ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

2023 COVID-19 VACCINATION STRATEGY RECOMMENDATIONS

NIAC | 11.04.2023, Version 1.1

About NIAC

NIAC membership includes nominees from the Royal College of Physicians of Ireland, its Faculties and Institutes, the Royal College of Surgeons in Ireland, the Irish College of General Practitioners, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

NIAC considers the evidence about vaccines and related products and provides advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.

Update 11 April 2023

A correction has been made to footnote 3 in 'SUMMARY OF 2023 COVID-19 VACCINE RECOMMENDATIONS BY AGE GROUP', pages 5-6.

Version 1.1 (corrected 11 April 2023)

Corrected text:

[3] for those aged 5 years and older with immunocompromise the primary series should be extended to include three doses, the third dose should be given at an interval of at least 28 days after the second dose.

Version 1.0 (28 March 2023)

[3] for those aged 12 years and older with immunocompromise the primary series should be extended to include three doses, the third dose should be given at an interval of four months after the second dose.

2023 COVID-19 VACCINE RECOMMENDATIONS

A. RECOMMENDATIONS FOR 2023 COVID-19 BOOSTER VACCINES

1. A spring COVID-19 booster vaccine is recommended for:
    - those aged 70 years and older
    - those living in long term care facilities for older adults
    - those aged 5 years and older with immunocompromise associated with a suboptimal response to vaccination.

2. The spring COVID-19 booster vaccination campaign should aim for completion by end May.

3. An autumn COVID-19 booster vaccine is recommended for:
    - those aged 50 years and older
    - those aged 5-49 years with immunocompromise associated with a suboptimal response to vaccination
    - those aged 5-49 years with medical conditions associated with a higher risk of COVID-19 hospitalisation, severe disease or death
    - health and care workers.

4. For pregnant adolescents and adults a COVID-19 booster vaccine once in pregnancy is recommended if it is more than six months since their previous COVID-19 vaccine or infection.
    - COVID-19 vaccine can be given at any stage in pregnancy
    - the booster is ideally given between 20-34 weeks' gestation
    - if it is more than 12 months since their previous COVID-19 vaccine or infection administration earlier in pregnancy should be considered.

5. For those healthy aged 18-49 years and who are up to date with their vaccines (primary schedule and first booster)
    - an autumn booster vaccine is not routinely recommended
    - access to an autumn booster vaccine should be available for those who, following discussion of their reasons with a health care provider (e.g., GP, pharmacist or vaccination centre), request vaccination.

6. For those healthy aged 12-17 years and who are up to date with their vaccines (primary schedule and first booster) an additional booster vaccine is not routinely recommended.

7. For those healthy aged under 12 years COVID-19 booster vaccination is not recommended.

8. COVID-19 booster vaccines as outlined above may be given irrespective of the number of previous booster doses or types of COVID-19 vaccines received as follows:

- for those aged 50 years and older an interval of six months is recommended following any previous COVID-19 vaccine dose or infection
- for those aged 5 and older with immunocompromise associated with a suboptimal response to vaccination, an interval of six months is recommended following any previous COVID-19 vaccine dose or infection
- for those aged less than 49 years an interval of nine months is recommended following any previous COVID-19 vaccine dose or infection
- a minimum interval of three months is permissible in exceptional circumstances e.g., heightened epidemiologic risk or for operational reasons.

9. mRNA COVID-19 bivalent vaccines are preferred for use as boosters however, Spikevax bivalent Original/Omicron BA.4-5 should not be administered to those aged under 30 years. For those aged 5-29 years, Comirnaty Original/Omicron BA.4-5 at the age appropriate dose is recommended.

10. Protein based vaccines (Nuvaxovid and VidPrevtyn Beta) may be used as alternatives for those for whom an mRNA vaccine is contraindicated or declined.
    - Nuvaxovid is the preferred alternate and can be used for primary and booster vaccination.
    - Data on VidPrevtyn Beta are more limited. It is only authorised as a booster.

11. The autumn campaign should coincide with the seasonal influenza vaccination campaign. COVID-19 booster and influenza vaccines may be administered at the same time with one vaccine in each arm.

B. RECOMMENDATIONS FOR PRIMARY COVID-19 VACCINATION

1. For those aged 30 years and older, recommendations regarding the primary COVID-19 vaccine schedule and the first booster vaccine are unchanged.

