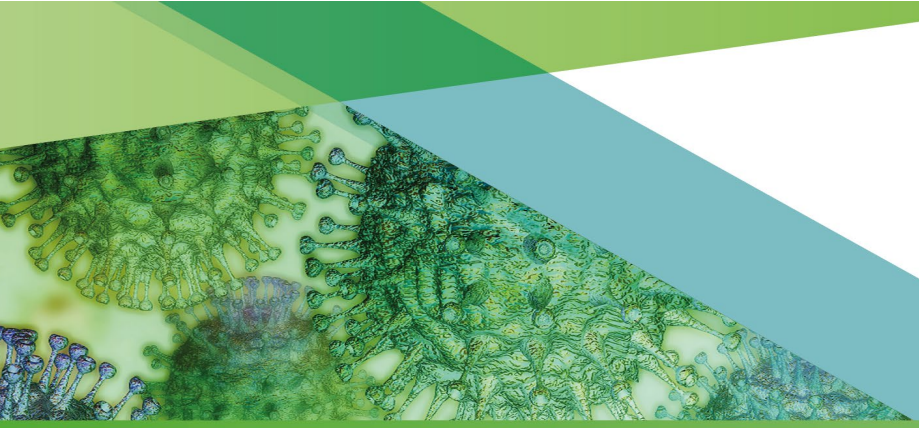

TECHNICAL REPORT

Interim public health considerations for COVID-19 vaccination roll-out during 2023

5 April 2023

Key messages

- Severe COVID-19 continues to disproportionately affect older adults and individuals with underlying comorbidities. Each time there has been a new wave of infection, EU/EEA countries' surveillance data from 2022 onwards indicate the largest increases in hospital, intensive care unit (ICU) admissions and deaths in the age groups 65–79 and 80 years and older. However, the height of the peaks for these indicators is lower than in the pre-Omicron period. Similarly, length of hospital stay increases with age, and is longest in individuals aged 65 years and above and especially those aged 80 years and above.
- At this stage of the pandemic, the main objectives of COVID-19 vaccination campaigns continue to be reducing COVID-19 hospitalisations, severe disease and deaths, and protecting healthcare systems.
- In 2022, all EU/EEA countries recommended the administration of COVID-19 booster doses, mostly for older population groups such as those aged 60 years and above, individuals with underlying medical conditions and other selected groups. In those aged 60 years and above, uptake of the primary series and first booster has levelled off in all countries over the last year (>90%; > 40%, respectively). The uptake of the second booster shows a less evident pattern and more heterogeneity across countries. In general, every subsequent booster dose added to vaccination campaigns shows lower uptake.
- Despite only a fraction of infections being detected, reported COVID-19 case rates fluctuate around levels comparable to those reported during late 2020 and 2021 – prior to Omicron circulation and when widespread free population testing was available. This suggests high levels of ongoing SARS-CoV-2 transmission in the EU/EEA and therefore an associated high risk of exposure for groups vulnerable to severe COVID-19.
- A predictable pattern of COVID-19 seasonality has not yet been established. Nevertheless, time series of severe COVID-19 outcomes (hospital, ICU admissions COVID-19 deaths) since the beginning of the pandemic show that the impact of the disease has been much higher during the period corresponding to the traditional influenza season.
- Omicron SARS-CoV-2 virus subvariants continue to dominate the SARS-CoV-2 virological landscape in the EU/EEA and globally. In the EU/EEA, several variants under investigation (VUI) including XBB.1.5, other XBB lineages and CH.1.1, have been increasing in proportion and XBB.1.5 became the dominant lineage by March 2023, without causing a deterioration in the epidemiological situation.
- Since September 2022, bivalent vaccines targeting the Omicron sub-lineages BA.1 and BA.4/BA.5 have represented approximately 94% of the total vaccine doses administered, according to data reported in the EU/EEA (18 countries reporting).
- Data currently available on vaccine effectiveness (VE) of monovalent and bivalent booster doses indicate added protection against severe outcomes in previously vaccinated individuals. In most cases, studies of the bivalent BA.4/5 mRNA COVID-19 vaccines were conducted during a time when Omicron BA4/5 or sub lineages of the Omicron variants were the dominant strains. For effectiveness of bivalent vaccines, longer follow-up is needed to determine the long-term protective effect of a bivalent booster against severe outcomes.
- Evidence suggests that hybrid immunity[1] confers strong protection against severe COVID-19, with high levels of protection lasting possibly beyond 12 months. However, it is likely that hybrid immunity has not developed uniformly across populations, with the elderly reportedly having the lowest rates.

[1] Hybrid immunity is defined as the immune protection in individuals who have had one or more doses of a COVID-19 vaccine and experienced at least one SARS-CoV-2 infection before or after the initiation of vaccination.

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- Mathematical modelling has been undertaken at ECDC, based on the observed epidemiology of COVID-19 in EU/EEA countries, observed vaccine uptake of boosters in EU/EEA countries, review of the literature on vaccine effectiveness, waning and hybrid immunity. Modelling scenarios of campaigns restricted to once/twice a year and with modelling restricted to the population aged 50 years and above and 80 years and above, respectively, in the main analysis indicates as follows:
  - **An autumn 2023 vaccination campaign** with an optimistic scenario of high vaccine uptake among individuals aged 60 years and above as a target group is expected to prevent an estimated 21–32% of the cumulative total all-age COVID-19-related hospitalisations across EU/EEA countries until 28 February 2024. The incremental gains in prevention are larger when targeting individuals aged 60 years and above instead of 80 years and above. The gains in prevention are similar, irrespective of whether individuals aged 50 years and above or 60 years and above are targeted.
  - Combining an **autumn 2023 vaccination campaign** targeting individuals aged 60 years and above **with a spring 2023 vaccination campaign** targeting individuals aged 80 years and above can result in a substantial increase in the impact of vaccination (an estimated 36–44% reduction in hospitalisations), but only if the vaccine uptake is high in both the autumn and spring campaigns. A low vaccine uptake in the spring 2023 campaign followed by a high vaccine uptake in the autumn 2023 campaign in the same age groups (80 and 60 years, respectively) is only marginally different to an autumn 2023 campaign alone. This indicates that for the spring campaign to be effective at population level it is important to achieve a high vaccine uptake.
  - Similar results were observed for prevented mortality and disability-adjusted life years (DALYs).
  - When contrasting the overall impact with the efficiency of the different vaccination campaign scenarios, the per-dose effect increases with age for the target population. However, no substantial difference in efficiency is observed when comparing autumn and spring campaigns.
- At present, four EU/EEA countries have published their approach/recommendations to COVID-19 vaccination campaigns for 2023. In four countries, spring vaccination campaigns are recommended, targeting vulnerable groups (individuals aged over 75 years, those who are immunocompromised and residents of long-term care facilities). For the autumn vaccination, two countries have announced campaigns targeting vulnerable groups, such as individuals aged 65 years and above, and individuals with underlying comorbidities.
- Based on the elements summarised above, to decrease the impact of COVID-19, and the related hospitalisations and mortality expected during 2023, countries should plan for a continued roll-out of COVID-19 vaccines, particularly during the autumn/winter season, and take into account the following considerations:
  - vaccination efforts should focus on protecting those aged over 60 years and other vulnerable individuals irrespective of age (such as those with underlying comorbidities and the immunocompromised) during the autumn/winter seasons 2023;
  - to maximise individual protection, the offer of COVID-19 vaccination during spring 2023 to individuals aged over 80 years and to other vulnerable adults, irrespective of age, should also be considered. This could also have a substantial effect at population level, if the uptake is projected to be high;
  - for the autumn/winter vaccination campaigns, countries should consider combined vaccination campaigns against COVID-19 and influenza, since this approach could be more efficient in terms of administration, logistics and costs.
  - If a spring COVID-19 vaccination campaign is undertaken, there should be adequate time allowed between the spring and autumn campaigns.
  - The above considerations are consistent with the recent highlights presented by WHO's Strategic Advisory Group of Experts on Immunization (SAGE), which has defined high-, medium- and low-priority groups for continued COVID-19 vaccination with respect to the current epidemiological scenario. In its updated roadmap highlights, SAGE recommends an additional booster dose for the high-priority groups, either six or 12 months after the last dose, with the timeframe depending on factors such as age and immunocompromising condition. SAGE indicates that these recommendations should not be seen as continuous annual COVID-19 vaccine boosters.
  - Overall, the decisions at country level related to COVID-19 vaccination for 2023 will continue to depend on a number of key evolving factors, such as the specific national epidemiological situation, possible virus evolution, availability of vaccines (including updated vaccines), vaccine effectiveness and protection over time, evidence on the effect of repeated boosters, degree of hybrid immunity across the population, projected vaccine uptake in different age groups, vaccine acceptance and the capacity of health systems to deliver vaccinations in the context of other competing public health priorities during the post-pandemic phase.
  - Promoting acceptance and uptake of COVID-19 vaccination becomes challenging in the context of diminishing population interest in getting vaccinated and a perception of 'return to normality'. Factors leading to declining uptake need to be identified, even in populations previously willing to be vaccinated. Future vaccination campaigns may consider developing targeted communication, focusing efforts on reaching high-priority groups through trusted channels and messengers, and providing clear information on which groups vaccination is being recommended to, the type of vaccines available and the timing. People should also be reminded why it is important to stay up-to-date with vaccination (particularly those in risk groups for severe COVID-19).

Background

There is consensus among international and national vaccination advisory groups that the main objectives of COVID-19 vaccination programmes have been the reduction of COVID-19 hospitalisations, severe disease and deaths, along with the protection of healthcare systems [1,2].

In the EU/EEA, severe COVID-19 continues to affect vulnerable individuals, influencing decision-making at national level on future vaccination campaigns targeting these population groups. A small number of countries have already made decisions for their 2023 vaccination campaigns focusing on the protection of vulnerable groups (Annex 1).

Scope of this document

This document offers an overview of the available scientific evidence and epidemiological situation and provides public health considerations to support discussions and decisions on the planning and implementation of COVID-19 vaccination campaigns for 2023.

The analysis presented in this document focuses on adults and on age as a risk factor for severe COVID-19. Adults with underlying comorbidities (including immunocompromised individuals) are at increased risk of severe COVID-19 irrespective of age [3]. In the past, National Immunisation Technical Advisory Groups (NITAGs) have provided recommendations prioritising vaccination of these population groups and emphasising the importance of high vaccination uptake.

The public health considerations presented in this document are based on:

- assessment of current epidemiological trends across the EU/EEA
- an overview of current vaccination campaigns and uptake
- modelling scenarios of age-based vaccination campaigns
- available knowledge on SARS-CoV-2, along with uncertainties related to its evolution
- a review of the effectiveness of COVID-19 vaccines
- a review of current knowledge on hybrid immunity
- programmatic considerations that may have an impact on future campaigns, including uptake of further doses and societal acceptance of vaccination.

The public health considerations presented in this document are preliminary and subject to change as more data become available. NITAGs are the bodies responsible for providing advice and/or recommendations on the use of COVID-19 vaccines at country level.

This document only focuses on vaccination and not on other non-pharmaceutical and pharmaceutical measures that may be necessary to prevent further spread or clinical manifestations of infection with SARS-CoV-2, especially in specific settings.

Target audience

The target audiences for this document are the EU/EEA NITAGs, national public health institutes and ministries of health in EU/EEA countries, as well as public health experts at national and sub-national level.

Considerations for vaccination strategies in 2023 in the EU/EEA

The primary public health objectives of COVID-19 vaccination campaigns have been to reduce severe disease, hospitalisations, and deaths in individuals at high risk of severe COVID-19 disease, as well as to protect healthcare systems.

While the risk of severe disease, hospitalisation and death due to COVID-19 has significantly decreased in the general population of the EU/EEA as a result of the vaccination campaigns carried out, the build-up of hybrid immunity and the emergence of the less virulent Omicron variants, evidence indicates that the risk persists, especially for certain population groups such as older individuals and those with underlying comorbidities [4].

There has recently been a general downward trend in the height of the peaks in reported cases, hospitalisations, ICU admissions and deaths [5]. Since early 2022, the volume of COVID-19 testing has reduced considerably, with many countries adapting testing strategies and limiting free testing to vulnerable groups. Despite only a fraction of all infections being detected, reported case rates fluctuate around levels comparable with those reported during late 2020 and 2021 – prior to Omicron variant dominance and when widespread population testing was available free of charge. This implies high levels of ongoing SARS-CoV-2 transmission in the EU/EEA and an associated high risk of exposure for groups vulnerable to severe COVID-19. EU/EEA countries' surveillance data show that, each time there is a new wave of infection, the age groups 65–79 years and 80 years and above continue to report the largest increases in hospital, ICU admissions and deaths. Available data indicate that, following admission individuals from these age groups can remain in hospital for longer than younger individuals, further increasing pressure on already strained healthcare systems.

A predictable pattern of COVID-19 seasonality has not yet been established. Since the large peak of infection at the beginning of 2022 due to the introduction of the Omicron variant of concern, the overall epidemiological picture for the EU/EEA has been characterised by periodic waves of infections every 2–3 months. These waves have been temporally associated with both increased circulation of different Omicron sub-lineages and seasonal population mixing patterns. Although no clear seasonal pattern of virus circulation has emerged, time series of severe COVID-19 outcomes (hospital, ICU admissions and deaths) since the beginning of the pandemic show that the disease's impact has been much higher during the autumn-winter period (corresponding to the traditional influenza season).

ECDC has created modelling scenarios on the impact of age-based COVID-19 vaccination strategies to reduce hospitalisation and mortality rates over a 12-month period in order to support public health considerations for 2023 vaccination campaigns in EU/EEA countries. The approach considered age as a risk factor - i.e. that the risk for COVID-19 hospitalisation and death increases with age - and was based on an annual or bi-annual vaccination campaign in 2023 for individuals aged 50 years and above. A selection of the possible scenarios is presented in detail, taking into account the anticipated epidemiological impact of the vaccination campaign along with other programmatic considerations.

In light of the epidemiological situation in the EU/EEA countries in 2022, with severe outcomes in older age groups increasing compared to younger age groups, the knowledge gathered on waning vaccine effectiveness and the age-groups targeted by an autumn/winter 2022/23 booster campaign, scenarios targeting those aged 80 years and above years in the spring and/or those aged 50 years and above in the autumn were deemed to be plausible. The population impact of the campaigns was explored, with modelling restricted to those aged 80 years and above and 50 years and above in the main analysis. This is also in line with decisions already made in some EU Member States for vaccination in 2023. However, it should be noted that national decisions on the best strategies and target groups suited for the local epidemiological context will ultimately be taken by Member States.

Mathematical modelling showed that an autumn 2023 vaccination campaign, with an optimistic scenario of high vaccine uptake targeting individuals aged 60 years and above, is expected to prevent an estimated 21–32% (IQR) of the cumulative total all-age COVID-19-related hospitalisations across EU/EEA countries until 29 February 2024. In the same model, a bi-annual campaign targeting individuals aged 80 years and above in the spring to restore immunity that may have waned after the previous vaccine dose, together with a campaign in the autumn targeting those aged 60 years and above, resulted in a substantial increase in the population impact of vaccination, with an estimated 36–44% (IQR) reduction in hospitalisations - if the vaccine uptake is high in both autumn and spring campaigns. A low vaccine uptake in the spring 2023 campaign, followed by a high vaccine uptake in the autumn 2023 campaign in the same age groups (80 and 60 years, respectively) would only be marginally different to a single autumn 2023 campaign targeting those aged 60 years and above. Modelling also showed that targeting individuals aged 50 years and above has a similar population impact to the targeting of individuals aged 60 years and above.

This suggests that the projected uptake in the different age groups could be one of the key parameters to evaluate in the decision-making process, since an additional spring campaign would only have a more substantial impact at population level than an autumn-only campaign if high uptake were achieved in both spring and autumn campaigns.

The above considerations based on mathematical modelling only use age as a risk factor. Available evidence suggests that immunity conferred by vaccination wanes a few months after the last dose, which may place individuals with underlying comorbidities at risk of severe disease and hospitalisation. Adults with underlying comorbidities (including immunocompromised individuals) are at increased risk of severe COVID-19, irrespective of age. In the past, NITAGs have provided recommendations to prioritise these population groups in order to achieve a high vaccination uptake.

It is important to note that there is a large variation in the expected burden of COVID-19, not only between countries but also due to considerable uncertainties in major drivers of future epidemiological dynamics. Such drivers can be the characteristics and timing of new variants of concern and their impact on immune escape and transmission; immunity levels and waning protection; time interval since last dose or infection; the role of hybrid immunity, social behaviour, contact mixing and mobility, and the potential vaccination uptake in different age groups. With regard to hybrid immunity, current evidence suggests that it offers superior and longer lasting protection against severe COVID-19 clinical outcomes compared to infection-induced or vaccine-induced immunity alone. However, this may not apply uniformly across age groups, with the elderly having the lowest rates of hybrid immunity.

Implications for vaccination policies

The primary objective of continued COVID-19 vaccination campaigns in 2023 is to reduce severe disease, hospitalisations, and deaths in individuals at high risk of severe COVID-19 disease, and to free up capacity in the healthcare system.

To decrease the impact of COVID-19, and the related hospitalisations and mortality expected during 2023 (particularly during the autumn/winter seasons), countries should plan for a continued roll-out of COVID-19 vaccines, and take into account the following considerations:

- vaccination efforts should focus on protecting adult individuals above the age of 60 years and other vulnerable individuals, irrespective of age (such as those with underlying comorbidities and the immunocompromised) during the autumn/winter seasons 2023;
- to maximise individual protection, consideration should also be given to offering COVID-19 vaccination to individuals above 80 years of age and other vulnerable adults, irrespective of age, during spring 2023. This could have a substantial effect at a population level, if the uptake is projected to be high;
- countries should consider the need for combined autumn/winter vaccination campaigns against COVID-19 and influenza, since this approach could be more efficient in terms of administration, logistics and costs;
- if a spring COVID-19 vaccination campaign is undertaken, there should be adequate time between the spring and autumn campaigns.

The above considerations are consistent with the recent highlights presented by WHO's Strategic Advisory Group of Experts on Immunization (SAGE), which has defined high-, medium- and low-priority groups for continued COVID-19 vaccination with respect to the current epidemiological scenario [6]. In its updated roadmap highlights, SAGE recommends an additional booster dose for the high-priority groups, either six or 12 months after the last dose, with the timeframe depending on factors such as age and immunocompromising condition. SAGE indicates that these recommendations should not be seen as continuous annual COVID-19 vaccine boosters.

Overall, the decisions at country level related to COVID-19 vaccination for 2023 will continue to depend on a number of key evolving factors, such as the specific national epidemiological situation, possible virus evolution, availability of vaccines (including updated vaccines), vaccine effectiveness and protection over time, evidence on the effect of repeated boosters, degree of hybrid immunity across the population, projected vaccine uptake in different age groups, vaccine acceptance and the capacity of health systems to deliver vaccinations in the context of other competing public health priorities during the post-pandemic phase.

