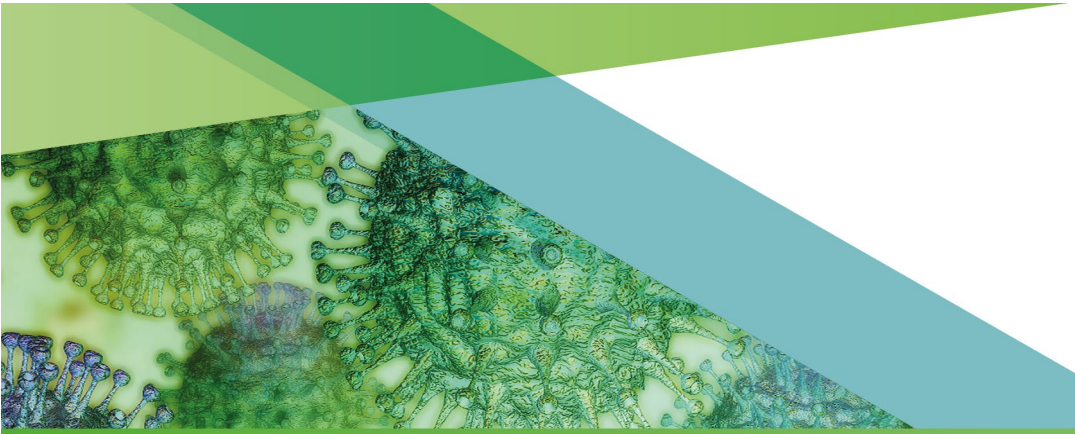

TECHNICAL REPORT

Public health considerations and evidence to support decisions on the implementation of a second mRNA COVID-19 vaccine booster dose

28 April 2022

Key messages

- Following the rise to dominance of the SARS-CoV-2 Omicron variant in January 2022, transmission and burden of severe disease among older age groups increased to very high levels, although this has recently started to decline in most European Union/European Economic Area (EU/EEA) countries. It remains uncertain whether, in the coming weeks/months, these indicators will stabilise at the low inter-wave levels observed prior to Omicron, or at an elevated plateau.
- Since completeness of vaccination status in COVID-19 cases reported to the European Surveillance System (TESSy) is limited, we are unable to attribute the observed increases in severe disease due to Omicron to individuals with a particular level of vaccination. However, a separate analysis of three countries with complete data on severe outcomes and vaccination status demonstrates that the highest burden of severe outcomes has been among unvaccinated people in all adult age groups and this continues to be the case.
- All EU/EEA countries are currently recommending a first booster dose at a defined interval following primary vaccination. At present, uptake of the first booster dose in the EU/EEA adult population is 64.2% (country range 11.0–87.9%).
- In general, vaccine effectiveness (VE) against infection due to Omicron has been shown to be reduced compared to other SARS-CoV-2 variants, and protection wanes over time.
- Published literature indicates VE against severe outcomes caused by Omicron remains high, with continued strong protection in the range of 80–90% around 2–3 months after receiving the first booster, albeit with some evidence of this waning slightly from around 3-4 months. In addition, analysis of severe outcomes among COVID-19 cases having received a first booster dose, as reported to TESSy, also shows that hospitalisation and death are extremely rare in this group; 0.38% and 0.1% respectively. Moreover, the adjusted risk of hospitalisation and death is higher in older populations, males and those who received a first booster dose more than three months ago.
- Evidence currently available indicates that a second mRNA booster dose is able to restore the humoral immune response to levels similar to those observed shortly after the first booster dose, and also to restore VE against infection, although this does appear to wane rapidly. Early data indicate that the risk of severe disease and/or death due to COVID-19 is reduced for up to 10 weeks after the administration of a second booster dose, compared to those receiving only the first booster dose. However, this is in populations already experiencing low levels of severe outcomes, thus providing small absolute reductions. The maximum duration of this protection is not yet known due to the short follow-up periods after the second booster in the studies available.
- Mathematical modelling suggests that increasing the proportion of the population who have been provided with immunity through a primary course and first booster has a substantial potential to reduce COVID-19 death burden by the end of October 2022. This is particularly relevant for countries where gaps in coverage are still large, and efforts to address these gaps remain a public health priority. With regard to the second booster, modelling shows that its roll-out in some vulnerable groups could avert a substantial proportion of COVID-19 deaths between now and mid-autumn 2022. Further indications are set out below.
  - The total number of averted deaths, both before and beyond autumn 2022, depends on the COVID-19 incidence, and as such is difficult to predict with certainty.
  - To reduce future COVID-19 burden through a second booster, the effect per dose is highest when targeting vulnerable populations, such as older age groups.
  - Given that vaccination and the boosting of immunity achieves the maximum impact at population level if administered before an epidemic wave and the minimum impact if administered at the end of an epidemic

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wave, a continuous high incidence or a large surge in cases in the early summer would imply greater benefit could be achieved by an early second booster roll-out. Alternatively, if surveillance shows relatively low incidence levels during the summer months, the optimal timing for a second booster roll-out would be later in the year, subject to further assessment of the risk of a surge in cases during autumn/winter 2022 and waning protection against severe outcome.

- Given data on the current epidemiological situation, vaccine effectiveness and mathematical modelling, it is suggested that EU/EEA countries consider the information set out below with respect to the administration of a second COVID-19 booster dose.
  - Due to the fragility of the population, continued high hospitalisation and ICU rates in many settings, lower immune response to vaccination, and the higher risk of severe COVID-19, the public health benefit of administering a second booster dose is clearest in those aged 80 years and above. Immediate administration of a second booster dose in this population would be optimal in situations of continued high or increasing viral circulation. Alternatively, in situations of low viral circulation, administration of a second booster dose should be considered prior to autumn 2022.
  - Mathematical modelling suggests that a second booster roll-out including those aged 60-79 years who are immunocompetent in the EU/EEA is likely to be beneficial, although the best timing for the roll-out depends on the highly uncertain future of COVID-19 incidence. Therefore, continued close epidemiological and vaccine effectiveness monitoring is essential in order to rapidly detect signals of increased SARS-CoV-2 circulation or risk of severe COVID-19 among vaccinated individuals. If such signals emerge, a second booster may be considered for all or some adults between the ages of 60 and 79 years and countries should have plans in place for a rapid deployment of booster doses in this population group.
  - For immunocompetent individuals below 60 years of age, the administration of a second booster dose at this time is not supported by the current epidemiological, modelling or VE data on the continued level of vaccine protection against severe disease or death.
  - Continued protection against severe disease will need to be monitored in those populations receiving a second booster dose in spring/early summer 2022 in order to consider the need for additional booster doses in relation to potential future autumn/winter 2022 waves.
  - Adapted vaccines may potentially be authorised later in the year and could be taken into account with regard to the timing of a second booster dose.
  - It remains essential that countries have strong surveillance systems to detect increased incidence, severity, and emerging variants of concern coupled with preparedness planning to quickly implement booster dose campaigns if deemed necessary.
  - Communication planning should consider when the efforts to promote uptake of the second COVID-19 booster dose are likely to be most effective. At this stage, focus should be on targeted communication for those population groups who are recommended a second booster, whilst also ensuring full vaccination and uptake of the first booster in those most at risk of severe disease who have not yet completed their recommended vaccinations.
  - In anticipation of possible new waves and the related need to adapt recommendations around a second booster dose (e.g. extending them to other age groups), planning of future campaigns should be based on good practices to promote vaccine acceptance and uptake identified during earlier phases of the vaccination programme, and taking into account behavioural insights research.
- Depending on the evolving epidemiology and forthcoming data on vaccine effectiveness over time, it will be necessary to re-assess recommendations on timing and with regard to the populations that may benefit from a second COVID-19 vaccination booster dose in the near future.

Background and rationale

Despite the sustained transmission of SARS-CoV-2 observed recently in many parts of the EU/EEA, including in older age groups, the continued expansion of the Omicron BA.2 variant sub-lineage, and the widespread lifting of public health measures, the rates of severe disease associated with COVID-19 have not been as significant as those seen during earlier COVID-19 waves. Nevertheless, the epidemiological situation remains fairly mixed across the EU/EEA, with transmission remaining high overall. At the same time, progress in deployment of COVID-19 vaccines has been slowing down in most EU/EEA countries, with vaccination uptake plateauing in most age groups, both for the primary course and the first booster dose [1].

Several countries have recently adopted or are considering adopting a policy on the administration of a second booster dose to ensure sufficient and sustained protection against infection and symptomatic disease and to guard against severe outcomes in certain vulnerable population groups (e.g. the elderly, those with underlying conditions, etc.) [2].

In this context, the COVID-19 task force (ETF) of the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) recently reviewed available evidence from studies and epidemiological data to provide a common position for EU/EEA countries on the current need and potential benefit of a second booster dose of mRNA COVID-19 vaccines [3]. In the EU/EEA, two mRNA COVID-19 vaccines (Comirnaty and Spikevax) are currently authorised for use as boosters in individuals aged 12 years or older (Comirnaty) and 18 years or older (Spikevax) following completion of a primary course. COVID-19 Vaccine Janssen is authorised for use as a booster in adults aged 18 years and older [4].

Scope of this document

This document offers a more detailed overview of the available scientific and epidemiological evidence and public health considerations in order to support decisions on the implementation of a second booster dose of COVID-19 vaccine. It aims to provide input to EU/EEA Member States for evidence-based decision-making when planning vaccination campaigns, both at present and during the coming months. Given the evidence available at this time, the document focuses on mRNA vaccines in immunocompetent individuals.

Target audience

The target audiences for this document are the EU/EEA National Immunisation Technical Advisory Groups (NITAGs) collaboration, and national public health institutes and ministries of health in the EU/EEA, as well as public health experts and decision-makers at national and subnational level.

Definitions

Primary vaccination course: dosage schedule provided according to authorisation in the EU/EEA [4]. For mRNA vaccines the primary course in immunocompetent individuals includes two doses, and in immunocompromised individuals three doses.

Additional dose: this refers to any additional dose of currently authorised vaccines in the EU that is provided to complement the primary vaccination course for individuals with severe immunocompromising conditions.

First booster dose: this refers to an additional dose of vaccine provided in order to boost immunity at an interval of at least three months after the primary vaccination course. In this document this is sometimes referred to as the first booster dose, or the third overall dose for immunocompetent individuals, unless otherwise specified.

Second booster dose: this refers to an additional dose of vaccine provided to an individual who has completed the primary vaccination course and received the first booster dose. According to existing national policies, the second booster is currently provided after an interval of at least three to six months following the first booster dose. In this document this is sometimes referred to as the second booster dose, or the fourth overall dose for immunocompetent individuals, unless otherwise specified.

Methods

This report is based on analysis of the following sources of data:

- Aggregate and case-based epidemiological data reported by EU/EEA countries to the European Surveillance System (TESSy) and aggregate data obtained from public sources.
- Summary of data reported by EU/EEA countries to TESSy on COVID-19 vaccine doses administered and uptake of the primary course and additional/booster dose in the total population and by age group.
- Summary of national policies on the administration of a second booster dose (responses received from EU/EEA countries to the vaccine-related questions for the Integrated Situational Awareness and Analysis report and a rapid desk review of official sources [2], including selected countries beyond the EU/EEA, as published on national health authority websites.
- Review of published and pre-print literature on vaccine effectiveness of the first booster dose (third dose) in different populations to assess waning protection against severe disease over time and in different populations.
- Review of published and pre-print literature to assess vaccine effectiveness of the second booster dose (fourth dose).
- An age-stratified compartmental model for all 30 EU/EEA countries was fitted to historically-observed data up to early-April 2022 to conduct a counterfactual scenario analysis for the next six months (to end of October 2022). In this scenario analysis, second booster dose roll-out targeting older adults is considered to be initiated at different timepoints. We compare the impact of the alternative roll-out timings in terms of the predicted burden (such as COVID-19 deaths and hospitalisations), providing information on the relative value of different second booster dose roll-out strategies.

Additional details regarding some of the analysis methods are included in the sub-sections of 'Results' below.

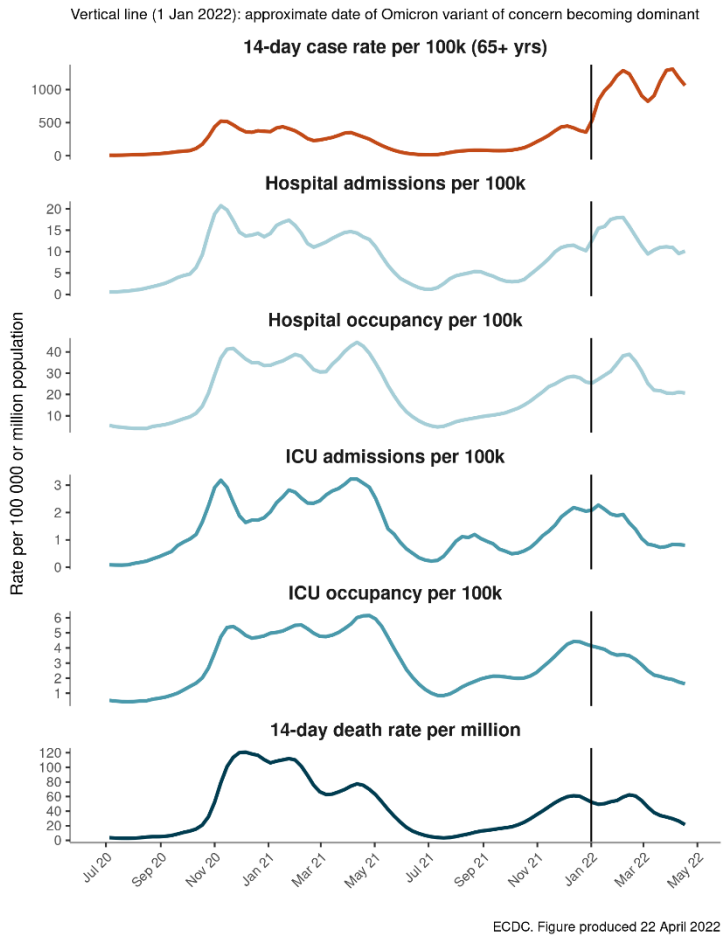
Results

Epidemiological overview based on European surveillance data

The elevated COVID-19 incidence due to the Omicron variant has resulted in a high proportion of reported hospitalisations and deaths among people with COVID-19, although a proportion of the hospitalisations and deaths may not have necessarily been due to COVID-19. It is difficult to quantify this proportion which is likely to change over time with disease incidence. At the same time, a shift in focus in many countries towards targeted testing of people in risk groups has made case rates in the total population, and test positivity, extremely difficult to interpret. These indicators are currently of limited value for comparison over time or between countries. ECDC therefore considers case rates among people aged 65 years and above to be the most reliable indicator of SARS-CoV-2 transmission, and ICU occupancy and ICU admissions the most reliable indicators of severity in the current context.

Since Omicron became dominant in January 2022, pooled all-age ICU indicators at the EU/EEA level have shown a steadily decreasing trend, despite two waves in which case rates among people aged 65 years and above reached record highs (Figure 1). However, age-specific notification rates of cases requiring hospitalisation, admission to ICU or ventilation reveal a more nuanced picture, with a considerable burden observed among the elderly.