2. For those aged 12-29 years, recommendations regarding the primary vaccine schedule and first booster vaccine remain. However, an interval of eight weeks between the first and second doses of an mRNA vaccine is now recommended, with a minimum interval of three weeks if there is urgency to achieve protection.

3. For those aged 5-11 years, recommendations regarding the primary vaccine schedule remain. However, an interval of eight weeks between the first and second doses of an mRNA vaccine is now recommended, with a minimum interval of three weeks if there is urgency to achieve protection.

4. For those aged 6 months to 4 years the COVID-19 vaccination recommendations are unchanged.

Recommendations may be updated when more information becomes available.

SUMMARY OF 2023 COVID-19 VACCINE RECOMMENDATIONS BY AGE GROUP		
Population by age	**Primary Vaccination Series**	**Booster Vaccination**
		A six month interval from previous booster vaccine or infection is recommended for those aged 50 years and older. **A nine month** interval from previous booster vaccine or infection is recommended for those aged under 50 years.
Adults aged 70 years and older	**Recommended** Schedule: two doses 4 weeks apart[1,3]	At least one booster is recommended for all adults aged 18 years and older. Irrespective of number of prior booster doses: • a booster vaccine **is recommended** in spring • a booster vaccine **is recommended** in autumn.

Adults aged 50-69 years	**Recommended**
	Schedule: two doses 4 weeks apart[1,3]
		At least one booster is recommended for all adults aged 18 years and older. Irrespective of the number of prior booster doses:
		• a booster vaccine **is recommended** in spring for:
		  ○ those living in long term care facilities for older adults
		  ○ those with immunocompromise associated with a suboptimal response to vaccination.
		• a booster vaccine is **recommended** for all in autumn.

Adults aged 18-49 years	**Recommended**
	Schedule: two doses 4-8 weeks apart[1,2,3]
		At least one booster is recommended for all adults aged 18 years and older. Irrespective of the number of prior booster doses:
		• additional booster vaccines are **not** routinely recommended
		• a booster vaccine **is recommended** in spring for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination.
		• a booster vaccine **is recommended** in autumn for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination
		  ○ those with medical conditions associated with a higher risk of COVID-19 hospitalisation, severe disease or death.
		• access to an autumn booster vaccine should be available for those who, following discussion of their reasons with a health care provider (e.g., GP, pharmacist or vaccination centre), request vaccination.

Adolescents aged 12-17 years	**Recommended**
	Schedule**:** two doses 8 weeks apart[2,3]
		At least one booster dose should be offered to all aged 12-17 years. Irrespective of the number of prior booster doses:
		• additional booster vaccines are **not** routinely recommended.
		• a booster vaccine **is recommended** in spring for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination
		• a booster vaccine **is recommended** in autumn for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination
		  ○ those with medical conditions associated with a higher risk of COVID-19 hospitalisation, severe disease or death.

Children aged 5-11 years	**Recommended** for those with underlying conditions
	Available to others
	
	Schedule: two doses 8 weeks apart[2,3]
		Booster vaccines are **not** routinely recommended.
		
		Irrespective of the number of prior booster doses:
		• a booster vaccine **is recommended** in spring for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination
		• a booster vaccine **is recommended** in autumn for:
		  ○ those with immunocompromise associated with a suboptimal response to vaccination
		  ○ those with medical conditions associated with a higher risk of COVID-19 hospitalisation, severe disease or death.

Children aged 6 months to 4 years	**Recommended** for those with underlying conditions **Available** to others Schedule: Three doses with first interval of 3 weeks, second interval of 8 weeks	Booster vaccines are **not recommended.**
Health and Care workers	**Recommended** Schedule: two doses 4-8 weeks apart[1,2,3]	At least one booster is recommended. Irrespective of the number of prior booster doses: • a booster vaccine is **recommended** for all in autumn
Pregnancy	**Recommended** Schedule: two doses 4-8 weeks apart[1,2,3]	For pregnant adolescents and adults a COVID-19 booster vaccine once in pregnancy is recommended if it is more than six months since their previous COVID-19 vaccine or infection. • COVID-19 vaccine can be given at any stage in pregnancy • the booster is ideally given between 20-34 weeks' gestation • if it is more than 12 months since their previous COVID-19 vaccine or infection administration earlier in pregnancy should be considered.