Promoting acceptance and uptake of COVID-19 vaccination becomes challenging in the context of diminishing population interest in getting vaccinated and a perception of 'return to normality'. Factors leading to declining uptake need to be identified, even in populations previously willing to be vaccinated. Future vaccination campaigns may consider developing targeted communication, focusing efforts on reaching high-priority groups through trusted channels and messengers, and providing clear information on which groups vaccination is being recommended to, the type of vaccines available and the timing. People should also be reminded why it is important to stay up-to-date with vaccination (particularly those in risk groups for severe COVID-19). Furthermore, a simplification of the COVID-19 vaccination regimen would contribute to better communication and may improve vaccine coverage.

These public health considerations are based on current scientific evidence and epidemiological trends and will be periodically reassessed. The scope of these considerations is focused on 2023 and primarily takes into account the impact of COVID-19 vaccination at population level. Ultimately, responsibility for national decisions on the best strategies suited for the local epidemiological context lies with ministries of health, taking into account the relevant advice and/or recommendations given by NITAGs.

Supporting evidence to the public health considerations for 2023 vaccination strategies

The following sections contain detailed evidence reviews to support public health considerations and implications for vaccination policies.

Epidemiological overview based on the EU/EEA surveillance data

Since the large peak of COVID-19 infection at the beginning of 2022 due to the introduction of the Omicron variant of concern, the overall epidemiological picture for the EU/EEA has been characterised by periodic waves of infections approximately every 2–3 months.

These waves have been temporally associated both with increased circulation of different Omicron sub-lineages and seasonal population mixing patterns.

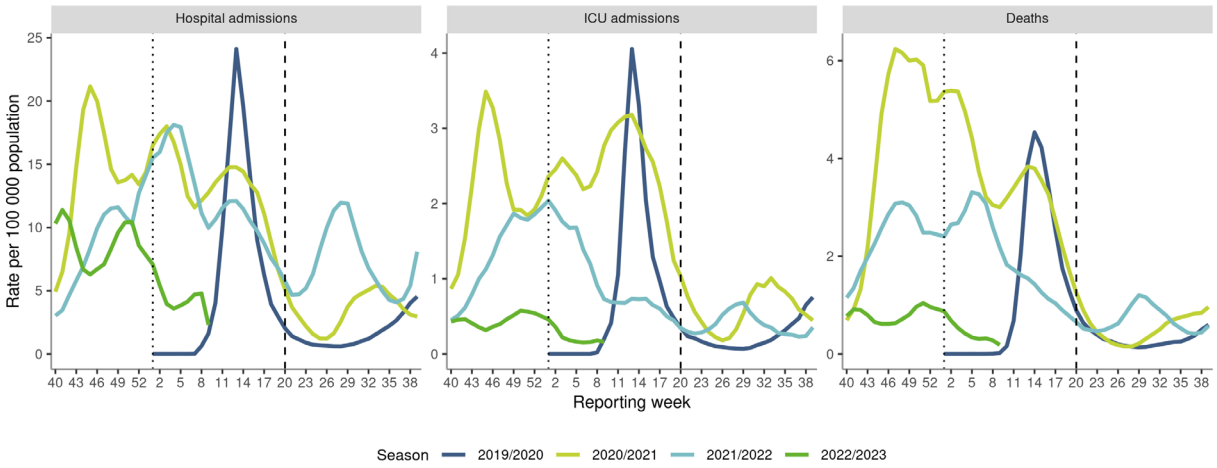
There has been a general downward trend in the height of the associated peaks in reported cases, hospitalisations, ICU admissions and deaths during this period [5].

Since early 2022, the volume of COVID-19 testing has decreased considerably, with many countries limiting free testing to vulnerable populations and those with severe disease. Despite only a fraction of infections being detected, reported case rates fluctuate around levels comparable to those reported during late 2020 and 2021 – prior to Omicron circulation, when widespread testing was available free of charge. This implies high levels of ongoing SARS-CoV-2 transmission in the EU/EEA and an associated high risk of exposure for vulnerable groups. Each time there is a new wave of infection, surveillance data show that the largest increases in hospital, ICU admissions and deaths are seen in the age groups 65–79 years and 80 years and above, albeit with the peaks for these indicators at lower levels than in the pre-Omicron period. Moreover, following admission, individuals from these older age groups can remain in hospital/ICU for longer periods, further increasing the pressure on healthcare systems which are already strained.

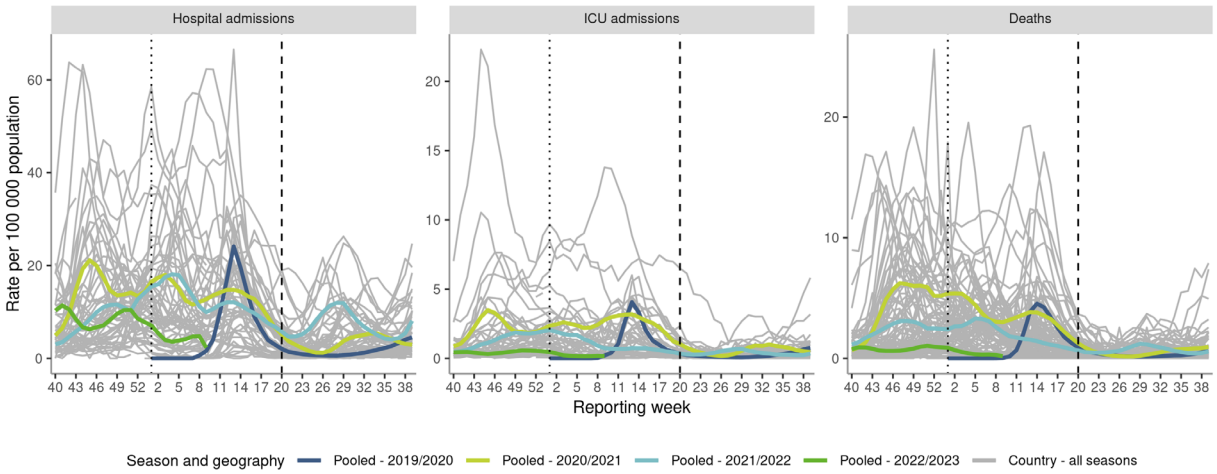
A predictable pattern of COVID-19 seasonality has not yet been established. However, time series of severe COVID-19 outcomes (hospital, ICU admissions and deaths) since the beginning of the pandemic show that the impact of the disease has been much higher during the period corresponding to the traditional influenza season (weeks 40 to 20) than during the 'inter-season' period (weeks 21 to 39). Nevertheless, smaller increases have been observed between weeks 21–39 in all years since the start of the pandemic. This is true for both pooled EU/EEA data and data from individual countries (Figure 1).

Figure 1. Rates of COVID-19 hospital, ICU admissions and deaths, by reporting week, seasons 2019/20 to 2022/23

a) pooled EU/EEA data



b) country-level with pooled EU/EEA data overlaid



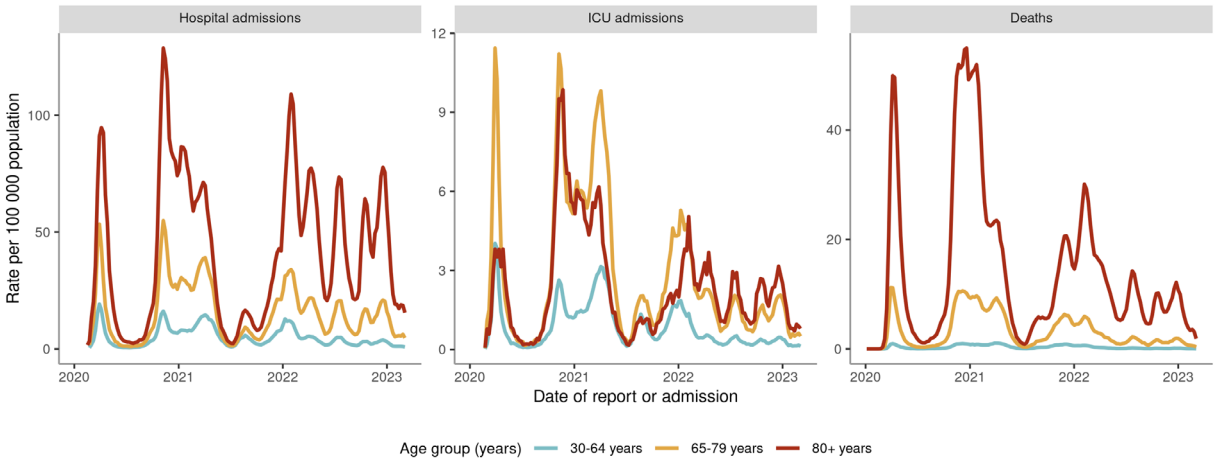
Note: dotted line indicates start of the calendar year (week 1), dashed line indicates the end of the influenza season (week 20).

Data sources: hospital admissions: ECDC database compiled from public online sources for Croatia, Denmark, Germany, Ireland, Norway and Slovenia; TESSy data from Belgium, Cyprus, Czechia, Estonia, France, Greece, Iceland, Italy, Latvia, Liechtenstein, Luxembourg, Malta, Netherlands, Portugal, Slovakia and Spain. ICU admissions: ECDC database compiled from public online sources for Ireland, Norway and Slovenia; TESSy data from Cyprus, Czechia, Estonia, France, Greece, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Slovakia, Spain and Sweden. Deaths: TESSy data for all 30 EU/EEA countries.

Age-specific rates of severe disease

Age-specific pooled rates of COVID-19 hospital, ICU admissions and deaths show that, despite an overall decreasing trend in the height of peaks during the Omicron period (since January 2022), the impact of severe disease is still disproportionately large among people aged 65 years and above, most notably in the age group 80 years and over (Figure 2).

Figure 2. Age-specific pooled rates of COVID-19 hospital, ICU admissions and deaths, 27 January 2020 to 5 March 2023



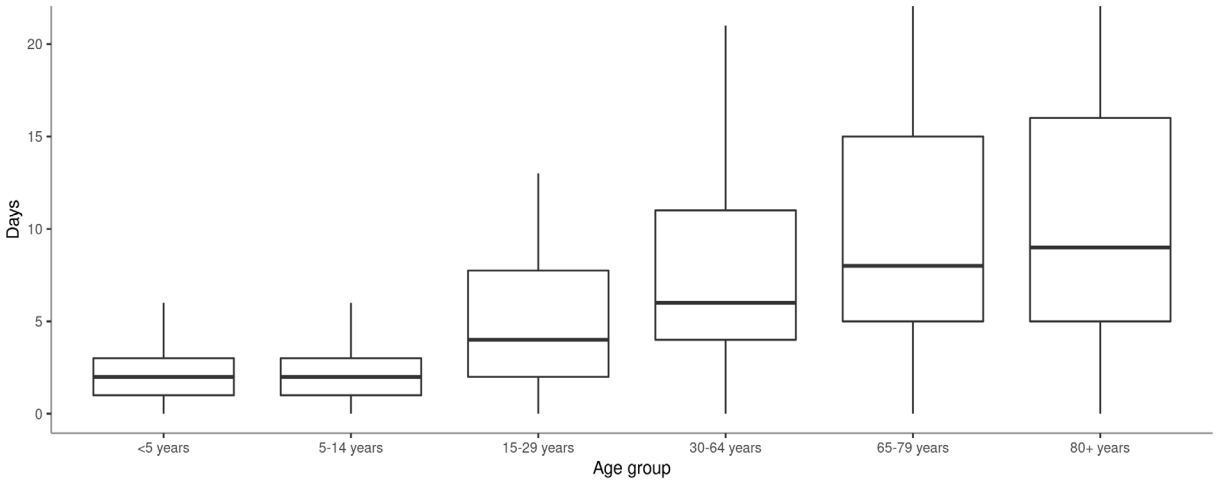
Note: the true burden of COVID-19 hospitalisations since 2022 is likely to be lower than shown in the reported data, since hospital admissions of people with COVID-19 (not due to COVID-19) have increased proportionately and have been estimated to account for 25–50% of reported admissions) [6,7].

Data sources: Hospital and ICU admissions: aggregate data submitted to TESSy RESPISEVERE or case-based data submitted to TESSy RESPISURV and/or NCOV. Hospital admissions data from Cyprus, France, Ireland, Italy, Luxembourg, Netherlands and Slovakia. ICU admissions data from Austria, France, Ireland, Italy, Luxembourg, Netherlands, Slovakia and Sweden. Date of admission was used for all countries except Austria and Ireland for which reporting date of the case was used. Deaths: data submitted to TESSy NCOVAGGR from Austria, Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Liechtenstein, Luxembourg, Malta, Netherlands, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

Length of stay and healthcare burden from severe COVID-19

Individual level data reported to TESSy show that length of stay among cases since January 2022 increases with age (Figure 3).

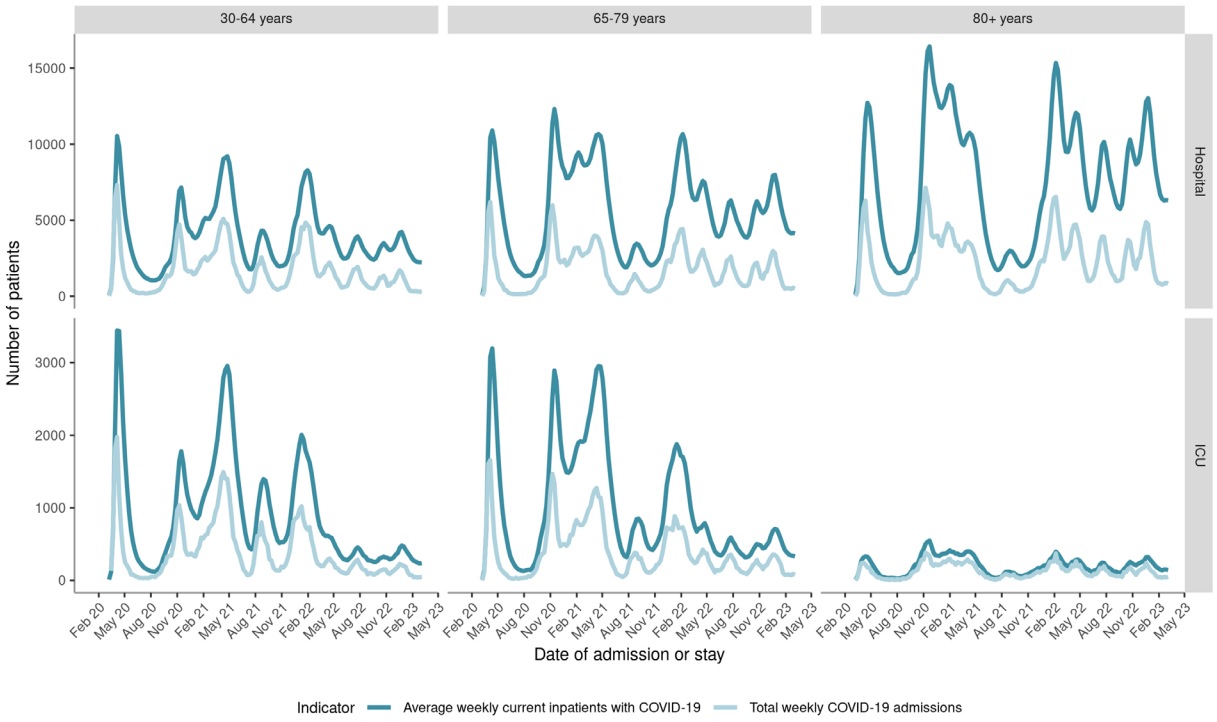
Figure 3. Length of stay in hospital for hospitalised cases reported 3 January 2022 to 5 March 2023



Data source: TESSy RESPISURV case-based data from Cyprus (12 582), Ireland (1 921), Malta (4 189) and Poland (3 469) Cases restricted to those in which date of onset occurred before date of hospital admission and for which age was known.

The impact of increased length of stay among older individuals is also visible in national data showing the total number of weekly COVID-19 hospital or ICU admissions, together with the average number of current COVID-19 hospital and ICU in-patients each week. With every increase in new admissions (light blue line, Figure 4) there is an increase in the number of current in-patients (dark blue line, Figure 4). Once new admissions fall again, the number of COVID-19 in-patients that remain in hospital stays high and remains higher for longer periods in the age groups 65–79 years and 80+ years than in those aged 30–64 years.

Figure 4. Counts of new COVID-19 admissions and the average number of current COVID-19 in-patients in hospital and ICU each week, 2 March 2020 to 5 March 2023



Source: TESSy RESPISEVERE, data from France.

Risk of hospitalisation and death among reported COVID-19 cases in relation to time since vaccination, according to indicator-based surveillance data reported to TESSy

This analysis included all cases aged 60 years and above with laboratory-confirmed symptomatic SARS-CoV-2 that had received at least three or more COVID-19 vaccine doses prior to disease onset, as reported to TESSy by EU/EEA countries from 1 January 2022 to 31 December 2022.

The risk of hospitalisation and death was compared between groups defined by sex, age (60–79, 80+ years) and time from last booster dose, adjusted by onset month.

Cases were then divided into groups according to the time elapsed since receipt of their last booster dose (irrespective of booster dose number): less than three months, between three and six months, 6–9 months or more than nine months prior to COVID-19 onset date. Unknown hospitalisation status and unknown deaths were recoded as 'Not hospitalised/alive'. Negative binomial regression models were run to calculate the Relative Risks (RR) and the 95% Confidence Intervals (95% CI) of hospitalisation and death.

Table 1. Main characteristics of COVID-19 cases who received at least three COVID-19 vaccine doses, by hospitalisation and case fatality status, 1 January 2022- 31 December 2022 (n=129 586)

	Total		Hospitalised		Died	
Characteristic	Number of cases	Proportion of cases (col %)	Number of cases	Proportion of cases (row %)	Number of cases	Proportion of cases (row %)
	129 586	100	1 264	1.0	123	0.09
Booster vaccination						
Last dose <3 months	72 274	55.8	593	0.8	37	0.05
Last dose between 3 and 6 months	50 345	38.8	578	1.2	58	0.12
Last dose between 6 and 9 months	5 654	4.4	60	1.1	19	0.34
Last dose >=9 months	1 313	1.0	33	2.5	9	0.69
Sex						
Female	71 067	54.8	535	0.7	50	0.07
Male	58 519	45.2	729	1.2	73	0.12
Age at diagnosis (years)						
60-79	110 907	85.6	796	0.7	38	0.03
80+	18 679	14.4	468	2.5	85	0.46
Onset month						
January 2022	30 207	23.3	258	0.8	20	0.07
February 2022	41 569	32.1	374	0.9	24	0.06
March 2022	39 137	30.2	388	1.0	34	0.09
April 2022	11 167	8.6	143	1.3	24	0.21
May 2022	2 687	2.1	23	0.9	4	0.15
June 2022	1 003	0.8	17	1.7	3	0.30
July 2022	1 736	1.3	17	1.0	3	0.17
August 2022	406	0.3	12	3.0	2	0.49
September 2022	392	0.3	9	2.3	1	0.26
October 2022	482	0.4	12	2.5	4	0.83
November 2022	480	0.4	10	2.1	3	0.63
December 2022	320	0.3	1	0.3	1	0.31

Cases included are from Cyprus (11 000), Luxembourg (6 734), Poland (111 852).