Figure 1. Epidemiological indicators at the EU/EEA level, week 26, 2021 to week 15, 2022



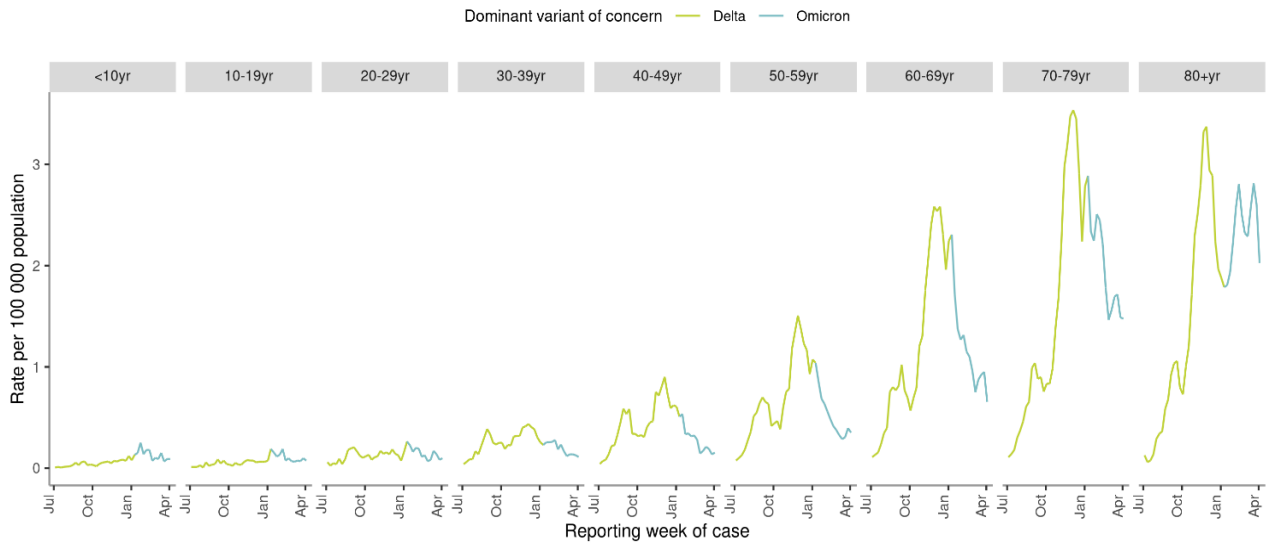
Note: rates of severe outcomes include cases with and due-to COVID-19 since most countries do not make this distinction in their routine surveillance data.

Pooled analysis of case-based data reported to TESSy by nine EU/EEA countries with sufficient data completeness show that, in the time since Omicron became dominant, increases in rates of severely ill cases in hospital (requiring admission to ICU and/or ventilation and/or extracorporeal membrane oxygenation) were reported among those aged 60 years and above. This effect was most substantial among those aged 80 years and above, for whom rates during the second Omicron wave in March 2022 (coinciding with the lifting of public health response measures and dominance of the more transmissible BA.2 Omicron sub-lineage) reached levels comparable to the first Omicron wave in January-February and almost as high as those during the peak of the Delta wave (Figure 2). However, country-specific patterns vary, with individual countries such as Austria, Germany and Italy appearing to drive this pooled trend (Figure A1, Annex 1).

The highest burden of notified cases requiring hospitalisation in the same nine countries also occurred in the oldest age groups, most strikingly in those aged 80 years and above (Figure 3; Figure A2, Annex 1). The interpretation of this is made difficult by the considerable uncertainty concerning the proportion of cases hospitalised due to or with COVID-19 since Omicron became dominant. It is not normally possible to make this distinction in routine surveillance data submitted to TESSy.

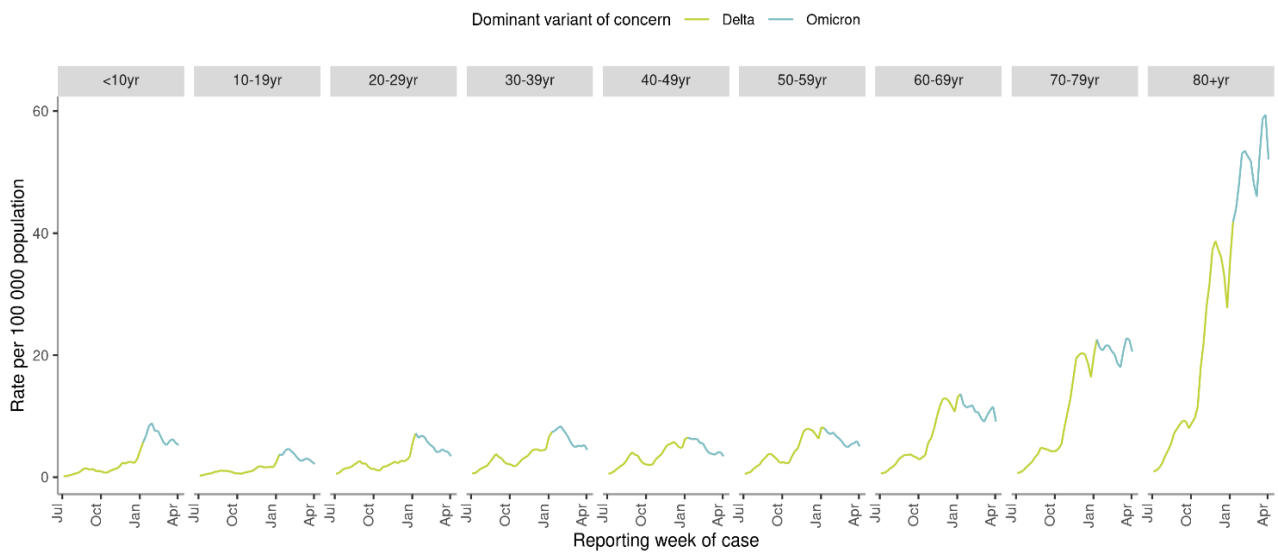
Transmission among those aged 65 years and above and the burden of severe disease among older age groups remain very high although they have started to fall in most countries. It remains uncertain whether in the coming weeks/months, these indicators will stabilise at the low inter-wave levels observed prior to Omicron or at an elevated plateau.

Figure 2. Age-specific notification rate of cases admitted to ICU and/or requiring ventilation and/or extracorporeal membrane oxygenation, week 26, 2021 to week 13, 2022



Source: TESSy case-based data pooled from Austria, Cyprus, Denmark, Germany, Ireland, Italy, Luxembourg, Slovakia and Sweden
Data reported to week 15, 2022; the most recent two weeks have been excluded to allow for delay to severe outcome

Figure 3. Age-specific notification rate of hospitalised cases, week 26, 2021 to week 13, 2022



Source: TESSy case-based data pooled from Austria, Cyprus, Denmark, Germany, Ireland, Italy, Luxembourg, Slovakia and Sweden
Data reported to week 15, 2022; the most recent two weeks have been excluded to allow for delay to severe outcome

Since completeness of vaccination status reported to TESSy is limited, we are unable to attribute the observed increases to individuals with a particular level of vaccination. A separate analysis of three countries with complete data on severe outcomes and vaccination status indicates that the highest burden of severe outcomes has been, and continues to be, among unvaccinated people in all adult age groups (Figures A3-6, Annex 2). Outcomes stratified by booster dose are not shown as this would have further limited the number of countries that could be included.

Risk of hospitalisation and death post-first COVID-19 booster dose

For this analysis, cases were considered for all adult individuals aged 18 years and older with laboratory-confirmed symptomatic SARS-CoV-2, as reported to TESSy by EU/EEA countries from 1 October 2021 to 27 March 2022 for hospitalisation and from 1 October 2021 to 27 March 2022 for case fatality, with a disease onset at least two weeks after receiving their first booster dose. Individuals were then divided into groups who had received their first booster less than or more than three months prior to the COVID-19 onset data. The risk of hospitalisation and death was compared between groups defined by sex, age (18–59, 60–79, 80+ years) and onset month.

Negative binomial models were run to calculate the Relative Risks (RR) and the 95% Confidence Interval (95% CI) of hospitalisation for vaccinated individuals with booster dose more than three months before, compared to those vaccinated with booster dose less than three months before, adjusting for sex, age group and onset month.

Table 1. Main characteristics of COVID-19 cases who had a disease onset at least two weeks after receiving their first COVID-19 vaccine booster dose, by hospitalisation status, 1 October 2021–27 March 2022 (N=281 967)

	Total		Not hospitalised		Hospitalised	
Characteristic	Number of cases	Proportion of cases (%)	Number of cases	Proportion of cases (%)	Number of cases	Proportion of cases (%)
	281 967	100	280 885	99.6	1 082	0.38
Booster vaccination						
Booster dose <3 months	218 180	77.4	217 460	99.7	720	0.33
Booster dose >=3 months	63 787	22.6	63 425	99.4	362	0.57
Sex						
Female	165 305	58.6	164 811	99.7	494	0.3
Male	116 662	41.4	116 074	99.5	588	0.5
Age at diagnosis (years)						
18-59	174 018	61.7	173 821	99.9	197	0.11
60-79	92 837	32.9	92 268	99.4	569	0.61
80+	15 112	5.4	14 796	97.9	316	2.09
Onset month						
October 2021	265	0.1	256	96.6	9	3.40
November 2021	1 672	0.6	1 635	97.8	37	2.21
December 2021	4 606	1.6	4 509	97.9	97	2.11
January 2022	84 065	29.8	83 816	99.7	249	0.30
February 2022	105 809	37.5	105 451	99.7	358	0.34
March 2022	85 550	30.3	85 218	99.6	332	0.39

Cases are from Estonia (84), France (2), Ireland (5), Liechtenstein (1), Luxembourg (17 993), Poland (263 882).

The main results for hospitalisation data are presented in Table 1. Of 281 967 individuals who had received a first COVID-19 booster dose and then acquired COVID-19 between October 2021 and March 2022, 0.38% required hospitalisation. This proportion was higher for the individuals who, at the time of onset, had received their booster dose more than three months before their diagnosis of COVID-19 (0.57%), compared to those who had received their booster dose less than three months before (0.33%). The proportion was also higher for males (0.5%) than females (0.3%), increased by age group and decreased by calendar time.

Table 2. Main characteristics of COVID-19 cases who had a disease onset at least two weeks after receiving their first COVID-19 vaccine booster dose, by case fatality, 1 November 2021−27 March 2022 (N= 264 831)

	Total		Survived		Died	
Characteristic	Number of cases	Proportion of cases (%)	Number of cases	Proportion of cases (%)	Number of cases	Proportion of cases (%)
	264 831	100	264 680	99.9	151	0.1
Booster vaccination						
Booster dose <3 months	230 507	87.0	230 400	99.95	107	0.05
Booster dose >=3 months	34 324	13.0	34 280	99.87	44	0.13
Sex						
Female	148 313	56.0	148 256	99.96	57	0.04
Male	116 518	44.0	116 424	99.92	94	0.08
Age at diagnosis (years)						
18-59	147 390	55.7	147 388	100.0	2	0.00
60-79	98 802	37.3	98 757	99.95	45	0.05
80+	18 639	7.0	18 535	99.44	104	0.56
Onset month						
November 2021	392	0.2	381	97.19	11	2.82
December 2021	3 201	1.2	3 184	99.47	17	0.53
January 2022	36 350	13.7	36 311	99.89	39	0.11
February 2022	98 039	37.0	97 999	99.96	40	0.04
March 2022	126 849	47.9	126 805	99.97	44	0.03

Cases are from Estonia (84), France (2), Ireland (5), Liechtenstein (1), Luxembourg (17 993), Netherlands (246 746).

The main results for case fatality data are presented in Table 2. Of 264 831 individuals who had received a first COVID-19 booster dose and then acquired COVID-19 between November 2021 and March 2022, 0.1% died. This proportion was higher for the individuals who, at the time of onset, had received their booster dose more than three months (0.13%) before their diagnosis of COVID-19, compared to those who had received their booster dose less than three months before (0.05%). The proportion was also higher for males (0.08%) than females (0.05%), increased by age group and decreased by calendar time.

Table 3. Adjusted relative risk of hospitalisation and death by time from booster vaccination, sex, age group, gender **

	Adjusted relative risk of hospitalisation (95% CI) [&]	Adjusted relative risk of death (95% CI) [$]
Booster vaccination		
Booster dose <3 months	Ref	Ref
Booster dose >=3 months	1.49 (1.27-1.75) *	3.52 (2.27-5.47) *
Sex		
Female	Ref	Ref
Male	1.53 (1.36-1.73) *	1.82 (1.31-2.55) *
Age at diagnosis (years)		
18-59	Ref	Ref
60 to 79	5.01 (4.32-5.99) *	30.52 (7.40-126.0) *
80	16.39 (13.60-19.75) *	295.75 (72.66-1203.89) *

** P-value<0.001 ** Further adjusted by onset month.*

[&] Cases are from Estonia (84), France (2), Ireland (5), Liechtenstein (1), Luxembourg (17 993), Poland (263 882)

$ Cases are from Estonia (84), France (2), Ireland (5), Liechtenstein (1), Luxembourg (17 993), Netherlands (246 746).

The main results for the Relative Risks (RR) and the 95% Confidence Interval (95% CI) of hospitalisation and death are shown in Table 3: the adjusted risk of hospitalisation increases by almost 50% for those having received the booster dose three months or more before diagnosis of COVID-19 (362 of 63 787 cases), compared to less than three months before (720 of 218 180 cases). A significant increase in the adjusted risk of hospitalisation is seen also among men compared to women (RR=1.53, 95% CI: 4.32−5.99) and among older age groups. With regard to the adjusted risk of death, those who received the booster dose three months or more before their diagnosis of COVID-19 have a 3.5 fold increase in the risk of dying after COVID-19 onset (44 of 34 324 cases) compared to those who received less than three months before (107 of 230 507 cases). A significant increase in the adjusted risk of death is seen also for men (RR=1.82, 95% CI: 1.31−2.55) and the elderly.

Current uptake of primary vaccination and first booster dose in the EU/EEA

As of week 16, 2022 (24 April 2022), the uptake of the primary vaccination course against COVID-19 in the total EU/EEA population had reached 72.6% and is levelling off, with a very small progression (average 0.05% weekly increase in the last month). The uptake of a first booster/additional dose (this includes both uptake of a first booster dose and uptake of an additional dose administered as extension of the primary course, for instance, in severely immunocompromised individuals) has reached 64.2% among adults aged 18 years and above and is still slowly increasing (average 0.2% weekly increase in the last month). In individuals above 60 years of age, the uptake of a first booster/additional dose has reached 82.0%. The increase in uptake of the first booster/additional dose is higher among younger adults aged 18–24 years (average 0.8% weekly increase in the last month) [1]. Table 4 summarises the uptake of the primary and first booster/additional dose by age group as of week 16 and Figure 4 displays the uptake of the first booster/additional dose among adults in the EU/EEA by age groups over time.

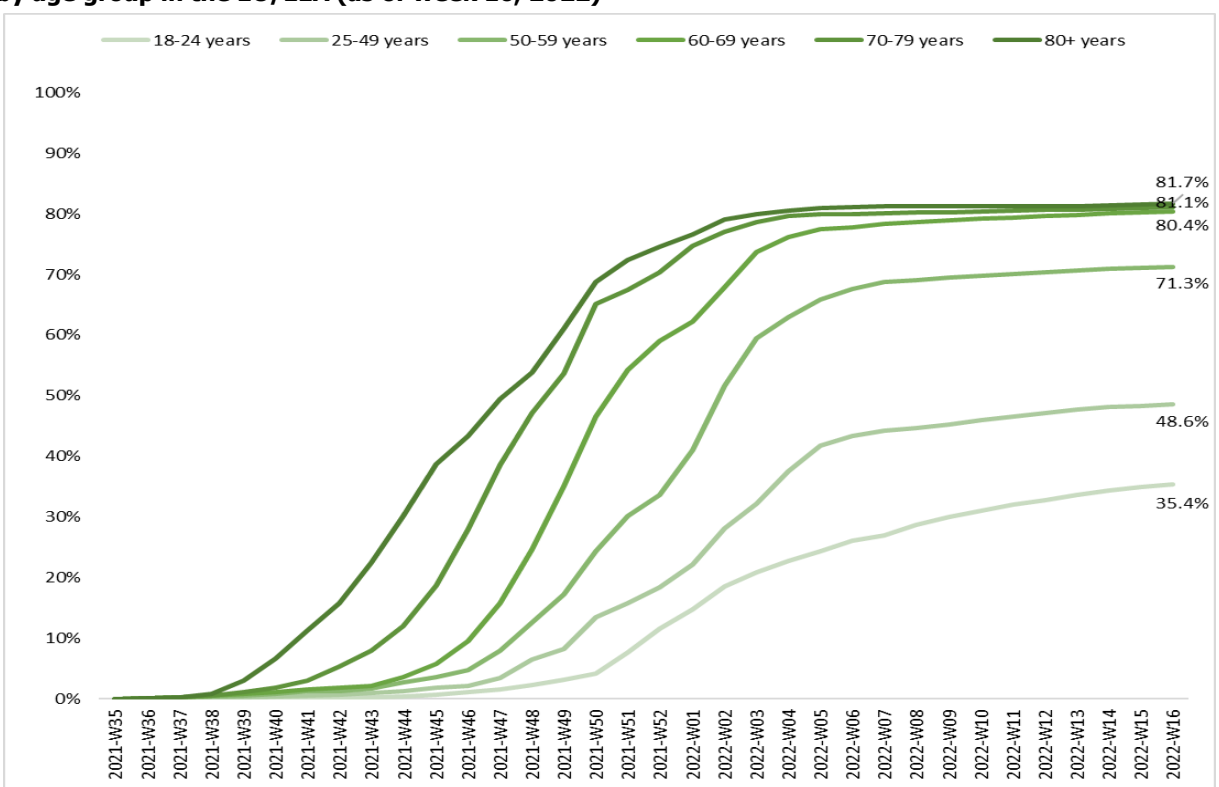
Table 4. Summary table of COVID-19 vaccine uptake as of week 16, 2022

Population group	Uptake of primary course (range)	Uptake of a first booster/additional dose (range)	Number of countries reporting
Total population	72.6% (29.7-86.0%)	53.2% (9.0-70.5%)	30
Adults (18+)	83.4% (35.5-94.3%)	64.2% (11.0-87.9%)	30
Persons aged 60+*	89.4% (38.2-100%)	82.0% (13.2-100%)	29
Persons aged 80+*	93% (26.1-100%)	81.7% (7.9-100%)	28

Notes: cumulative uptake of the primary vaccination course based on the dosing schedule authorised in the EU/EEA; cumulative uptake of a first booster/additional doses. This includes uptake of the first booster dose after the primary course as well as uptake of a first additional dose administered as an extension of the primary course - for example, in certain immunocompromised individuals.

