 vaccine.

Other variant-containing vaccines

To date, available vaccines with an updated antigen composition are predominantly mRNA-based, and most of the vaccine effectiveness data are derived from mRNA vaccines. The paucity of data from vaccines other than those based on mRNA technology is problematic given the diversity of vaccines in use globally.

Safety of variant-containing vaccines

Reactogenicity and safety data from the human immunogenicity studies using the variant-containing mRNA vaccines as a booster are comparable with the safety data for the primary series and boosters with ancestral virus-containing vaccines. This would suggest that the safety profiles of all variant-containing vaccines can be expected to be comparable to the already approved mRNA vaccines, for which a large amount of data is available from hundreds of millions of vaccinated people.

For the CoV2 preS dTM-AS03 (B.1.351) vaccine, safety was evaluated from the phase 3 study for 705 participants that received the CoV2 preS dTM-AS03 (B.1.351) vaccine as a booster with a median safety follow-up of 145 days. No serious adverse events were observed. The median duration of local and systemic adverse reactions was 1 to 3 days with most occurring within 3 days following vaccination and being mild to moderate in severity (21). Supportive safety data from 7093 participants 18 years of age and older who received the adjuvanted vaccine as a primary series or as a booster vaccine as well as combining with those that received the bivalent (B.1.351 + D614) vaccine and the AS03 adjuvant in general, showed a similar profile to the 705 study cohort (21). The adjuvant AS03 is assumed to enhance the quality and quantity of the immune response by promoting a more balanced T-helper (Th)1/Th2 response and has been used in several vaccines including influenza vaccines.

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Despite considerable virus evolution, the original COVID-19 vaccines, based on the ancestral virus, maintain relatively high vaccine effectiveness against severe disease in the context of the Omicron variant and its descendent lineages, in particular when booster doses have been administered. However, some immune evasion has been observed in the context of the Omicron variants that are currently circulating. Recently-authorized bivalent variant-containing vaccines may broaden and enhance the immune response to the Omicron and its descendent lineages when administered as a booster dose *(7)*. As data become available for other variant-containing vaccines, SAGE will review such data and will update this guidance as appropriate.

Primary series:

For the primary series, any of the WHO Emergency Use Listing (EUL) COVID-19 vaccines can be used.

WHO considers it acceptable that the bivalent original/Omicron BA.5 mRNA vaccine currently authorised for boosting may also be used to deliver a primary series should this become necessary to support vaccination campaigns. However, for the time being, this use is considered off-label.

Achieving very high and equitable vaccine coverage rates of the primary series globally remains the highest priority, particularly among groups that are at higher risk of severe disease and death *(5)*. Increasing the primary vaccination series coverage rate has a greater impact on reducing hospitalizations and deaths per dose than use of equivalent vaccine supply to increase the booster dose coverage rate.

Booster doses:

Following vaccination with the primary series, protection against infection or mild disease declines quite rapidly and so, to a much lesser extent, does protection against severe disease. A first booster is part of the initial vaccine series. With the greater immune evasion of Omicron and its descendent sub-lineages, the use of further booster doses of vaccines may be justified to restore vaccine effectiveness, particularly for persons at highest risk of developing severe COVID-19.

WHO recommends that any of the WHO EUL COVID-19 vaccines or authorized variant-containing vaccines can be used for booster vaccination.

Bivalent variant-containing vaccines used as booster doses may have modestly enhanced vaccine effectiveness compared with the monovalent original vaccines at a time of circulating Omicron sub-lineages. However, there are no head-to-head comparisons for the extent of vaccine effectiveness for bivalent mRNA vaccines compared with other platforms or heterologous schedules. When deciding which vaccine to use as booster, each country needs to take into account access to such vaccines and costs. Countries should not delay implementing booster doses while waiting for access to variant-containing vaccines. There is greater benefit in ensuring that persons at high risk of developing severe COVID-19 receive a booster, rather than extending this interval in anticipation of a variant-containing vaccine.

There is increasing evidence that boosters using a different COVID-19 vaccine platform from that used for the primary series (heterologous boosting) may provide superior immunogenicity to use of a homologous booster *(7, 17, 22, 23)* .

For countries considering heterologous boosters, WHO recommends the following on the basis of equivalent or favourable immunogenicity or effectiveness for heterologous versus homologous schedules, depending on product availability *(19, 21):*

- countries implementing WHO EUL inactivated vaccines for initial doses may consider using WHO EUL vectored or mRNA vaccines for subsequent doses;
- countries implementing WHO EUL vectored vaccines for initial doses may consider using WHO EUL mRNA vaccines or protein subunit vaccines for subsequent doses;
- countries implementing WHO EUL mRNA vaccines for initial doses may consider using WHO EUL vectored vaccines or protein subunit vaccines for subsequent doses.

When deciding to implement second boosters or further boosters, each country needs to take into account the age structure of the population, the current and potential burden of severe COVID-19 disease and hospitalizations, the availability and access to vaccines, including variant-containing vaccines, as well as opportunity costs, coverage rates with the primary series and community acceptance of boosters.

