21st meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE)

Excerpt of conclusions

Virtual meeting

16-18 November 2021
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Abbreviations

ETAGE  European Technical Advisory Group of Experts on Immunization
EUL  Emergency Use Listed
SAGE  Strategic Advisory Group of Experts on Immunization
VOC  Variant of Concern
VPI  Vaccine-preventable Diseases and Immunization Programme of the WHO Regional Office for Europe
Introduction
The 21st meeting of the European Technical Advisory Group of Experts on Immunization (ETAGE) took place virtually on 16–18 November 2021 to review and discuss immunization activities and developments in the WHO European Region and provide advice to the WHO Regional Office and its Member States.

The objectives of the meeting were to request advice and guidance from ETAGE on the following key topics and issues:

- resuming and scaling-up routine immunization in the WHO European Region: identifying the magnitude of the problem and understanding the underlying factors; issues to be considered while planning the resuming and scaling-up; development of country action plans and monitoring the implementation performance;
- COVID-19 vaccination issues addressed at the Strategic Advisory Group of Experts on Immunization (SAGE) October meeting with particular relevance to the WHO European Region.

Highlights, conclusions and recommendations on COVID-19 additional and booster doses as well as coadministration with seasonal influenza vaccine are summarized below.

Highlights

- The primary public health objective of COVID-19 vaccination is to reduce severe disease and deaths and maintain essential health care services. Therefore, vaccination of vulnerable populations and health care workers should remain the highest priority.

- Based on the available evidence, an additional dose is needed to enhance immune response in the following specific cases as these people remain vulnerable even after receiving the standard number of priming doses.
  - Immunocompromised people should receive an additional dose of COVID-19 vaccine 1-3 months after receiving the standard number of priming doses. Currently, there is no contraindication to receiving any of the WHO Emergency Use Listed (EUL) COVID-19 vaccines (which are all non-live) for immunocompromised people.
  - People 60 years and over who received two doses of inactivated Sinovac-CoronaVac or Sinopharm-BIBP vaccine should receive a third dose 3-6 months after receiving the second dose.

Routine testing for antibodies is not recommended prior to or following the administration of the additional dose.

- Emerging evidence demonstrates that:
  - vaccine effectiveness against SARS-CoV-2 infection and mild COVID-19 disease provided by the standard number of primary vaccine doses declines over time while protection against severe disease and death remains high;
  - a booster vaccine dose significantly increases immune responses particularly in older adults.
• Considering the current upsurge of COVID-19 cases in the WHO European Region\(^1\) and in light of emerging evidence, ETAGE suggests that countries offering a booster dose should focus first on people aged ≥60 years and other population groups at high risk of severe COVID-19 disease to minimize increases in severe COVID-19 cases and on healthcare workers to maximize resilience of and safety in healthcare facilities. ETAGE recommends that the following criteria be taken into account: local epidemiology of COVID-19, current and predicted vaccine supply and programmatic capacity.

ETAGE will provide guidance on the provision of a booster dose for the wider adult population as further evidence become available.

• ETAGE concurs with the SAGE consideration that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable.

“Additional” dose

“Additional” doses of COVID-19 vaccines may be needed as part of an extended primary series for target populations in whom typical immune responses following the standard primary series are deemed insufficient. The objective of an additional dose in the primary series is to optimize or enhance immune responses and thus to increase effectiveness against disease\(^2\).

