

# Good practice statement on the use of second booster doses for COVID-19 vaccines

18 August 2022



## Background

This good practice statement has been developed based on the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on [11 August 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 Working Group website](#).

The guidance is based on the evidence outlined in this document, which was presented to SAGE on 11 August 2022. All referenced documents are available on the SAGE COVID-19 webpage: <https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials>.

## Methods

The details of the literature review and the summary of the available evidence serving as the basis for this guidance are outlined below. The recommendations apply to all COVID-19 vaccines that have received WHO Emergency Use Listing (EUL) as of 11 August 2022 (Ad26.COV2.S, Ad5-nCoV-S, BBV152, BNT162b2, ChAdOx1-S [recombinant], mRNA-1273, Sinopharm-BIBP, Sinovac-CoronaVac, and Novavax).

There is increasing evidence on the benefits of a second booster dose of COVID-19 vaccines in terms of restoring waning vaccine effectiveness (VE). The data mainly exist for mRNA vaccines with very limited data for other COVID-19 vaccines. The available heterogeneous body of evidence was deemed not to lend itself to formal GRADE<sup>a</sup>ing of evidence. Nevertheless, SAGE considered the available data from multiple sources as sufficient to proceed with issuing this good practice statement.<sup>b</sup> WHO has not issued EUL for second booster doses.

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<sup>a</sup> GRADE: Grading of Recommendations, Assessment, Development and Evaluation.

<sup>b</sup> Good practice statements represent recommendations that guideline panels feel are important but that are not appropriate for formal ratings of quality of evidence. Good practice statements characteristically represent situations in which a large and compelling body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action.

## Context

As eradication of SARS-CoV-2 infection is unlikely to be achieved with existing infection control tools, and even local elimination of infection is unlikely to be sustainable, the strategic goals for vaccination are to: i) minimize deaths, severe disease and overall disease burden including post COVID condition; ii) curtail the impact on the health system; iii) mitigate negative impact on socioeconomic activity; and iv) reduce the risk of new variants (1). These four goals are interdependent, and each is important. The protection conferred by currently available COVID-19 vaccines against SARS-CoV-2 transmission declines substantially within a few months of vaccination, particularly in the context of each variant of concern. However with severe disease, protection is relatively well maintained against each variant of concern including Omicron and its sub-lineages (1).

Countries that achieved high levels of vaccine uptake in priority groups have seen reductions in rates of COVID-19-related hospitalization and death. Most countries have relaxed public health and social measures with a consequent rise in community infection rates, but a concomitant rise in rates of severe disease and death has been much less marked. The longer-term impacts of post-COVID-19 condition due to increased infection rates are yet to be fully understood and quantified. Questions remain on the trajectory of the pandemic and if and when SARS CoV-2 will become an endemic virus.

Omicron (including its various sub-lineages BA.1, BA.2, BA.4 and BA.5) is associated with less severe disease compared to the ancestral strain and pre-Omicron variants. However, it 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 and lower VE. While effectiveness is still relatively well maintained 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 VE in such vulnerable persons will translate into a rise in severe disease and deaths.

This guidance pertains to the need for a second booster dose to restore VE in the context of Omicron; it does not take into account future variants or variant-containing vaccines. Variant-containing vaccines are in late-stage development and have not yet received regulatory approval.

The objective of this good practice statement is to provide a review of the evidence and policy recommendations for a second booster dose. The document also addresses future additional booster doses.

## Definitions used in this document

Primary series: For most COVID-19 vaccines, a primary series consists of two doses. For the Ad26.COV2.S (Janssen) and Ad5-nCoV-S (CanSino) vaccines, a single dose has received regulatory approval.

Extended primary series: An extended series consists of an additional dose to the primary series for moderately and severely immunocompromised persons (ICPs) who are known to mount a lower immune response and have less clinical protection against COVID-19 (2). The full primary series therefore has three doses (for most COVID-19 vaccines) to enhance the immune response in this subpopulation.

First booster dose: A first booster dose is an additional dose, administered usually 4–6 months after completion of the primary series to improve the immune response after it has waned over time. For most COVID-19 vaccines, this will be a third dose (for ICPs, a fourth dose).

