

7 April 2022
EMA/204784/2022

COVID-19: Joint statement from ECDC and EMA on the administration of a fourth dose of mRNA vaccines

EMA's COVID-19 task force (ETF) and the European Centre for Disease Prevention and Control (ECDC) have reviewed currently available studies and epidemiological data to provide a common position for EU/EEA countries on the current need and potential benefit of a fourth dose (second booster dose) of mRNA COVID-19 vaccines. This statement is based on the currently available scientific evidence and, as such, is preliminary and may be subject to change as more data become available. This statement should not be interpreted as a regulatory decision in terms of changes to the product information. National recommendations regarding COVID-19 vaccines policies are made by National Immunisation Technical Advisory Groups.

Administration of a fourth dose of mRNA vaccines to immunocompromised individuals whose immune system may have mounted a suboptimal response to earlier vaccination is already recommended and should be part of current vaccination campaigns. There are currently no data on immunogenicity, safety or effectiveness of additional further doses in this population. Additionally, in severely immunocompromised subjects, passive immunisation with monoclonal antibodies should be considered as an additional shield to protect against infection and disease.

The main source of empirical evidence on the potential public health impact of a fourth dose of mRNA vaccines as a second booster in immunocompetent individuals comes from data from Israel. These data indicate that a fourth dose of an mRNA vaccine given to immunocompetent individuals at least 4 months after the third dose is able to restore humoral immunity to the level seen after the third dose without raising any new safety concerns. Immunogenicity data are available for a follow-up period of 3 weeks. No longer-term data are available on the duration of the achieved antibody levels however available data indicate that protection against Omicron infection may wane at a similar rate to that observed following the receipt of a third dose. Only preliminary data from Israel with respect to vaccine effectiveness against severe disease following a fourth dose are currently available.

There are currently no data with respect to a second booster dose of an mRNA vaccines in people who have received a primary series with another type of vaccine, e.g. a viral vector vaccine.

Although data on the rate of waning protection among the very elderly (adults above 80 years of age) following the first booster dose are still limited, due to the fragility of this population, the lower immune response to vaccination and the higher risk of severe COVID-19 a second booster could be administered. Data on safety and efficacy are only available for a fourth dose administered at least 4 months after a third dose, and this interval, together with local epidemiological data, should be taken into account when deciding on vaccination strategies.

In the context of continued high SARS-CoV-2 incidence, rates of severe outcomes and deaths remain low. For immunocompetent individuals between 60 and 80 years of age, there are currently no clear epidemiological signals from the European region of substantial waning of vaccine protection against severe COVID-19. Therefore there is no indication of an imminent need for a second booster dose in

this population. However, continued close epidemiological and vaccine effectiveness monitoring is essential in order to rapidly detect signals indicating the emergence of an increasing risk of severe COVID-19 among vaccinated individuals. If such signals emerge, a fourth dose may be considered for adults between the ages of 60 and 80 years. Furthermore, local data on the epidemiological profile of severe COVID-19 cases may warrant a tailored use of a second booster dose in population groups identified as being at particular risk. If made available, vaccines adapted to better match recently circulating variants would be in principle preferable for additional boosters.

For immunocompetent individuals below 60 years of age, the administration of a second booster dose is not supported by the available data on continued level of vaccine protection against severe disease or death.

While seasonality is not yet established for SARS-COV-2, it is known that respiratory viruses tend to spread more consistently during the cold season. Therefore, plans for catch-up and re-vaccination campaigns should take this into account. In addition, in view of the possibility of new variants of concern (VOCs) emerging rapidly, the need to increase immunological breadth from available vaccines is a priority warranting the investigation of updated vaccine composition. However, it is still unclear when data on such updated vaccines will be available for a possible approval during the summer. Depending on whether waning protection against severe outcomes is observed in the coming months and on the evolving epidemiological situation, additional booster doses in anticipation of future waves or in advance of the next autumn/winter season may be needed in some or all age groups. Such additional doses will be of greatest value if administered closer to expected periods of increased viral circulation.