**Median uptake among reporting countries.*

Figure 4. Median cumulative uptake of first booster/additional dose of COVID-19 vaccine among adults by age group in the EU/EEA (as of week 16, 2022)

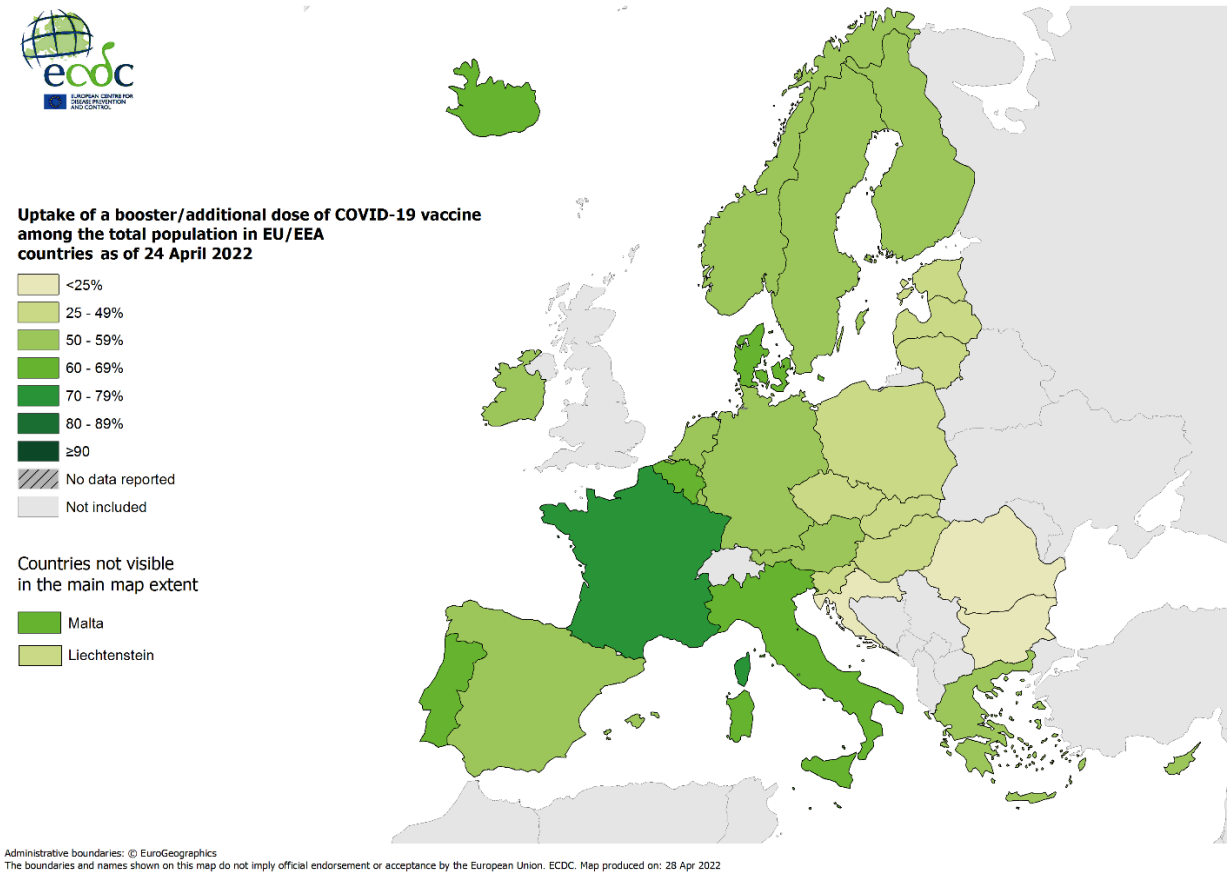


Source: TESSy data reported by 29 countries as of week 16, 2022 (missing the Netherlands)

Overall, the progress in vaccine uptake remains unequal across EU/EEA countries, with the uptake of the first booster/additional dose among adults ranging from 11.0 to 87.9% (Figure 5).

More information on COVID-19 vaccine doses administered and vaccine uptake rates can be found in the ECDC Vaccine Tracker [5].

Figure 5. Uptake of first booster/additional dose of COVID-19 vaccine among adults aged 18 years and above in EU/EEA countries (as of week 16, 2022)



Evidence for impact of the Omicron variant on transmissibility and severity

The SARS-CoV-2 Omicron variant of concern (VOC) rapidly replaced the previous SARS-CoV-2 Delta variant in all EU/EEA countries during the first months of 2022 and as of weeks 12−13, it accounted for nearly 100% of sequenced samples in the EU/EEA (range 79−100%)[1]. Presently the BA.2 sub-lineage of Omicron accounts for 89% of the samples sequenced (58−99%). As indicated by earlier in vitro and in vivo studies, Omicron can evade the protective effects of antibodies elicited by vaccination or natural infection to a certain extent [6]. The immune evasion capability of Omicron resulted in sharp increases in the number of COVID-19 cases between January and March 2022, leading to unprecedentedly high community transmission across the region [1].

In comparison with earlier circulating variants, Omicron infections appear less likely to lead to severe clinical outcome requiring hospitalisation or ICU admission [6]. Although the reduction in severity is partially due to the inherent characteristics of the virus, results from vaccine effectiveness studies have shown that despite the observed element of immune evasion, a significant role is played by vaccination in preventing severe clinical outcomes from Omicron infection, with effectiveness against severe illness increasing significantly among people having received three vaccine doses.

Vaccine effectiveness and duration of protection following booster doses against the Omicron variant

The latest ECDC Rapid Risk Assessment, published on 27 January 2022, included a review of the available scientific evidence on vaccine effectiveness against infection, transmission and severe disease due to the Omicron variant up until date of publication [6]. The updated overview of COVID-19 vaccine effectiveness in this section of the report is largely based on an ongoing systematic review of COVID-19 vaccine effectiveness studies conducted by the International Vaccine Access Center, John Hopkins Bloomberg School of Public Health and the World Health Organization (WHO) [7], with the latest update provided on 14 April 2022, and also through regular monitoring of published and preprint literature up to 21 April 2022.

In general, VE against infection due to Omicron has been shown to be reduced compared to other variants, and protection against infection also wanes over time, both for the primary series and for the first booster dose. First booster doses also seem to have a modest-to-limited effect in preventing Omicron transmission in the population. In

terms of vaccine effectiveness against severe outcomes caused by the Omicron variant, this is shown to be high following the administration of a first booster dose, with estimates in the range of 80–90% at around 2–3 months after receiving the booster, while there is some evidence of a decrease in protection from around 3–4 months. At present, available evidence indicates that the second booster dose can restore the humoral immune response to levels similar to those shortly after the first booster dose and it can also restore VE against infection. However, this does seem to wane rapidly. In relation to severe disease, available evidence indicates that the second booster dose can restore the reduced protection seen four months after the first booster dose. However, the follow-up period is currently short and at this stage it is not known how long protection from second booster doses will continue.

Vaccine effectiveness and duration of protection for first booster dose (third dose)

Vaccine effectiveness against infection over time with the Omicron variant

Studies investigating VE against infection have found protection to wane over time, starting from around two to three months after completing the primary series. In addition, there are several studies available on the vaccine effectiveness of the first booster dose against infection with the Omicron variant over time. As was seen after the primary series, the protective effect decreases over time, although the follow-up period of the studies was limited. In the studies available, VE against documented infection is generally estimated to be within the range of 45–66% at 0 to 3 months after the first booster dose (the majority of studies looked at mRNA vaccines in particular as the booster), and in the range of around 25–45% between over three months and less than six months after the first booster dose [8-13]. Estimates for symptomatic infection are in a slightly higher range than when the outcome is all infections (also including asymptomatic infections), but direct comparisons between studies should be avoided due the different study designs, study population, settings, etc. [12,14-16]. In addition, some studies measure VE after the first booster dose compared with those having received primary vaccination, whereas others compare with the unvaccinated population. Studies either include or exclude those previously infected and a few studies go into vaccine effectiveness for hybrid immunity in more depth. Studies from the Delta and Omicron-dominant periods have shown that hybrid immunity gained from both prior infection and vaccination provides additional protection, compared to vaccine doses alone [9,11,17-19].

Vaccine effectiveness against transmission with the Omicron Variant

One study from the UK that compared VE against transmission of Omicron and Delta variants after vaccination found a protective effect in contacts (adjusted risk ratio (aRR) 0.88, 95% CI: 0.79–0.97, p=0.0129) or exposures (aRR 0.78 (95% CI: 0.69–0.88) having received three doses (compared to two doses) in household settings. In non-household settings, a protective effect was observed for contacts having received three doses compared to two doses (0.76 (95% CI: 0.61–0.94) but there was no evidence of differences in protection based on the number of doses received by those exposing the contacts. This protective effect of a first booster dose was less pronounced for Omicron compared to Delta [20]. In summary, this and other studies suggest that booster doses in general have a modest to limited effect in preventing Omicron transmission in the population [21-23].

Vaccine effectiveness against severe disease due to the Omicron Variant by time since first booster (third dose)

Several studies have estimated vaccine effectiveness at sequential time points after the administration of a first booster dose, in order to investigate any indications of waning protection against severe disease or hospitalisation (Annex 3). In summary, these studies suggest that vaccine effectiveness against severe outcomes caused by the Omicron variant is high following the administration of a booster dose, with estimates around 80–90% protection for up to 2-3 months after receiving the booster [11,16,24]. Studies with a follow-up period of three months or more after the booster dose show some decline in effectiveness compared to the initial period [14,17,25-28], with estimates in the range of 60–80% against hospitalisation for a follow-up period of more than four months [14,25].

From the studies available, it is not possible to conclude whether the waning of protection after the first booster dose follows a different pattern in elderly groups than the general population. The available studies of elderly groups show high vaccine effectiveness up to three months after the booster dose [17,24,27], but studies with longer follow-up times that specifically investigate the waning of vaccine effectiveness in older age groups are still lacking.

The estimates of vaccine effectiveness should be interpreted with caution since there are relatively few studies available, especially with longer follow-up periods, and several of the available studies are preprints that have not yet been peer-reviewed. It should also be acknowledged that the studies have used different measures of hospitalisation or severe disease, with some studies including all hospitalised cases, and others using emergency department visits or more restrictive definitions of COVID-19 disease, such as inclusion of a diagnosis code for respiratory disease. Including all generalised hospitalisations may result in an analysis of both individuals hospitalised due to COVID-19 and those hospitalised with COVID-19 who are not primarily being treated for it, which can result in an under-estimation of the vaccine effectiveness estimates. In addition, as in most observational studies of vaccine effectiveness, there might be bias in the estimates relating to differences in behaviour, and socio-demographic and clinical characteristics between vaccinated and unvaccinated individuals. Studies and collection of real-life data are ongoing to further assess the duration of protection after a booster and patterns of waning in specific target groups.

Vaccine efficacy and effectiveness of the second booster (fourth dose)

Vaccine efficacy and effectiveness of a second booster dose against infection and severe disease

Data on the efficacy and effectiveness of a second booster (fourth dose) is still scarce at this point, with little evidence on duration of protection due to short follow-up times. In addition, most of the estimates provided so far are mainly calculated as a relative benefit compared to a third dose given three or four months earlier, rather than against those who are unvaccinated. Moreover, the studies are carried out in populations where the risk of severe disease and mortality is already low. The majority of studies on second booster dose effectiveness against infection and severe disease are currently from Israel, most probably due to the early roll-out of their vaccination campaign. In early January 2022, a second booster dose was authorised in Israel for those over 60 years of age, immunocompromised individuals and healthcare workers, to be given at least four months after the first booster dose. The few studies available have several limitations. As mentioned, most are from the same setting (Israel), in the context of a fast and early vaccine roll-out performed when transmission levels of the Omicron variant were very high. As yet, the follow-up period is short (10 weeks maximum), not allowing for any conclusions on duration of vaccine effectiveness for the second booster dose. More follow-up is needed in order to evaluate the protection of the second booster dose against severe illness over longer periods.

From the evidence available so far, a second booster does seem to restore the humoral immune response to levels similar to those seen shortly after the first booster dose [29]. A second booster improves VE against infection, but this seems to wane rapidly, which has also been seen within the short follow-up period available so far after the second booster dose [30-34]. After a second booster dose, VE against severe disease remains high during the short follow-up period covered in the studies available so far, and the second booster dose seems to restore protection which has waned slightly four months after the first booster dose (Annex 3 and 4) [30,32-35].

Estimating the reduction of COVID-19 burden by future vaccine campaigns through mathematical modelling

We apply a mathematical compartment model of SARS-CoV-2 transmission dynamics and COVID-19 disease to estimate the future COVID-19 burden (to end of October 2022) that would be avoided with a roll-out of a second booster dose. A detailed description of an earlier version of this model can be found in a previous ECDC report [36]. In brief, our model is a deterministic, SEIR-type compartment model that further divides the population into groups according to age (0-4, 5-9, 10-14, 15-17, 18-24, 25-49, 50-59, 60-69, 70-79, 80+ years), vaccination status (dose 1 of a two-dose primary vaccination schedule, complete primary vaccination, first booster, second booster), and previous infection with a pre-Omicron as well as an Omicron variant. We model viral transmission and disease progression, based on our current knowledge of SARS-CoV-2. The model considers differential contact rates between age groups, as well as the waning of vaccine-induced and natural protection. Given the increasing uncertainties towards the end of 2022 due to factors such as seasonal forcing, our predictions focus on the period from end of April to end of October 2022. We assume that, at the time of modelling, BA.2 is the dominant variant across the EU/EEA.

Scenarios

We conduct scenario analyses until end of October 2022, for which we explore different scenarios for the roll-out of the second booster dose. In addition, to compare the impact of a second booster dose roll-out with other public health measures, we explore scenarios of closing the gaps in vaccination by increasing coverage of the primary schedule and/or first booster vaccinations. We consider the following scenarios:

- **Second booster dose roll-out.** We vary the age group that receives a second booster dose (minimum age of 60 years, or 80 years, respectively). We consider that 75% of targeted individuals having received a first booster dose receive a second booster (see Table in Annex 5 for the discussion of this assumption).
- **Closing the vaccination coverage gap for the primary vaccination course.** We consider a 50% reduction of the coverage gap for the primary vaccination course in individuals older than 18 years or 60 years by 1 August 2022.
- **Closing the vaccination coverage gap for the first booster dose.** We consider a reduction of the coverage gap for the first booster dose by 50% for individuals between 18 and 59 years and by 75% for individuals older than 60 years by 1 August 2022.
- **Baseline scenario**. In the baseline scenario, we consider that there are no further vaccine campaigns, while current vaccination uptake trends continue.