[1] a minimum interval of three weeks may be used if there is urgency to achieve protection

[2] for mRNA vaccines a four week interval between dose one and dose two of the primary vaccination series is standard in Ireland. For those aged 5-29 years an eight week interval between dose one and dose two is now recommended, a minimum interval of three weeks may be used if there is urgency to achieve protection.

[3] for those aged 5 years and older with immunocompromise the primary series should be extended to include three doses, the third dose should be given at an interval of at least 28 days after the second dose.

[4] high risk categories as listed in Chapter 5a

1. EXECUTIVE SUMMARY

- The continuing aim of the vaccination programme is to reduce hospitalisations, severe disease and death from COVID-19 and to reduce the burden on the health care system particularly in winter.
- The primary COVID-19 vaccination schedule affords very good protection against severe disease that is further enhanced by a first booster dose and/or by COVID-19 infection. Each subsequent booster dose restores protection that has waned.
- The primary COVID 19 vaccine series is recommended for all aged five years and older and is available to those aged six months to four years. A first booster is recommended for all aged 18 years and older and is available to those aged 12-17 years. All are encouraged to be up to date with recommended vaccines.
- Wastewater surveillance and other surveillance systems indicate that the SARS-CoV-2 virus continues to circulate in the community at relatively high levels.
- Circulating variants are highly transmissible and more immune evasive than those previously encountered, however they do not appear to be associated with increased disease severity.
- In 2023, the rates of COVID-19 cases, hospitalisation and deaths had been decreasing in Ireland and in Europe, however a recent small increase in cases and hospitalisations has been noted.
- The baseline number of cases between surges is remaining higher than after the first and second waves of infection, representing persistent risk for vulnerable members of the community.
- Age is the strongest risk factor for severe COVID-19 outcomes with the risk increasing incrementally with age, those aged over 70 years are at the highest risk for hospitalisation and death.
- COVID-19 vaccination uptake rates in Ireland are among the highest in Europe, especially among those over 65 years of age. However, uptake rates have declined with each subsequent booster offer.
- COVID-19 vaccines are very effective in preventing severe COVID-19. Protection peaks four to eight weeks after vaccination and wanes gradually thereafter. Overall protection is sustained against hospitalisation and severe disease to at least nine months and beyond.
- Hybrid immunity confers the most robust and durable protection against severe COVID-19 outcomes, with studies indicating protection extending beyond 12 months.
- Those aged 70 years and older are least likely to have had SARS-CoV-2 infection and are more reliant on vaccination for protection than younger age cohorts. For these, modest declines in protection from vaccination are associated with greater risk of severe COVID-19.
- Based on studies from the UK, Nordic countries, US and Israel, mainly involving those aged 50 years and older, bivalent mRNA vaccination is anticipated to modestly enhance

protection compared with monovalent vaccines. Data on younger cohorts are more limited.

- Compared to younger cohorts, the lower levels of hybrid immunity and greater impact of waning protection in older persons means that more frequent vaccination will be required to sustain their protection against hospitalisation, severe disease and death.
- SARS-CoV-2 seasonality is not yet established. Surges in case numbers, hospitalisations and deaths occur in all seasons. However, as the impact is potentially greatest in winter, timing the COVID-19 vaccination campaign for the autumn should maximise benefit both for the individual and the health care system.
- Combining the roll out of influenza and COVID-19 vaccination is safe and will result in a more streamlined and efficient implementation and may increase vaccine uptake.
- VidPrevtyn Beta, a protein based monovalent vaccine based on the Beta variant spike antigen, is authorised for use in the EU as a COVID-19 booster for adults who were previously vaccinated with a primary series of mRNA or adenoviral vector COVID-19 vaccine.
- Clinical trials that compared VidPrevtyn Beta to Comirnaty (monovalent) as a booster dose reported similar adverse events and similar or increased immunogenicity. No post-marketing safety data or studies comparing VidPrevtyn Beta to bivalent mRNA vaccines are available.
- Nuvaxovid is the preferred alternate for use in Ireland as data on VidPrevtyn Beta are more limited.
- mRNA vaccines are the preferred COVID-19 vaccines in Ireland. The risk of vaccine associated myocarditis that mainly occurs in those aged less than 30 years can be reduced by extending the interval between the first and second mRNA COVID-19 vaccine dose in the primary schedule.
- Consideration must be given to the potential need for a rapid escalation of vaccination should the epidemiological situation deteriorate.