It must also be emphasized that, based on current evidence from longitudinal studies, routine surveillance and observational vaccine effectiveness studies, a primary course of vaccination remains the most efficient way to limit the disease burden and impact of COVID-19. COVID-19 vaccines continue to be very protective against severe disease, hospitalisation and death after completion of primary series and administration of the first booster dose. With vaccine uptake stagnating and in view of the significant variation in uptake across countries (only 63.5% of subjects aged 18 years and above in EU/EEA countries had received the first booster as of the end of March 2022), additional efforts are needed to increase vaccination uptake with a focus on the first booster dose as a public health priority.

ECDC and EMA will continue to closely follow vaccine effectiveness and epidemiological data, along with the progress in the development of adapted vaccines and will update advice accordingly. In addition, as more data are generated and submitted by marketing authorisation holders, these data may be reflected in the relevant product information where applicable.

The data and scientific evidence providing the basis for this statement are provided in the Annex.

Annex: Supporting rationale

Current epidemiological context

- Elevated COVID-19 incidence is resulting in a high proportion of reported hospitalisations and deaths among people with, but not necessarily due to, COVID-19. It is difficult to quantify this proportion which is likely to change over time with disease incidence. ECDC therefore considers ICU occupancy and ICU admissions to be the most reliable indicators of severity in the current context and the most stable over time.
- Many countries reported their highest case notification rates between January and February 2022 due to the highly transmissible Omicron variant of concern. Although this initial Omicron wave coincided with generally falling trends in all-age ICU admission rates since January 2022¹, some increases in early 2022 were observed in the number of older cases requiring admission to ICU, ventilation or ECMO, most notably among the 80+ age group.
- Despite the context of substantial co-circulation of influenza in most EU/EEA countries, all-cause mortality among age groups 65 and older and older adults (45 to 64) is currently declining².
- The EU/EEA has recently experienced an increase in COVID-19 cases among people aged 65 years and above, coinciding with the lifting of public health response measure and the more transmissible BA.2 Omicron sub-lineage becoming dominant. While ICU indicators are currently still low, the impact of this resurgence in the coming weeks will depend in part on the susceptibility of those who are infected to severe disease.
- Analysis of European COVID-19 surveillance data indicates that the highest rates of severe outcomes has been, and continues to be, among unvaccinated people. Within all age groups, occurrence of severe disease is extremely rare among those who have completed the primary vaccination course and/or received an additional booster dose.
- Although great progress has been achieved in uptake of COVID-19 vaccinations in the EU/EEA, there are significant variations in uptake across and within countries and population groups for the primary vaccination series and boosters. In the EU/EEA (as of end of March 2022) 83.3% of the adult (+18 years) population have received a full primary course of vaccination, 63.5% received a booster vaccination³. We also observe that vaccine uptake is stagnating. Therefore, continued efforts are needed to increase uptake in primary vaccination series and booster doses.

Vaccine effectiveness and impact in averted morbidity and mortality

- The rapid development and administration of COVID-19 vaccines has provided protection from severe disease and death globally. In 33 countries across the WHO European Region, an estimated 470,000 lives had been saved among those aged 60 years and over⁴, as of November 2021⁵.
- The number of cases of severe COVID-19 has been significantly decreased by the administration of a booster dose of COVID-19 vaccines after the primary vaccination.^{6,7}

¹ ECDC. <https://www.ecdc.europa.eu/en/covid-19/country-overviews>

² EuroMOMO. <https://www.euromomo.eu/bulletins/2022-12/>

³ [ECDC Vaccine Tracker](#)

⁴ [Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021 | Eurosurveillance](#)

⁵ [Estimated number of deaths directly averted in people 60 years and older as a result of COVID-19 vaccination in the WHO European Region, December 2020 to November 2021 | Eurosurveillance](#)

⁶ [Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel | NEJM](#)

⁷ [BNT162b2 Vaccine Booster and Mortality Due to Covid-19 | NEJM](#)

- The effectiveness of current vaccines in preventing infections with the Omicron variant is lower than it was for previous variants,^{8,9} however COVID-19 vaccines continue to be highly effective in protecting all age groups against severe disease, hospitalisation and death.