Data sources: TESSy RESPISURV (Cyprus) and NCOV (Luxembourg and Poland).

The main results for hospitalisation and case fatality data are presented in Table 1.

Of 129 586 reported cases with onset of COVID-19 symptoms between 1 January 2022 and 31 December 2022, and at least three COVID-19 vaccine doses:

- In all, 1.0% of the total cases were hospitalised and 0.09% of total cases had a fatal outcome.
- In 99.4% of total cases (n= 128 794), disease onset was reported after the third dose of the vaccine. The remaining of cases (n=792) had a disease onset after the fourth dose.

The proportion of hospitalisation was higher for those individuals who, at the time of disease onset, had received their last booster dose more than nine months before their COVID-19 diagnosis (2.5%), compared to those who had received their booster dose less than three months before (0.8%). The proportion was also higher for males (1.2%) than females (0.7%), and by age group.

With regard to case fatality, the proportion of deaths was higher among cases who, at the time of disease onset, had received their booster dose more than nine months before (0.69%), compared to those who had received their booster dose less than three months before (0.05%). The proportion was also higher in males (0.12%) than females (0.07%) and increased by age group.

Table 2. Adjusted relative risk of hospitalisation and death by time since last booster vaccination, sex, age group

	Adjusted relative risk of hospitalisation (95% CI)	Adjusted relative risk of death (95% CI)
Booster vaccination		
Last dose <3 months	Ref	Ref
Last dose between 3 and 6 months	1.05 (0.91–1.20)	1.14 (0.72–1.79)
Last dose between 6 and 9 months	0.80 (0.57–1.11)	**2.23 (1.08–4.62) ***
Last dose >=9 months	**1.94 (1.10–3.41) ***	**4.78 (1.30–17.56) ***
Sex		
Female	Ref	Ref
Male	**1.69 (1.51–1.89) *****	**1.83 (1.28–2.63) ****
Age at diagnosis (years)		
60- 79	Ref	Ref
80	**3.52 (3.12–3.96) *****	**13.08 (8.79–19.45) *****

** P-value<0.05 ** P-value<0.01 *** P-value<0.001.*
Data are further adjusted by the other variables presented in the table and by onset month.

Source: TESSy RESPISURV (Cyprus) and NCOV (Luxembourg and Poland); Cases are from Cyprus (11 000), Luxembourg (6 734), Poland (111 852).

The main results for adjusted Relative Risks (RR) and the 95% Confidence Intervals (95% CI) of hospitalisation and death are shown in Table 2: compared to individuals who received the booster dose less than three months before the onset date, the adjusted risk of hospitalisation almost doubled (RR=1.94, 95% CI: 1.10-3.41) more than nine months after receiving the booster dose. There was also a significant increase in the adjusted risk of hospitalisation in men compared to women (RR=1.69, 95% CI: 1.51-1.89) and among those aged 80+ years (RR=3.52, 95% CI: 3.12–3.96) when compared to those aged 60–79 years. Adjusted risk of death was higher for those who received the booster dose between six and nine months (RR= 2.23, 95% CI: 1.08–4.62) and after more than nine months since the receipt of a booster dose (RR=4.78, 95% CI: 1.30–17.56) compared to those who received the booster less than three months earlier. A significant increase in the adjusted risk of death was also seen for men (RR=1.83, 95% CI: 1.28–2.63) and those aged 80+ years (RR=13.08, 95% CI: 8.79–19.45).

A stratified analysis by number of doses received (three versus four doses) could not be performed as among the 792 cases with four doses, only 17 cases were hospitalised and four had died.

Table 3. Adjusted relative risk of hospitalisation by time from last booster vaccination and sex, stratified by age group

	Adjusted relative risk of hospitalisation (95% CI) among those aged 60-79 years	Adjusted relative risk of hospitalisation (95% CI) among those aged 80+ years
Booster vaccination		
Last dose <3 months	Ref	Ref
Last dose between 3 and 6 months	0.98 (0.82–1.16)	0.82 (0.66–1.02)
Last dose between 6 and 9 months	0.71 (0.44–1.13)	0.64 (0.41–1.00)
Last dose >=9 months	1.42 (0.67–2.99)	**2.63 (1.17–5.93) ***
Sex		
Female	Ref	Ref
Male	**1.86 (1.61–2.15) *****	**1.45 (1.21–1.75) *****

** P-value<0.05 ** P-value<0.01 *** P-value<0.001. Data are further adjusted by age (continuous) and onset month.*

Source: TESSy RESPISURV (Cyprus) and NCOV (Luxembourg and Poland); Cases are from Cyprus (11 000), Luxembourg (6 734), Poland (111 852).

The interaction between time from the booster dose and age group was tested for both hospitalisation and case fatality and was found significant for the former. Therefore, Table 3 shows the stratified adjusted risk of hospitalisation among individuals aged 60-79 and 80+ years separately. The results show that the higher risk of hospitalisation seen in Table 3 among those who received the booster dose after more than nine months is driven by the individuals aged 80+ years (RR= 2.63, 95% CI: 1.17–5.93).

We believe that a very small proportion of unknown hospitalisation status and unknown deaths should be categorised as 'Hospitalised/dead', and therefore the overall proportion of hospitalisations and deaths could be slightly underestimated. However, the misclassified observations are very likely to be equally distributed among the groups under comparison. Moreover, given the limited completeness of data, the estimates could not be adjusted by existing comorbidities.

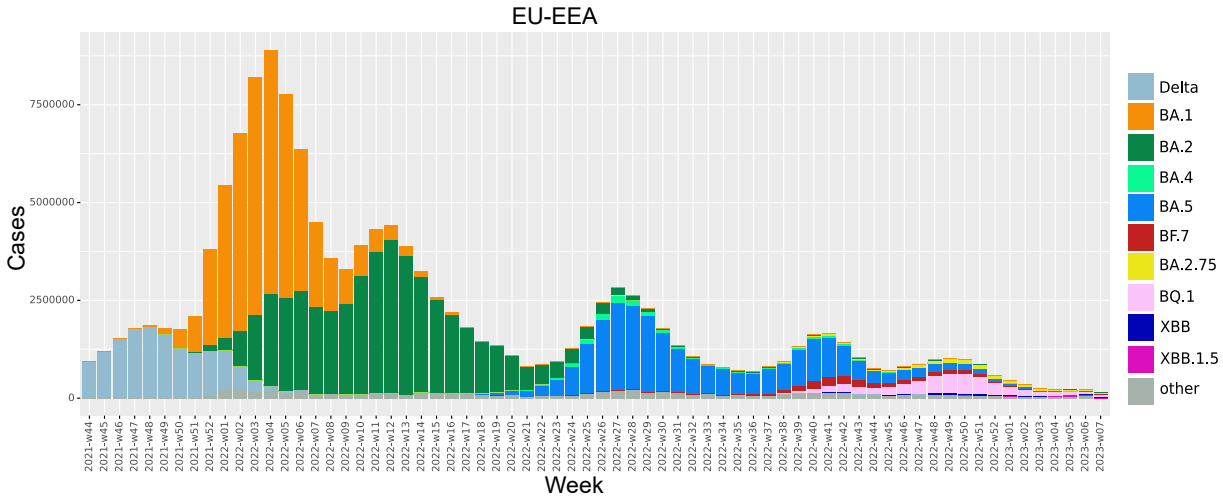
In addition, as the adjusted relative risk of severe outcome (hospitalisation or death) estimated above only takes into account individuals already infected, these estimates do not include complete vaccine protection against severe outcome (i.e. protection against an infection and against subsequent severe outcome). Therefore, since the protection against infection wanes more quickly than protection against severe outcomes, and since the adjusted relative risks of severe outcome for those individuals not yet infected are likely to be higher than those estimated here, the adjusted relative risks estimated above are underestimated.

SARS-CoV-2 variants

SARS-CoV-2 continued to evolve on a global scale during 2022 and the epidemiological situation in the EU/EEA was largely dominated by the Omicron variant and its subvariants. The initial Omicron variant B.1.1.529 emerged in November 2021 and was classified as a variant of concern (VOC) by ECDC on 26 November 2021. In January 2022, its sub-lineage BA.1 became the dominant SARS-CoV-2 virus in the EU/EEA. Since then, several more Omicron lineages and Omicron-Omicron recombinant viruses have developed, some of which became dominant in the EU/EEA, driving overlapping COVID-19 waves. Some Delta-Omicron recombinant viruses emerged over time, but none were successful in replacing circulating variants in the EU/EEA.

The initial Omicron variant BA.1 was first replaced as the dominant lineage in the EU/EEA by BA.2 in March 2022, followed by BA.5 in July 2022. After August, overall case notifications decreased further in the EU/EEA and several sub-lineages of BA.2 and BA.5 with growth advantages, as a result of acquiring different immune escape mutations, started to emerge simultaneously. BA.5 sub-lineages BA.5.2 and BQ.1 were dominant in September and December 2022, respectively (Figure 5).

Figure 5. Average number of weekly confirmed COVID-19 cases for EU/EEA countries, with the relative proportion of circulating variants



Note: the average number of confirmed cases from EU/EEA countries extracted from WHO's COVID dashboard were plotted on the y-axis. The proportion of the circulating variant was estimated from the SARS-CoV-2 sequences submitted to the GISAID EpiCoV database [8] based on the collection date of the submissions.

The overall decline in case notifications in most recent months needs to be interpreted carefully in connection with current testing behaviour and strategies.

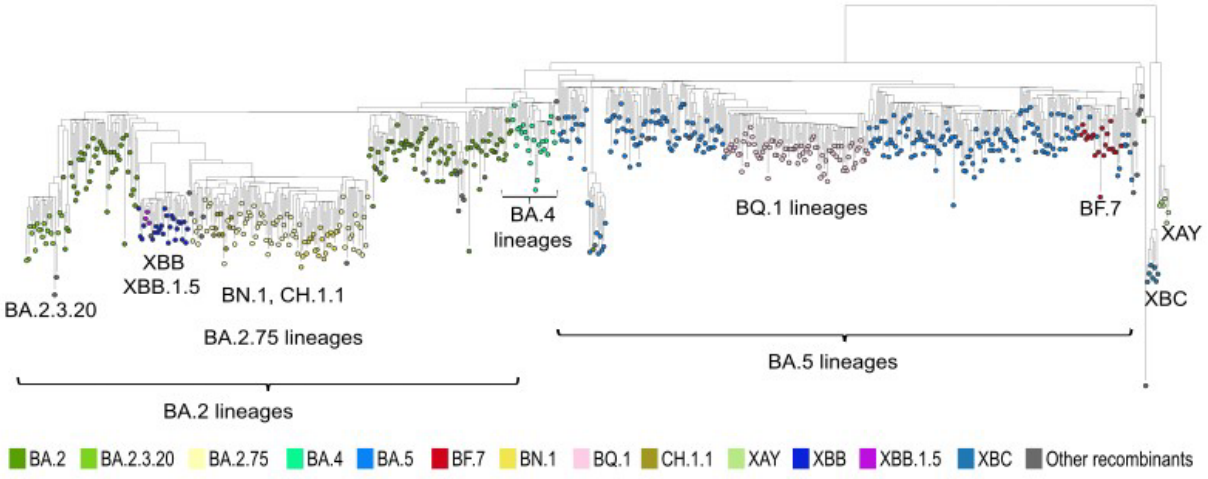
In March 2023, increasing proportions were detected for several variants under investigation, including XBB.1.5 and other XBB lineages (e.g. XBB.1.9, XBB.1.16) which are recombinants of the Omicron sub-lineages BA.2.10.1 and BA.2.75 as well as BA.2.75 sub-lineage CH.1.1 [5]. More specifically, XBB.1.5 showed a higher growth advantage and became the dominant variant in the USA [9], the UK [10] and the EU/EEA [11], without causing a worsening of the epidemiological situation in the EU/EEA.

As of 3 March 2023, earlier VOCs BA.2, BA.4 and BA.5 were de-escalated by ECDC as these parental lineages were no longer circulating in the EU/EEA [12]. As of 15 March 2023, WHO also de-escalated these earlier VOCs from the WHO VOC list [13]. In addition, WHO revised the current working definitions for SARS-CoV-2 VOC and VOI (variants of interest) [14], thereby allowing the monitoring of Omicron as separate sub-lineages, reserving Greek letter designations for VOCs only and increasing the specificity of the VOC definition to large SARS-CoV-2 evolutionary steps that require major public health interventions. ECDC's internal mechanisms and definitions for variant classification allow for such granularity and flexibility and remain unchanged; classification of variants continues to be closely aligned with that of WHO.

SARS-CoV-2 will continue to evolve and acquire mutations that may alter its virulence properties towards increased immune escape, higher transmissibility, and/or increased disease severity. Previous VOCs have represented significant evolutionary jumps in terms of these characteristics, with several underlying amino acid substitutions and no intermediate variants detected. The three main hypotheses presented for acquiring these mutations are: i) prolonged infections, likely in immunocompromised patients, allowing the virus to accumulate mutations without any of the evolutionary bottlenecks associated with human-to-human transmission; ii) transmission of SARS-CoV-2 to an animal host (most probably wild) and prolonged circulation in an animal population, where mutations could then have accumulated, and iii) circulation in countries with little or no genomic surveillance, where mutations could have accumulated without being detected. Of the three hypotheses, the prolonged infections hypothesis has the most direct supporting evidence, with studies showing that immune escape mutations can arise during prolonged infections, particularly in combination with convalescent plasma treatment [15,16].

The diversification within the Omicron variant represents a different situation in which intermediate lineages are detected and acquisitions of single amino acid substitutions determine new sub-lineage assignments (Figure 6). However, the emergence of a new, as yet undetected VOC is still possible. In mid-December-2022, China lifted long-standing and far-reaching IPC measures, resulting in the spread of the disease in a large proportion of the population over a short period. As of 16 March 2023, no novel variant of concern has emerged as a result of this spread in China, based on assessments of the sequence data both deposited by China in GISAID EpiCoV and detected by European countries in travellers from China [17] and in aircraft and airport wastewater surveillance [18].

Figure 6. The complex landscape of SARS-CoV-2 variants circulating from July 2022 to February 2023



Note: nodes are coloured based on their parental lineage (pangolin lineage assignment using Nextclade). Global sequence data were downloaded from GISAID EpiCoV [8] and analysed using the Augur pipeline [19] with default settings and visualised using MicroReact [20].

Immune evasion mutations and antiviral resistance mutations in the SARS-CoV-2 virus genome are continuously monitored [21,22]. Hotspots of mutations for immune evasion and viral fitness are identified and tools have been developed to estimate their impact [23-25]. Research groups study the antigenic relatedness of SARS-CoV-2 variants and illustrate these using antigenic cartography. This shows that Omicron subvariants are antigenically distinct from earlier subvariants [26], allowing them to partially evade a primed immune response from earlier variants, which has implications for vaccine composition [27]. This trend has been continuing for lineage XBB [11] and evidence is emerging that it is also continuing with the Omicron sub-lineages CH.1.1 and XBB.1.5 [10,28,29].

Transmissibility of the virus is affected by a range of viral properties including cell/receptor tropism, receptor binding and entry, viral replication efficiency and viral load kinetics, and the ability of virus particles to stay viable in the environment. Subsequent variants of concerns have demonstrated evolution towards increasing transmissibility [16], as has also been indicated for XBB.1.5 [28,30].

Pathogenicity of the virus and the ability to cause severe disease is a factor that is closely investigated for new variants and, with the exception of the Delta VOC, evolution of viral properties such as the cell/receptor tropism and fusogenicity [31] have trended towards lower pathogenicity [32,33]. Preliminary findings from New York, USA, where XBB.1.5 was circulating, indicate comparable severity to BQ.1 [34].

SARS-CoV-2 will continue to evolve, with the selective pressure from vaccination and hybrid immunity promoting variants with increased immune evasion properties or increased transmissibility, although the exact future trajectory is uncertain. Therefore, monitoring the genetic diversity of SARS-CoV-2 remains a priority in order to follow the viral evolution and identify variants with a potentially high impact on the epidemiological situation, and to inform future vaccine composition.

Update of data on vaccine effectiveness following booster doses

Vaccines used in the EU as booster vaccination and relative vaccine effectiveness

In September 2022, the first Omicron adapted bivalent vaccines were authorised as booster doses in the EU, including Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5 and Spikevax bivalent Original/Omicron BA.1. In October 2022, Spikevax Original/Omicron BA.4-5 was authorised as a booster dose.

The bivalent mRNA COVID-19 vaccines are authorised for use in people aged 12 years and over and are adapted versions of the original vaccines Comirnaty and Spikevax to target the Omicron BA.1 or BA.4-5 lineages in addition to the original strain of SARS-CoV-2. The aim of the bivalent mRNA COVID-19 vaccines was to better match the circulating variants of SARS-CoV-2 and to broaden protection against different variants, thereby helping to maintain optimal protection against COVID-19 as the virus evolves [35]. A statement by the European Medicine Agency (EMA) Emergency Task Force (ETF) on 6 December 2022 concluded that the bivalent original/Omicron BA.4-5 mRNA vaccines were expected to prime against SARS-CoV-2 and that they would have a similar safety profile to the originally approved mRNA vaccines in those previously unvaccinated [36]. The ETF considers it acceptable that the bivalent original/Omicron BA.4-5 mRNA vaccines, currently authorised in the EU/EEA for boosting, may also be used to deliver a primary series, should this become necessary to support vaccination campaigns.

According to data reported in in the EU/EEA (18 countries reporting), as of 10 February 2023, and since mid-September 2022, Comirnaty bivalent vaccines and Spikevax bivalent vaccines targeting the Omicron sub-lineages BA.1 and BA.4/BA.5 represent approximately 94% of the total number of vaccine doses administered as booster doses [37].

Since the bivalent vaccines have gradually replaced monovalent booster vaccine doses in individuals from 12 years of age, the vaccine effectiveness (VE) data presented in this section focuses on the bivalent adapted mRNA vaccines containing either the BA.4-5 strains or the BA.1 strain in addition to the original SARS-CoV-2 strain. Due to the fact that the bivalent vaccines were only recently introduced, little or no evidence on duration of protection is available. However, it is possible that the duration of protection will be similar to that seen for the (more extensively studied) monovalent mRNA COVID-19 vaccines, where waning of protection can be observed from around four months after the last booster dose for severe outcomes, as described in more detail below.