2. INTRODUCTION

The SARS-CoV-2 virus continues to circulate at high prevalence in our community as indicated by its detection in wastewater samples throughout Ireland. The current circulating strains are highly transmissible and the most immune evasive encountered thus far. The predominant Omicron strain, XBB.1.5 does not appear to be associated with increased disease severity. Should the numbers infected increase a proportionate rise in hospitalisations, severe disease and deaths might be anticipated.

In Ireland, with a highly vaccinated population and seroprevalence studies indicating high levels of prior SARS-CoV-2 infection, the overall population protection from COVID-19 hospitalisation,

severe disease, or death is good. However, the robustness of the protection afforded varies across the population by age, health status, and time since prior vaccination or infection.

While the current circulating stains are more immune evasive than earlier variants and protection against infection is short-lived, protection against hospitalisation, severe disease and death is much more durable. However, protection wanes over time and the impact is greatest for older persons and those with immunocompromise.

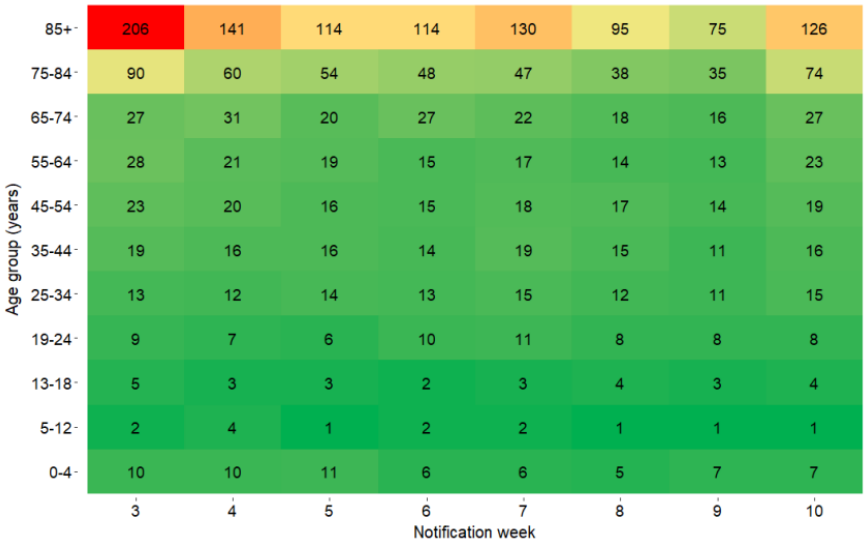
In these 2023 COVID-19 vaccine recommendations, the lower risk that the circulating variants pose to those who are young, healthy and who, importantly, are up to date with the recommended COVID-19 vaccines, is recognised, while the value of additional COVID-19 vaccination doses in sustaining protection of those more vulnerable is addressed.

3. EPIDEMIOLOGY IN IRELAND

In 2023, the rates of COVID-19 cases, hospitalisation and deaths had been decreasing in Ireland, however a recent small increase in cases and hospitalisations has been noted. Case numbers and hospitalisations remain at a higher baseline between surges than after the first and second waves of infection.