Additional booster doses: Additional doses given beyond the first booster are intended to restore or further improve the immune response after waning since the previous booster dose. Booster doses (first and/or second or subsequent boosters) could potentially use a vaccine with the ancestral strain, or a vaccine incorporating a variant strain. For vaccines with a two-dose primary regimen, the second booster dose refers to a fourth dose overall (fifth among ICPs); for vaccines with a single dose primary series, a second booster dose is a third dose overall (fourth among ICPs).

This document concerns second booster doses but also elaborates on the potential need for further future booster doses.

## WHO Roadmap

All WHO EUL vaccines have provided substantial protection against severe disease and death due to currently circulating variants of concern (3). As outlined in the WHO SAGE Roadmap (1), vaccinating individuals at highest risk with a primary series and a first booster dose prior to embarking on further vaccination with additional booster doses is a public health priority, and will result in the highest public health gains. In countries with large gaps in vaccine coverage rates, especially in highest and high priority-use groups, all efforts should be taken to address these gaps.

## Rationale for a second booster

In the context of the Omicron variant, waning of VE was documented as relatively minor against severe disease and significant and rapid against symptomatic illness. A recent systematic review and meta-regression assessing VE over time since vaccination, examined data from 3 December 2021 to 21 April 2022 during an Omicron-dominant period (BA.1). Using random-effects meta-regression, the mean change in effectiveness was estimated 1–4 months after the first booster vaccination (i.e. third dose). The booster dose increased VE against all outcomes initially. Over time the decrease in effectiveness against severe disease was found to be 5% (95% CI: 2–9) 1–4 months after booster vaccination, and 8% (95% CI: 4–14) when projected to 6 months after booster vaccination. In contrast, against symptomatic disease, there was a decrease in VE over time of 24% (95% CI: 20–29) 1–4 months after the booster vaccination, and of 29% (95% CI: 18–41) when projected to 6 months (4).

The rationale for a second booster is to restore and possibly enhance protection. In some countries, second booster doses are currently being offered (i.e. fourth doses to older adults and fifth doses to immunocompromised persons) (5-7). Because these doses have been administered relatively recently, data are limited on the additional protection they confer in terms of the duration of VE, and may differ by vaccine platform.

## Performance of a second booster dose

The following section summarizes the data on duration of protection after a third dose (primary series and a booster) and a second booster dose (fourth dose) as of July 2022.

### mRNA COVID-19 vaccines:

Studies available for review on the use of mRNA vaccines as a second booster dose include eight from Israel (8-15), one from Canada (16) and one from the United States of America (17). All were conducted during a time when Omicron was the predominant circulating strain globally. The study from the United States examined the different circulating sublineages of Omicron (17). While the studies vary in design and population investigated, most evaluated the relative effectiveness of a fourth dose of mRNA vaccine (given approximately 4 months after the third dose) compared to those who received three vaccine doses. This relative VE provides evidence on the additional protection induced by four doses compared to protection induced by three doses. The relative effectiveness may vary according to the initial VE provided by three doses and how much waning of protection has occurred subsequent to the third dose. In contrast, absolute VE compares vaccinated with unvaccinated individuals. Two studies provide data on this (comparing people in a fourth-dose schedule to those who are unvaccinated, described below. The maximum follow-up in the available studies was short, ranging from 2 to 10 weeks after the fourth dose; potential waning of protection after the fourth dose is therefore not captured by the data presented.

Of the studies that investigated the use of a fourth dose of COVID-19 vaccine, two from Israel reported specifically on outcomes of infection and any symptomatic disease (12, 15). The two studies used mRNA vaccines (BNT162b2 or mRNA-1273) for the fourth dose and included health workers as their population of interest. After the fourth dose, immunogenicity showed a 9–10-fold increase in IgG antibodies against SARS-CoV-2 receptor-binding domain and neutralizing antibody titres, levels that were slightly higher than those achieved immediately after the third dose; no significant difference was observed between the two mRNA vaccines (12). The second study investigated breakthrough infections in health workers and found a reduction of approximately 50% in those who had received a fourth dose of BNT162b2 compared to those who had received only three doses (15).