General considerations

Vaccination should be offered regardless of a person's history of symptomatic or asymptomatic SARS-CoV-2 infection. Vaccination of recently-infected persons is not known to be associated with increased adverse effects. WHO does not recommend pre-vaccination screening for prior infection. Individuals who have had SARS-CoV-2 infection (confirmed by PCR or antigen test) could consider delaying the booster dose by 4–6 months; however, such considerations should not interfere with the programmatic roll-out of booster doses. The optimal interval for vaccination after documented previous infection is currently not known. Hybrid immunity has been shown to increase the magnitude and duration of vaccine effectiveness *(24)*.

WHO recommends that countries consider co-administration of COVID-19 vaccines (including variant-containing vaccines) with seasonal influenza vaccines, whenever epidemiologically justified. 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, or any time before or after, other vaccines for adults and adolescents, including live attenuated, inactivated, adjuvanted, or non-adjuvanted vaccines (30). When administered concomitantly, the vaccines should be injected in separate sites, preferably different extremities. Continued pharmacovigilance monitoring is recommended. WHO aims for a life course approach for the implementation of all vaccines including COVID-19 vaccines. Such a programmatic approach will help to achieve a higher uptake of vaccines, increase the efficiency of vaccine roll-out and protect stretched health-care systems.

The high incidence of mild-to-moderate symptomatic COVID-19 illness continues to cause significant disruption to society, including the risk of post-COVID-19 conditions. SARS-CoV2 infections, even if not severe and not requiring hospitalization, may have an impact on economies, the resilience of the workforce due to the loss of productivity and absenteeism, and the ability to travel, although the extend of these impacts depends on policy settings. The impact of currently available ancestral virus vaccines on reducing symptomatic illness and transmission in the context of Omicron is limited.

Considerations for further evolution of the SARS-CoV-2 virus

This statement does not address the question whether annual boosters will be needed in the future. For longer-term considerations, there are significant uncertainties related to the evolution of the virus, the characteristics of future variants, and the trajectory of the epidemic given increasing vaccine- and infection-induced immunity globally. Further adaptations of the composition of COVID-19 vaccines may be needed in order to address future circulating variants.

The optimal timing for updating variant-containing vaccines remains uncertain. The breadth of vaccine immunity might be achieved by selecting a strain that is at the greatest antigenic distance from the previous vaccine strain as possible.

Novel vaccine platforms that elicit broader protection against antigenically diverse viruses are needed in order to address the challenges of the continuous evolution of SARS-CoV-2, but also the risk of other emerging coronaviruses with pandemic potential.

Pan-SARS-CoV2 or pan-sarbecovirus vaccines, as well as vaccines with greater impact on infection and virus transmission (i.e. vaccine platforms that elicit strong mucosal immunity), are urgently needed. However, the time frame for their development remains uncertain.

Recommendations on addressing current knowledge gaps through further research

The currently available evidence base has several limitations which should be addressed by research as per the recommendations on addressing the knowledge-gaps below.

Global sequencing and surveillance capacity for SARS-CoV-2 must be strengthened and combined with multidisciplinary studies of infectivity, virulence and immune escape, in order to track the unpredictable evolution of the ongoing COVID-19 pandemic(25).

WHO calls for the generation of relative vaccine effectiveness data using variant-containing vaccines compared to ancestral virus-containing vaccines as soon as possible after they have been introduced into populations. In addition, variant-containing vaccines should be tested urgently in order to understand their comparative efficacy when used as the primary vaccination series.

WHO recommends the following monitoring activities and research, especially in low- and middle-income country settings:

- performance of variant-containing vaccines as booster doses across all COVID-19 platforms with regard to:
- vaccine effectiveness, immunogenicity and safety,
- vaccine effectiveness stratified by disease outcome (asymptomatic, mild, moderate, severe, death),
- vaccine effectiveness by priority groups,
- breadth, magnitude and durability of humoral and cell-mediated immune responses to variants,
- need and timing of further booster doses,
- hybrid immunity performance against severe disease outcomes;
- data on variant-containing vaccines as primary vaccine series across all COVID-19 platforms relating to:
- clinical data on immune responses in humans to a primary series and/or booster dose;
- bivalent variant-containing vaccines using platforms other than mRNA platforms;
- data on co-administration of WHO EUL COVID-19 vaccines with other routine vaccines;
- performance of heterologous boosters across all COVID-19 platforms with regard to vaccine effectiveness by disease outcome;
- development of pan-SARS-CoV-2 or pan-sarbecovirus vaccines;
- development of vaccines with the ability to decrease transmission.

Table of updates

Section	Rationale for update
Monovalent Sanofi-GSK Vidprevtyn Beta (CoV2 preS dTM-AS03 (B.1.351)) vaccine against COVID-19 was added to this Good Practice Statement	European Medicine Agency authorized Vidprevtyn Beta as a vaccine for preventing coronavirus disease 2019 (COVID-19) in people aged 18 years and older. It can be used once as a booster in people who have already received an mRNA or adenoviral vector COVID-19 vaccine.
Benefit of bivalent versus monovalent mRNA COVID-19 vaccines as booster doses	This paragraph was updated to reflect emerging evidence.
Primary series	This paragraph was updated to: WHO considers it acceptable that the bivalent original/Omicron BA.5 mRNA vaccine currently authorised for boosting may also be used to deliver a primary series should this become necessary to support vaccination campaigns. However, for the time being, this use is considered off-label.
Heterologous schedules	This section was updated to also include protein subunit vaccines

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