Recent VE studies have mainly investigated the relative vaccine effectiveness (rVE) of a booster dose (i.e. comparing with those that have received prior doses) rather than the absolute vaccine effectiveness (aVE, i.e. comparing with those who are unvaccinated). The relative (or incremental) VE is the level of protection that the booster dose provides in addition to the remaining protection conferred by previous doses given at different points in time. Therefore, these estimates are not directly comparable with estimates where VE is calculated relative to the unvaccinated. Comparison between different studies is difficult because the rVE estimate is dependent on time since previous vaccination dose, and this varies considerably between studies. Since rVE estimates measure the additional protective effect of a vaccine dose, estimates are often lower than those of aVE estimates. In addition, studies are subject to several methodological limitations in terms of profile diversity of the compared groups. This includes number of previous infection(s) at different points in time, differences in behaviour according to vaccination status, and different strategies at country-level for deployment of non-pharmaceutical interventions.

Vaccine effectiveness of bivalent and monovalent vaccines

In most cases, studies of the bivalent BA.4-5 vaccines were conducted during a time when these were the dominant sub-lineages of the Omicron variant. Available evidence on the bivalent mRNA COVID-19 vaccines indicates that the relative VE against symptomatic infection ranges between 14% (among individuals aged 60–85 years) and 56% when more than eight months have passed since the previous dose (for adults aged over 18 years). For hospitalisation as outcome, rVE ranged between 31% and 81%, where the lower estimate compares against two, three or four doses only 2–4 months earlier, when the protection from the earlier doses is still quite high. Data currently available on severe outcomes indicate a strong added layer of protection with a booster dose.

In terms of the monovalent vaccines, studies of VE against severe disease due to the Omicron variant suggest that monovalent vaccine effectiveness against severe outcomes is high following the administration of a first booster dose, for up to 2–3 months after receiving the booster. Studies with a follow-up period of 4–6 months after the first booster dose continue to show protection against severe disease up to six months post mRNA booster, with some slight waning over time. Among studies looking at VE >6 months following a first booster dose, a UK study found that VE against severe outcomes decreased further by 25 to 39 weeks (approximately six to eight months) after the booster vaccine [38]. A second booster improves VE against infection, but this seems to wane rapidly. VE following a second booster dose against severe disease appears to restore the slightly reduced protection seen four months after the first booster dose. Depending on the specific outcome and study, protection is in the range of 40–77% when compared to the third dose (incremental or relative VE*) and in the range of 66–86% when compared to the unvaccinated. Some studies have found similar declines in protection over time following the second booster dose, as seen with the first booster dose [39,40].

UK data show no difference in VE against the outcomes of infection, symptomatic infection nor hospitalisation between monovalent and bivalent mRNA vaccines when used as booster doses, including over time [41]. It should be noted that the bivalent boosters used in the UK were either Comirnaty bivalent Original/Omicron BA.1 or Spikevax bivalent Original/Omicron BA.1I, during a period when Omicron BA.4 and BA.5 were the dominant circulating lineages [38]. By way of comparison, a study from the Nordic countries found a comparative VE of 32.3% between a bivalent booster dose (BA.4-5) and a monovalent booster for preventing severe disease [42] . Similarly, a US study found that the difference in VE against hospitalisation or death was 36.9% higher for a bivalent booster than a monovalent booster [43].

The studies available are described in more detailed below.

Vaccine effectiveness of bivalent vaccines against severe outcomes (hospitalisation and death)

In the US, a large cohort study on VE of the bivalent vaccines against severe infection with Omicron BA.4.6, BA.5, BQ.1, and BQ.1.1 found that bivalent boosters provided substantial additional protection against severe Omicron infection in those who had previously been vaccinated or received a booster. The effectiveness of bivalent boosters was higher than that of monovalent boosters. VE against severe disease resulting in hospitalisation or death was 24.9% (95% CI 1.4 to 42.8) for one monovalent booster dose and 61.8% (95% CI, 48.2 to 71.8) for one bivalent booster dose. The difference in VE against this outcome between the bivalent booster and the monovalent booster was 36.9 percentage points (95% CI 12.6 to 64.3) , with similar VE estimates for those 18 years and above and those 65 years and above [43]. The researchers found that the vaccine effectiveness following bivalent vaccination peaked at approximately four weeks before starting to wane.

A study (preprint) from the Nordic countries (Denmark, Finland, Norway and Sweden) estimated the relative VE of the two different bivalent mRNA COVID-19 vaccines (BA.4-5 and BA.1, both Comirnaty and Spikevax) during a period when BA.4-5 sub-lineages were predominant. Compared with having received three vaccine doses, receipt of a bivalent BA.4-5 booster as a fourth dose was associated with a country-combined rVE against COVID-19 hospitalisation of 80.5% (95% CI 69.5% to 91.5%). The corresponding rVE for bivalent BA.1 boosters was 74.0% (95% CI 68.6% to 79.4%). The rVE against COVID-19 death was 77.8% (95% CI 48.3% to 100%) and 80.1% (95% CI 72.0% to 88.2%) for bivalent BA.4-5 and BA.1 boosters as a fourth dose, respectively. Comparing the effectiveness of bivalent BA.4-5 versus BA.1 boosters found a comparative VE of 32.3% (95% CI 10.6% to 53.9%) for COVID-19 hospitalisation and 12.3% (95% CI -36.1% to 60.7%) for death (the latter only being possible to estimate in Denmark). The authors concluded that vaccination with either bivalent mRNA COVID-19 vaccine booster as fourth dose is associated with an increased protection against hospitalisation or death due to COVID-19, compared to three doses of vaccine [42].

In another US study, VE of a bivalent BA.4-5 booster dose (after two, three or four doses of the COVID-19 mRNA vaccine targeting the original strain of SARS-CoV-2) against hospitalisation was 59% (95% CI 44% to 70%) compared with no vaccination, 42% (95% CI 20% to 58%) compared with receipt of last monovalent dose 5–7 months earlier, and 48% (95% CI 30% to 62%) compared with receipt of last monovalent dose ≥11 months earlier. Previous SARS-CoV-2 infection was not accounted for in this study. The authors concluded that the study findings support efforts to improve coverage with bivalent vaccines, although the optimal timing for receipt of bivalent vaccine booster doses needs to be established [44].

A recently published (preprint) retrospective cohort study from Israel, which included over 600 000 participants aged ≥65 years, evaluated the real-world effectiveness of the Comirnaty BA.4-5 bivalent booster vaccine for preventing COVID-19 hospitalisations [45]. Hospitalisations and death due to COVID-19 among participants who received the bivalent vaccine were compared with those who had not receive the bivalent vaccine but were eligible for it. For hospitalisation due to COVID-19, the adjusted hazard ratio (HR) was 0.19 (95% CI 0.08 to 0.43) and for death, the HR was 0.14: (95% CI 0.02 to 1.04). The study findings suggest that in adults aged ≥65 years, the relative VE of a bivalent booster is 81% for COVID-19 related hospitalisations and 86% for COVID-19 death.

In the UK, bivalent boosters targeting both the ancestral strain and Omicron BA.1 were offered to those in clinical risk groups and those aged 50 years and above from September 2022. The incremental VE (protection on top of at least six months waned protection from the bivalent boosters) was estimated against hospitalisation in the period following 5 September 2022 for all Omicron subvariants in circulation at the time. The incremental protection conferred by the bivalent vaccines estimated relative to those with waned immunity was 43.1% for Comirnaty after two weeks, and 57.8% for Spikevax. Effectiveness remained high 10 or more weeks after vaccination, at 46.4% for the Comirnaty booster and 47.5% for the Spikevax booster [38].

Vaccine effectiveness of bivalent vaccines against symptomatic infection

A recent study from the US analysed data from the Increasing Community Access to Testing (ICATT) national pharmacy programme for SARS-CoV-2 testing to estimate the VE of the bivalent mRNA COVID-19 vaccines against symptomatic infection caused by either BA.5 or XBB/XBB.1.5 related sub lineages. Among adults who had previously received 2–4 monovalent mRNA COVID-19 vaccine doses, the relative VE of a bivalent booster dose given 2–3 months earlier compared with no bivalent booster in those aged 18–49 years was 52% against symptomatic BA.5 infection and 48% against symptomatic XBB/XBB.1.5 infection. VE remained similar across age

groups, with slightly lower estimates for individuals aged ≥65 years (37% against BA.5 and 43% against XBB/XBB.1.5-related infection). Only minimal waning of protection was seen after 2–3 months [46].

Another VE study from the US (also using data from the ICATT) on the Omicron updated mRNA BA.4-5 bivalent COVID-19 vaccines indicates that in the short term bivalent boosters restore the previously waned protection against symptomatic infection. Absolute vaccine effectiveness (aVE) of a bivalent booster dose received after ≥2 monovalent doses (compared with being unvaccinated) was similar among those aged 50–64 years (28%) and ≥65 years (22%), but varied depending on the number of previous monovalent vaccine doses. Among adults aged 18–49 years, aVE after ≥2 monovalent doses (43%) was higher than that for older age groups and did not vary among those who received two or three previous monovalent vaccine doses. However, >90% of adults have received at least one COVID-19 vaccine dose in the US and aVE should be interpreted with caution since unvaccinated persons might significantly differ in terms of behaviour and or differential rate of previous infection. Relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥2 monovalent vaccine doses among those last vaccinated with a monovalent dose 2–3 months and ≥8 months previously was 30% and 56% among persons aged 18–49 years, 31% and 48% among persons aged 50–64 years, and 28% and 43% among persons aged ≥65 years, respectively [46].

A recent US study (preprint) to evaluate whether the bivalent COVID-19 vaccine protects against COVID-19 (as defined by positive NAAT test) found that the current bivalent vaccines were about 30% effective overall in protecting against infection with SARS-CoV-2, when the Omicron BA.4/BA.5 lineages were the predominant circulating strains. Being vaccinated with a bivalent vaccine was independently associated with a lower risk of COVID-19 (HR 0.70; 95% CI 0.61 to 0.80), leading to an estimated VE of 30% (95% CI 20% to 39%). Compared to last exposure to SARS-CoV-2 by infection or vaccination within 90 days, last exposure 6–9 months previously was associated with twice the risk of COVID-19, and last exposure 9–12 months previously with 3.5 times the risk [47].

A study from the Netherlands (preprint) estimates the effect of a bivalent BA.1 booster dose relative to primary series and one or two monovalent booster doses. The study found the overall relative VE among those aged 18–59 years to be 31% (95% CI 18% to 42%) and 14% (95% CI 3% to 24%) among those aged 60–85 years. In those with a previous Omicron infection, the rVE was lower, 20% (95% CI -7% to 40%) and 6% (95% CI -31% to 31%) in those aged 18–59 years and 60–85 years, respectively. In addition, the study data showed higher protection from prior Omicron infection than the protection from bivalent vaccination among persons without prior infection, despite a longer time since prior Omicron infection than time since bivalent vaccination [48].

A recent matched cohort study (n=136 852) conducted in France, when both bivalent and monovalent vaccines were used, showed that an mRNA Original/BA.4-5 bivalent booster (Comirnaty BA 4/5 bivalent) conferred an additional 8% [95% CI: 0–16%] protection against symptomatic infection, compared to a monovalent booster [49].

Other considerations

The potential effect of immune imprinting on protection against COVID-19 is unclear. It has been hypothesised that the protective effect of adapted vaccines based on new variants will be limited, due to an already primed immune system in the majority of individuals. There are studies indicating that prior imprinting of an earlier variant does impact subsequent immune protection to new variants, potentially affecting the usefulness of variant-specific vaccines. However, studies also indicate that previous infections and vaccinations create a broad immune response which is likely to protect against new variants and most probably maintaining the protective effect against severe disease. Imprinting also raises the question as to whether future updated vaccines against COVID-19 should use a bivalent formulation or an updated single-strain vaccine [50-53]. The above-described evidence on monovalent and bivalent boosters indicates that the bivalent boosters provide greater protection when targeting the dominating circulating strain. However, it remains to be seen how this will translate into protection against new variants.

ECDC and EMA Vaccine Monitoring Platform

Vaccine Effectiveness, Burden and Impact Studies – VEBIS project

In 2020, the European Commission stressed the importance of continuously monitoring the safety and effectiveness of vaccines in the EU/EEA in the post-authorisation phase, with particular emphasis on COVID-19 vaccines in the context of the ongoing pandemic. The 2018 Council Recommendation on Strengthened Cooperation against Vaccine-preventable Diseases asked ECDC and EMA to cooperate in ensuring the continued monitoring of vaccines and vaccination in use in EU/EEA vaccination programmes [54]. This request was subsequently formalised as part of the extended EMA regulatory mandate [54] and ECDC's newly amended mandate [55], whereby the two Agencies will develop a structured and independent post-authorisation vaccine monitoring platform, initially prioritising COVID-19 vaccines. ECDC and EMA officially established and launched this platform in May 2022, with the intention of bringing together public health and regulatory experts to discuss the studies needed to generate real-life evidence on the safety and effectiveness of vaccines used in EU/EEA immunisation programmes.

At the end of 2020, ECDC started to build an infrastructure to support a multi-country project on Vaccine Effectiveness, Burden and Impact studies (VEBIS). This undertaking is now considered to be related to the ECDC EMA Vaccine Monitoring Platform which will monitor the COVID-19 and influenza vaccine effectiveness against various outcomes.

The VEBIS project generates VE estimates using different data sources and/or recruitment settings:

- Multi-country study 1: COVID-19 and influenza VE against hospital admission with Severe Acute Respiratory Infection (severe disease) – 14 countries participating [56].
- Multi-country study 2: COVID-19 and influenza VE against infection evaluated in a cohort of healthy individuals (healthcare workers) – seven countries participating [57].
- Multi-country study 3: COVID-19 and influenza VE against moderate disease (patients presenting to primary care) – 10 countries participating.
- Multi-country study 4: COVID-19 VE against severe disease using health and vaccination population registries – six countries participating [58].

While there are no specific VE data on the bivalent mRNA COVID-19 vaccines from these studies yet, future results will be an important addition to the current evidence base. Countries have made progress in applying agreed EU-level protocols, their participation has increased over time, and they have taken opportunities to leverage other systems, such as Severe Acute Respiratory Infection (SARI) surveillance, or to pilot new methodologies.

Recent results from the hospital study (multi-country study 1) indicated that aVE of first monovalent booster dose in preventing SARI hospitalisations associated with laboratory-confirmed SARS-CoV-2 infection was moderate at 54% (95% CI: 45–61%), and rVE of the first booster dose to complete primary series vaccination was 29% (95% CI: 14–42%). VE and rVE of the first monovalent booster dose vaccination remained high in the first four months after vaccination but decreased substantially after that point in time. A similar pattern was observed for the age groups 60–79 years and ≥80 years, but VE could not be estimated for the younger group (20–59 years) due to small sample size. However, a longer period since receiving a booster dose coincided with onset during the dominance of BA.4/BA.5 Omicron sub-lineages, and it is challenging to attribute the apparent decrease in vaccine effectiveness to either the impact of waning immunity alone or the immune escape properties of these Omicron sub-lineages [59].

Similarly, in multi-country study 3, among patients with mild to moderate illness presenting to primary care settings between December 2021 and January 2023, VE following a primary or booster dose was highest in the first three months following vaccination. Among patients aged 50 years and above, primary series VE was 70% (95% CI 44% to 85%) among those vaccinated 14–89 days before symptom onset (unpublished data). In the same population following the first booster, VE was 73% (95% CI 63% to 81%) among those vaccinated 14–89 days before symptom onset. However, the VE among those vaccinated 90-179 days before onset was 48% (95% CI 28% to 63%), and 28% (95% CI -68% to 69%) among those vaccinated ≥180 days before onset (unpublished data).

Results from real time monitoring of vaccine effectiveness using a retrospective cohort study design and data from population based electronic health registries in six EU countries (multi-country study 4) show waning of protection for the first booster falling to less than 50% six months after booster administration. Furthermore, the level of protection of the second booster dose waned to around 50% after 12 weeks since administration in countries that implemented a spring vaccination campaign in 2022. Similar vaccine effectiveness was observed for recently administered doses, as part of the vaccination campaign for autumn 2022, irrespective of them being second or third boosters (depending on country vaccination policy). Most recent vaccine effectiveness estimates (1 November 2022 to 26 December 2022) of booster(s) compared to complete primary course against hospital admission due to COVID-19 for the age groups 65–79 years and 80+ years were: first booster (44%/42%), second booster (78%/75%), and third booster (NA/65.2%) (unpublished data).

Evidence of the protective effect of hybrid immunity

SARS-CoV-2 infection and vaccination both induce a wide range of adaptive immune responses. Memory B cells produce different classes of antibodies to neutralise the virus or support the removal of virus-infected cells, while memory T cells support B cell antibody production and kill virus-infected cells. There are two important differences between immunity induced by the current COVID-19 vaccines and natural infection. Firstly, whilst the vaccines were designed to induce B cell and T cell responses specifically targeting the SARS-CoV-2 spike protein, natural infection induces responses to several other SARS-CoV-2 proteins, such as nucleoprotein. Secondly, vaccines administered by intramuscular injection do not induce immune responses in the respiratory mucosa, whereas infection induces mucosal immunity, which includes tissue-resident memory T cells and memory B cells. These site-specific responses are advantageous for protecting against infection, partly because they counter the virus at the site of entry, but also because the type of antibody secreted into the mucosa (dimeric secretory IgA) has been shown to neutralise SARS-CoV-2 more effectively than serum IgG antibodies induced by intramuscular vaccination [60-63].

Serum is convenient to collect, store and analyse. Consequently, serum antibodies—particularly anti-spike IgG—have been the focus of studies evaluating immune responses to infection or vaccination. These serum antibodies can be evaluated quantitatively (by measuring their amount - e.g. total anti-spike IgG) or functionally (by measuring their capacity to perform specific actions that play a role in protection - e.g. virus neutralisation in vitro). In naïve individuals, natural infection typically induced lower or variable serum antibody levels than vaccination, hence the recommendation for previously infected individuals to complete a primary vaccination course [64]. Hybrid immunity is defined as the immune protection in individuals who have had one or more doses of a COVID-19 vaccine and experienced at least one episode of SARS-CoV-2 infection before or after initiation of vaccination [65]. Hybrid immunity has consistently been shown to generate higher serum anti-spike IgG titres and broader neutralising capacity against newly emerged variants when compared to serum from individuals with non-hybrid immunity [66-69].