All remaining studies from Israel that evaluated relative VE were conducted among individuals older than 50 or 60 years of age who had received mRNA vaccines; individuals who had known previous SARS-CoV-2 infection were excluded. Three of the studies were retrospective cohort studies using administrative data. The first study found the relative vaccine effectiveness against severe disease to be 66% (95% CI: 57–72), 15–21 days after a fourth dose, and 77% (95% CI: 62–86), 36–42 days after a fourth dose (8). The second reported on death as the outcome measure and found a relative effectiveness of 78% (95% CI: 72–83), 7 or more days post fourth dose; the absolute risk reduction conferred by the fourth dose was 0.07% (11). The third study found the relative VE against hospitalization to be 89% (95% CI: 87–91), 0–2 months post fourth dose (14). Using a test negative design with severe disease as the outcome of interest, a relative VE of 87% (95% CI: 0–98) was reported 49–69 days post fourth dose. In this study severe disease was reported as a relatively rare event, occurring among less than 1% of recipients of both four and three doses (10). A matched cohort study applying trial design principles from random control trials to the analysis of observational data (18) found a relative VE of 62% (95% CI: 50–74) against severe COVID-19, and 74% (95% CI: 50–90) against COVID-19-related death comparing recipients of three doses against recipients of four doses. A further analysis of the risk of severe COVID-19, 7–30 days post fourth dose found 42.1 events per 100 000 persons, compared to 110.8 events per 100 000 persons in the three-dose comparison group. This corresponds to a difference

in risk of 68.8 cases per 100 000 persons (95% CI: 48.5–91.9) (9). A prospective study in residents of long-term care facilities reported a relative VE of 67% (95% CI: 57–75) against severe hospitalization, 7 or more days after a fourth dose, and 72% (95% CI: 54–83) against death (13).

Two studies include analysis of the absolute vaccine effectiveness of a fourth dose compared to unvaccinated individuals. The study from Canada found the absolute VE to be 82% (95% CI: 75–88) among individuals vaccinated 84 or more days after their third dose, and 92% (95% CI: 87–95) among those vaccinated 7 or more days after their fourth dose, which corresponds to a relative VE of 54% (95% CI: 31–70) (16). The study from the United States included 4094 individuals aged over 50 years who received a fourth dose during the period of BA.2 predominance. Vaccine effectiveness against COVID-19-associated hospitalization was 80% (95% CI: 71–85), 7 or more days after the fourth dose, in contrast to 52% (95% CI: 44–59), 120 or more days after the third dose (17).

#### **Viral-vectored vaccines:**

A study conducted in Thailand used ChAdOx1-S as a fourth vaccine dose. The study used a test negative design in a subset of individuals aged 18–59 years who received Sinovac-CoronaVac vaccine, and a subset aged over 60 years who received ChAdOx1-S for their primary series and then a third dose of one of the following vaccines: Sinovac-CoronaVac, or Sinopharm COVID-19 vaccine BIBP, or ChAdOx1-S, or BNT162b2, or mRNA1273. A fourth dose of either an mRNA vaccine or ChAdOx1-S was provided starting in the fourth quarter of 2021. Approximately 40 days after administration of the fourth dose, absolute VE against symptomatic infection with Omicron was calculated to be 73% (95% CI: 48–89) (19); when separated by vaccine product of fourth dose, no difference in effectiveness was observed between ChAdOx1-S and the mRNA vaccines (19). Too few severe Omicron cases occurred after the fourth dose to evaluate the VE against severe outcomes. It is currently not known whether repeated homologous doses could lead to the emergence of substantive anti-vector immunity.

#### **Inactivated vaccines:**

Three inactivated vaccines have received WHO EUL (BBV152, Sinopharm BIBP, and Sinovac-CoronaVac). To date, no ongoing or completed studies have been found on the effectiveness or safety of an additional booster dose for either the BBV152 or Sinopharm vaccine. Studies are ongoing on the additional booster dose for Sinovac. Both Sinovac and Sinopharm have received regulatory approval for an additional booster dose in some countries but have not submitted for this variation with WHO.

#### **Protein-based vaccines:**

No published data have been found on an additional dose using protein-based vaccines. Currently-available data underpin the broadening of protection with a third vaccine dose. However, protein-based vaccines such as Novavax have been used for a relatively short period of time, and currently no data exist on the waning of immunity over time after the third dose.