Waning vaccine effectiveness of protection from severe disease

- Vaccine effectiveness (VE) against severe outcomes is high following the administration of a first booster dose, with estimates of around 80 to 90% protection against severe disease and hospitalisations up to 2 to 3 months after administration of a booster dose, with slight decreases after approximately 4 months.
 - In elderly people (aged 70 years and older) in Finland before and after the emergence of the Omicron variant of concern, VE increased to 96% (95% CI, 95 to 97) 14 to 60 days after the third dose.¹⁰ VE of other homologous and heterologous 3-dose series was similar. Protection against severe COVID-19 requiring ICU treatment was even better. Since 1 January 2022, the VE of Comirnaty was 91% (95% CI, 79 to 96) and 76% (95% CI, 56 to 86) 14 to 90 days and 91 to 180 days after the second dose, respectively, and 95% (95% CI, 94 to 97) 14 to 60 days after the third dose.
 - In the Czech Republic, the VE of a Comirnaty booster against Omicron hospitalisation was 86% (95% CI, 84 to 89) 14 to 74 days after administration of the booster and reduced to 79% (95% CI, 74 to 82) after more than 75 days.¹¹ The VE against the need for oxygen therapy following a booster dose was 90% (95% CI, 87 to 92) 14 to 74 days after administration and reduced to 85% (95% CI, 80 to 88) after more than 75 days. The VE against the need for intensive care following a booster was 83% (95% CI, 75 to 89) 14 to 74 days after administration and 60% (95% CI, 37 to 74) after more than 75 days.
 - A test-negative, case-control study from Qatar investigated vaccine effectiveness and the effectiveness of natural and hybrid immunity after the administration of a booster dose. The VE against hospitalisation and death was over 90% for both Comirnaty and Spikevax, around 7 weeks after the third dose. The authors concluded that hybrid immunity resulting from prior infection and recent booster vaccination confers the strongest protection against either Omicron subvariant (BA.1 and BA.2) and that vaccination enhances protection of those with a prior infection.¹²
 - Among adults in the United States during the Omicron period, VE against hospitalisations was 91% during the first 2 months after a first booster, which decreased to 78% when more than 4 months passed since the first booster.⁴
 - A case control mRNA vaccination study¹³ performed in the United States focused exclusively on the most severe outcomes of COVID-19, including invasive mechanical ventilation (IMV) and death in adults aged 18 years and above. An overall high VE against IMV or in-hospital death of 90% was estimated. Sub-analysis indicated that while VE hardly decreases with age, it does reduce to a large extent depending on health status (from 92% in immunocompetent people to

⁸ [Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants| Nature Medicine](#)

⁹ [Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study| medrxiv](#)

¹⁰ [High vaccine effectiveness against severe COVID-19 in the elderly in Finland before and after emergence of Omicron—medrxiv.org](#)

¹¹ [Protection by vaccines and previous infection against the Omicron variant of SARS-CoV-2—medrxiv.org](#)

¹² [Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar](#)

¹³ [Effectiveness of mRNA Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death — United States, March 2021–January 2022 \(cdc.gov\)](#)

74% in immunocompromised people), demonstrating that high levels of durable VE can be obtained by mRNA vaccination in healthy subjects.

- A nationwide cohort analysis from Denmark estimated the vaccine effectiveness against COVID-19-associated hospitalisation. The effectiveness after a booster dose of Cominarty was estimated to 88.8% (95% CI: 87.3 to 90.1%), declining to 79.0% (76.5 to 81.3%) in the fourth month, and 66.2 (61.1-70.7) at 4+ months after the booster dose. For Spikevax, the initial effectiveness was 90.2% (87.3 to 92.5%), declining to 83.6% (77.7 to 88.0%) in the fourth month, and 77.3 (63.1-86.1) at 4+ months.¹⁴
- Another study¹⁵ showed that with the generally milder disease seen with Omicron, contamination of data on hospitalisations with incidental cases reduces VE estimates. With more precise VE estimates, high levels of booster VE against hospitalisation with the Omicron variant have been observed (up to 96%), in particular among older adults who are at greatest risk and against more severe outcomes. Nevertheless, there is evidence of limited waning of protection from 3-4 months after administration of a booster dose.
- Due to the recent exposure of large numbers of the population to the Omicron variant, hybrid immunity, gained from documented previous infection and receipt of a full-vaccination course, is likely to play an increasingly important role in protection at population level.^{16,17,18} When combined with three vaccine doses, hybrid immunity provides additional population protection in the current context.