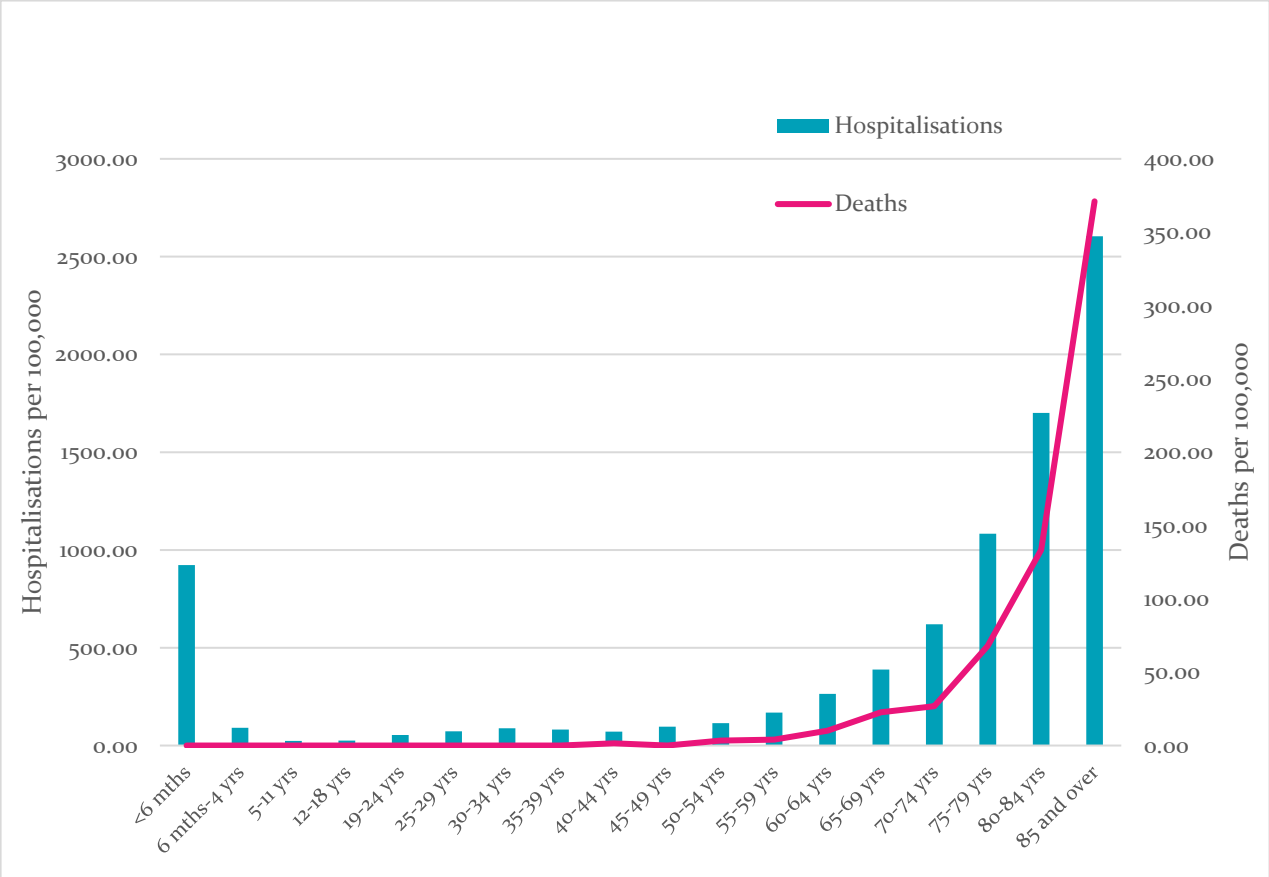
Although overall case numbers have declined in 2023, the increased susceptibility of older persons to infection and adverse outcomes remains. The general trend of decreasing incidence rate with decreasing age with those aged 85 years and older having the highest age specific incidence rates this year.[1] (Figure 1)

Figure 1. Heat map of weekly age-specific incidence rates of confirmed COVID-19 cases per 100,000 population in Ireland from 15 Jan to 11 March 2023. Source: HPSC.[1]



The number of hospitalisations among confirmed COVID-19 cases have also decreased since the beginning of January 2023. The rate of hospitalisations remains higher in those aged less than six months compared to older infants and children. Amongst those aged 45 years and older, the hospitalisation rates increase incrementally for each five-year cohort with the highest rates seen in those aged 70 years and older. COVID-19 death rates are highest in those aged 70 years and older.[2] (Figure 2) In the latest estimates 36% of those hospitalised with a positive SARS-CoV-2 PCR are admitted because of COVID-19 as opposed to it being an incidental finding.[3]

Figure 2. Hospitalisations and deaths per 100,00 among confirmed COVID-19 cases from 1 Sept 2022 to 13 March 2023. Source: HPSC CIDR extract 14.02.2023 (Cases notified to 13.03.2023).