#### **Hybrid immunity**

Hybrid immunity is defined as the immune protection in individuals who have received one or more doses of a COVID-19 vaccine and experienced at least one SARS-CoV-2 infection before or after the initiation of vaccination. In the context of the current epidemic wave dominated by the Omicron variant and subvariants, a high proportion of the global population has had

an Omicron infection, thereby possibly enhancing vaccine-induced immunity through hybrid immunity. Hybrid immunity enhances vaccine effectiveness (20, 21).

### Heterologous boosting

Heterologous schedules refers to the administration of a vaccine product that differs from the product(s) previously used. Although homologous COVID-19 vaccination schedules are considered standard practice based on the substantial data on safety, immunogenicity, and efficacy for each WHO EUL vaccine, heterologous schedules are commonly considered where there is a lack of availability of the same vaccine product. Interchangeability of vaccine products allows for added programmatic flexibility as well as reducing reactogenicity, increasing immunogenicity, and enhancing vaccine effectiveness. In addition, there is increasing evidence that heterologous schedules may provide superior immunogenicity to homologous schedules (22).

In the context of second booster doses, limited data on heterologous boosting are available. The study from Thailand used a test negative design and provides data on heterologous boosting. mRNA vaccines or ChAdOx1-S were used as a second booster, with Sinovac-CoronaVac or ChAdOx1-S used for initial vaccination (19). The study suggests that a second booster dose with vaccines from either of these two platforms provides a similar increase in VE. Extrapolating from data on the performance of primary series and first booster doses using heterologous schedules (previously reviewed (22)) suggests that heterologous boosters with any of the WHO EUL vaccines are likely to be safe and immunogenic (23). Data are limited but the expectation is that the response will vary depending on the vaccine used.

For countries considering heterologous schedules, WHO recommends the following on the basis of equivalent or favourable immunogenicity or effectiveness for heterologous versus homologous schedules depending on product availability (further information can be obtained from the good practice statement (22)):

- 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.

### Safety of second booster doses

Limited data are available on the safety of a fourth dose of WHO EUL COVID-19 vaccines; most are from studies using an mRNA vaccine platform and show that the majority of adverse events are similar to those following previous doses and resolve on their own (12, 24). After the second dose, a risk of myocarditis/pericarditis was identified in individuals aged 12 years and older, with most reported cases of myocarditis and myopericarditis occurring less than 7 days after vaccination in those aged 12–39 years. The risk of myocarditis and myopericarditis after the fourth dose was less than that seen after the second dose in the primary series. Among those aged 40 years and older, cases were predominantly pericarditis, and the small, elevated risk was more spread out over the 3 weeks after the first booster dose (6).

## Good practice statement

Achieving high and equitable vaccine coverage rates of primary series and first booster doses globally among the groups at higher risk of severe disease and death remains the greatest priority. The combination of waning vaccine- and infection-induced SARS-CoV-2 immunity against infection and mild disease, and to a lesser extent severe disease, the widespread relaxation of public health and social measures, temporal fluctuations in virus transmission, and the potential emergence of new SARS-CoV-2 variants, may lead to one or more surges in SARS-CoV-2 activity in the coming months, with the need to introduce a second booster dose in a risk-based approach. Evolving evidence from studies suggests that additional protection of the most vulnerable populations, at least for several months, is likely to be achieved through administration of a second booster dose, although follow-up time for these studies is limited.

When deciding to implement second boosters, each country needs to take into account the age structure, current and potential burden of severe COVID-19 disease and hospitalizations, availability and access to vaccines, opportunity costs, coverage rates with primary series and community acceptance of second boosters. The incremental benefit of a second booster dose is likely lower compared to primary series and first booster doses. The number needed to vaccinate to avert one death with a second booster is higher compared to that for primary series.

To reduce the risk of severe disease, deaths and disruption to health services, WHO recommends that countries consider a second booster dose for the following population groups:

- i) all older persons (age specific cut-off should be defined by countries based on local COVID-19 epidemiology);
- ii) all persons with moderately and severely immunocompromising conditions<sup>c, d</sup>
- iii) adults with comorbidities<sup>e</sup> that put them at higher risk of severe disease;
- iv) pregnant women; and
- v) health workers.