Available evidence demonstrates that individuals with immunocompromising conditions and those receiving immunosuppressive therapy often fail to mount an adequate response to a standard primary series of COVID-19 vaccination, while being at higher risk of COVID-19 disease progression to severe stages requiring hospitalization, intensive care and also potentially leading to death when compared to the general population.\(^3,4\) Evidence strongly indicates that the risk of serious disease and death increases exponentially with age and older adults are at the highest risk of morbidity and mortality due to COVID-19\(^5\). Emerging evidence demonstrates that the effectiveness of inactivated Sinovac-CoronaVac and Sinopharm-BIBP vaccines against severe disease and death is lower in older persons than in younger adults.\(^6\)


\(^6\) Post-introduction vaccine effectiveness studies are not yet available for the inactivated Bharat Biotech BBV152 COVAXIN® vaccine against COVID-19, which was granted WHO Emergency Use Listing on 3 November 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin
Expanded primary vaccination series for immunocompromised individuals

**ETAGE notes:**

- A rapid literature review conducted for the Strategic Advisory Group of Experts (SAGE) Working Group on COVID-19 Vaccines\(^7\) suggests that immunocompromised persons often fail to mount an adequate response to a primary series of COVID-19 vaccination. Multiple studies have demonstrated lower mean antibody responses and lower effectiveness against symptomatic and severe disease in immunocompromised persons in comparison to people without immunocompromising conditions. According to observational studies conducted in Israel\(^8\) and the United States\(^9\), \(\geq40\%\) of breakthrough COVID-19 cases were observed in vaccinated immunocompromised people, who comprise only a small fraction of the total population.

- Evidence suggests that an additional dose has a reactogenicity profile similar to that of previous doses and increases immune responses in most immunocompromised persons who have received a primary vaccination series, including induction of immune responses in 25-50\% of immunocompromised individuals who failed to respond immunologically to the standard primary vaccination series\(^10\).

- The benefit of an additional dose in an extended primary series administered to immunocompromised people has largely been assessed using the same vaccine product for the initial dose(s) and the additional dose. Evolving evidence in non-immunocompromised people suggests that using a different vaccine (a heterologous series) may sometimes be more immunogenic than a homologous series. Although these heterologous schedules have not been specifically tested in immunocompromised populations, it seems reasonable to expect similar effects in terms of immune responses.

- Some countries in the WHO European Region have policies in place which outline immunocompromising conditions or immunosuppressive therapy as contraindications to COVID-19 vaccination, leaving immunocompromised persons unprotected against COVID-19. Currently there is no contraindication to receiving any of the WHO Emergency Use Listed (EUL) COVID-19 vaccines (which are all non-live) for people with any of these conditions. On the contrary, immunocompromised people are at significantly higher risk of severe COVID-19 outcomes and should be a priority target group for vaccination.

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**ETAGE recommendations:**

- In the light of available evidence, ETAGE concurs with SAGE recommendations\(^{11}\) that:
  - the primary vaccination series of all COVID-19 vaccines in moderately and severely immunocompromised persons should be extended to include an additional dose 1-3 months after the last dose in the primary series;
  - using a homologous series (same vaccine product for the initial dose(s) and the additional dose) should currently be considered a standard practice, but an alternative heterologous series (using a vaccine product from a different platform) for the additional dose may also be considered.
- Countries may use the case definition suggested by SAGE\(^{12}\) to identify moderately and severely immunocompromised persons (active cancer, transplants recipients, immunodeficiency, treatment with immunosuppressives, people living with HIV with a current CD4 cell count of <200 cell/\(\mu\)l, evidence of an opportunistic infection, not on HIV treatment, and/or with a detectable viral load (i.e., advanced HIV disease)) or consider developing their own case definitions.
- ETAGE re-emphasizes that vaccination of immunocompromised persons, who are at high risk of developing severe COVID-19 outcomes, should be prioritized in all countries. Immunocompromising conditions and immunosuppressive therapy are not contraindications to vaccination. On the contrary, vaccination should be offered to immunocompromised persons as soon as possible\(^{13}\).
- Routine testing for antibodies is not recommended prior to or following the administration of the additional dose.

**Additional primary dose for older adults who received two doses of inactivated COVID-19 vaccines**

**ETAGE notes:**

- 18 countries of the WHO European Region have reported using inactivated Sinovac-CoronaVac and/or Sinopharm-BIBP vaccines in their national COVID-19 vaccination programmes.