To capture the uncertainty concerning future viral circulation, we assess each of these intervention scenarios for a range of parameter settings relating to the waning of protection against infection and severe disease, as well as currently prevailing transmission levels. The results are presented as ranges of estimates across these different settings.

Modelling results

A second booster roll-out can avert a substantial proportion of COVID-19 deaths between now and the end of October 2022, but its impact on absolute death numbers strongly depends on future COVID-19 incidence. Specifically, a second booster roll-out targeting 60+ year-olds in the EU/EEA may avert: 0.40 deaths/100 000 population (10% to 90% quantile range: 0.0004−26.2/100 000) in countries with low first booster coverage in the total population (we divide countries into three equal groups based on their uptake level of first booster dose – Figure 5); 4.2 deaths/100 000

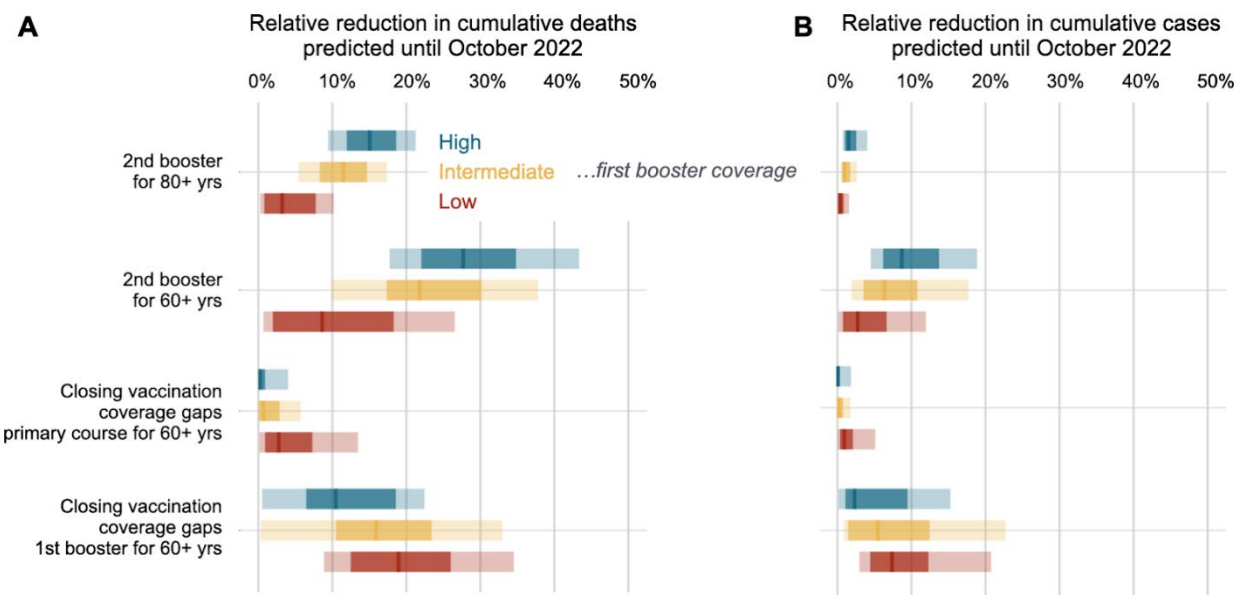
population (range:0.03−20.9) in intermediate first booster coverage countries; and 6.9 deaths/100 000 population (range:0.3−41.5) in high first booster coverage countries. These large ranges are a consequence of the considerable uncertainty in major drivers of future epidemiological dynamics (we discuss some of them in Annex 5 Table). Furthermore, our model also indicates that the averted number of deaths roughly halves in size when the second booster roll-out targets the 80+ years population only.

It is important to note that the model also shows that the older the target population of a vaccine campaign, the higher the per-dose impact on projected COVID-19 deaths. For instance, closing the gaps in coverage of primary vaccination and the first booster for individuals aged 60 years and above prevents 3.5 deaths/10 000 doses (range: 0.02−12.8) and 1.50 deaths/10 000 doses (range: 0.015−9.2) for those aged 18 years and above. In comparison, a second booster roll-out including individuals aged 60 years and over prevents 3.6 deaths/10 000 doses (range: 0.005−24.2), while a second booster roll-out including only individuals aged 80 years and older prevents 7.0 deaths/10 000 doses (range:0.01−53.9). This is because COVID-19 disease severity strongly increases with age, and because the main benefit of vaccines comes from reducing disease severity. Note that these estimates only cover the burden until 31 October 2022.

Figure 6A shows the relative reduction of deaths predicted until the end of October 2022 when comparing different enhanced vaccination campaigns against a baseline assuming no change in current vaccination uptake. Between-country differences in the effect of a second booster campaign across the EU/EEA correlate strongly with the achieved coverage of the first booster dose, where countries with a higher first booster dose coverage show a larger proportional reduction in deaths through a second booster. Furthermore, our model indicates that, when compared to prevented deaths, a second booster roll-out reduces disability-adjusted life years (DALYs) and cases to a lesser degree (Annex 6 Figure A7 and Figure 6B, respectively). This is because a second booster has a larger effect on predicted severe outcomes than on cases.

Figure 6A also shows that closing the gaps in coverage of primary vaccination and the first booster in individuals aged 60 years and older by 1 August 2022 (see Annex 6 Figure A8 for effects on closing the gaps for individuals aged 18 years and older) yields large benefits that are comparable with those from a broad (targeting the 60+ years population) second booster roll-out in terms of preventing COVID-19 deaths. These benefits will increase further with a wider target population as a result of a campaign to close vaccine coverage gaps (see Annex 6 Figure A8). As expected, the benefits of closing the gaps are largest for countries with low current uptake of the primary vaccination course and first booster (Figure 6A). Therefore the optimal vaccination strategy varies for each country. In particular, attention should be given to the large unvaccinated proportion of the population for some countries, which has a disproportionate impact on the burden of COVID-19.

Figure 6. Reduction in cumulative predicted deaths and SARS-CoV-2 cases by second booster rollout or closure of vaccine coverage gaps in different age groups



Relative reduction in cumulative deaths (A) and cases (B) by various scenarios compared to the baseline scenario, predicted until 31 October 2022. Different colours show groupings of countries depending on their first booster vaccination levels in the total population (we split countries into three groups of equal size – see Figure 5). The variation of each colour bar is due to the different characteristics of countries in the same vaccination group and the uncertainties of epidemiological parameters (speed of waning protection against infection and severe outcome, current viral transmissions and changes in test availability). The dark lines in the centre of each distribution show the median value, the darker shaded areas correspond to the 25th and 75th quantile, and light shaded areas correspond to the 10th and 90th percentile. The scenario 'Closing the vaccination coverage gaps' is assumed to close the gaps in vaccination coverage of 50% for the primary series and 75% for the first booster. The roll-out of the second booster is 15 May but we explored other timings as well although these are not shown here.

It should be emphasised that the impact of a second booster roll-out in terms of averted mortality and morbidity will strongly depend on the continuously evolving COVID-19 epidemic trajectory. A continuous high incidence or a large surge in cases in the early summer would imply a strong benefit from an early second booster roll-out. Alternatively, for a relatively low incidence level during the summer months, the optimal timing of second booster roll-out will probably be later in the year, depending on the risk of a surge in cases over autumn/winter 2022 and waning protection against severe outcome. The value of implementing the second booster in different population groups should therefore be re-assessed over time, and Annex 5 lists several factors that are expected to play a role in this assessment. We emphasise that our model only projects the COVID-19 burden until October 2022, without considering the following winter. Because model projections become highly uncertain towards the end of the year, and a winter wave may be likely, the benefits of a second booster roll-out in advance of the winter need to be reassessed before autumn 2022. It should also be noted that we assume the same uptake of the second booster for the different scenarios. However, it is likely that for various reasons (fatigue, hesitancy, travel over the summer, trust in public health authorities) certain campaigns and timings may lead to a higher uptake than others, and that these effects are highly context-specific. Such factors are outside the scope of this modelling analysis but will be important for choosing successful vaccine campaigns.

Summary of the mathematical modelling conclusions

- A second booster roll-out in some vulnerable groups before the end of summer can avert a substantial relative number of COVID-19 deaths between now and mid-autumn 2022, however the optimal timing of the roll-out and the total number of averted deaths by a second booster roll-out depend on the highly uncertain future incidence of COVID-19.
- To reduce the future COVID-19 death burden through a second booster, the effect per dose is highest when targeting vulnerable populations such as those aged 80+ years. With regard to the total reduction of averted deaths (not taking into account the number of administered doses), the effect of a roll-out that includes those aged 60+ years is roughly twice as high as a roll-out that includes only those aged 80+ years. However, this should be put into context in terms of the proportion of people in these age groups - 27.4% and 6%, respectively.
- A second booster roll-out for immunocompetent 60−79 years olds will probably be beneficial, but the best timing for the roll-out depends on the highly uncertain future of COVID-19 incidence and needs continuous reassessment.
- Closing the vaccination coverage gaps of the primary course, and especially the first booster vaccination, has substantial potential to reduce the COVID-19 death burden. This is particularly relevant for countries where these gaps are still large and efforts to address these gaps remain a public health priority.
- We also note that the expected vaccine uptake and the required communication and infrastructure will differ depending on the target age group, and these important factors are outside the scope of the model.

Current recommendations on booster doses in EU/EEA countries

All 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 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 also recommend boosters for adolescents (either to those over 12 years or those over 16 years).

As of 5 April 2022, nine countries are recommending a second booster dose (fourth dose) for different vulnerable population groups, such as residents in long-term care facilities (LTCFs) and the elderly, with different age cut-offs (Cyprus, Finland, France, Germany, Greece, Hungary, Ireland, The Netherlands and Sweden) (Table 5) [2]. The recommendation of a second booster for vulnerable people and certain at-risk groups aims to restore serological responses and overall vaccine effectiveness. The basis for the recommendation is the recorded waning of protection from the first booster against infection and symptomatic disease over time, as well as local epidemiological considerations [3,26,42,43].

Table 5. EU/EEA Country recommendations for second booster doses of COVID-19 vaccinations

Country	Country recommendations for second booster doses of COVID-19 vaccination	Timing of second booster dose
Cyprus	Second booster for those aged >70 years, residents and staff at LTCF, health professionals.	At least five months since the first booster dose.
Finland	Second booster for individuals aged ≥80 years, residents of LTCF.	At least three months since the first booster dose.
France	Second booster for individuals aged ≥80 years, residents of LTCF, those aged >65 years who are at risk of severe disease and want to have it.	At least six months since the first booster dose.
Germany	Second booster for individuals aged >70 years, residents of LTCF and people at risk of developing severe illness in support facilities, workers in medical and nursing facilities (especially in direct contact with patients and residents).	At least three months after first booster dose for those at risk. For personnel in medical and nursing facilities the second booster dose is given at least six months after the first booster dose.
Greece	Second booster for ≥60 years (the vaccine rollout will start with those aged 80 years and above and continue with the lower age groups).	At least four months after the first booster dose.
Hungary	Second booster dose for elderly, and those with chronic disease and also available to anyone who asks for it.	At least four months after the first booster dose.
Ireland	Second booster dose for individuals aged ≥65 years.	At least four months after the first booster dose.
The Netherlands	Second booster dose for individuals aged ≥60 years, residents in LTCF and adults with Down syndrome.	At least three months after the first booster dose.
Sweden	Second booster dose for individuals aged ≥65 years, LTCF residents, people who have home care or home healthcare and individuals aged ≥18 years with Down syndrome.	At least four months after the first booster dose.

Key: LTCF=long-term care facility

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

The UK Government has recently decided to offer an additional mRNA booster dose for people aged 75 years and older, those in care homes, and those aged 12 years and over with a weakened immune system. This second booster should be offered around six months after the first booster dose, and not earlier than three months after the first booster dose [39]. On 25 March 2022, the Australian Technical Advisory Group on Immunization made recommendations on a fourth COVID-19 vaccine dose to increase vaccine protection before their winter season for some groups, including adults aged 65 years and older, residents in long-term care facilities and the severely immunocompromised, suggesting the use of an mRNA vaccine unless contra-indicated or declined (in which case Vaxzevria can be used, or Nuvaxovid if no other vaccine is considered suitable) [40]. 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 aged 50 years and older, at least four months after receiving a first booster dose [41]. Following this authorisation, the US Centers for Disease Control and Prevention (CDC) updated their recommendations to allow certain immunocompromised individuals and people aged over 50 years who had received an initial booster at least four months earlier to be eligible for another mRNA booster [42]. The Canadian National Advisory Committee on Immunization has provided guidance on a second booster dose of COVID-19 vaccines in Canada and strongly recommends that adults aged 80 years and over living in the community and residents in long-term care or other congregated living settings for seniors receive the offer of a second mRNA booster dose (or the offer of Nuvaxovid for those unwilling or unable to receive an mRNA dose). The Committee gave a discretional recommendation that jurisdictions may also consider offering a second mRNA booster dose to adults aged 70–79 years living in the community [43].

Public health considerations when assessing the need for a second COVID-19 booster dose

A number of public health considerations should be taken into account when assessing the need for a second booster dose of the COVID-19 vaccine. Some of them have been outlined in a previous ECDC report [6] and in the recent joint statement from EMA and ECDC on the administration of a fourth dose of mRNA vaccines [3]. These considerations are based on scientific evidence currently available and, as such, may be subject to change as more data become available. Given the many factors that may influence decision-making around the implementation of a second booster dose recommendation, or for different sub-groups of the population, it is essential that close attention be paid to emerging epidemiological and scientific data which should be re-assessed frequently in the coming months.

Objectives of the vaccination strategy

When assessing the need for possible additional booster doses of COVID-19 vaccine from a public health perspective, it is important to keep in mind the main objective of the vaccination strategy (i.e. preventing severe cases of COVID-19). Vaccine effectiveness against severe disease should preferably be chosen as the primary outcome of interest for assessing when there is a clear need for an additional booster dose in specific groups. Close monitoring of vaccine effectiveness data, particularly among vulnerable groups at risk of severe COVID-19 and those living in closed settings, should be continued and decisions adapted accordingly, should a substantial decrease in effectiveness be noted in one or more population groups.

Viral circulation and hybrid population immunity

Even though the recent resurgence of cases observed in the EU/EEA appears to have slowed down, SARS-CoV-2 transmission remains at quite high levels in many EU/EEA countries. There are still many uncertainties around the future incidence of SARS-CoV-2 and large outbreaks and high levels of strain on healthcare systems may still periodically occur. Issues that could impact viral circulation and the epidemiological situation in the EU/EEA during the coming months include increased contact rates during the summer, waning protection against infection or severe disease, changes in COVID-19 testing and surveillance, the emergence of new variants of concern and seasonal forcing of viral transmission (see Annex 5). It remains essential that countries have strong surveillance systems to detect increased incidence, severity, and emerging variants of concern.

When evaluating the need for additional booster doses, overall population immunity against SARS-CoV-2 and viral circulation are key factors to be considered. Population immunity could be broadly estimated by knowing the vaccination coverage and the proportion of the population with a previous natural infection. While the cumulative COVID-19 vaccine uptake is currently 72.6% for the primary course in the total EU/EEA population and 64.2% for the first booster and additional dose among adults, uptake is higher among those aged 60 years and over (89.4% and 82.0% respectively for the primary course and booster/additional dose). In general, vaccine uptake rates are levelling off, with considerable differences among EU/EEA countries. Due to the recent exposure of large numbers of the population to the Omicron variant, hybrid immunity, gained from previous infection and a complete primary vaccination course, is likely to play an increasingly important role in protection at population level. When combined with three vaccine doses, hybrid immunity provides additional population protection in the current context [9,11,17-19].