While neutralising antibodies in serum are important for (and predictive of) protection against infection and severe disease, they are not definitive correlates of protection against COVID-19 clinical outcomes. Epidemiological studies of effectiveness are required to fully assess the contribution of all adaptive immune responses induced by hybrid immunity [70]. A recent systematic review and meta-regression analysis of studies published between January 2020 and June 2022, compared protective effectiveness of hybrid immunity (monovalent vaccines plus infection) with protection induced by previous infection alone or vaccination alone. The effectiveness of previous infection against hospital admission or severe disease waned from ~83% at two months to ~75% at 12 months, with protection against reinfection waning from ~70% at two months to ~25% at 12 months. The effectiveness of hybrid immunity (following primary series vaccination) against hospital admission or severe disease was sustained at ~97% at 12 months, with protection against reinfection waning from ~72% at two months to ~42% at 12 months. The effectiveness of hybrid immunity (following first booster vaccination) against reinfection waned from ~75% at two months to ~47% at six months [71]. These results demonstrate that while hybrid immunity robustly improves the magnitude and duration of protection against severe COVID-19 outcomes, protection against infection still wanes rapidly due to the emergence of new SARS-CoV-2 variants. Previous infection was found to provide higher protection against re-infection and more sustained protection against hospital admission or severe disease than vaccination alone. However, individuals with hybrid immunity had the highest magnitude and durability of protection against all outcomes, emphasising the importance of providing vaccination to previously infected individuals [71]. This systematic review predates the emergence of the most immune-evasive Omicron sub-lineages to date – BQ.1 and XBB.1 – as well as newly licenced bivalent mRNA booster vaccines. Evidence from in vitro neutralisation studies for these sub-lineages to date indicates that serum from previously infected patients receiving the bivalent booster substantially outperforms serum from individuals who received the bivalent booster but had no prior infection history [72] In addition, BA.2 or BA.4/5 breakthrough infections in individuals receiving monovalent vaccines generally induced higher neutralising antibody titres to the recent SARS-CoV-2 Omicron sub-lineages BQ.1 and XBB.1 than a monovalent or bivalent booster dose as a fourth vaccination [73]. Hybrid T cell-mediated immunity is less SARS-CoV-2 variant-dependent as it targets more than the spike protein alone, and T cell immunity to emerging Omicron spike variants is better preserved, despite mutations that can cause some loss of recognition [74,75]. Epidemiological data comparing the protective effectiveness for bivalent-boosted, hybrid immune versus non-hybrid immune individuals against these sub-lineages are still not available.

Taken together, current evidence indicates that hybrid immunity offers superior protection against severe COVID-19 clinical outcomes than infection-induced or vaccine-induced immunity alone, with high levels of protection lasting at least 12 months. However, it is likely that hybrid immunity has not developed uniformly across the population, particularly among vulnerable and elderly groups. We are approaching a stage in the COVID-19 response where population immunity encompasses an increasingly complex and heterogenous hybrid immune landscape, with individuals experiencing multiple undocumented prior infections with different variants, as well as different vaccines being used. Monitoring protective effectiveness against clinical outcomes will be critical to inform public health decision-making and should seek to address key evidence gaps for the populations most at risk. These include outcome data for unvaccinated individuals who have experienced one or multiple prior asymptomatic SARS-CoV-2 infections, as well as outcome data for vulnerable and elderly populations who may be less likely to develop hybrid immunity [76,77]. While the high transmissibility and immune evasion capabilities of Omicron and its subvariants ensure most of the population will develop hybrid immunity, age-stratified population serosurveys estimating the proportion experiencing prior infection before, during and after the emergence of Omicron show that, despite

observed increases in all age groups, older age groups appear less likely to be exposed to or experience Omicron infections [78,79]. In contrast to younger adults, individuals aged 60 years and above have faced the highest rates of hospitalisation and death, while having the lowest rates of hybrid immunity [76,77]. These age-specific trends dispel the notion that hybrid immunity is developed uniformly across the population and highlight the importance of population serosurveys [65]. In the majority of population-based seroprevalence studies, presence of anti-SARS-CoV-2 antibodies is qualitatively assessed by detecting presence/absence above a specific titre threshold, as determined by the sensitivity of the assay used. In the context of an increasingly complex and heterogenous hybrid immune landscape, age-stratified population serosurveys should evolve to incorporate quantitative anti-spike assays (measuring exact titre values for everyone sampled) in studies that disaggregate results by prior infection (anti-nucleocapsid positive) status [79] and functional assays (measuring the capacity of antibodies to perform specific actions that play a critical role in protection such as virus neutralisation). This would help us to better understand the distribution and magnitude of hybrid immunity at population level [78].

Mathematical modelling to estimate the impact of future COVID-19 vaccination campaigns on preventing the hospitalisation burden

ECDC presents its internal modelling results from an age-structured compartmental model that investigated the benefits of performing a spring and/or an autumn COVID-19 vaccination campaign in the EU/EEA countries between now and the end of February 2024. We compared the estimated disease and healthcare burden relative to the baseline scenario of no further vaccination campaign for various possible vaccination campaigns in 2023. Here, we focus on assessing the impact of vaccination in reducing the disease and healthcare burden in terms of the number of COVID-19 related infections, hospitalisations, deaths and DALYs, without taking into account potential adverse vaccination events in the mathematical modelling.

We conducted a scenario analysis to assess the impact of future COVID-19 vaccination campaigns in 2023. We considered two kinds of scenarios for the vaccination campaigns. Firstly, we considered different autumn-only vaccination campaigns, for which we explored four eligible age groups (80+, 70+, 60+, and 50+ years). Secondly, we considered a combined spring and autumn vaccination campaign, where we explored potentially different age groups for the spring and the autumn campaign (e.g. 80+ years in spring and 60+ years in autumn). Furthermore, for each autumn-only and spring-and-autumn scenario, we explored three sub-scenarios for the possible vaccine uptake that differ by age:

- low uptake (assumed 80+years of age: 25%, 70–79 years of age: 25%, 60–69 years of age: 20%, 50–59 years of age: 15%)
- intermediate uptake (80+ years of age: 50%, 70–79 years of age: 45%, 60–69 years of age: 40%, 50–59 years of age: 30%)
- high uptake (80+ years of age: 95%, 70–79 years of age: 90%, 60–69 years of age: 80%, 50–59 years of age: 60%).

The three vaccine uptake scenarios are drawn from data regarding the uptake of the second booster in the EU/EEA, which varied considerably across the Member States (see Table T1).

In our analysis, impact is defined as the percentage decrease in one of the studied outcomes; burden is defined as the cumulative number of infections, hospitalisations, or deaths in the next 12 months.

Figure 7 shows the estimated impact of the different vaccination campaign scenarios. For ease of exposition, Figure 7 only shows the autumn campaign, both alone and in combination with a spring vaccination campaign in 2023 for those aged 80+ years. The combined campaigns with an eligible age group under 80+ years for the spring campaign are shown in Figure S1.

Further details of the modelling and assumptions can be found underneath Figure 7 and in the annexes.

ECDC's novel modelling results indicate the following:

A higher vaccine uptake and/or expanding the eligibility of age groups leads to larger decreases in the relative burden compared to no further vaccination in 2023. A larger effect is achieved from a high uptake in a given age group than an expansion in the eligible age groups targeted for vaccination. In general, a high uptake in any age groups leads to larger decreases in the relative burden compared to expanding vaccination to younger age groups but with a lower uptake. The effects were explored with the age groups included in the scenarios.

Adopting an autumn vaccination campaign only:

- With a low vaccine uptake can prevent an estimated 3–10% of COVID-19-related hospitalisations.
- With a high vaccine uptake can prevent an estimated 13–20% interquartile range (IQR) of the total all-age hospitalisations when targeting individuals aged 80 years and above, and 21–32% (IQR) when targeting individuals aged 60 years and above (see Fig 7, first row). It is important to note that modelling indicates that targeting individuals aged 50 years and above results in a similar impact to targeting individuals aged 60 years and above (Fig 7).

Combining the autumn vaccination campaign with a spring vaccination campaign in those aged 80 years and above can substantially increase the impact of vaccination if the vaccine uptake is high in both autumn and spring campaigns. Targeting individuals aged 80 years and above in spring and those aged 60 years and above in autumn can lead to an estimated 36−44% (IQR) decrease in hospitalisations when uptake is high in both campaigns - see Fig 7, second row. Vaccination campaigns with a high uptake in older age groups but a low or intermediate uptake in younger groups (e.g. high uptake for 80+ years but low uptake for 70−79 years) have not been modelled explicitly. However, it is reasonable to expect the impact of such vaccination campaigns to be in between the high uptake scenario for all considered age groups (e.g. high uptake for those aged 80+ years and high uptake for those aged 70−79 years) and the scenario that does not target the younger age group (e.g. high uptake for those aged 80+ years and no uptake for those aged 70−79 years).

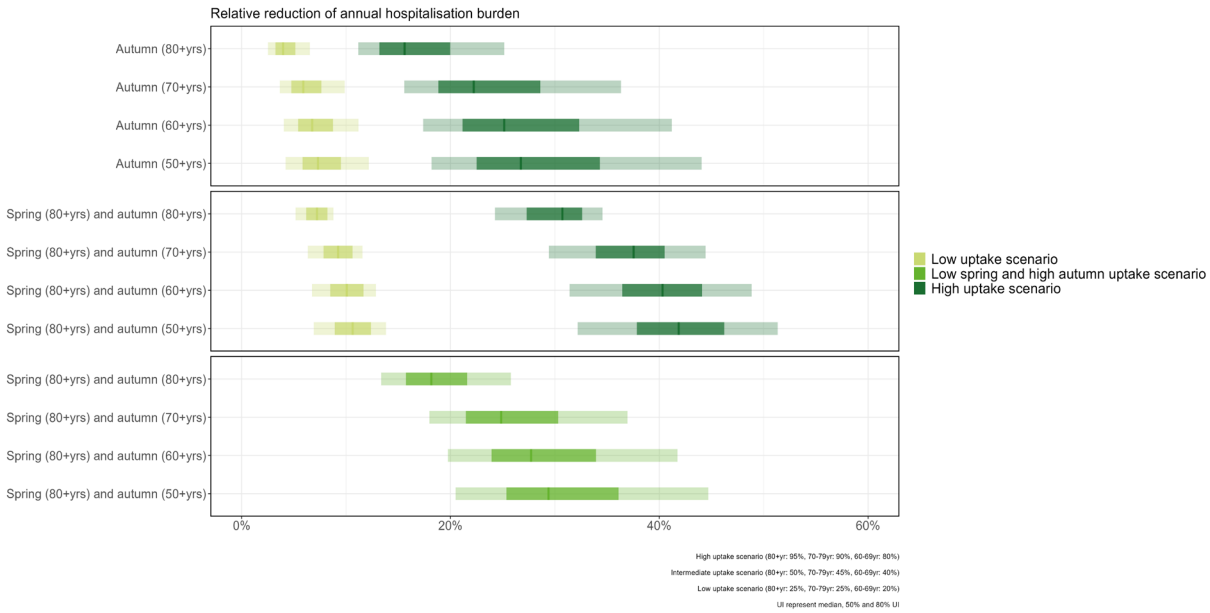
A low vaccine uptake in the spring campaign followed by a high vaccine uptake in the autumn campaign is estimated to give marginal benefit compared to only running an autumn campaign, indicating the importance of a high vaccine uptake for the spring campaign to be effective (see Fig 7, third row). Only by extending low-uptake vaccination campaign to a lower age group in both spring and autumn (e.g. 70 years and above in spring and 50 years and above in autumn) do we start observing reductions similar to those for a high uptake of an autumn campaign in the 80+ years alone (see supplementary Fig S1 in Annex 2).

In terms of outcomes other than hospitalisations, similar results are observed for infections, mortality, and disability-adjusted life years (DALYs) but with lower values (see Figs S2A-C and S5A-C in Annex 2). It is worth noting that the modelling indicates that any vaccination campaign targeting individuals aged 50 years and above will have a minimal impact on the total number of infections prevented (<10% for any vaccine uptake, Figs S2A and S5B, Annex 2). Moreover, mortality is expected to continue to contribute a large proportion of the DALY burden for all scenarios (Fig S3 in Annex 2).

The model also shows that the **efficiency in terms of the per-dose effect** (defined as averted burden per administered dose) increases as the target population of a vaccination campaign gets older. There is large and overlapping variability between scenarios stemming from the many uncertainties faced. For these reasons, there is also no substantial difference in efficiency when comparing an autumn campaign with a campaign in both spring and autumn. Meanwhile, the impact on the reduction of infections does not depend significantly on age, indicating that modelled scenarios for 2023 do not see a substantial indirect protection from the vaccines (Fig S4A, Annex 2).

It is important to note that overall there is still a large variation in the expected burden, not only between countries but also due to **considerable uncertainties in major drivers of future epidemiological dynamics**. Examples of these drivers are the characteristics and the timing of new variants of concern and their impact on immune escape and transmission; under-ascertainment of reported COVID-19 cases, hospitalisations and deaths; immunity levels and waning protection; time interval since last dose; role of hybrid immunity; social behaviour of contact mixing and mobility, and potential vaccination uptake in different age groups.

Figure 7. Relative reduction in cumulative hospitalisations under various vaccination campaigns and vaccine uptake scenarios compared to the baseline scenario, predicted until 28 February 2024



Row 1 shows an autumn vaccination campaign in 2023 only at a low or high uptake;
Row 2 shows the combination of both spring and autumn vaccination campaigns in 2023 where uptake is low or high in both campaigns;
Row 3 shows the combination of a spring and autumn vaccination campaigns in 2023 where uptake is low in spring and high in autumn.

Different colours show different vaccination uptake of the spring and autumn vaccination campaigns. 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 roll-out of the spring and autumn campaign starts on 1 April and 1 October and ends on 1 July and 31 December 2023, respectively.

The variation of each colour bar is due to the different characteristics of EU/EEA countries and the uncertainties of epidemiological parameters: (i) characteristics and the timing of new variants of concern and their impact on immune escape and transmission (no new variant, a new variant appearing before the vaccination campaigns on 1 March and 1 September, or a new variant appearing after the vaccination campaigns on 1 June and 1 December, with all future variants of concern having 20% decrease in their protection against infection and no decrease in protection against severe outcomes compared to the previously dominant one); (ii) immunity levels and waning protection (optimistic and pessimistic immunity and waning protection following [71] (iii) under-ascertainment of reported COVID-19 cases (10 and 60), and (iv) social behaviour - contact mixing and mobility (sinusoidal yearly impact with 5–20% amplitude).

Programmatic overview and considerations

This section details autumn/winter 2022 vaccination policies and uptake of booster vaccination. It also discusses considerations for communication campaigns before launching a new vaccination campaign, in light of the lessons learned from the earlier roll-out of COVID-19 vaccination.

Fall/winter 2022 COVID-19 vaccination policies

EU/EEA countries recommendations – autumn and winter 2022/23

For autumn and winter 2022/23, EU/EEA countries implemented targeted vaccination campaigns focusing on older adults, individuals with comorbidities irrespective of age (see Table 5 in Annex 3), pregnant women, residents of long-term care facilities (LTCF) and healthcare workers [80]. A majority of EU/EEA countries (21/30) recommended a booster dose from 60 years of age.

Countries' previous approaches to the administration of vaccine doses to their populations were based on the number of booster doses (i.e. first booster dose, second booster dose.) For the autumn/winter 2022 campaign, the approach many countries adopted was based on the interval between the doses (i.e. at least three months since last vaccine dose), rather than the number of booster doses actually received.

Uptake of COVID-19 vaccination in the EU/EEA

COVID-19 vaccine uptake – booster vaccination

As of 5 February 2023, approximately 29.3 million doses of Comirnaty bivalent vaccines and 950 000 doses of Spikevax bivalent vaccines targeting the Omicron sub-lineages BA.1 and BA.4/BA.5 had been administered in the EU/EEA (18 countries reporting), representing approximately 94% of the total number of vaccine doses administered in these countries since mid-September 2022.

Since the inception of the COVID-19 vaccination roll-out in EU/EEA countries, the cumulative uptake of the primary vaccination course in the total EU/EEA population has reached 73% (range: 30.0–86.4%) and 54.7% of the first booster dose (range: 9.2–75.8%) (30 countries reporting) (Table 4). Primary vaccination uptake has been levelling off for over a year in all EU/EEA countries – despite heterogeneity in uptake across countries; reported average uptake for primary series changed from 90.1% in week 3-2022 to 91.2% in week 10-2023 for individuals over the age of 60 years.

Table 4. Summary table of COVID-19 vaccine uptake in the EU/EEA (as of 5 February 2023)

Population group (years)	Uptake of primary course (range)	Uptake of first booster (range)	Uptake of second booster (range)	Countries reporting	Uptake of third booster (range)	Countries reporting
Persons aged 60+*	**91.1%** (38.5–100%)	**84.9%** (13.6–100%)	**35.2%** (0.4–86.6%)	**30**	**2.3%** (<0.1–37.8%)	**20**
Persons aged 80+*	**94.0** (26.3–100%)	**83.8%** (8.0–100%)	**46.3%** (0.3–96.4%)	**29**	**4.1%** (<0.1–57.2%)	**18**
Adults (18+)**	**82.4%** (35.8–96.4%)	**65.4%** (11.3–87.0%)	**17.1%** (0.2–41.9%)	**30**	**2.0%** (<0.1–11.5%)	**20**
Total population**	**73.0%** (30.0–86.4%)	**54.7%** (9.2–75.8%)	**14.1%** (0.2–33.6%)	**30**	**1.6%** (<0.1–9.3%)	**20**

** Values are the median across the reporting countries.*

***Note that not all countries actively promote second/third booster vaccination for these age groups.*

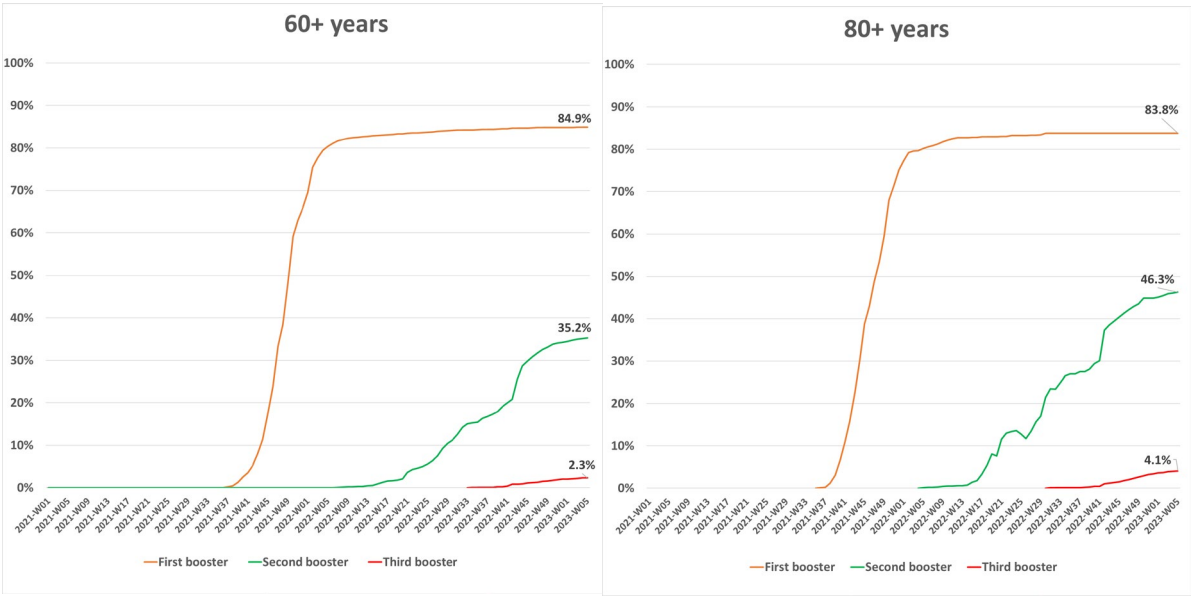
More detailed information on the vaccine roll-out and country-specific disclaimers on the data may be found in the ECDC Vaccine Tracker.

