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

17 October 2022

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.

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 these variant-containing mRNA vaccines and provides guidance on their use in the context of the continued availability of ancestral virus-based COVID-19 vaccines. The recommendations apply to all COVID-19 vaccines; however, at this point only variant-containing mRNA vaccines have received emergency authorization.

The strategic goals for vaccination against SARS-CoV-2 are: 1) to minimize deaths, severe disease and overall disease burden, including post-COVID-19 condition; 2) to curtail the impact on the health system; 3) to mitigate negative impacts on socioeconomic activity; and 4) to reduce the risk of new variants. These four goals are interdependent and each is important.

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 and BA.5) 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, Omicron is more transmissible and circulates faster, and has caused many hospitalizations and deaths due to the high incidence. 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)*. Consequently, WHO has issued guidance on the use of the first booster *(5)* and a Good practice statement for second booster doses *(6)*.

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)*, a number of manufacturers have developed variant-containing vaccines, including a number of bivalent formulations that retain the index virus/ancestral virus(7). 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.4/5 subvariant.

Methods

The available evidence that served as the basis for this guidance is outlined below, and was obtained from scientific publications, preprints, materials presented to the US FDA and ACIP, and data presented directly by the companies Moderna and Pfizer-BioNTech to the SAGE Working Group. The available supportive body of evidence was deemed not to lend itself to formal GRADE[2]-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.[3] 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 *(8, 9)* 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.

Original[4]/Omicron BA.1 developed by Pfizer-BioNTech:

A randomized controlled trial evaluated a fourth dose of Pfizer Original (30 mcg) or Pfizer Original/Omicron BA.1 (15/15 mcg) in persons who had received their third dose ("Original" recipients ranged from 5.3 to 13.1 months previously versus "Bivalent" recipients who ranged from 4.7 to 11.5 months previously*) (10).* The study was conducted in adults older than 55 years (N=610) who had received three prior doses of the Original 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 Original/Omicron BA.1 relative to the response elicited by a dose of Pfizer Original.

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 Pfizer Original/Omicron BA.1 over Pfizer Original *(10)*.

Original/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 *(11)*.

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.

Original/Omicron BA.4 and 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.4/5-containing vaccine, met superiority criteria (approximately a 2.6-fold increase, neutralization titres of 2075 compared to 800) *(12)*. Further human immunogenicity data on Pfizer Original/Omicron BA.4/5 are being generated but are not yet available.

Original/Omicron BA.4 and 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.4/5 vaccine met superiority criteria (approximately 4.5-fold increase, with titres of 267 compared to 73 *(13)*.

Further human immunogenicity data are being generated.

In summary, currently authorized variant-containing bivalent vaccines appear to broaden and enhance protection against the Omicron lineages while maintaining protection against the pre-Omicron variants and the ancestral virus. Data indicate that the immune responses induced by such Omicron subvariant-containing vaccines covers other Omicron subvariants beyond the vaccine-specific strains.

To date, there are no data on vaccine effectiveness using the variant-containing COVID-19 vaccines. Consequently, it is unknown whether these modestly superior immunogenicity results will translate into improved clinical vaccine effectiveness, and whether this will differ by disease outcome (severe versus non-severe COVID-19) or differ between the four variant-containing vaccines. Neutralization levels have been shown to be predictive of immune protection *(14, 15)*. 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) *(13)*. 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) (15). 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, $p=0.00032$) *(15)*.

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.

Safety of variant-containing mRNA 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.

Good practice statement

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 mRNA 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 bivalent vaccines using vaccine platforms other than the mRNA platform, SAGE will review such data and will update this guidance as appropriate.

Primary series:

Until supportive evidence or regulatory approval become available, variant-containing vaccines should not be used as the primary series. For the primary series, any of the WHO Emergency Use Listing (EUL) COVID-19 vaccines can be used.

Achieving very high and equitable vaccine coverage rates of the primary series with the ancestral virus COVID-19 vaccines 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 lesser extent, does protection against severe disease. With the now widespread relaxation of public health and social measures to prevent infection, and the greater immune evasion of new SARS-CoV-2 variants (in particular Omicron and its descendent lineages), the use of further booster doses of vaccines may be justified, particularly for persons at highest risk of developing severe COVID-19.

Booster doses should be offered based on evidence that doing so would optimize impact against severe disease, hospitalization, and death, and to protect health systems.

Data that are currently available are not sufficient to support the issuance of any preferential recommendation for bivalent variant-containing vaccine boosters over ancestral-virus-only boosters. The immunogenicity data comparing bivalent Omicron-containing boosters to the monovalent ancestral boosters demonstrate only modest superiority, and the impact on vaccine effectiveness remains to be demonstrated. Consequently, at this time, WHO recommends that any WHO EUL COVID-19 vaccines or authorized mRNA bivalent variant-containing vaccines can be used for booster vaccination.

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 *(14, 15)*. There are currently no data comparing the vaccine effectiveness of heterologous boosters with variant-containing boosters.

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 *(16, 17):*

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

Further information can be obtained from the Good practice statement.

First booster dose:

According to the Roadmap, WHO recommends a first booster to all persons aged 12 and above, particularly to the highest priority-use groups *(5)*, with an interval of 4–6 months after completion of the primary series. The order of implementing booster doses should follow that for primary vaccination series – i.e., booster doses should be prioritized first to the higher priority-use groups before extending to lower priority-use groups, unless there is adequate justification not to do so. WHO recommends that any of the WHO EUL vaccines, or any of the authorized bivalent variant-containing vaccines, can be used for the first booster dose.

Second booster dose:

For countries considering second boosters, WHO recommends a targeted approach with focusing second boosters for all older persons, all persons with moderately and severely immunocompromising conditions,[5,6] and adults with comorbidities[7] that put them at higher risk of severe disease, as well as for pregnant women and health workers *(6)*. Such booster doses are recommended 4–6 months after the previous dose. WHO recommends that any of the WHO EUL vaccines or any of the authorized bivalent variant-containing vaccines can be used. 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.

Countries could consider offering second boosters to persons who do not fall into the high-risk categories as listed above depending on the cost-effectiveness of such additional booster doses, programmatic considerations and other priorities.

General considerations

When deciding between using the ancestral virus WHO EUL COVID-19 vaccines or using new variant-containing vaccines for either the first or second booster dose, each country needs to take into account access to such vaccines and costs. Countries should not delay implementing first or second boosters 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 4–6 months after the previous dose, rather than extending this interval in anticipation of a variant-containing vaccine.

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) after the previous dose 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 between vaccination after infection is currently not known.

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. The impact of currently available ancestral virus vaccines on reducing symptomatic illness and transmission in the context of Omicron is limited, and it is not yet known whether boosting with variant-containing vaccines will enhance vaccine effectiveness against mild infections compared to boosting with the ancestral virus vaccines. On the basis of the immunogenicity data, some clinical benefit might be anticipated against infection and mild disease when using the bivalent boosters; however, the extent of this clinical benefit is not yet known, and may be modest and short-lived. In light of these unknowns, a strong research agenda – including vaccine effectiveness data for variant-containing vaccines when used as first and second boosters that include outcomes such as mild infection through to severe disease and death – should be conducted.

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