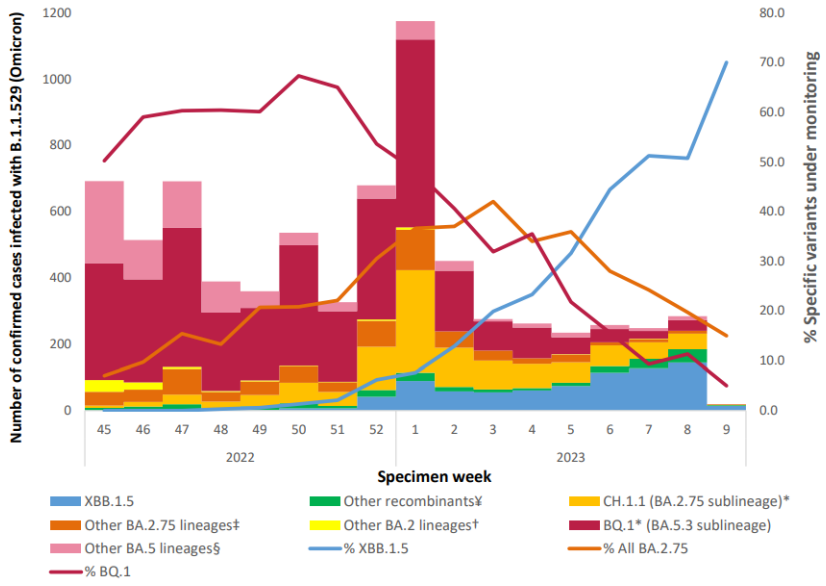


SARS-CoV-2 Variants

The initial Omicron wave was caused by the BA.1 sublineage. Four distinct Omicron sublineages, BA.2, BA.3, BA.4 and BA.5 subsequently emerged. A number of recombinant lineages have also been reported globally, some of which have been detected in low numbers in Ireland. Globally, the XBB recombinants, XBB.1.5 and XBB.1.9.1, have emerged as dominant and display a growth advantage over previous variants. As yet the new recombinants have not been associated with an

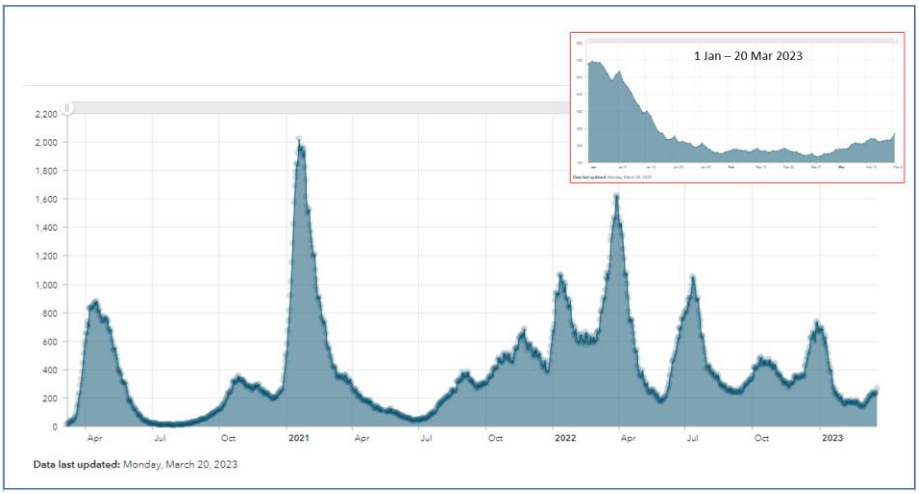
increase in severity. In Ireland, since the beginning of 2023 the percentage of Omicron cases of XBB.1.5 sublineage has steadily increased. As of 4 March 2023, XBB.1.5 accounted for 70% of sequenced cases in Ireland.[4] (Figure 3)

Figure 3. Confirmed Omicron cases identified in Ireland from 6 November 2022 to 4 March 2023. Source: HPSC.[4]



The recent increase in case numbers in fifteen countries in Europe and in hospitalisations in seven countries in Europe has been attributed to the spread of the newer variants e.g., XBB.1.5, XBB.1.9.1. However, pooled estimates across all countries remain low. A small increase in case numbers in hospital has been noted in Ireland in March. (Figure 4)

Figure 4. Confirmed COVID-19 cases in hospital March 2020 to March 2023 (Inset: 1 January to March 2023). Source: COVID-19 Data Hub.[5]



4. VACCINATION UPTAKE AND SEROPREVALENCE

Vaccination uptake

The uptake of COVID-19 vaccinations in Ireland is amongst the highest in Europe.[6] However, with each subsequent booster vaccine offered and with decreasing age the percentage uptake decreases. (Table 1)