WHO supports a flexible approach to homologous versus heterologous vaccination schedules, for both primary series and booster doses. Heterologous boosters should be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

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<sup>c</sup> Moderately and severely immunocompromised individuals include those with: i) **Active cancer** (Active immunosuppressive treatment for solid tumour or haematological malignancy (including leukaemia, lymphoma, and myeloma), or within 12 months of ending such treatment. ii) **Transplant recipients** (Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy). iii) **Immunodeficiency** (Severe primary immunodeficiency, chronic dialysis). iv) **HIV** (HIV with a current CD4 cell count of <200 cells/μl, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e. advanced HIV disease)). v) **Immunosuppressives** (Active treatment causing significant immunosuppression, including high-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, or other highly immunosuppressive drugs; immunosuppressive chemotherapy or radiotherapy within the past 6 months).

<sup>d</sup> Data on second booster doses for immunocompromised children are limited. As vaccine effectiveness against COVID-19 in moderately and severely immunocompromised people is lower and wanes more rapidly than in immunocompetent individuals, and such individuals usually suffer from more severe disease, a second booster dose (fifth dose) could be offered to all children with these conditions, in accordance with the regulatory approval for the age indication of a given COVID-19 vaccine product.

<sup>e</sup> Comorbidities that increase the risk of severe disease and death due to COVID-19 include diseases such as diabetes, hypertension, chronic cardiac, lung and kidney diseases, neurodegenerative diseases, and conditions associated with immunosuppression are associated with a higher risk of severe disease etc.

As vaccine effectiveness wanes over a period of 4–6 months, a second booster dose should be offered 4–6 months after the last dose or, if this time period is missed, as soon as possible thereafter. Individuals at high risk for disease and death should receive a second booster dose in this time interval. Once authorized for use, variant-containing vaccines can be considered; however individuals at high risk should not delay receiving a booster dose in anticipation of these.

WHO recommends that countries consider co-administration of COVID-19 vaccines with seasonal influenza vaccines, whenever feasible, dependent on seasonality. The known risk of serious illness is substantial for older adults and many other priority groups infected either with influenza virus or SARS-CoV-2. Other adult vaccines may also be co-administered with COVID-19 vaccines: WHO aims for a life course approach for the implementation of COVID-19 vaccines. Such a programmatic approach will help to reach a higher uptake of vaccines, increase efficiency and protect stretched health-care systems.

The high incidence of mild to moderate symptomatic COVID-19 illness continues to cause significant disruptions to society. SARS-CoV-2 infections, even if not severe and not requiring hospitalization, may impact economies, the resilience of the work force due to the need for isolation, loss of productivity, and the ability to travel. The impact of currently-available vaccines on reducing symptomatic illness and transmission in the context of Omicron is modest. The effects of a second booster dose on restoring VE against symptomatic illness will be transient and likely not last longer than a few months. Countries considering methods to reduce the socioeconomic impact due to mild and moderate SARS-CoV-2 infections need to take into account cost–benefit, affordability, opportunity costs to other vaccination programmes, and community acceptance of a second booster dose before offering second boosters to individuals who do not fall into the high risk categories as listed above.

Infection-induced immunity provides some additional benefit to vaccine-induced immunity, however the benefit of such hybrid immunity may be lower in older and vulnerable populations (21). From a programmatic point of view, pre-vaccination screening for past infections may be impractical and could hamper roll-out.

WHO recognizes that the need for and optimal timing of the primary vaccination series and booster dose may be different in an individual who has had a prior SARS-CoV-2 infection or who has experienced a breakthrough infection after initiation of the primary series when compared to a previously uninfected individual. The optimal interval between vaccination after natural infection is currently not known. In the context of second boosters, individuals who have had a SARS-CoV-2 infection (confirmed by PCR or antigen test) after the first booster dose, could consider delaying the second booster dose by 4–6 months. To date, no safety issues have been seen when giving the booster dose earlier than 4–6 months post infection. Seropositivity rates may vary within sub-populations and are generally lower in older age groups compared to younger adults (25).

WHO recommends that countries consider the broader integration of COVID-19 vaccination and booster doses into primary health care through national immunization programmes.



## Considerations for future additional doses

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. It is likely that additional doses may be needed within 4–12 months after the second booster, especially in persons most vulnerable to severe disease and death.