As yet, no absolute serum antibody titre threshold has been established as a correlate of protection against SARS-CoV-2 infection, and immune correlates have not been established for protection against severe disease [49,50]. However, serum neutralising antibody titres are well-established predictors of protection against SARS-CoV-2 infection [45]. Nationally representative, age-stratified sero-epidemiological studies provide a basis for estimating the proportion of the population with SARS-CoV-2-specific antibodies in a given country. These, in turn, provide a basis for estimating projected disease burden and evaluating the potential benefit of additional booster doses during periods of increased viral circulation. Such studies are particularly informative when they use quantitative assays to determine the level of both natural and vaccine-induced antibodies in participating individuals in order to estimate the contribution of natural, vaccine-derived and hybrid immunity in the population [12,51,52]. Given that serum antibodies wane over time, longitudinal or repeated studies with the same sampling strategy and common testing methodology are essential for understanding temporal trends and risks, as is continued vigilance for the immune escape capabilities of newly emerging variants.

Prioritisation of population groups

It should also be emphasised that, based on current evidence from longitudinal studies, routine surveillance and observational vaccine effectiveness studies, a complete primary vaccination course followed by a first booster dose remains the most effective way to limit the disease burden and impact of COVID-19. Analysis of European COVID-19 surveillance data indicates that the highest rates of severe outcomes have been among unvaccinated people, and this continues to be the case. 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. With vaccine uptake stagnating and given the

significant variation in uptake across countries, additional efforts are needed to increase vaccination uptake, focussing on closing the vaccination coverage gap of the primary course and the first booster dose as a public health priority, especially among individuals from vulnerable groups at risk of severe disease who are still unvaccinated, or only partially vaccinated.

When assessing the need for a second booster of COVID-19 vaccine and the prioritisation for its administration in specific groups, the evidence of vaccine effectiveness and waning protection against severe disease, including death, should preferably be chosen as the primary outcome of interest.

Immunocompromised: administration of a fourth dose of mRNA vaccines to immunocompromised individuals whose immune system may have mounted a sub-optimal response to earlier vaccination is already recommended and should be part of current vaccination campaigns. In these individuals, the fourth dose corresponds to a first booster dose after a three-dose primary series. There are currently no data on immunogenicity, safety or effectiveness of additional further doses in this population. Furthermore, in severely immunocompromised subjects, passive immunisation with monoclonal antibodies should be considered as an additional shield to protect against infection and disease.

People aged 80 years and older: epidemiological data presented above show how during the Omicron wave rates of severely ill cases in hospital increased most substantially in individuals aged over 80 years, although part of this increase could have been driven by unvaccinated individuals. The risk of hospitalisation among individuals who had received a first booster dose is highest for those over 80 years. The mathematical modelling presented in this report suggests that the roll-out of a second booster dose among the elderly could avert a substantial proportion of COVID-19 deaths between now and the end of October 2022, and a second booster roll-out targeting those aged 80 years and above would yield the highest per dose impact on projected COVID-19 deaths.

Due to the fragility of the population, continued high hospitalisation and ICU rates in many settings, lower immune response to vaccination, and the higher risk of severe COVID-19, the public health benefit of administering a second booster dose is clearest in those aged 80 years and older. Immediate administration of a second booster dose in this population would be optimal in situations where viral circulation remains high or is increasing. Alternatively, in situations where viral circulation is low, administration of a second booster dose should be considered before autumn 2022.

People aged 60 to 79 years: mathematical modelling suggests that a second booster roll-out, including immunocompetent peopled aged 60–79 years in the EU/EEA will probably be beneficial, but the best timing for the roll-out depends on the highly uncertain future of COVID-19 incidence. Therefore continued close epidemiological and vaccine effectiveness monitoring is essential in order to rapidly detect signals of increased SARS-CoV-2 circulation or the risk of severe COVID-19 among vaccinated individuals. If such signals emerge, a second booster may be considered for all or some adults between the ages of 60 and 79 years and countries should have plans in place for a rapid deployment of booster doses in this population group.

People under 60 years: for immunocompetent individuals below 60 years of age the administration of a second booster dose is not supported by the current epidemiological, modelling or VE data on he continued level of vaccine protection against severe disease or death. The main focus for this age group in the immediate future should be on improving vaccine uptake of the primary course and first booster dose in populations who have yet to receive them. 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 second booster may be considered for some individuals under 60 years of age and countries may consider plans for the deployment of booster doses in this population.

In addition to the age group-specific considerations listed above, 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.

Timing of boosters

In general, vaccination and boosting of immunity achieve the maximum impact at population level if administered before an epidemic wave and the minimum impact if administered at the end of an epidemic wave. Timing is also important for diseases that follow a seasonal pattern, such as respiratory infections. Vaccinating before the beginning of the autumn, when people start spending more time indoors, is an example of such an approach - anticipating an epidemic wave and maximising the impact of the vaccination. 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, including the possibility of combined COVID-19 and flu vaccination campaigns.

Modelling results indicate that continuous high incidence or a large surge in cases in the early summer would imply considerable benefit from an early second booster roll-out. Alternatively, for a relatively low incidence level during the summer months, the optimal timing of second booster roll-out will probably be later in the year, depending on the risk of a surge in cases during autumn/winter 2022 and waning protection against severe outcome.

The value of implementing the second booster in different population groups should therefore be re-assessed over time and monitoring the epidemiological situation will be the key to deciding when an additional booster dose could be best administered, in the presence of clear signs of reduced vaccine effectiveness against severe COVID-19 in some target groups. The continued protection against severe disease will need to be monitored in

those populations receiving a second booster dose in spring/early summer 2022 in order to consider the need for additional booster doses in relation to potential future autumn/winter 2022 waves.

If made available, vaccines with updated composition, adapted to better match the recently circulating variants of concern (VOCs), would in principle be preferable for the additional boosters. As data on adapted vaccines will be available in the near future and will possibly lead to the authorisation of adapted vaccines later in the year, this could be an additional factor to take into account with regard to the timing of a second booster dose for some populations.

Finally, preparedness planning is essential in order to quickly implement second booster dose campaigns, if deemed necessary, in response to increased or high viral circulation or signals of increased waning protection.

Other pharmaceutical interventions for COVID-19

Along with COVID-19 vaccines, other pharmaceutical interventions may become increasingly available as a means of reducing the risk of severe disease, especially among the most vulnerable population groups. A number of pharmaceutical agents have been studied for prophylaxis of COVID-19. A combination of two long-acting antibodies – tixagevimab and cilgavimab (Evusheld) – have shown a relative risk reduction of 76.7% (95% confidence interval [CI], 46.0 to 90.0; P<0.001) for symptomatic COVID-19 compared to a placebo when administered to adults with an increased risk of inadequate response to vaccination (e.g. people with immunosuppression, or those with increased risk of exposure to SARS-CoV-2) [48]. Such options can be made available to people with contraindications to vaccination or for whom an inadequate response is expected, however they cannot substitute vaccination. Another combination of monoclonal antibodies against SARS-CoV-2, casivirimab/imdevimab, has also been studied and authorised for prophylaxis [49]. However, in vitro data show that the efficacy of casivirimab/imdevimab against the Omicron VOC is lower compared to previously circulating variants [50] possibly leading to lower effectiveness in preventing COVID-19, if administered as prophylaxis. Clinical guidelines consider that casirivimab/imdevimab and bamlanivimab/etesevimab are not active against the Omicron VOC, and are recommended only where other SARS-CoV-2 variants are still circulating and causing substantial numbers of cases [51].

The availability of oral antiviral treatments, such as nilmatrevir/ritonavir and to a lesser degree molnupiravir, for the prevention of severe disease when administered early after disease onset, particularly in people at high risk of severe COVID-19, is also a welcome addition to the options available for mitigating the impact of COVID-19, also for those with an increased risk of inadequate response to vaccination. In addition, the early administration of IV remdesivir, up to five days after disease onset, can also prevent progression to severe disease [51,52].

Communication, vaccination acceptance and uptake

Communication to promote uptake of a second booster dose of COVID-19 vaccine will need to take into account a number of challenges. The lifting of measures and a perception that the 'pandemic is over' may contribute to complacency regarding the threat of COVID-19 [53]. People – including those at increased risk of severe disease – may also question the need for recurring vaccination. The levelling off of uptake for primary vaccination and the first booster which has been observed [5] indicates the increasing challenges in reaching those as yet unvaccinated. In addition, some people willing to get vaccinated may prefer to wait for variant-adapted vaccines [54].

Initiatives to promote uptake of a second booster dose will need to take into account optimal timing, the specific focus of the campaigns, lessons learned and current uncertainties:

- Planning should consider when the efforts to promote uptake are likely to be most effective. In addition to promoting uptake of primary vaccination and first booster for those most at risk of severe disease and who have not yet completed their recommended vaccinations, at this stage, the focus should be on targeted communication for the population groups being prioritised to receive a second booster, in accordance with national recommendations. Clear information should be provided around the rationale for the recommendations and the benefits of the primary course and boosters for these population groups [39]. Barriers to uptake also need to be identified and addressed.
- In anticipation of possible new waves and the related need to adapt recommendations concerning a second booster dose (e.g. extending them to other age groups), planning of future campaigns should be based on good practices identified during earlier phases of the vaccination programme. This can also include considerations on how to optimise resources by combining efforts with flu vaccination campaigns.
- Taking into account one of the key principles of risk communication, uncertainty should be acknowledged [55]. This could apply within the context of unexpected changes in the epidemiological situation, possible emergence of new variants, and further evidence on vaccine effectiveness and the waning of protection. Furthermore, it is not yet known when adapted vaccines might be available. Developments on any of these issues may lead to changes in national recommendations on additional booster doses, and this possibility should be communicated.

Communication efforts to promote vaccination acceptance and uptake should be based on an understanding of people's knowledge, expectations and concerns about the vaccine and their perceptions of the threat posed by COVID-19. Such an understanding can be derived through behavioural insight research, ideally based on a model or framework delineating the factors that may either facilitate or hinder vaccination acceptance and uptake. One such model is the '5Cs', which looks at confidence, constraints, complacency, calculation and collective responsibility [56].

While all EU/EEA countries track COVID-19 vaccine coverage in their countries, and some track reported confidence in COVID-19 vaccines, not all of them seek to identify the full range of possible reasons for lower-than-desired vaccination coverage in different population groups. Strategies aimed at promoting vaccination acceptance and uptake may therefore be targeting the wrong combination of the '5Cs', and this could undermine their effectiveness, while also wasting financial resources and time. One of the most widely used behavioural insight survey tools in the EU/EEA – which also includes questions about the '5Cs' – has been made available by WHO's Regional Office for Europe and has been adapted for use in several countries [57,58].

It is important that strategies promoting COVID-19 vaccination and uptake of boosters for different priority groups, such as people over the age of 80 years, are based on insights derived specifically from the priority group in question. For example, key questions concern the extent to which elderly people currently consider themselves to be at risk from COVID-19 (this could relate to the confidence or complacency of the '5Cs'). How willing and able are they to access a (second) booster vaccine (this could relate to constraints)? Are they subjected to misinformation about COVID-19 or the vaccine, and, if so, to what extent and how does this influence their vaccination beliefs and behaviour (this could relate to calculation)? Another area that may be relevant for campaigns scheduled for the coming autumn is the potential willingness of elderly people to receive both the influenza vaccine and the COVID-19 vaccine at the same time.

In addition to these considerations for communication concerning a second booster dose, continued efforts are currently needed to increase uptake of the primary vaccination series and first booster in the wider population, in particular in areas with sub-optimal coverage. The importance of primary vaccination and first booster for prevention of severe disease and hospitalisation needs to be continuously stressed.

Conclusions and potential implications

- Following the rise to dominance of the SARS-CoV-2 Omicron variant in January 2022, transmission and burden of severe disease among older age groups increased to very high levels, although this has recently started to decline in most EU/EEA countries. It remains uncertain whether, in the coming weeks/months, these indicators will stabilise at the low inter-wave levels observed prior to Omicron, or at an elevated plateau.
- Since completeness of vaccination status in COVID-19 cases reported to the European Surveillance System (TESSy) is limited, we are unable to attribute the observed increases in severe disease due to Omicron to individuals with a particular level of vaccination. However, a separate analysis of three countries with complete data on severe outcomes and vaccination status demonstrates that the highest burden of severe outcomes has been among unvaccinated people in all adult age groups, and this continues to be the case.
- All EU/EEA countries are currently recommending a first booster dose at a defined interval following primary vaccination. At present, uptake of the first booster dose in the EU/EEA adult population is 64.2% (country range 11.0-87.9%).
- In general, vaccine effectiveness (VE) against infection due to Omicron has been shown to be reduced compared to other SARS-CoV-2 variants, and protection wanes over time.
- Published literature indicates VE against severe outcomes caused by Omicron remains high, with continued strong protection in the range of 80−90% around 2-3 months after receiving the first booster, albeit with some evidence of this waning slightly from around 3-4 months. In addition, analysis of severe outcomes among COVID-19 cases having received a first booster dose, as reported to TESSy, also shows that hospitalisation and death are extremely rare in this group; 0.38% and 0.1% respectively. Moreover, the adjusted risk of hospitalisation and death is higher in older populations, males and those who received a first booster dose more than three months ago.
- Evidence currently available indicates that a second mRNA booster dose is able to restore the humoral immune response to levels similar to those observed shortly after the first booster dose and also to restore the VE against infection, although this does appear to wane rapidly. Early data indicate that the risk of severe disease and/or death due to COVID-19 is reduced for up to 10 weeks after the administration of a second booster dose, compared to those receiving only the first booster dose. However, this is in populations already experiencing low levels of severe outcomes, thus providing small absolute reductions. The maximum duration of this protection is not yet known, due to short follow-up periods after the second booster in the studies available.
- Mathematical modelling suggests that increasing the proportion of the population who have been provided with immunity through a primary course and first booster has a substantial potential to reduce the COVID-19 death burden by end of October 2022. This is particularly relevant for countries where gaps in coverage are still large, and efforts to address these gaps remain a public health priority. With regard to the second booster, modelling shows that its roll-out in some vulnerable groups could avert a substantial proportion of COVID-19 deaths between now and mid-autumn 2022. Further indications are set out below.
  - The total number of averted deaths, both before and beyond autumn 2022, depends on the COVID-19 incidence, and as such is difficult to predict with certainty.
  - To reduce future COVID-19 burden through a second booster, the effect per dose is highest when targeting vulnerable populations, such as older age groups.

  - Given that vaccination and the boosting of immunity achieves the maximum impact at population level if administered before an epidemic wave and the minimum impact if administered at the end of an epidemic wave, a continuous high incidence or a large surge in cases in the early summer would imply greater benefit could be achieved by an early second booster roll-out. Alternatively, if surveillance shows relatively low incidence levels during the summer months, the optimal timing for a second booster roll-out would be later in the year, subject to further assessment of the risk of a surge in cases during autumn/winter 2022 and waning protection against severe outcome.

- Given data on the current epidemiological situation, vaccine effectiveness and mathematical modelling, it is suggested that EU/EEA countries consider the information set out below with respect to the administration of a second COVID-19 booster dose.
  - Due to the fragility of the population, continued high hospitalisation and ICU rates in many settings, lower immune response to vaccination, and the higher risk of severe COVID-19, the public health benefit of administering a second booster dose is clearest in those aged 80 years and above. Immediate administration of a second booster dose in this population would be optimal in situations of continued high or increasing viral circulation. Alternatively, in situations of low viral circulation, administration of a second booster dose should be considered prior to autumn 2022.
  - Mathematical modelling suggests that a second booster roll-out including those aged 60-79 years who are immunocompetent in the EU/EEA will probably be beneficial, although the best timing for the roll-out depends on the highly uncertain future of COVID-19 incidence. Therefore, continued close epidemiological and vaccine effectiveness monitoring is essential in order to rapidly detect signals of increased SARS-CoV-2 circulation or risk of severe COVID-19 among vaccinated individuals. If such signals emerge, a second booster may be considered for all or some adults between the ages of 60 and 79 years and countries should have plans in place for a rapid deployment of booster doses in this population group.
  - For immunocompetent individuals below 60 years of age, the administration of a second booster dose at this time is not supported by the current epidemiological, modelling or VE data on the continued level of vaccine protection against severe disease or death.
  - Continued protection against severe disease will need to be monitored in those populations receiving a second booster dose in spring/early summer 2022 in order to consider the need for additional booster doses in relation to potential future autumn/winter 2022 waves.
  - Adapted vaccines may potentially be authorised later in the year and could be taken into account with regard to the timing of a second booster dose.
  - It remains essential that countries have strong surveillance systems to detect increased incidence, severity, and emerging variants of concern coupled with preparedness planning to quickly implement booster dose campaigns if deemed necessary.
  - Communication planning should consider when the efforts to promote uptake of the second COVID-19 booster dose are likely to be most effective. At this stage, focus should be on targeted communication for those population groups who are recommended a second booster, whilst also ensuring full vaccination and uptake of the first booster in those most at risk of severe disease who have not yet completed their recommended vaccinations.
  - In anticipation of possible new waves and the related need to adapt recommendations around a second booster dose (e.g. extending them to other age groups), planning of future campaigns should be based on good practices to promote vaccine acceptance and uptake identified during earlier phases of the vaccination programme, and taking into account behavioural insights research.