**Evidence to support the need for an additional dose:**

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• Some published studies, not yet peer-reviewed, report that effectiveness of inactivated Sinovac-CoronaVac and Sinopharm-BIBP vaccines against severe disease and death was lower in older persons than in younger adults. Furthermore, immune responses generated following a complete vaccination series were lower in persons above 60 years of age in whom seropositivity declined more rapidly than in younger persons\textsuperscript{14,15}.

• Administration of an additional dose of inactivated Sinovac-CoronaVac or Sinopharm-BIBP vaccine to older adults 3-6 months after the second dose generates peak antibody titers that are higher than the titers generated after the second dose. Unpublished data from Chile showed an increase in vaccine effectiveness in older persons after a third dose was administered.

• Emerging evidence suggests that a heterologous series (using a vaccine product from a different platform for the additional dose) is well tolerated and may be more immunogenic than a homologous series. However, data on safety and effectiveness of heterologous doses are currently limited.

**ETAGE recommendations:**

• Based on available evidence, ETAGE concurs with the SAGE recommendation that individuals aged 60 years and above who received two doses of inactivated COVID-19 vaccines Sinovac-CoronaVac or Sinopharm-BIBP should be offered an additional (third) primary dose 3-6 months after the second dose to enhance vaccine-induced protection. The same vaccine product as for the first two doses (homologous doses) should be used for the third dose. Heterologous series (a COVID-19 vaccine from another vaccine platform such as mRNA or viral-vector vaccines) can be used for the additional dose if the vaccine used for primary vaccination is not available.

• Countries should consider the following criteria when deciding on the introduction of a third dose for older adults who have received two doses of inactivated Sinovac-CoronaVac or Sinopharm-BIBP vaccine:
  - COVID-19 vaccine coverage: countries should continue to focus on vaccinating and completing the standard dose series in the entire older population group.
  - COVID-19 vaccine supply: countries should ensure that the available vaccine stock and predicted vaccine supply are sufficient to reach high vaccination coverage in priority population groups as well as to offer the third dose to older adults who have received two doses of inactivated Sinovac-CoronaVac or Sinopharm-BIBP vaccine.


• Any dose of COVID-19 vaccines, when offered, should be recorded in COVID-19 vaccination certificates to document the updated vaccination status of the individual for the continuity of care.

“Booster” dose
WHO has defined “booster” doses of COVID-19 vaccines as doses administered to a vaccinated population that has completed the primary vaccination series when, with time, the immunity and clinical protection have fallen below a rate deemed sufficient in that population. The objective of a booster dose is to restore vaccine effectiveness that is no longer sufficient to provide adequate protection to the recipient.

ETAGE notes:

Effectiveness of primary series

• Available evolving evidence from the studies with severe COVID-19 disease as endpoints suggest that protection against hospitalization and death from the primary vaccination series of currently available vaccines remains sufficiently high for at least 6 months for most individuals, although the degree of protection varies by vaccine type, age-groups, and setting (including different circulating variants of concern (VOCs).

• Emerging evidence indicates that the initial vaccine effectiveness achieved after completion of a primary vaccination course for some COVID-19 vaccines against SARS-CoV-2 infection and mild COVID-19 declines over a period of several months.

Immune response from, protection by and safety of booster doses

• Clinical trials have demonstrated that booster vaccines increase immune responses.

• Observational studies from Chili and Israel suggest high relative protection in individuals receiving a Pfizer booster dose. When comparing the effectiveness of the third vaccine dose to two vaccine doses, the reduction of risk of severe outcomes was particularly high in older adults and people with underlying medical conditions.

• Identified research gaps include systematic collection of real-world safety and effectiveness data for more vaccines, optimal timing of boosting, and better understanding of vaccine effectiveness against variants of concern.