The composition of the currently-available COVID-19 vaccines is being updated to offer broader protection against new variants of concern (26). Despite the potential benefit of variant-containing vaccines, current vaccines, based on the index virus, appear to maintain high VE against severe disease in the context of the Omicron variant and its sub-lineages. The administration of a second booster dose, as recommended by this guidance, should not be delayed in anticipation of future variant-containing vaccines. Once variant-containing vaccines are available, WHO will assess their performance and update guidance, as needed. Pan-SARS-CoV-2 or pan-sarbecovirus vaccines, as well as vaccines with greater impact on virus transmission (i.e. nasal vaccines), are urgently needed, however the time frame for their development is uncertain (26).

## Recommendations on addressing current knowledge gaps through further research

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

- Second dose performance of current WHO EUL COVID-19 vaccines with regard to:
  - vaccine effectiveness, immunogenicity and safety data;
  - duration of protection of mRNA vaccines, inactivated, protein subunit and viral vectored vaccines over time;
  - disease outcome (asymptomatic, mild, moderate, severe, death)
  - priority groups;
  - breadth, magnitude, and durability of humoral and cell-mediated immune responses to variants;
  - need and timing of regular booster doses;
  - vaccine correlates of protection and correlates of durability of protection in persons with and without previous COVID-19 infection;
  - hybrid immunity performance against severe disease outcomes.
- Data on variant-updated COVID-19 vaccines relating to:
  - clinical data on immune responses in humans to a primary series and/or boosters dose of updated vaccine across all available COVID-19 vaccine platforms;
  - vaccine effectiveness, immunogenicity and safety data;
  - duration of protection of mRNA vaccines, inactivated, subunit and viral-vectored vaccines over time;
  - disease outcome (asymptomatic, mild, moderate, severe, death);
  - priority groups;
  - breadth, magnitude, and durability of humoral and cell-mediated immune responses to variants.
- Data on WHO EUL COVID-19 vaccines co-administration with other routine vaccines.
- Development of pan-SARS-CoV-2 or pan-sarbecovirus vaccines.
- Development of vaccines with the ability to decrease transmission.

**Annex. Current WHO recommendations for a first booster dose (1):**

For ease of use, the current recommendations for the first booster dose are summarized below. These recommendations have not changed.

Booster doses should be offered based on evidence that doing so would have substantial impact on hospitalization, severe disease and death, and on protecting health systems. The order of implementing booster doses to different population groups should follow that which has been laid out for primary vaccination series – i.e. the first booster dose should be prioritized for higher priority-use groups before lower priority-use groups, unless there is adequate justification not to do so. Such justification may include programmatic constraints or acceptability obstacles to uptake in higher priority-use groups that would result in vaccine wastage. In such cases, strategies should be prioritized to improve vaccine delivery, community engagement, and social mobilization efforts to reach higher priority-use groups.

Within a given priority-use group, primary series vaccination will have greater impact per dose than booster doses. Across priority-use groups, the benefits of booster doses for higher priority-use groups versus primary series doses for lower priority-use groups depends on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection. When high primary series coverage rates have been achieved among subgroups at higher risk of severe disease and death (e.g. older adults), booster doses for these subgroups may yield greater reductions in severe disease and death than use of equivalent vaccine supply for primary series vaccination of lower priority-use groups.

The optimal interval between completion of a primary series and administration of booster doses has yet to be determined, and depends on epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation and frequency of specific variants of concern. As a general principle, an interval of 4–6 months since completion of the primary series could be considered, especially in the context of variants of concern.

Booster doses should be considered for all COVID-19 vaccines having received WHO emergency use listing (EUL).

**Additional doses in immunocompromised persons (extended primary series)**

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in immunocompromised persons (ICPs), compared to persons without immunocompromising conditions. An additional dose included in an extended primary series enhances immune responses in some ICPs (27, 28). Given the significant risk of severe COVID-19 for ICPs, if infected, WHO has already issued a recommendation for an extended primary series (i.e. third dose) as well as a booster dose (i.e. fourth dose) for ICPs, for all COVID-19 vaccines (1, 2). Homologous (same vaccine platform) and heterologous (different vaccine platform) vaccines can be used for such booster doses (22).

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