- Depending on the evolving epidemiology and forthcoming data on vaccine effectiveness over time, it will be necessary to re-assess recommendations on timing and with regard to the populations that may benefit from a second COVID-19 vaccination booster dose in the near future.

Knowledge gaps and research priorities

There are still substantial gaps in the evidence available to guide considerations on the timing and administration of a second COVID-19 booster dose. Further or continued research in the following areas should be a matter of public health priority:

- Studies and collection of real-life data on longer-term duration of protection and patterns of waning protection against severe outcomes following first and second booster doses in different population groups, especially in older age groups (in response to currently circulating and potential future SARS-CoV-2 variants) as well as immunosuppressed individuals, and those with underlying conditions associated with more severe COVID-19 outcomes;
- Kinetics of the antibody response to repeated COVID-19 vaccine doses in different populations;
- Effectiveness of eventual future variant-specific vaccines compared to currently available vaccines;
- Continuous monitoring of safety following additional booster doses;
- Vaccine effectiveness for individuals receiving mRNA vaccine booster doses following administration of a primary vaccine series with another type of vaccine (i.e. viral vector) and for boosters with non-mRNA vaccines;
- High-quality studies on the current sero-epidemiological situation in different EU/EEA countries will be crucial for high-quality modelling predictions, including an understanding of optimal roll-out timing for future vaccine boosters.

Consulted experts (in alphabetical order)

ECDC experts: Agoritsa Baka, Kim Brolin, Nick Bundle, Rok Grah, John Kinsman, Gaetano Marrone, Rene Niehus, Kate Olsson, Ajibola Omokanye, Lucia Pastore Celentano, Anastasia Pharris, Diamantis Plachouras, Bastian Prasse, Giovanni Ravasi, Frank Sandmann, Karin Wilbe Ramsay, Andrea Würz.

European Medicines Agency: Arnold Anderweg, Marco Cavaleri, Grossens Mathijs.

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Annex 1. Country-specific epidemiological data

Figure A1. Country- and age-specific notification rate of cases admitted to ICU and/or requiring ventilation and/or extracorporeal membrane oxygenation, week 26, 2021 to week 13, 2022

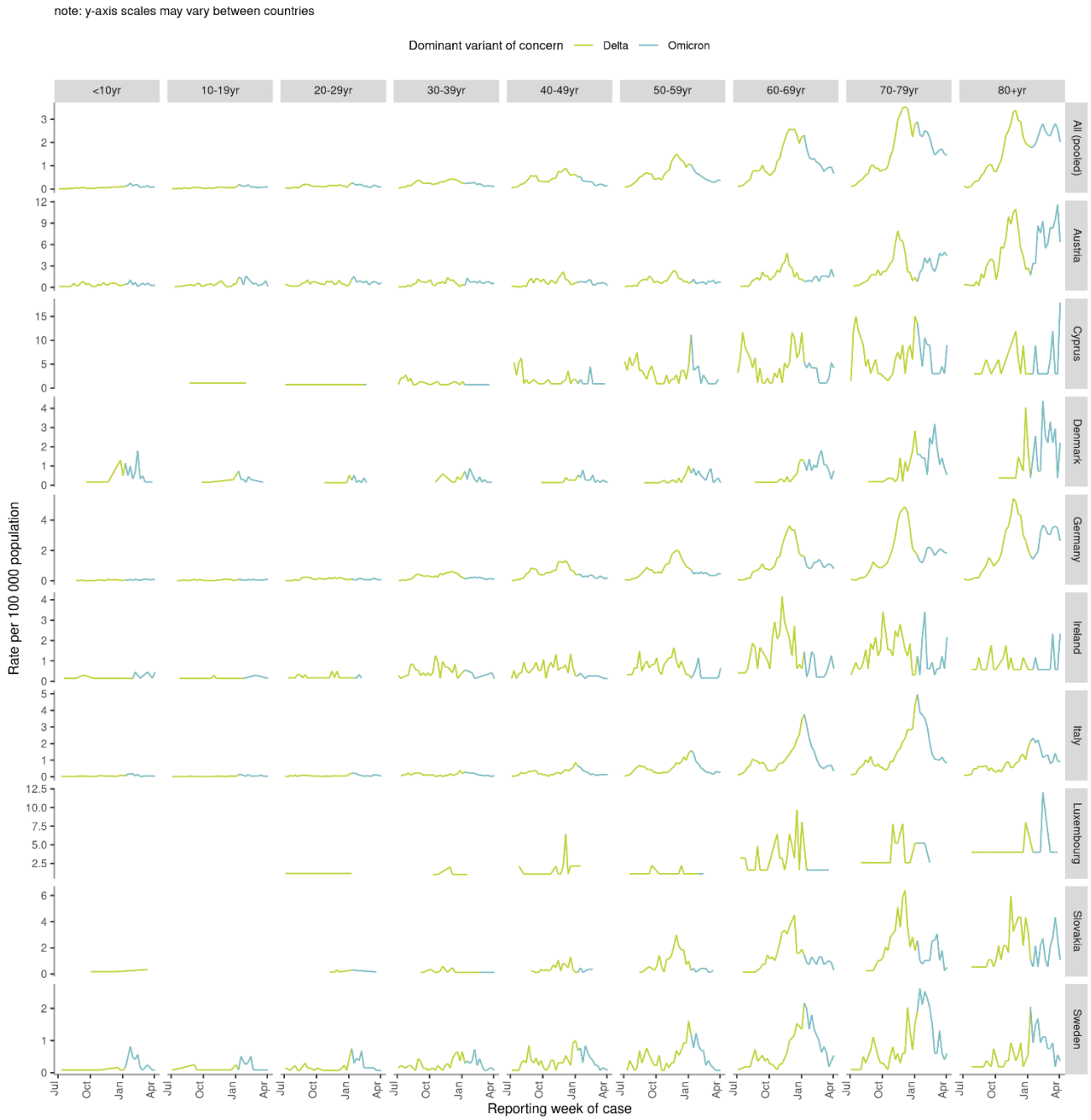
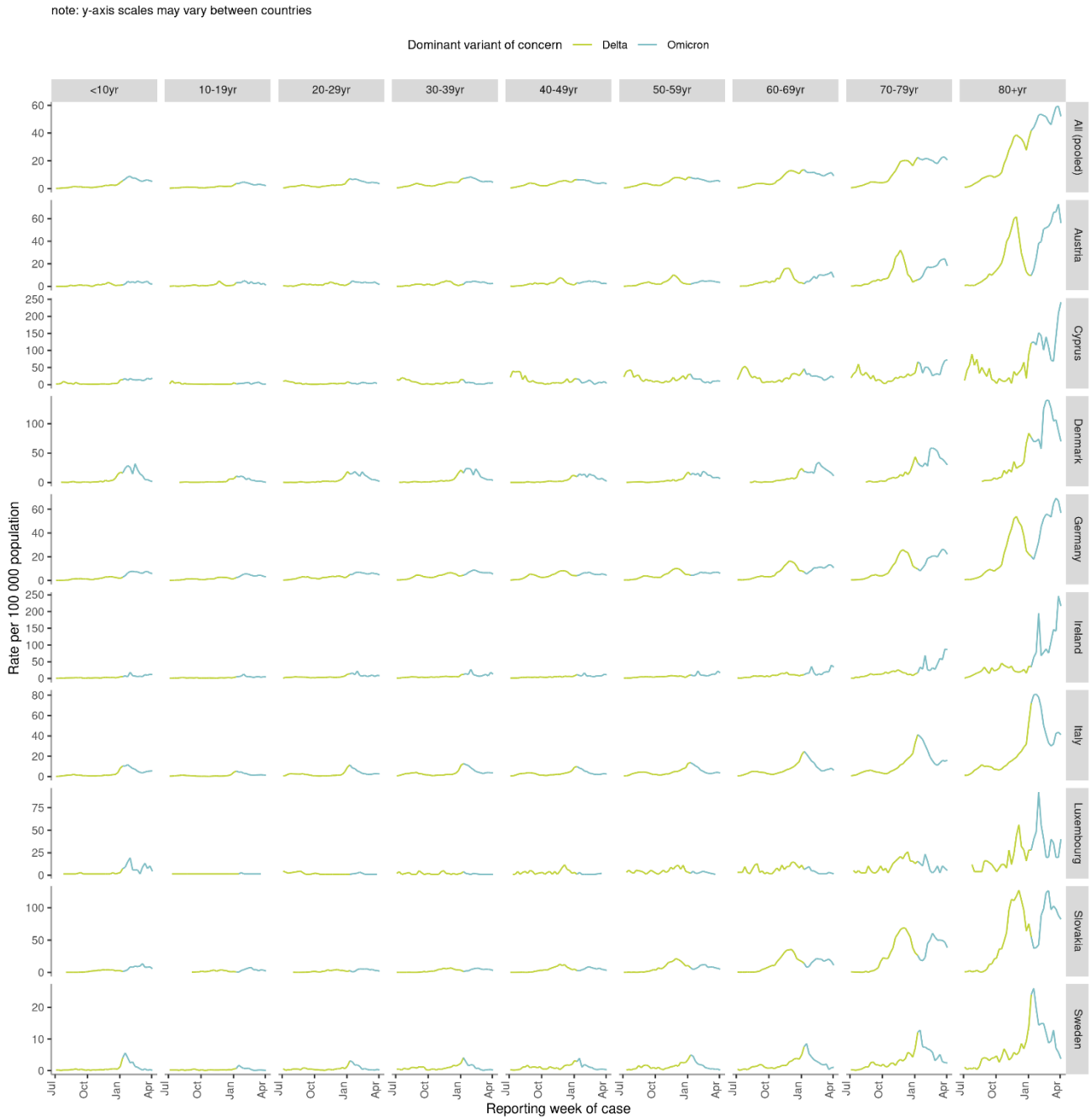


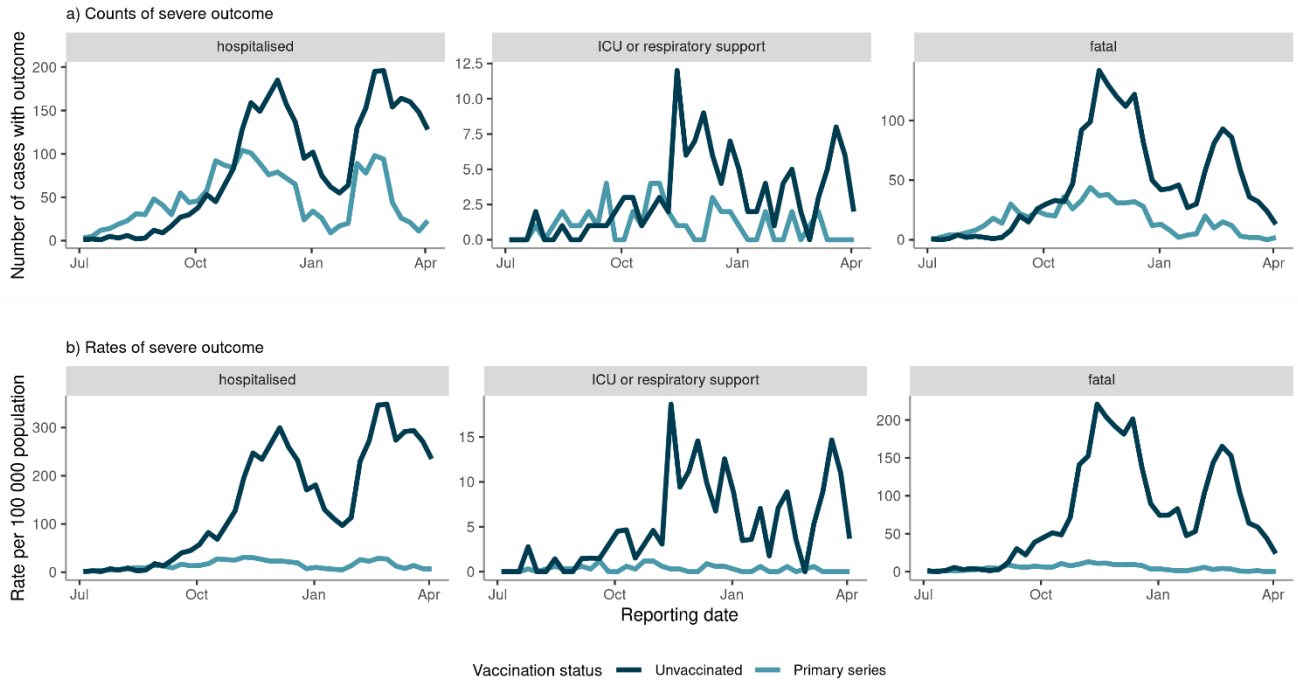
Figure A2. Country- and age-specific notification rate of hospitalised cases, week 26, 2021 to week 13, 2022



Source: TESSy case-based data
Data reported to week 15, 2022; the most recent two weeks have been excluded to allow for delay to severe outcome

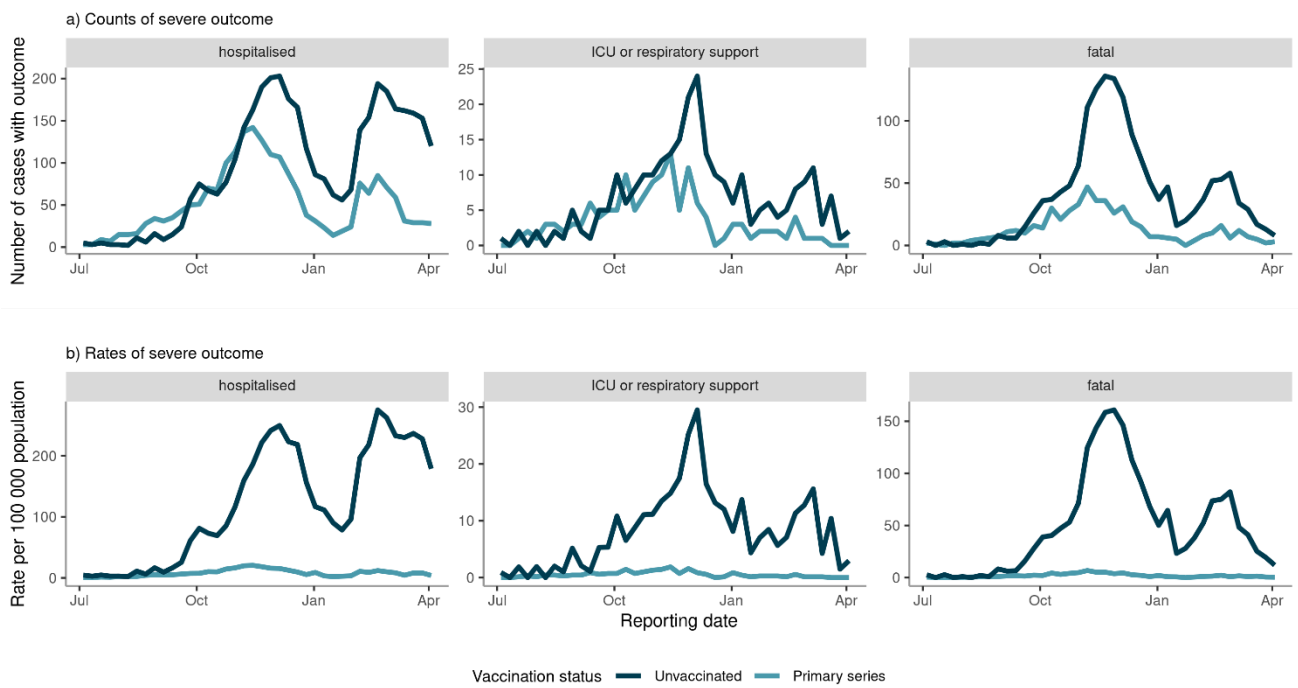
Annex 2. Severe outcomes and vaccination status