Current recommendations on booster doses in EU/EEA countries

- Many EU/EEA countries are currently recommending booster doses at a defined interval following primary vaccination, in light of evidence of waning protection over time.
- For immunocompromised individuals, all 30 EU/EEA countries recommend an **additional primary dose** as an extension of the primary vaccination course. Twenty countries also recommend a booster dose for immunocompromised individuals following the extended primary three-dose vaccination series (i.e. four doses).
- For the general population, all 30 countries also recommend **first booster doses** to different age groups due to waning protection. Half of the EU/EEA countries (15/30) recommend booster doses for all adults aged 18 years and over. Fifteen countries recommend boosters for adolescents (either to those over 12 years or those over 16 years).
- As of 5th April 2022, nine countries recommend a **second booster dose** (fourth dose) for different vulnerable population groups such as residents in long-term care facilities and the elderly, with different age cut-offs (Cyprus, Finland, France, Germany, Greece, Hungary, Ireland, The Netherlands and Sweden). The recommendations for a fourth dose for vulnerable people and certain at-risk groups aim to restore serological responses and overall vaccine efficacy. The basis

¹⁴ [Vaccine effectiveness against infection and COVID-19-associated hospitalisation with the Omicron \(B.1.1.529\) variant after vaccination with the BNT162b2 or mRNA-1273 vaccine: A nationwide Danish cohort study](#)

¹⁵ [Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study \(khub.net\)](#)

¹⁶ [Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection | NEJM](#)

¹⁷ [Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden - The Lancet Infectious Diseases](#)

¹⁸ [Effectiveness of CoronaVac, ChAdOx1 nCoV-19, BNT162b2, and Ad26.COV2.S among individuals with previous SARS-CoV-2 infection in Brazil: a test-negative, case-control study - The Lancet Infectious Diseases](#)

for the recommendations is the recorded waning over time of protection afforded by the third dose against infection and symptomatic disease, as well as local epidemiological considerations.^{19,20,21}

Current recommendations on additional booster doses in other parts of the world

- The Australian Technical Advisory Group on Immunization made recommendations on 25 March 2022 on a fourth COVID-19 vaccine dose to increase vaccine protection before their winter season for some groups, including adults aged 65 and older, residents in long-term care facilities and the severely immunocompromised. On 29 March 2022, the United States Food and Drug Administration (FDA) authorised the use of a second booster dose of either the Pfizer-BioNTech COVID-19 vaccine (Comirnaty in the EU) or the Moderna COVID-19 vaccine (Spikevax in the EU) for individuals 50 years of age and older at least 4 months after receipt of a first booster dose. Following this authorisation, the US Centers for Disease Control and Prevention (CDC) updated their recommendations to allow certain immunocompromised individuals and people over the age of 50 who received an initial booster at least 4 months earlier to be eligible for another mRNA booster.