Analysis of booster vaccination uptake over time in older adults (60+ years and 80+ years)

The median cumulative uptake of booster doses (first, second and third) has been relatively similar in the two age groups (60+ years and 80+ years) and over time; with those aged 80 years and above having a slightly higher uptake of the second and third booster dose than those aged 60 years and above (Figure 8 and Annex 4). The evolution of uptake has shown a similar pattern over time for the two age categories (see Figure 8).

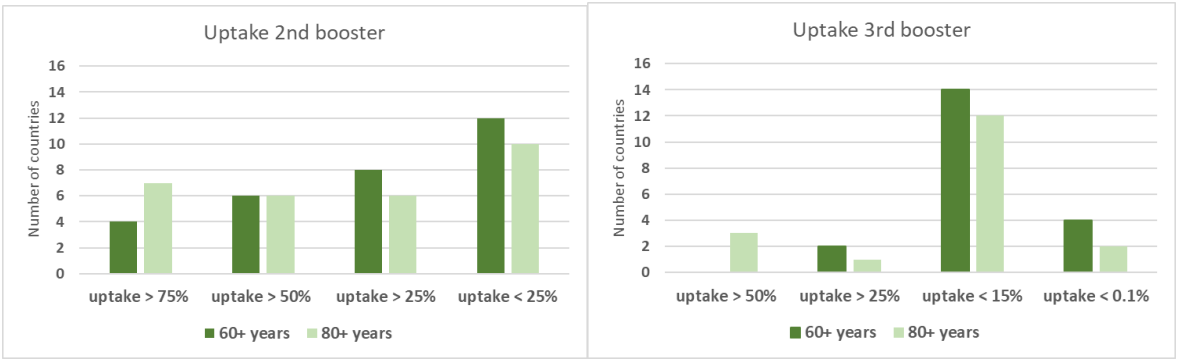
For almost a year, first booster vaccination uptake has levelled off for all EU/EEA countries – despite heterogeneity in uptake across countries. Reported average uptake for first booster changed from 51.9% in week 3-2022 to 54.7% in week 10-2023 for individuals above the age of 60 years.

Figure 8. Median cumulative uptake of first, second and third booster dose among those aged 60 years and above and 80 years and above in the EU/EEU (week 1-2021 to week 3-2023)



If the data is explored from a perspective other than the overall median in the EU/EEA and the countries are categorised according to the average in different age groups, the number of countries reporting on second booster doses with an uptake of over 50% is approximately one third of the total number of countries for those over 80 years. This distribution is similar for individuals aged over 60 years. On the other hand, for the third booster almost all countries have an uptake below 15% for both age categories. (Figure 9 below and Table 6 in Annex 3).

Figure 9. Countries' median cumulative uptake of second and third booster among those aged 60 years and above and 80 years and above in the EU/EEU (week 51-2022/week 5-2023)



Note: 30 countries reporting data to TESSy on second booster for those aged 60+ years; 29 countries – on second booster for those aged 80+ years; 20 countries - on third booster for those aged 60+ years; 18 countries - on third booster for those aged 80+ years.

Analysis of vaccination uptake in the EU/EEA countries according to time of implementation

The uptake of the second booster dose among individuals aged 60+ years was influenced by the timing of the decision to roll out second boosters, which was taken at different times in the various countries.

In order to map uptake of different booster doses in the various countries over time, countries were classified in four groups, based on the time period when each EU/EEA country reached 5% of the cumulative vaccine uptake for the second booster:

- Group 1: countries exceeding 5% of the cumulative vaccine uptake for the second booster by the end of June 2022 (before week 26 2022): Belgium, Cyprus, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Portugal, Sweden.
- Group 2: countries exceeding 5% of the cumulative vaccine uptake for the second booster between July and August 2022 (weeks 26-35 2022): Austria, Czechia, Estonia, Norway, Poland.
- Group 3: countries exceeding 5% of the cumulative vaccine uptake for the second booster starting from the middle of September 2022 (starting from week 36 2022): Denmark, Hungary, Latvia, Liechtenstein, Slovenia, Spain.
- Group 4: countries that did not meet the 5% of the cumulative vaccine uptake for the second booster at time of analysis: Bulgaria, Croatia, Lithuania, Romania, Slovakia.

Grouping the countries according to the time period when they reached a 5% uptake for the second booster dose, the median cumulative uptake of the first, second and third booster dose is presented in Figure 10.

As of 5 February 2023, the median cumulative uptake of the first booster dose has reached 88.7% for countries in Group 1, 72.6% for countries in Group 2, 71.5% for countries in Group 3, and 50.3% for countries in Group 4. The curve of the median cumulative uptake for the first booster dose was stable across Groups 1, 2 and 3, starting from week 05-2022 (end of January-beginning of February). The median uptake for the first booster dose in Group 4 was stable starting from week 05-2022 (end of January-beginning of February) with some increase between weeks 41 and 45-2022 (from mid-October to mid-November 2022) and has been stable since then.

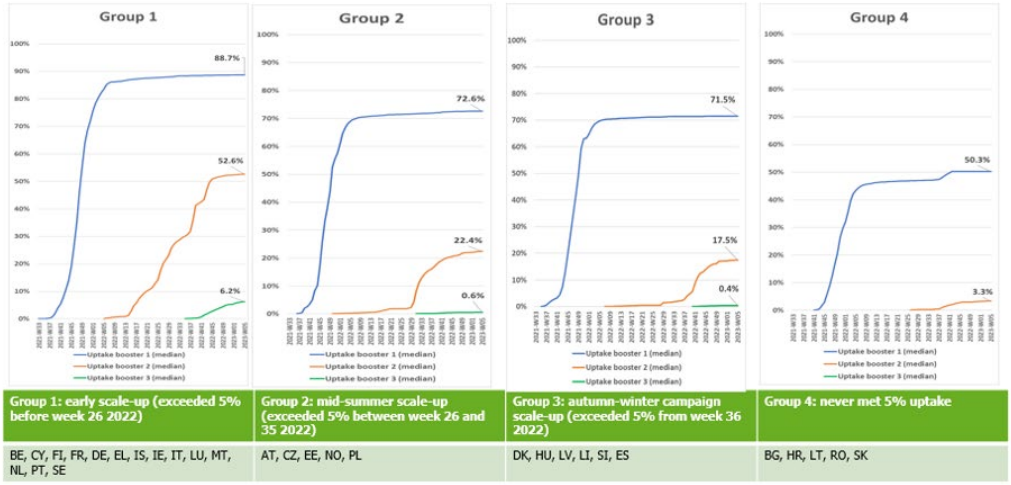
The median cumulative uptake for the second booster dose has reached 52.6% for countries in Group 1, 22.4% for countries in Group 2, 17.5% for countries in Group 3, and 3.3% for countries in Group 4. Curves of the median cumulative uptake for the second booster dose are slowly increasing in all four groups.

The median cumulative uptake for the third booster dose has reached 6.2% for countries in Group 1, 0.6% for countries in Group 2 and 0.4% for countries in Group 3.

The scale-up of the third booster dose seems to be progressing more significantly in Group 1, where eligible individuals may have already received their second booster three to six months before, which is not yet the case for Groups 2 and 3, where roll-out of the second booster dose only began in the middle of summer.

To summarise, these findings indicate that the uptake of the second and third booster was higher in countries defined in our analysis as having an 'early scale-up' of the first booster. A plateau effect is clear for the uptake of the first booster, while it is less evident for the second booster, with more inter-country variation. Furthermore, these findings indicate that the uptake of the second booster and, consequently, uptake of the third booster is more heterogeneous among EU/EEA countries than the uptake of the first booster.

Figure 10. Median uptake of first, second and third booster among those aged 60+ years in EU/EEA countries by time of scale-up of the second booster (as of week 05-2023); grouping based on update for second booster as of 5 February 2023



Group 1: early scale-up (exceeded 5% before week 26 2022)	Group 2: mid-summer scale-up (exceeded 5% between week 26 and 35 2022)	Group 3: autumn-winter campaign scale-up (exceeded 5% from week 36 2022)	Group 4: never met 5% uptake
BE, CY, FI, FR, DE, EL, IS, IE, IT, LU, MT, NL, PT, SE	AT, CZ, EE, NO, PL	DK, HU, LV, LI, SI, ES	BG, HR, LT, RO, SK

Communication, vaccination acceptance and uptake considerations for future vaccination campaigns

Future vaccination campaigns need to consider which approaches can be most effective and practical to promote acceptance and uptake of regular COVID-19 vaccination and draw on lessons learned from the vaccine roll-out so far. This becomes challenging in the context of peoples' diminishing interest in getting vaccinated with subsequent COVID-19 vaccine doses, and the perception of a 'return to normality' with the lifting of measures and overall improvement of epidemiological indicators.

Data on uptake of COVID-19 vaccines show that for each additional vaccine dose that is recommended, uptake in general has been lower than for the previous dose, including in the older population groups at higher risk of severe disease. The fact that the population in general may not accept repeated vaccination against COVID-19 also needs to be considered [81].

Since the vaccines became available, some of the factors that have affected uptake of COVID-19 vaccines in different population groups include perceptions that they had not been sufficiently tested; the belief that they are not effective, and worries about possible side effects [82]. However, as the pandemic and the related vaccination programmes have progressed, other perceptions can play a role in the declining uptake, even in those who have been willing to get vaccinated to date. For example:

- a recent study in the US found that the most common reasons in previously vaccinated people for not receiving a bivalent booster dose were lack of awareness of eligibility for vaccination or of vaccine availability, and perceived immunity against infection [83];
- in a survey carried out in Quebec, Canada, at the end of 2022, the main reasons given by those who do not intend to receive new vaccine doses were that they considered themselves well protected, and that there are too many doses and they do not want to receive them on a regular basis. A small percentage (6%) of those surveyed even said that they would rather build up their immunity by catching COVID-19 than receive a new booster dose [84].

The US Centers for Disease Control and Prevention (US CDC) have identified 'COVID-19 message fatigue' as a powerful barrier to vaccine uptake. The US CDC also caution against always assuming that those who have not taken the vaccine are necessarily hesitant, as there could still be some access barriers at play [85]. In addition to these factors, multiple COVID-19 vaccine compositions (e.g. different primary series and boosters) and immunisation schedules further complicate the communication around these vaccines [86].

Taking all these factors into account, preparations for future COVID-19 vaccination campaigns may consider:

- Developing targeted communication, focusing efforts on reaching high-priority groups through trusted channels and messengers such as healthcare providers, those caring for the elderly and community-level advocates [85]. Health professionals, doctors, nurses and pharmacists are considered by the public as the most trusted sources for reliable information on COVID-19 vaccines [82]. They can be supported via professional organisations that represent them at national/regional level, and with communication materials that help them to address questions, concerns and misinformation from service users. Initiatives could involve frontline healthcare workers providing advice to the specific risk groups (healthcare providers working with elderly patients, obstetricians/gynaecologists in the event of any specific recommendations for pregnant women).
- Providing clear information on which groups are recommended for vaccination, type of vaccines available and timing. People should also be reminded why it continues to be important to keep up-to-date with vaccination, in particular those in risk groups. Given possible overestimation of own immunity, communication should also address waning of protection [83] .

- A simplification of the COVID-19 vaccination regimen would contribute to better communication and may improve vaccine coverage [86].
- It is useful to continue to gather insights on people's beliefs, concerns and expectations, to inform strategies for facilitating vaccination acceptance and uptake. The '5Cs' model – that looks into Confidence, Constraints, Complacency, Calculation, and Collective responsibility – provides a framework to support this work [87].
- Developing communication initiatives in connection with regular campaigns that promote vaccination at specific times of the year – e.g. during the autumn/winter and linked to other vaccine recommendations as per national guidelines.

Knowledge gaps and research priorities

- Lack of long-term bivalent vaccine effectiveness data.
- Virus evolution and possible emergence of new SARS -CoV-2 VOCs or sub lineages.
- Evaluation of the need to harmonise the strain composition of COVID-19 vaccines on an annual basis in a similar manner to influenza and to define criteria for the decision-making process. Strain selection and options for monovalent versus multivalent vaccines to be further discussed by EMA and international regulators.
- Waning immunity for both cellular and humoral responses to emerging VOCs (both vaccine-induced and naturally acquired – in all age groups with emphasis on vulnerable groups such as older adults and the immunocompromised).
- Better assessment of the burden of COVID-19 disease related to the post-acute phase, which includes post COVID-19 condition (PCC), or 'long COVID'.
- More data are needed on the impact of vaccination, prior infection and hybrid immunity on the risk of developing PCC symptoms, and PCC symptom duration.
- Cost-effectiveness of COVID-19 vaccination programmes.
- Correlates of protection.

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Annex 1. Plans for vaccination campaigns in 2023 – EU/EEA countries and globally

This section focuses on countries that have announced recommendations for vaccination in 2023. Information on current applicable recommendations is available in the latest ECDC deployment report [80].

Country	Recommendations – 2023 COVID-19 vaccination campaign
Sweden [88]	**Date of implementation:** 1 Mar 2023 – 29 Feb 2024 **Target population:** • People aged 80 years and above and people living in care homes for elderly: **two doses**, one in the spring and one in the autumn/winter, with an interval of at least six months between doses. • For people aged 65–79 years and people aged 18–64 years in risk groups: **one dose** recommended, and regions **may offer one additional dose** at least six months after the initial dose in the autumn/winter season. NB: recommendations are to be announced for people aged 18–64 years **with no risk factors.**
France [89]	**Spring 2023** **One dose recommended:** people aged 80 years and above, those who are immunosuppressed, people at very high risk of severe disease. **Autumn 2023** One dose recommended: people aged 65 years and above, people of any age with co-morbidities, pregnant women**,** people at risk of severe disease and their contacts (including social and medical professionals).
Finland [90]	**Spring 2023** Booster doses are recommended for people with severe immune deficiencies from 12 years of age, where each case will be assessed individually by a physician. **Autumn 2023** Under consideration
Norway [91]	**Spring 2023** Booster dose recommended for people aged 75 years and above, including residents of long-term care facilities, if interval since last dose is more than six months. **Autumn 2023** Under consideration.

Country	Recommendations – 2023 COVID-19 vaccination campaign	Timing and type of vaccines offered
United Kingdom [92]	Interim advice from the Joint Committee on Vaccination and Immunisation (JCVI) • In autumn 2023, persons at higher risk of severe COVID-19 could be offered a booster vaccine dose in preparation for winter 2023 to 2024. • For a smaller group of people (such as the elderly and those who are immunosuppressed) an extra booster vaccine dose may be offered in spring 2023. • Emergency surge vaccine responses may be required, should a novel variant of concern emerge with clinically significant biological differences to the Omicron variant. • JCVI advises on the discontinuation of the autumn 2022 vaccination campaign, specific offer for healthy people aged 5 to 49 years who develop a new health condition in 2023 and targeted vaccination of people at higher risk of severe COVID-19.	
Canada - Quebec [84]	The Comité sur l'immunisation du Québec (CIQ) recently recommended a booster dose of bivalent vaccine for high-risk individuals* who had not yet had the disease and had never received a bivalent vaccine, to be given six months after the last dose received.	Bivalent COVID-19 vaccines

Country	Recommendations – 2023 COVID-19 vaccination campaign	Timing and type of vaccines offered
	The CIQ is extending this recommendation to all high-risk individuals who have not yet been infected and whose last dose was administered at least six months ago, irrespective of the product previously used. (* age 60 years and over, nursing homes and long-term care facilities, individuals from five years of age with at-risk conditions, healthcare workers, pregnant women, adults living in remote areas.)	
Australia [93]	**Recommended** All adults aged 65 years and over. Adults aged 18–64 years who have medical comorbidities that increase their risk of severe COVID-19, or disability with significant or complex health needs. **Vaccination to be considered** • All adults aged 18–64 years without risk factors for severe COVID-19. • Children and adolescents aged 5–17 years who have medical comorbidities that increase their risk of severe COVID-19, or disability with significant or complex health needs. **Not recommended** Children and adolescents under the age of 18 years who do not have any risk factors for severe COVID-19.	Prior to June 2023 and from six months after a last COVID-19 vaccine dose or confirmed infection. Bivalent vaccines preferred

Annex 2. Mathematical modelling estimates of the impact of future COVID-19 vaccination campaigns on preventing the hospitalisation burden

The variation of the age-specific second booster uptake across the EU/EEA. The data is obtained from ECDC's COVID-19 Vaccine Tracker [37].

Table T1

Uptake of the second booster across the EU/EEA	80+ years	70-79 years	60-69 years	50-59 years
Maximum	96.4%	89.9%	79.5%	60.4%
Median	46.3%	38.1%	21%	6.9%
Minimum	0.3%	0.5%	0.3%	0.2%

Relative reduction in cumulative hospitalisations by an extended set of vaccination campaigns and vaccine uptake scenarios compared to the baseline scenario, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.