Figure A3. Counts and notification rates of severe COVID-19 outcome by vaccination status among cases aged 80 years and above, week 26, 2021 to week 13, 2022



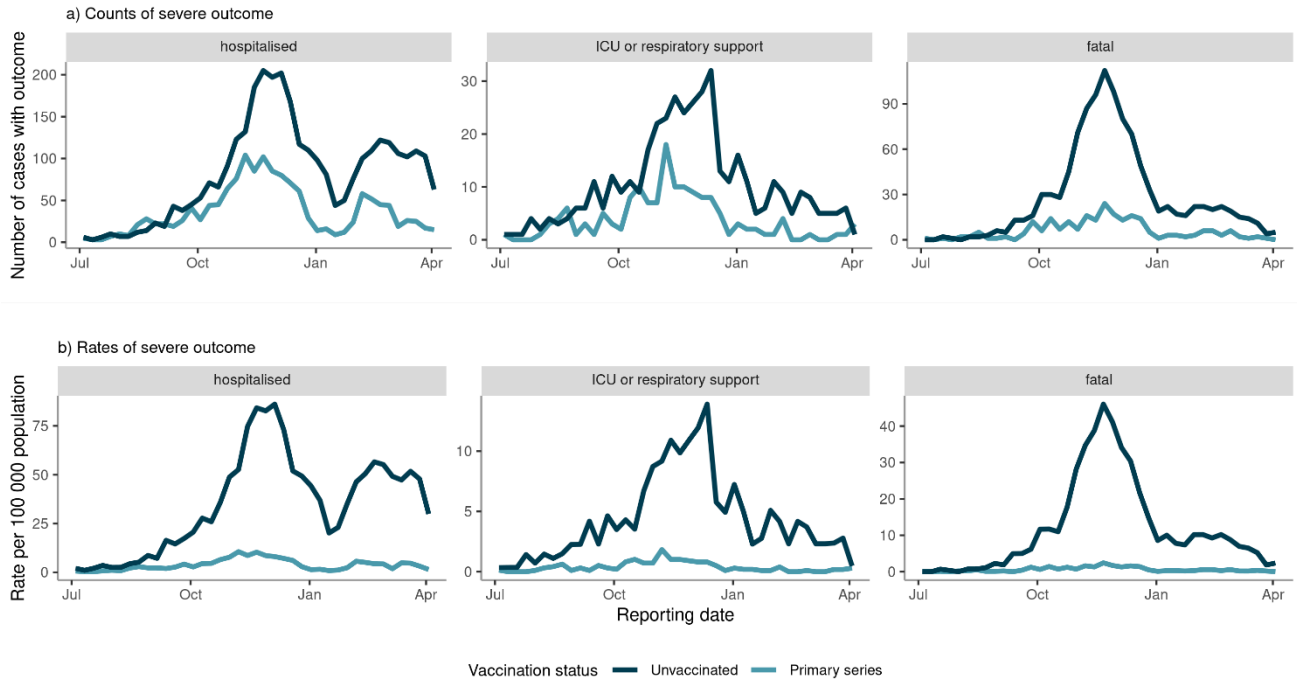
Source: TESSy case-based data reported by Ireland, Luxembourg and Slovakia

Figure A4. Counts and notification rates of severe COVID-19 outcome by vaccination status among cases aged 70–79 years, week 26, 2021 to week 13, 2022



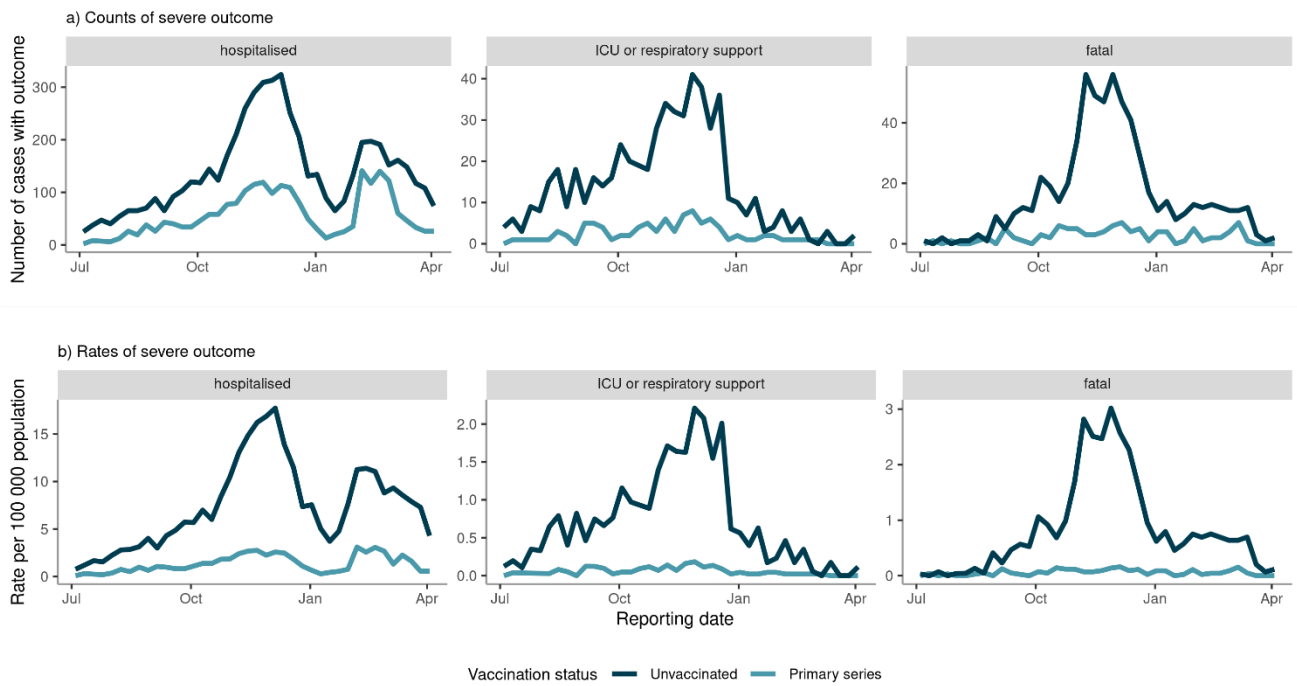
Source: TESSy case-based data reported by Ireland, Luxembourg and Slovakia

Figure A5. Counts and notification rates of severe COVID-19 outcome by vaccination status among cases aged 60–69 years, week 20, 2021 to week 13, 2022



Source: TESSy case-based data reported by Ireland, Luxembourg and Slovakia

Figure A6. Counts and notification rates of severe COVID-19 outcome by vaccination status among cases aged 18–59 years, week 20, 2021 to week 13, 2022



Source: TESSy case-based data reported by Ireland, Luxembourg and Slovakia

Annex 3. Description of studies on vaccine effectiveness after the first and the second booster

Studies of vaccine effectiveness against severe disease with a follow-up time of seven days to < 3 months after the first booster dose (third dose)

A matched, test-negative, case-control study (pre-print) from Qatar estimated the effectiveness against COVID-19 hospitalisation and death to be in the range of 70–80% any time after primary vaccination, increasing to 90% (95% CI: 79–96%) after a first booster dose of Comirnaty. The effectiveness remained at this level ≥7 weeks after the booster dose. The vaccine effectiveness against hospitalisation after a booster dose of Spikevax was also estimated, but lacked statistical precision due to few cases. The vaccine effectiveness was similar against the BA.1 and BA.2 variants [15]. The results of this study are in line with another pre-print study from Qatar that estimated the effectiveness against hospitalisation and death to over 90% about seven weeks after a booster dose of Comirnaty or Spikevax [9]. When the protection of a first booster dose of Comirnaty was investigated in a matched retrospective national cohort study from Qatar, the effectiveness against COVID-19–related hospitalisation and death due to Omicron infection, as compared with the primary series, was 77% (95% CI, 57–88%) [8].

A retrospective analysis of nationwide data from the Czech Republic (pre-print study) estimated the effectiveness against hospitalisation after administration of a first booster dose of Comirnaty to 86% (95% CI: 84–89%) at 14–74 days after the booster dose, declining to 79% (95% CI: 74–82%) at ≥75 days. The effectiveness against the need for oxygen therapy following a booster dose was 90% (95% CI: 87–92%) at 14–74 days and 85% (95% CI: 80–88%) at ≥75 days. The corresponding estimate regarding need for intensive care was 83% (95% CI: 75–89%), declining to 60% (95% CI: 37–74%). A recent combination of a previous infection and vaccination was more protective then either alone, with a slight benefit from a vaccination preceding an infection. Once infected, the rates of hospitalisation, need for oxygen therapy and ICU admission were lower for Omicron infections than for Delta infections [11].

The vaccine effectiveness against severe COVID-19 among individuals aged ≥70 years was investigated in a nationwide register-based cohort study (pre-print) in Finland. The effectiveness against COVID-19 -related hospitalisation (with a primary diagnosis of COVID-19 or respiratory infection) was 87% (95% CI: 84–89%) at 3–6 months after primary vaccination and increased to 91% (95% CI, 79–96%) at 14–60 days after administration of a first booster dose of Comirnaty during the Omicron-dominant period. The protection against need for ICU treatment was somewhat higher. Analyses of various homologous and heterologous three-dose series yielded similar estimates of effectiveness [23].

In addition to the above-mentioned studies that report vaccine effectiveness at sequential time points after the first booster dose, other studies have provided estimates from a single time point after administration of a first booster dose. Most of these studies estimated the effectiveness against hospitalisation to be in the range 86–99% in the initial period (from 14 days and up to 10 weeks) after the first booster [15,60-63].

Studies of vaccine effectiveness against severe disease with follow-up time of three months to < 6 months after the first booster dose (third dose)

A test-negative case-control study from the US estimated vaccine effectiveness against hospitalisation and emergency department/urgent care (ED/UC) visits by comparing the odds of a positive SARS-CoV-2 test result between vaccinated and unvaccinated patients between August 2021 and January 2022 in adults aged ≥18 years after three doses of an mRNA vaccine (Comirnaty or Spikevax). The VE against hospitalisation using data from 93 408 individuals was estimated to 91% (95% CI: 88–93%) initially at less than two months and declined to 88% (95% CI: 85–90%) at 2–3 months, and 78% (95% CI: 67–85%) at ≥4 months after the booster dose. The estimates for ED/UC visits were somewhat lower, estimated at 87% during the first two months after a third dose and decreasing to 66% among those vaccinated 4–5 months earlier. Variations in the waning of VE by age group, immunocompromised status, other indicators of underlying health status, or vaccine product were not studied [34].

Another test-negative case-control study evaluated the effectiveness of two and three doses of Comirnaty against hospital and emergency department (ED) admission for Delta and Omicron-related illness in a large US integrated health system. Data from 1 December 2021 to 11 January 2022 showed that two-dose effectiveness against Omicron related hospital admission was 68% (95% CI: 58–75%), and three-dose effectiveness was 89% (95% CI: 84–92%). The waning of effectiveness against Omicron-related hospitalisation after two or three doses was not observed in the study. Up to four months after a third dose of Comirnaty, VE remained high (≥89%) against Omicron-related hospitalisation. Three doses of Comirnaty were also effective at preventing Omicron-related ED admission with the disease presenting in a milder form, however, protection waned from 78% (95% CI: 73–82%) at <3 months to 48% (95% CI: 14–69%) at ≥3 months [28].

A test-negative, case-control study from the UK estimated the VE against COVID-19 related hospitalisation over time using different measures of hospitalisation. After administration of a booster dose of any vaccine (Comirnaty, Spikevax or Vaxzevria), the VE among 18 to 64-year-olds against hospitalisations admitted through emergency care peaked at 82% and dropped to 54% by ≥15 weeks. Using more specific data for hospitalisation caused by COVID-19 respiratory disease, effectiveness peaked at 91% and declined to 67% at ≥15 weeks, and the effectiveness of preventing need for oxygen/ventilation/intensive care ranged from 97% down to 76%. In the older age group of 65+ years, the corresponding VE estimates were 92%, declining to 77% for emergency care admission, 91% down to 85% for respiratory disease, and 96% down to 87% for oxygen/ventilation/intensive care at ≥15 weeks [27]. The somewhat higher estimates in the elderly were probably explained by contamination of hospitalisations with incidental cases of COVID-19 in the younger age group.

A nationwide cohort analysis in over three million people aged 12+ years from Denmark estimated the vaccine effectiveness against COVID-19-associated hospitalisation over the time period 21 December 2021 to 15 February 2022. The effectiveness after a first booster dose of Cominarty was estimated to 89% (95% CI: 87−90%) for up to one month, declining to 79% (77−81%) in the fourth month, and 66% (95% CI: 61−71%) at ≥4 months after the booster dose. For Spikevax, the initial effectiveness was 90% (95% CI: 87−92%), declining to 84% (95% CI: 78−88%) in the fourth month, and 77% (95% CI: 63−86%) at ≥4 months [25].

The vaccine effectiveness against COVID-19-associated hospitalisation after the first booster dose of a COVID-19 vaccine was also estimated from German data on ≥60-year-olds in a report from the Robert Koch Institute. The effectiveness was estimated to 98% (95% CI: 97−98%) in the first month after administration of the booster dose, and 93% (95% CI: 91−94%) at 2−3 month after the booster. At >3 months after the booster dose, the effectiveness had declined to 80% (95% CI: 77−84%) [16].

A report published by La Haute Autorité de Santé (HAS) in France estimated vaccine effectiveness against hospitalisation and critical care following a booster dose at different time points in older age groups. They found that vaccine effectiveness against hospitalisations was 83% among 60–79-year-olds who received a booster dose less than three months earlier and declined to 66% at more than three months after the booster dose. The corresponding estimates among those aged 80+ years were 77%, decreasing to 71%. Vaccine effectiveness against critical care and death for the two age groups is between 80% and 90% at the earlier time point, decreasing to between 70% and 85% after three months. The authors note that the loss of vaccine protection in people aged 80 years and over is most probably underestimated because this population is less likely to be transferred to the intensive care unit [26].

Effect of Omicron sub-lineages on vaccine effectiveness

It is not fully understood whether the different sub-lineages of Omicron influence vaccine effectiveness. A pre-print case control study from the southern part of Sweden reported on a rapid decline in vaccine effectiveness against severe COVID-19 that coincided with the transition from Omicron BA.1 to BA.2 dominance in the region [63]. The decline was observed among persons who had received two vaccine doses only, while the effectiveness from the first booster (three doses) remained stable. The authors suggest that the decline is explained by the immune evasiveness properties of BA.2, and not by waning VE alone. Other studies from Qatar and the UK have reported similar vaccine effectiveness estimates for the sub-lineages BA.1 and BA.2 in relation to symptomatic infection [16,65], and hospitalisation or death [9].

Studies of vaccine effectiveness against infection and severe disease after the second booster dose (fourth dose)

An open-label, non-randomised clinical study from Israel assessed the immunogenicity and safety of a second booster of either Comirnaty or Spikevax administered four months after the first booster dose in a series of three doses of Comirnaty. The study included 1 050 second booster dose eligible healthcare workers, of which 154 received Comirnaty and 120 Spikevax. The study found that a second booster dose restored the humoral response to levels similar to those after the first booster dose. Vaccine efficacy against any SARS-CoV-2 infection was 30% (95% CI: -9 to 55) for Comirnaty and 11% (95% CI: -43 to 44) for Spikevax. For symptomatic disease, vaccine efficacy was slightly higher; 43% (95% CI: 6.6 to 65) for Comirnaty and 31% (95% CI: -18 to 60) for Spikevax. However, confidence intervals are very wide and below zero for some values [29].