• Clinical trial data generally support the safety of booster doses: rates of local or systemic adverse events after a booster dose being similar to those following the last dose of a primary vaccination course. No serious adverse events considered related to vaccines were reported for booster doses. However, not all vaccines have a controlled or systematic analysis of post-authorization safety data and the risk of serious adverse events after a COVID-19 vaccine booster dose are therefore not yet well understood.

WHO interim statement on booster doses

- WHO is working closely with countries and researchers to gather sufficient evidence to assess how well vaccine-induced protection is sustained over time and the optimal timing for a booster dose for the wider adult population.
- The focus remains on urgently increasing vaccination coverage with the primary series driven by the objective to protect against severe disease.
- Offering a booster dose broadly to lower-risk population groups may divert limited resources and supply from vaccinating vulnerable populations.

Use of booster doses in the WHO European Region

- Since August 2021, 42 countries of the WHO European Region have introduced booster doses: 36 countries offer booster doses for priority target groups and 6 countries offer boosters to all adults who received a complete primary vaccination series. Most countries offer booster doses regardless of vaccine product used for the primary series, while some countries recommend booster doses only for specific vaccines. The priority population groups for booster vaccination vary between countries.

ETAGE recommendations:

- The primary public health objective of COVID-19 vaccination programmes in every country should remain to reduce severe disease and deaths and to maintain essential health care services. Therefore, primary vaccination of vulnerable populations (i.e., people with co-morbidities and health conditions, socio-demographic groups who are at significantly higher risk of severe COVID-19 diseases and adverse outcomes, and close contacts of immunocompromised people) and health care workers should remain a priority.
- All countries should undertake efforts to increase coverage with a primary COVID-19 vaccination series and strive to reach global (70% of total population) and regional (80% of adult population) targets by mid-2022.
- All countries should make adequate efforts using all available tools at hand to identify areas or population groups with low vaccination uptake, understand the reasons for low coverage, population demand and acceptance of the vaccines, including potential access barriers, in these areas or population groups and tailor strategies to address them.
- Countries that do not collect disaggregated coverage data should undertake urgent efforts to update their immunization information systems to obtain vaccination coverage data for each of the priority population groups.

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17 Interim statement on COVID-19 vaccine booster doses (who.int)
19 WHO Regional Office for Europe Weekly Media Monitoring. 2021; unpublished.
In the context of declining protections against SARS-CoV-2 infection and threat of COVID-19 resurgence, ETAGE suggests that countries offering a booster dose should focus first on:

- the following high risk population groups to minimize increases in severe COVID-19 cases:
  - residents and staff of long-term care settings;
  - people aged ≥60 years - starting with the oldest individuals and progressing to younger age categories;
  - adults <60 years with underlying medical conditions that put them at significantly higher risk of severe COVID-19 outcomes;
  - adults who are in close contact with moderately and severely immunocompromised persons;
- and health workers, to maximize resilience of and safety in healthcare facilities.

The countries should consider the following criteria while making a decision on introduction of a booster dose:

- epidemiology of COVID-19
- coverage with primary vaccine doses in in priority population groups
- current and predicted vaccine supply
- programmatic capacity.

ETAGE, along with SAGE, will continue to monitor and review emerging evidence to provide further advice on a booster dose for the wider adult population.

Co-administration of COVID-19 and influenza vaccines

ETAGE notes:

- Limited evidence suggests that coadministration of COVID-19 vaccines with inactivated influenza vaccine is acceptable both in terms of safety and of immunogenicity\(^\text{20}\).
- Administration of COVID-19 and influenza vaccines during the same visit would reduce the number of health care visits needed and will allow for more programmatic ease and potentially increase uptake of both vaccines.

ETAGE recommendations:

- ETAGE concurs with the SAGE consideration that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable despite

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limited available evidence, given that the known risk of serious illness of those infected with influenza virus or SARS-CoV-2 is substantial\textsuperscript{19}.

- ETAGE recommends that countries implement pharmacovigilance monitoring of coadministration of the two vaccines and report data on any safety events to WHO.
The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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