Fig S1 (see Fig S5 for the intermediate vaccine uptake scenario)

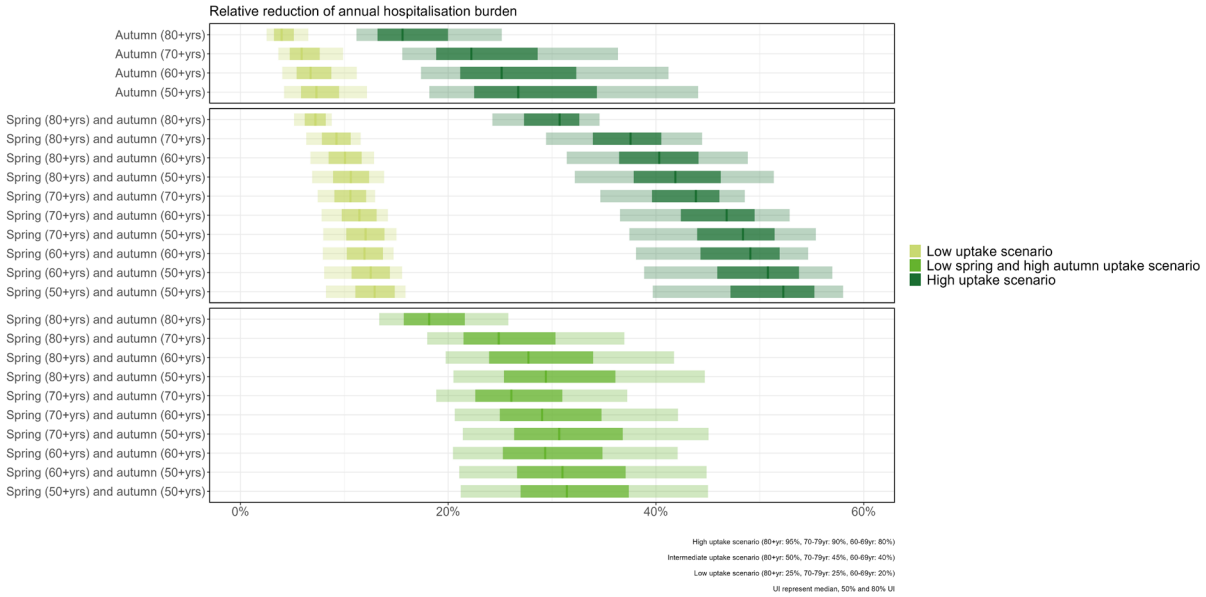
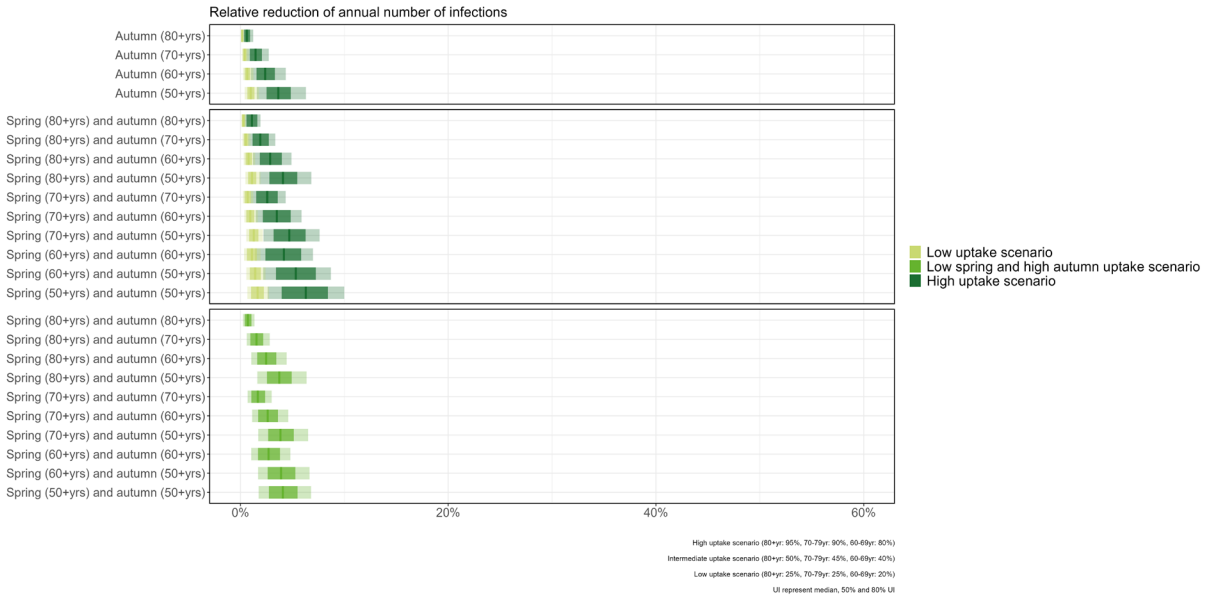
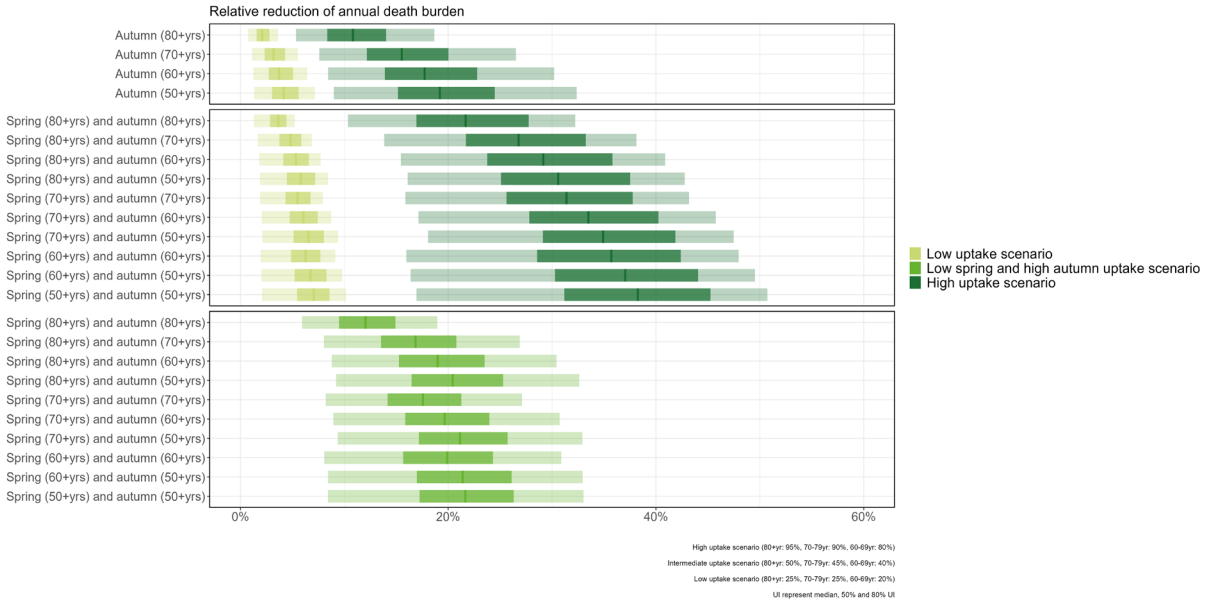


Fig S2A-C (see Fig S5 for the intermediate vaccine uptake scenario)



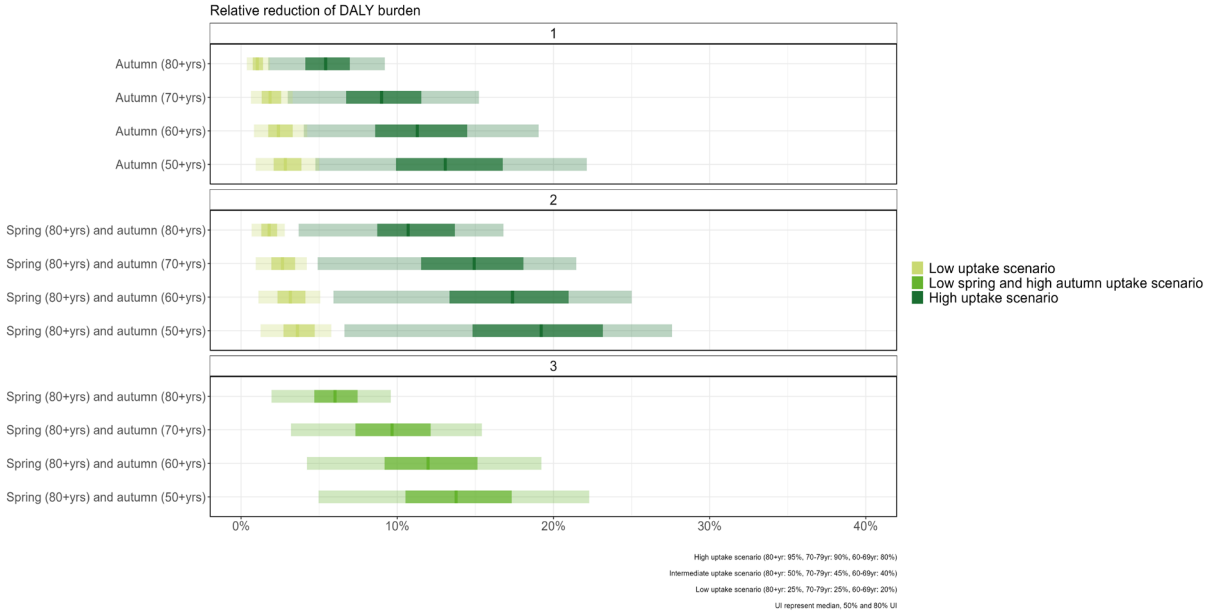
A. Relative reduction in cumulative infection by various vaccination campaigns and vaccine uptake scenarios compared to the baseline scenario, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.



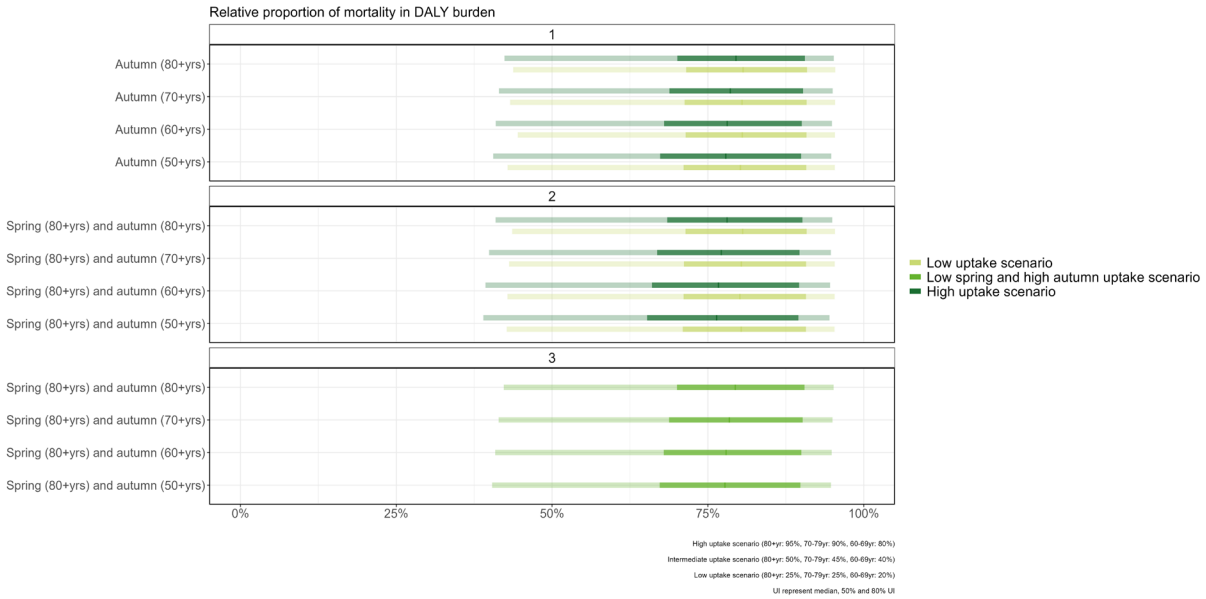
B. Relative reduction in cumulative death by various vaccination campaigns and vaccine uptake scenarios compared to the baseline scenario, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.



C. Relative reduction in disability-adjusted life years (DALY) burden by various vaccination campaigns and vaccine uptake scenarios compared to the baseline scenario, predicted until 28 February 2024.
Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.

Fig S3



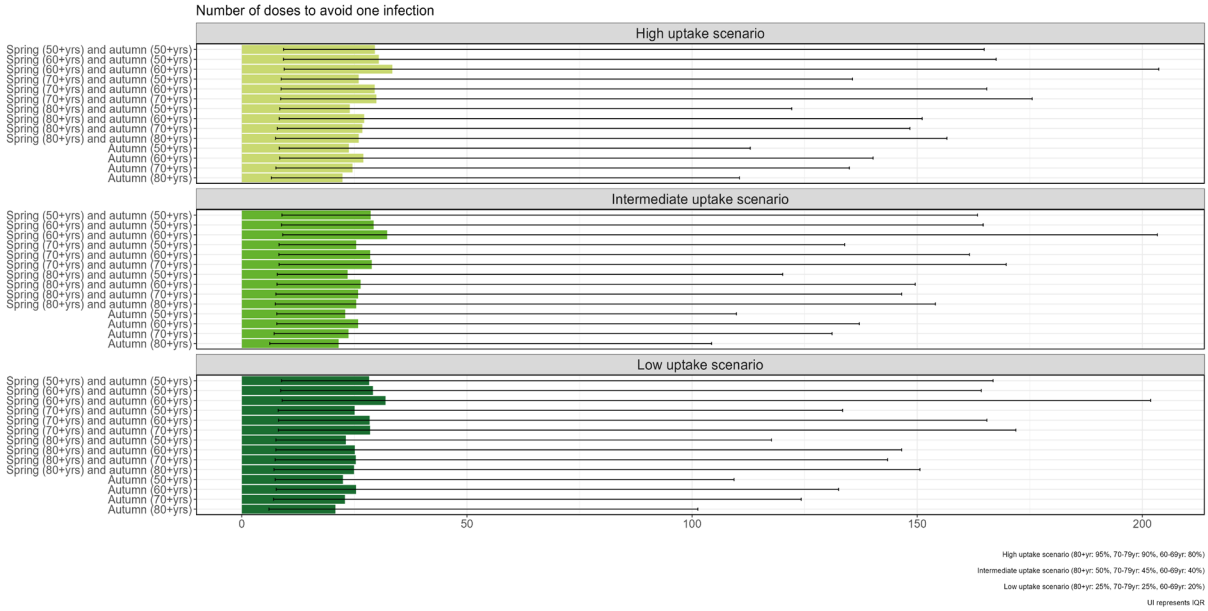
Proportion of mortality within the DALY burden by various vaccination campaigns and vaccine uptake scenarios, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.

A. Number of doses required to avoid one infection by various vaccination campaigns and vaccine uptake scenarios, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.

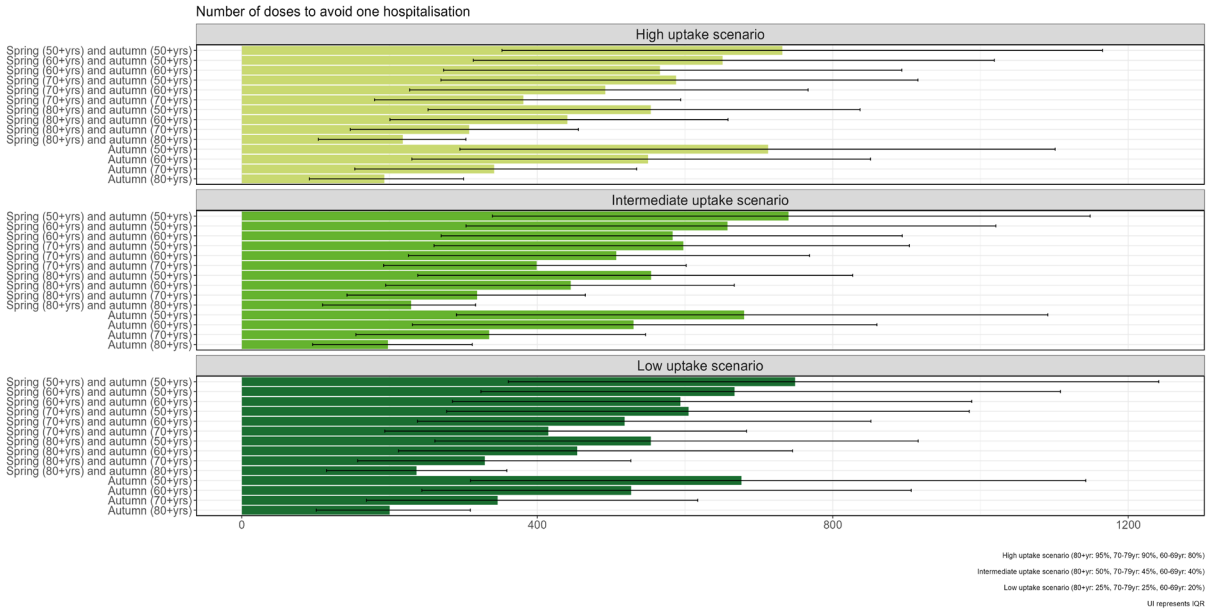
Fig S4A-C. Number of doses needed to prevent infection, hospitalisation, or death for various vaccination scenarios



Please note the differences in x axis.

B. Number of doses required to avoid one hospitalisation by various vaccination campaigns and vaccine uptake scenarios, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.



C. Number of doses required to avoid one death by various vaccination campaigns and vaccine uptake scenarios, predicted until 28 February 2024.

Rows and colours, as well as variations, are defined in the same way as in Figure 7 in the main text.