Effectiveness and safety of a second booster vaccination with mRNA vaccines

- The vaccine effectiveness of a second booster dose has been studied mainly in subpopulations considered to be at higher risk for severe COVID-19. Data are still limited, and all data pertain to the Omicron variant. Effectiveness in preventing infection is observed for a few weeks after the administration of the fourth dose but decreases quickly over time. Early data from Israel indicate that the risk of severe infection and/or death due to COVID-19 is decreased for up to 10 weeks after the administration of a fourth dose as compared to those receiving only the third dose, albeit in populations already experiencing very low levels of severe outcomes and thus providing minimal absolute reduction in severe outcomes. The maximum duration of this protection is not yet known due to short follow-up times in the studies available.
 - In an open-label, nonrandomized clinical study²² conducted during the Omicron period in Israel, the immunogenicity, safety and efficacy of a fourth dose of either Comirnaty or Spikevax was evaluated in healthcare workers when administered at least 4 months after the third dose of Comirnaty. All participants were actively screened for SARS-CoV-2 infection on a weekly basis. The data from this small interventional study showed that administration of a fourth dose does not reveal new serious adverse events and that it restores humoral responses to the highest level seen post-third dose. Only subjects expected to be at higher risk of infection were enrolled in the study (whose IgG antibody levels are below the 40-percentile). Breakthrough infections, nearly all asymptomatic, were very common and VE against SARS-COV-2 infection was not established (point estimates 10-30%, and non-statistically significant). There are no data to show that a fourth vaccination may be of benefit in healthy younger adults.
 - During the Omicron period, real-world evidence collected from electronic medical records in Israel and summarized in a pre-print study showed that subjects aged 60 to 100 years, including patients with comorbidities, were significantly less likely to die from COVID-19 if they received a second booster compared to those immunized with only 3 doses at least four months earlier. The absolute risk reduction conferred by the fourth dose was 0.07% in

¹⁹ [Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study - ScienceDirect](#)

²⁰ [Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance – VISION Network, 10 States, August 2021–January 2022 \(cdc.gov\)](#)

²¹ [COVID-19 vaccine surveillance report - week 9 \(publishing.service.gov.uk\)](#)

²² [Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron | NEJM](#)

circumstances of high circulation of Omicron variant.²³ Similarly, a preprint for a retrospective test-negative case-control study in Israel showed that subjects 60 years of age or older who received a second booster was 73% effective in preventing severe breakthrough COVID-19 (defined as COVID-19-related hospitalisation or death) during at least 9 weeks of follow-up compared with those who received only the first booster, although severe disease was a rare event (<1%) in both groups and relative effectiveness appeared to wane somewhat over time in the fourth dose group relative to the third dose group.²⁴ Both studies adjusted their results for differences between the groups with regards to age, gender, socioeconomic status, underlying comorbidities and calendar week of testing.

- Another study among 1.2 million Israelis aged 60 and older estimated vaccine effectiveness of the fourth dose of Comirnaty against SARS-CoV-2 infection and severe illness due to COVID-19.²⁵ The results showed a 2-times lower rate of confirmed infection and a 3.5-times lower rate of severe COVID-19 in adults in this age group in the fourth week after receiving a fourth dose compared to adults who received a third dose more than four months before. Protection against confirmed infection waned in the later weeks, whereas protection against severe illness did not wane during the short follow period of 6 weeks after receipt of the fourth dose.
- The waning of protection from a second booster dose has not yet been sufficiently studied due to the limited follow-up period. Existing studies are observational and, thus, unavoidably present limitations, including residual confounding factors. Several of the studies are still awaiting peer review. Although studies make adjustments for calendar time, age, and other potential confounders, it cannot be guaranteed that there are no remaining differences between the groups that can influence the VE estimate.
- Despite the relatively small size of the safety database, no major safety issues have emerged following administration of the second booster dose, a finding which is consistent across studies. The EMA will continue monitoring the safety of the second booster closely.

Implementation considerations

- As data on adapted vaccines will be available in the near future and possibly lead to the authorisations of adapted vaccines later on in the year, vaccination campaigns should take into account the impact of repeated booster doses on vaccine acceptance and uptake in the general population. The offer of a fourth dose should be promoted on the basis of an understanding of: (a) public concerns and expectations regarding the vaccines and (b) people's perceptions and concerns about the disease itself. Behavioural research can offer important insights into vaccination 'fatigue' and the low risk perception of the disease among many people today, and thereby providing direction to vaccination campaigns.

²³[Second Booster Vaccine and Covid-19 Mortality in Adults 60 to 100 Years Old | Research Square](#)

²⁴[Relative Effectiveness of Four Doses Compared to Three Doses of the BNT162b2 Vaccine In Israel | medRxiv](#)

²⁵[Protection by a Fourth Dose of BNT162b2 against Omicron in Israel | NEJM](#)