The recently published study by Bar-On et al. included 1 252 331 persons aged 60 years and above who were eligible for the second booster dose during the Omicron-dominated period (10 January 2022 until 2 March 2022 for confirmed infection and 18 February 2022 for severe illness). The study compared the rate of confirmed COVID-19 and severe illness between those who had received a fourth dose of Comirnaty at least 12 days earlier, those who had received only the third dose, and those who had received the fourth dose seven days earlier. This second control group included the same individuals as the treatment group, but at times when the fourth dose was not expected to be effective. The rate of confirmed infection was lower in people four weeks after their fourth dose than among those who received only three doses and those three to seven days after their fourth dose by factors of 2.0 (95% CI 1.9 to 2.1) and 1.8 (95% CI 1.7 to 1.9), respectively. The adjusted rate of infection in the eighth week after the fourth dose was very similar to those in the control groups. These findings suggest that protection against confirmed infection wanes quickly [30]. VE against confirmed infection amounted to 50% (50−53) 12 or more days after the fourth dose, and to 48% (45−50) 3−7 days after the second booster [7]. For severe illness, the rate was lower by factors of 3.5 (95% CI: 2.7 to 4.6) in people four weeks after their fourth dose than among those who received only the third dose, and 2.3 (95% CI: 1.7 to 3.3) three to seven days after receiving the third dose. Severe illness continued to occur at lower rates in the four-dose groups than in the control groups in the weeks after receipt of the fourth dose, and no signs of waning were evident by the sixth week after receipt of the fourth dose, in contrast to the waning seen for protection against infection [30]. VE against severe illness amounted to 77% (59−87) 12 or more days after the fourth dose, and to 75% (55−87) 3−7 days after the fourth dose [7].

A published study by Magen et al from the Israeli nationwide setting evaluated the early effectiveness of a fourth dose of Comirnaty in preventing COVID-19 related outcomes. They analysed data recorded in Israel from 3 January to 18 February 2022 using 182 122 matched pairs and compared the relative effectiveness of a fourth dose compared to a third dose given to individuals aged 60 years and above at least four months earlier. Relative vaccine effectiveness in days 7 to 30 after the fourth dose was estimated to be 45% (95% CI: 44 to 47) against polymerase-chain-reaction–confirmed SARS-CoV-2 infection, 55% (95% CI: 53 to 58) against symptomatic COVID-19, 68% (95% CI: 59 to 74) against COVID-19–related hospitalisation, 62% (95% CI: 50 to 74) against severe COVID-19, and 74% (95% CI: 50 to 90) against COVID-19–related death. In days 7 to 30 after a second booster dose, the difference in the absolute risk (three doses versus four doses) was 180.1 cases per 100 000 persons (95% CI: 142.8 to 211.9) for COVID-19–related hospitalisation and 68.8 cases per 100 000 persons (95% CI: 48.5 to 91.9) for severe COVID-19. The authors conclude that a second booster dose of Comirnaty was effective in reducing the short-term risk of COVID-19–related outcomes among those who had received a third dose at least four months earlier [34].

A pre-print study from Israel examined the short-term marginal effectiveness of a fourth dose compared to the third dose over the span of 10 weeks. The study involved 97 499 individuals aged 60 or older who were eligible to receive a second booster dose and performed at least one PCR test during the study period. In total, 27 876 received the fourth dose and 69 623 received only the third dose. The study found that the fourth dose provided considerable additional protection against both SARS-CoV-2 infection and severe disease compared to three doses of the vaccine. However, vaccine effectiveness against infection (defined as having tested positive with a PCR test) varied over time, peaking during the third week with a VE of 64% (95% CI: 62.0%−65.9%) and declining to 29.2% (95% CI: 17.7%−39.1%) by the end of the 10-week follow-up period. In addition, effectiveness of the fourth dose against infection seems to wane sooner than that previously seen for the third dose, although this could potentially be explained by a reduced effectiveness of Comirnaty against the Omicron variant. Unlike VE against infection, the relative effectiveness of a fourth dose against severe COVID-19 was maintained at high level (>73%) throughout the nine-week follow-up period. However, severe disease was a relatively rare event in both those receiving the second booster and those only receiving the first booster dose, occurring in under 1% of the study participants [32].

Another pre-print study from Israel compared mortality among participants who received a second booster with those who received only the first booster. Over half a million individuals aged 60−100 years were included in the study, 58% of whom had received a second booster dose during the 40-day study period. Deaths due to COVID-19 occurred in 92 second booster recipients and 232 participants who received one booster, with an adjusted hazard ratio of 0.22 (CI 0.17-0.28). Despite the substantial reduction in COVID-19 mortality due to the second booster, this 78% relative reduction in mortality in the elderly population is lower than the observed effect of the first booster in the elderly in Israel which was 90%. While the data indicate that a fourth dose may reduce mortality in those above 60 years of age, this reduction is from a low absolute mortality risk (<0.5% in all groups). It should be noted that there was a difference between the two groups and there were confounding variables (higher age group, male sex, ultra-orthodox Jewish, chronic heart failure, chronic obstructive pulmonary disease, and diabetes) that had a significant association with death due to COVID-19. Limitations of the study include the short follow-up time and the possibility that study participants died from other causes but were reported as death due to COVID-19 for having tested positive in screening for SARS-CoV-2 when they died [35].

A recent pre-print study from Israel reported on the risk of COVID-19 breakthrough infection in healthcare workers at eleven hospitals who had received three or four doses of Comirnaty. The risk ratio for infection at ≥7 days after four doses of vaccine compared to three doses only was 0.61 (95% CI: 0.54 to 0.71) when matched for sex, age group, profession, and hospital [31]. The corresponding vaccine effectiveness was estimated to be 44% (95% CI: 37−50%) [7]. Protection against severe disease was not evaluated.

A recent test-negative design cohort study (pre-print) from Canada among LTCF residents investigated the marginal vaccine effectiveness against Omicron ≥7 days after a fourth dose of COVID-19 mRNA vaccine compared to a third dose received ≥84 days prior to testing. Study participants received either Comirnaty or Spikevax as their first three doses, but 97% received Spikevax as the fourth dose. The study found the marginal VE to be 40% against infection (any), 63% against symptomatic infection and 54% against severe disease (including death). Compared to unvaccinated individuals, VE estimates against infection (65%), symptomatic infection (87%), and severe outcomes (92%) were consistently higher after a fourth dose than VE for a third dose received ≥84 days prior. The findings from this study indicate that in the short term a fourth dose of a COVID-19 mRNA vaccine successfully increased protection against any SARS-CoV-2 infection, symptomatic infection, and severe outcomes among LTCF residents in an Omicron-dominant period if ≥84 days had elapsed since their third dose. However, the long-term protection provided by the fourth dose is unknown at this stage [33].

Annex 4. Table of vaccine effectiveness studies for the fourth dose

Author, country	Population	Outcome	Reference group	Vaccine for fourth dose	VE of fourth dose (95% CI)	Timing
Gazit, et al. Israel	97 499 60+ years	Breakthrough infection	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	64% (62.0−65.9)	Three weeks
					29.2% (17.7−39.1)	Ten weeks
		Severe disease (hospitalisation or mortality)			Above 73%	Nine weeks
Grewal et al. Canada	9 957 Omicron cases and 46 849 test-negative controls, LTCF residents	Infection (any)	Complete vaccination with three doses of Comirnaty ≥84 days prior to testing	Comirnaty or Spikevax	40%	≥7 days
			Unvaccinated individuals		65%	
		Symptomatic disease	Complete vaccination with three doses of Comirnaty ≥84 days prior to testing		63%	
			Unvaccinated individuals		87%	
		Severe disease (including death)	Complete vaccination with three doses of Comirnaty ≥84 days prior to testing		54%	
			Unvaccinated individuals		92%	
Arbel et al. Israel	563 465, 60-100 years	Death	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	Adjusted HR 0.22 (0.17−0.28).	40 days
Cohen et al. Israel	29 612 HCW receiving the fourth dose during January	Breakthrough infection	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	44% (37−50)	≥7 days
Magen et al. Israel	182 122 matched pairs, 60+ years	Confirmed infection	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	45% (44−47)	7-30 days after the fourth dose
		Symptomatic infection			55% (53−58)	
		Hospitalisation			68% (59−74)	
		Severe disease			62% (50−74)	
		Death			74% (50−90)	
Bar-On et al. Israel	1 252 331, 60+ years	Confirmed infection	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	50 (50−53)	12+ days post first booster
					48 (45−50)	3-7 days post dose 4
		Severe illness			77 (59−87)	12+ days post first booster
					75 (55−87)	3-7 days post dose 4
Regev-Yochay et al, Israel	1 050 HCWs (non-randomised clinical trial)	Infection	Complete vaccination with three doses of Comirnaty at least four months prior	Comirnaty	30 (-9 to 55)	8-29 days
				Comirnaty primary Spikevax booster	11 (-43 to 43)	8-23 days
		Symptomatic disease		Comirnaty	43 (7 to 65)	8-29 days
				Comirnaty primary Spikevax booster	31 (-18 to 60)	8-23 days

Note: All studies were performed at a time when Omicron was the dominant SARS-CoV-2 variant.

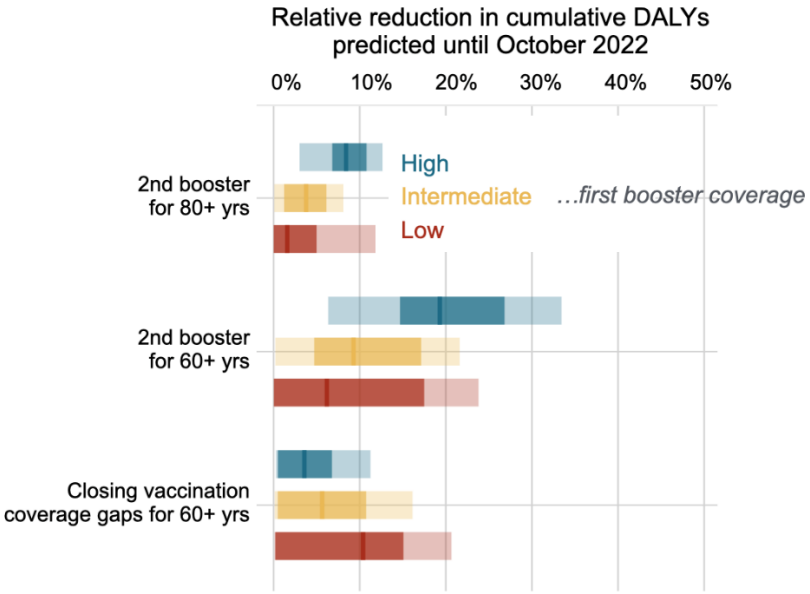
Annex 5. Factors for consideration in assessing the future epidemiology and considerations for a second COVID-19 vaccination booster

Factor	Expected effect on future epidemiology	Considerations for second booster roll-out
Contact rates during summer season	A clear risk factor for an early transmission increase in the summer, as well as sustained high levels of transmission.	If a high burden is observed in the summer, an earlier second booster will be more effective, while a second booster late in the summer will have greater effectiveness during the autumn/winter period.
Waning protection against infection*	Faster waning would mean relatively early increase in transmission, within a few months.	Would increase benefit of an early second booster roll-out.
Waning protection against severe disease*	Faster waning would mean a higher hospitalisation rate and death burden.	Higher burden and thus larger effect of second booster roll-out. Smaller impact on best timing for second booster roll-out within our modelling timeframe.
Change in COVID-19 testing and surveillance	Reduced testing and surveillance will delay visibility of and response to increases in transmission.	Will delay second booster vaccination in response to increases in transmission and diminish the short-term impact of this vaccine roll-out.
New variants of concern	Important risk factor for a rapid increase in transmission. Potential for reduction of VE against severe disease and thus an increased infection rate.	Second booster should be strongly considered in the wake of an increase in transmission caused by a variant (assuming that protection against severe disease is conferred by the booster against the variant).
Seasonal forcing of viral transmission	Seasonal forcing of transmission (due to environment and/or social factors) will increase risk of an increase in transmission towards the winter months.	Will make autumn increases in transmission more likely with greater benefit from a later second booster roll-out.
Expected second booster uptake	Relatively muted impact on epidemiological trajectory.	High uptake will result in a larger impact of the second booster campaign, but might increase vaccine fatigue in future campaigns.

**These factors are included in the uncertainty of our modelling analysis.*

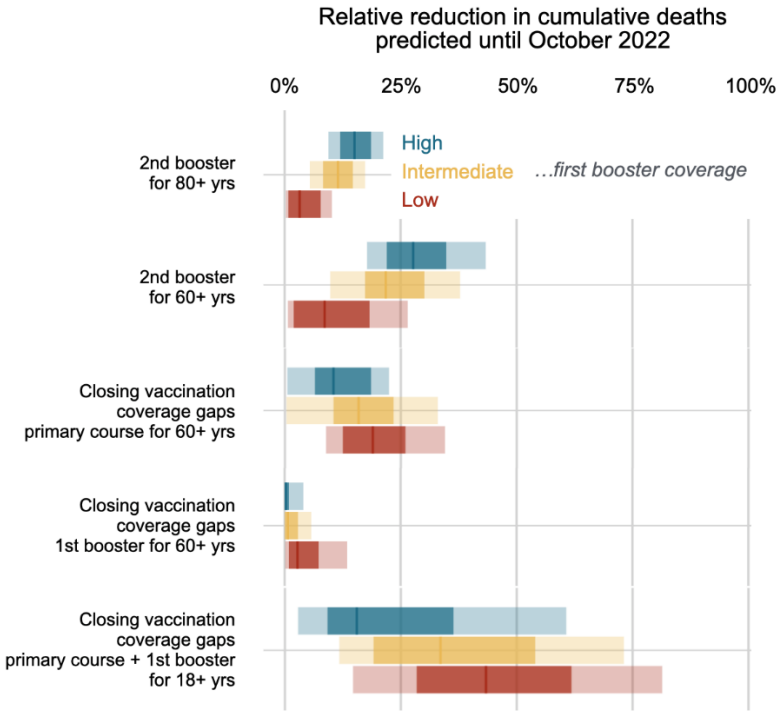
Annex 6. Supplementary figures of modelling analysis

Figure A7. Reduction in disability-adjusted life years (DALYs) by a second booster roll-out



Relative reduction in cumulative disability-adjusted life years (DALYs) under various scenarios, predicted until 31 October 2022. Different colours show groupings of countries depending on their first booster vaccination levels in the total population. (We split countries into three groups of equal size, depending on the vaccination uptake of the first booster). The variation of each colour bar is due to the different characteristics of countries in the same vaccination group and the uncertainties of epidemiological parameters (speed of waning of protection against infection and severe outcome, current viral transmissions, and changes in test availability). The dark lines in the centre of each distribution show the median value, the darker shaded areas correspond to the 25th and 75th quantile, and the light shaded area corresponds to the 10th and 90th percentile. The scenario 'Closing vaccination coverage gaps' targets the age group 60+ years and corresponds to closing the vaccination coverage gaps by 50% for the primary series and by 75% for the first booster. These analysis results are only based on a subset of EU/EEA countries due to the scarcity of hospitalisation data.

Figure A8. Reduction in deaths by a second booster roll-out



Relative reduction in deaths under various scenarios, predicted until 31 October 2022, showing a larger effect from closing the vaccination coverage gaps of the first booster than for the primary course. Different colours show groupings of countries depending on their first booster vaccination levels in the total population. (We split countries into three groups of equal size, depending on the vaccination uptake of the first booster). The variation of each colour bar is due to the different characteristics of countries in the same vaccination group and the uncertainties of epidemiological parameters (speed of waning of protection against infection and severe outcome, current viral transmissions, and changes in test availability). The dark lines in the centre of each distribution show the median value, the darker shaded areas correspond to the 25th and 75th quantile, and the light shaded area corresponds to the 10th and 90th percentile. The scenario 'Closing vaccination coverage gaps first booster' corresponds to closing the vaccination coverage gaps by 75% for the first booster. The scenario 'Closing vaccination coverage gaps primary course' targets the age group 60+ years and corresponds to closing the vaccination coverage gaps by 50% for the primary course vaccination. When targeting those aged 18+ years, the vaccination gaps for those aged 18–59 years are closed by 50% for both first booster and primary course.