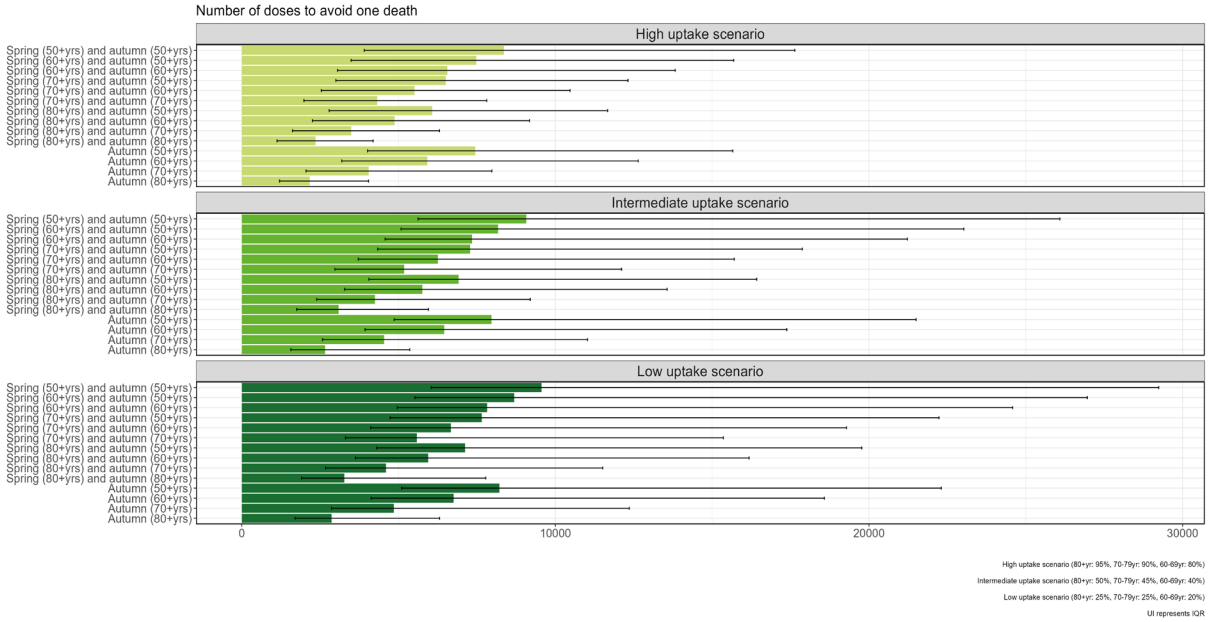
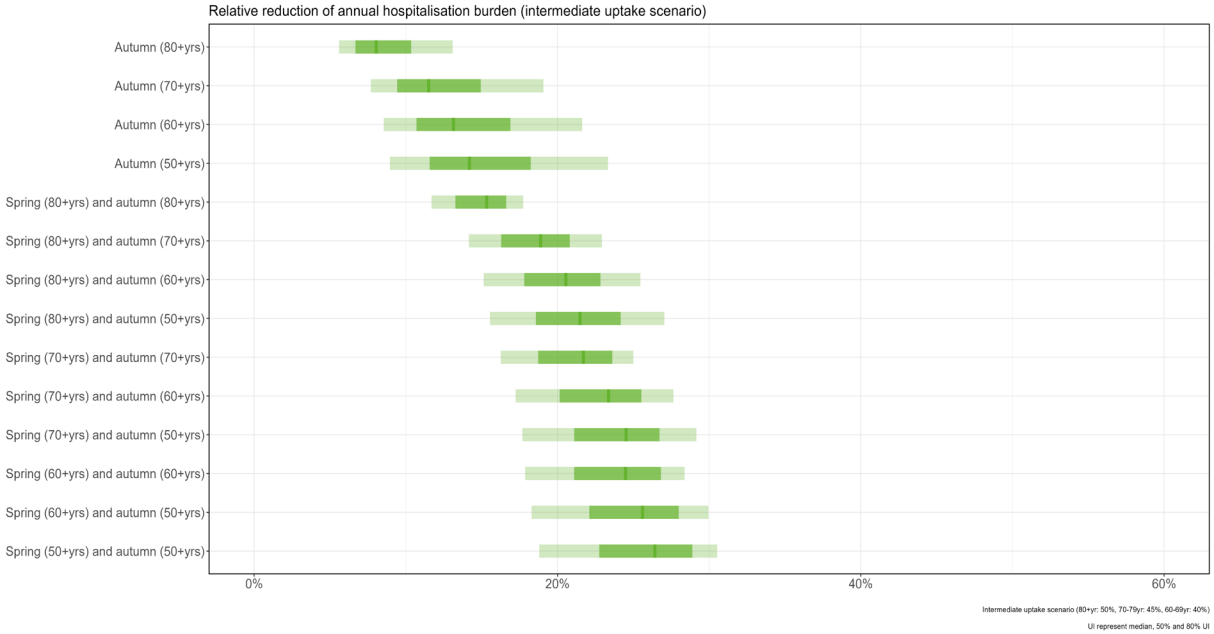
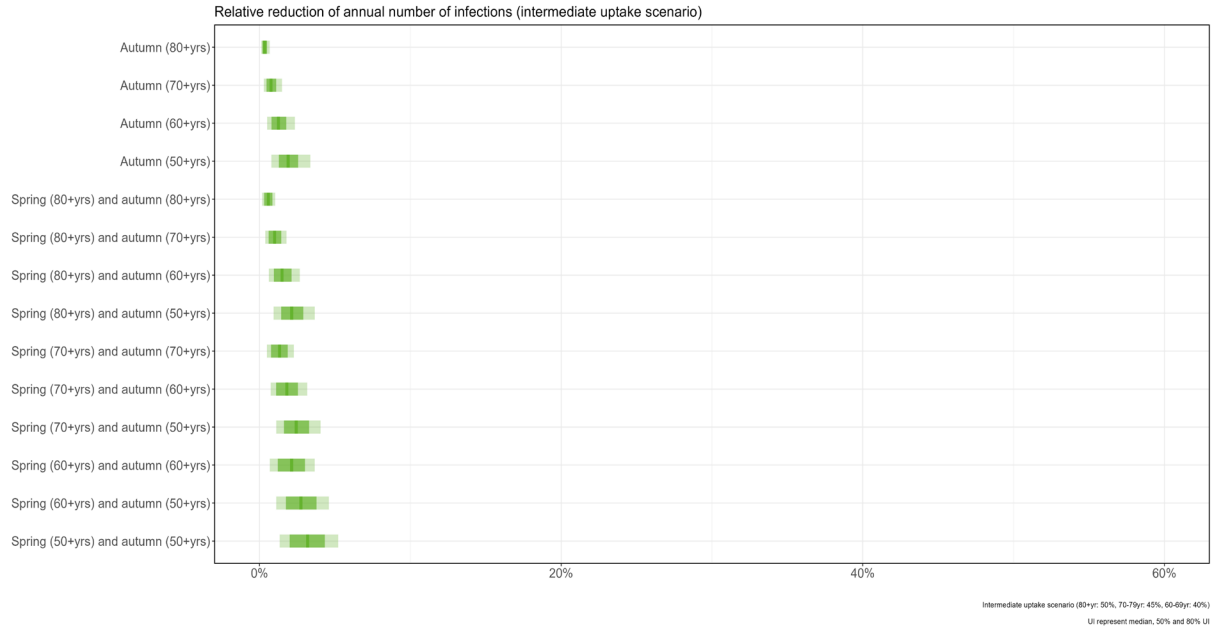


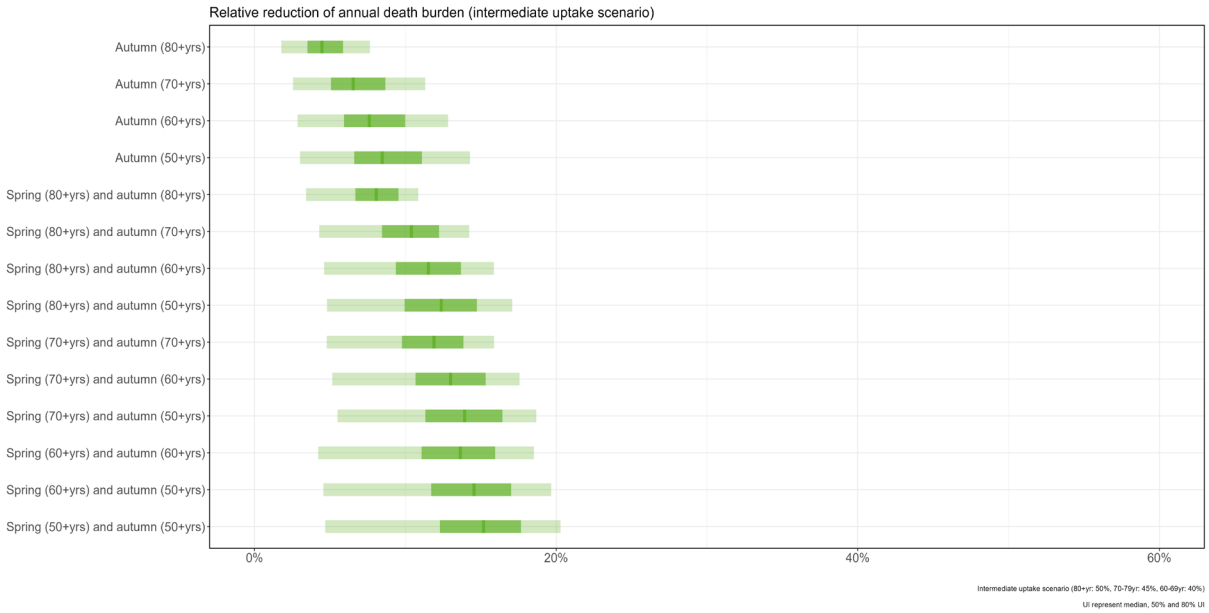
Fig S5A-C. Relative reduction in cumulative burden (hospitalisations, infections, deaths) by various vaccination campaigns and the intermediate vaccine uptake scenario compared to the baseline scenario (see Figs S1 and S2 for other vaccine uptake scenarios)



A. Relative reduction in cumulative hospitalisations by an extended set of vaccination campaigns and the intermediate vaccine uptake scenario compared to the baseline scenario, predicted until 28 February 2024.



B. Relative reduction in cumulative infection by various vaccination campaigns and the intermediate vaccine uptake scenario compared to the baseline scenario, predicted until 28 February 2024.



C. Relative reduction in cumulative death by various vaccination campaigns and the intermediate vaccine uptake scenario compared to the baseline scenario, predicted until 28 February 2024.

List of assumptions and limitations for the mathematical model

For the mathematical modelling presented in this report, we used a deterministic mean-field metapopulation model that was age-structured into ten age groups and the vaccine status of individuals in the EU/EEA countries. The compartmental model follows a Susceptible-Exposed-Infectious-Recovered (SEIR)-type structure with reinfections. For a vaccination programme targeting specific age groups, the vaccine impact will still be seen across all ages as the model captures the dynamics in the total population (i.e. both direct and indirect effects.) For the vaccination scenarios that we explored in this report, we made the following assumptions:

Timeframe of simulations: 1 March 2023 – 28 February 2024

1. Protection from prior infection and waning over time:
   i. Source: values from Table 2 in 'Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the Omicron variant and severe disease: a systematic review and meta-regression' [71]
   ii. Using pessimistic values and optimistic values (lower and upper values of 95% UI).
2. Protection from vaccines and waning over time:
   i. We assume that second booster and later doses have the same vaccine effectiveness (VE) and waning profile as first booster.
   ii. Source: Table 1-4, 6-7 for 'Any vaccine' [40].
3. Immunocompromised and specific settings (e.g. hospitals, long-term care facilities) have not been explicitly modelled. Even in a low uptake scenario, if the uptake is achieved among immunocompromised individuals or other people at higher risk of severe disease, then the individual-level effect of the vaccine protection could be higher.
4. Impacts from other respiratory viruses have not been included.
5. New variants:
   i. Baseline Scenario: no new variant.
   ii. Scenario 1 (pessimistic, before the vaccination campaigns): new variant introduced on 1 March 2023 and 1 September 2023.
   iii. Scenario 2 (optimistic, after the vaccination campaigns): new variant introduced on 1 June 2023 and 1 December 2023.
   iv. All new variants are assumed to represent at least 0.1% of daily cases for the first 30 days.
   v. All new variants are assumed to have a 20% decrease in protection (VE, prior infection, or hybrid immunity) against infection and 0% decrease in protection against severe outcomes.

6. Vaccination campaign:
   i. Spring: from 1 April to 1 July
   ii. Autumn: from 1 October to 31 December
   iii. Vaccination uptake: linear increase in vaccine uptake from 0% to the final uptake level.
   iv. Vaccination uptake - values obtained from the range for COVID-19 second booster uptake:
      a) Low vaccination uptake- assumed 80+ yrs: 25%, 70-79 yrs: 25%, 60-69 yrs: 20%, 50-59 yrs: 15%
      b) Intermediate vaccination uptake - assumed 80+ yrs: 50%, 70-79 yrs: 45%, 60-69 yrs: 40%, 50-59 yrs: 30%.
      c) High vaccination uptake - assumed 80+ yrs: 95%, 70-79 yrs: 90%, 60-69 yrs: 80%, 50-59 yrs: 60%.
7. Age-specific parameters:
   i. Relative susceptibility by age [94].
   ii. Relative symptom severity (used both to estimate age-specific IFT and IHR, proportional constant estimated by fitting most recent data) by age [95].
8. DALY assumptions:
   i. Disability-adjusted life years (DALYs) are an aggregated outcome measure for the overall burden of disease that combines morbidity and mortality. The DALYs consist of the years lived with disability (YLD) and the years of life lost (YLL) due to premature mortality, using country-specific life tables. Our calculations are subject to large uncertainty in parameters, particularly for the post-COVID-19 condition (PCC). However, they can give an indication of the relative importance of morbidity and mortality from the total burden of COVID-19 expected in 2023, without over-interpreting precise numbers.
   ii. Calculations include acute symptomatic infections, hospitalisations, ICU stays and deaths (undiscounted and with no age-weighting), as well as disability from post-COVID-19 condition (PCC).
   iii. Sources: we used the same duration of outcomes as in the dynamic transmission model, while for PCC we assumed a low proportion of 0.0005 of cases with disability for 120 days. We used disability weights assigned to the different outcomes of COVID-19 [96].
9. 'Seasonality and social behaviour of contact mixing and mobility' is assumed to be of sinusoidal shape with peak value on 15 January and proportionally affects reproductive number; the amplitude is a random variable (and thus part of UI in each modelling results/figure) following logit-normal distribution with mean and standard deviation (in logit unit) of -2.2 and 1.05, respectively. Using these parameters, we ascertain that the amplitude of the sinusoidal curve is below 5% in (on average) 25% of examples, and below 20% in 80% of examples. The precise values defining these parameters were obtained in consultation with ECDC experts internally.

Annex 3. Recommendations for fall/winter 2022 COVID-19 vaccination for general population, individuals with comorbidities and other high-risk groups

Table 5. Autumn/winter 2022 booster vaccination in the general population, individuals with comorbidities and other high-risk groups

Country	Minimum recommended age for COVID-19 booster vaccination in the autumn/winter of 2022 for the general population	Recommendations for autumn/winter 2022 vaccination for individuals with comorbidities and other high-risk groups
Austria	60 years	People at risk of developing a severe disease, pregnant women, residents of long-term care facilities, healthcare workers.
Belgium	50 years	People with weakened immunity working in the healthcare sector.
Bulgaria	65 years	Long-term care facility residents, healthcare workers, immunocompromised individuals, and those with underlying conditions.
Croatia	60 years	People under the age of 60 years with an increased risk of developing severe forms of COVID-19 (persons with moderate or severe immunosuppression, persons with severe diseases of the respiratory system, severe forms of diseases of the heart and circulatory system, metabolic and endocrine diseases).
Cyprus	60 years	Long-term care facility residents, healthcare workers, those aged 12 years and above with underlying conditions (including immunocompromised), pregnant women.
Czechia	60 years	Persons between the ages of 12 and 59 years with underlying medical conditions, long-term care facility residents, healthcare workers, pregnant women.
Denmark	50 years	People at increased risk of serious illness, healthcare personnel, those who have close contact with patients or people who are at increased risk of serious COVID-19, pregnant women.
Estonia	60 years	People over 12 years of age who are at risk.
Finland	65 years	Persons aged 18 years and over who belong to risk groups, severely immunocompromised persons aged 12 years and over.
France	60 years	Immunocompromised people, irrespective of age, people suffering from one or more comorbidities, pregnant women, residents of long-term care facilities, healthcare workers.
Germany	60 years	Long-term care facility residents, people at increased risk, people from the age of 5 years with immunodeficiency and underlying diseases who have an increased risk of severe COVID-19 progression, healthcare personnel.
Greece	60 years	People aged 12-59 years who belong to high-risk groups (including immunocompromised), long-term care facility residents, healthcare workers, people aged 30 to 59 years who do not belong to the above categories, with the consent of the attending physician.
Hungary	Everyone aged 18 years and older	
Iceland	60 years	Individuals aged 18-59 years who belong to high-risk groups, those who are immunocompromised, healthcare workers.
Ireland	65 years	Those aged 12 years and above who are immunocompromised; people between 12 and 64 years with an underlying medical condition. Earlier recommendation for second booster: 50 to 64 years, 12 to 49 years with underlying medical conditions. Residents of long-term care facilities, healthcare workers, pregnant women.

Country	Minimum recommended age for COVID-19 booster vaccination in the autumn/winter of 2022 for the general population	Recommendations for autumn/winter 2022 vaccination for individuals with comorbidities and other high-risk groups
Italy	60 years	Long-term care facility residents, people aged 60 years and over with pre-existing diseases. People aged 60 years and older can receive a third booster dose upon request. Bivalent vaccines are recommended as a second booster dose for people aged 60 years and older, individuals aged 12 years and older with pre-existing conditions, pregnant women, health professionals, residents, and workers in care units for the elderly.
Latvia	65 years	Immunosuppressed people, people with chronic diseases, seniors aged 65 and over, healthcare personnel, long-term care facility residents, pregnant women, and the rest of society (after consultation with the family doctor).
Liechtenstein	aged 12 years and older, with a priority given to those 65 years and older	People with chronic diseases, pregnant women.
Lithuania	all individuals aged 18 years and older can receive their second booster dose, with the priority given to those 60 years and older,	Individuals with chronic diseases.
Luxemburg	60 years	People between 12 and 59 years old with underlying conditions, immunocompromised people, pregnant women, healthcare professionals.
Malta	55 years	Priority given to those aged 60 years and older, 12 years and older in risk groups, healthcare workers.
Netherlands	60 years	People aged 12 to 59 years who are eligible for the annual flu jab, long-term care facility residents, people with Down's syndrome, healthcare workers, pregnant women, people aged 12-59 years who are not medically at risk.
Norway	65 years	People in the 18-64 age group with an underlying risk of serious illness, young people in the age group 12-17 years with a serious underlying illness, pregnant women in the 2nd and 3rd trimester. People in the age group 18-64 years with no risk factors may be vaccinated if they so wish.
Poland	60 years	Individuals over 12 years of age with underlying conditions, healthcare personnel, all those aged 12 years and over.
Portugal	50 years	People aged 5-49 years with underlying conditions, long-term care facility residents, healthcare workers. People between 18 and 49 years old without associated risk diseases can also have access to the seasonal booster dose after an individual evaluation of the risk/benefits.
Romania	65 years	Those with underlying conditions, irrespective of age, healthcare personnel, long-term care facility residents.
Slovakia	Aged 12 years and older	
Slovenia	60 years	Vulnerable patients with chronic diseases, other persons aged 18 years and above can also be vaccinated with a second booster if they desire.
Spain	60 years	Long-term care facility residents, people under 60 years with underlying medical conditions.
Sweden	65 years	Long-term care facility residents, people over 18 years belonging to risk groups, pregnant women.

Table 6. Cumulative vaccine uptake of the second and the third booster dose in each EU/EEA country for people aged 60 years and above, and 80 years and above (as of 10 February 2023)

Country	60+ years		80+ years	
	Uptake of the second booster dose*	Uptake of the third booster dose**	Uptake of the second booster dose^	Uptake of the third booster dose^^
Austria	44.2%	1.3%	52.9%	1.6%
Belgium	70.9%	13.7%	73.3%	40.8%
Bulgaria	4.4%	-	4.3%	-
Croatia	3.0%	-	4.3%	-
Cyprus	29.5%	6.7%	39.2%	11.2%
Czechia	22.4%	< 0.1%	30.0%	< 0.1%
Denmark	86.6%	2.2%	96.4%	2.8%
Estonia	19.3%	0.6%	23.4%	0.8%
Finland	68.9%	30.7%	85.1%	50.3%
France	44.3%	10.2%	47.9%	14.6%
Germany	39.3%	3.7%	-	-
Greece	26.5%	5.7%	28.9%	6.6%
Hungary	12.7%	0.4%	15.5%	0.7%
Iceland	68.4%	< 0.1%	84.5%	-
Ireland	77.0%	37.8%	93.1%	57.2%
Italy	31.2%	2.4%	46.3%	5.4%
Latvia	8.4%	< 0.1%	10.0%	0.1%
Liechtenstein	22.2%	-	45.3%	-
Lithuania	3.4%	-	4.3%	-
Luxembourg	49.2%	0.6%	63.3%	0.7%
Malta	44.1%	5.4%	79.0%	8.6%
Netherlands	55.9%	-	64.2%	-
Norway	59.9%	-	72.7%	-
Poland	21.5%	-	20.1%	-
Portugal	75.0%	13.1%	87.5%	54.1%
Romania	0.4%	-	0.3%	-
Slovakia	3.8%	< 0.1%	4.8%	< 0.10%
Slovenia	11.0%	-	16.8%	-
Spain	59.8%	0.3%	74.8%	0.2%
Sweden	75.7%	-	85.8%	-

**30 EU/EEA countries reporting data to TESSy*
***20 EU/EEA countries reporting data to TESSy*
^29 EU/EEA countries reporting data to TESSy
^^18 EU/EEA countries reporting data to TESSy.