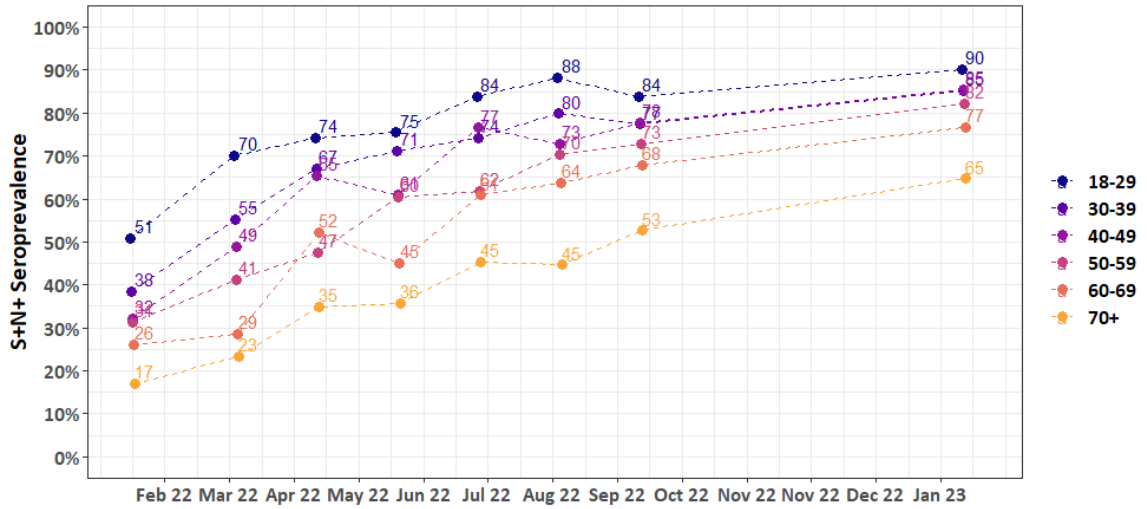
Table 1: Uptake of COVID-19 vaccinations in Ireland. Source HPSC and HSE.[7] [8]

Age Group	Primary course uptake (%)	Booster 1 uptake (%)	Booster 2 uptake (%)	Booster 3 uptake (%)
80+ years	100	100	89	56.5
65+ years	99.9	95.3	76.8	45.7
50+ years	99.9	92.3	59.6	23.3
18+ years	98.1	80.5	33.5	10.9
12-17 years	70.2	33.1	0.6	0
12+ years	95.3	77.1	31.1	10.1
5+ years	87.6	75.2	-	-

Seroprevalence

As of 29 January 2023, testing of residual samples from the Irish Blood Transfusion Service found that 98% of adults tested had evidence of either infection or vaccination (S+) and 85% had evidence of previous infection (S+ and N+).[9] These data may not accurately reflect community seroprevalence as blood donors are a select group. They are generally healthy and the number of blood donors aged 60 years and older is small. The Laboratory Surveillance Network data includes test results of residual blood samples sent by GPs and captures more data from older adults and those with underlying medical conditions. Similar trends with very high seroprevalence rates are observed in both testing programmes. There has been an increase in S+N+ seroprevalence across all age groups over the past 12 months. The proportion that are S+N+, indicative of past infection, decreases with age. Those aged 70 years and older are least likely to have had SARS-CoV-2 infection, have less evidence of hybrid immunity as protection, and are more reliant on vaccination for protection than younger age cohorts. (Figure 5)

Figure 5. Percentage of people with evidence of prior SARS-CoV-2 infection. Source: Lab Surveillance Network data provided directly to NIAC by the Seroepidemiology Unit.



5. VACCINE SAFETY

In authorising the BA.4-5 bivalent vaccines, the EMA based their recommendations on the safety of the bivalent BA.1 mRNA COVID-19 vaccines and a large body of cumulative data on original mRNA vaccines that are very similar to the adapted vaccines and whose safety profile is well established.[10] [11] In their analysis of safety data after the administration of 22.6 million booster doses the bivalent BA.4-5 vaccines, the US Centers for Disease Control and Prevention (CDC) found the safety profile to be similar to that of the monovalent vaccine boosters.[12] The preliminary results of a nationwide Danish study of 2.2m individuals aged 50 years or older found no evidence of increased risk of adverse events after the bivalent vaccine was given as a fourth COVID-19 vaccine dose.[13]

In Ireland, as of 31 January 2023, the HPRA had received 2,147 reports of suspected side effects following a booster COVID-19 vaccine dose. Of these, 118 reports related to a bivalent vaccine. Overall, side effects of bivalent booster vaccines are consistent with those seen following the primary vaccination course with the majority mild to moderate in nature. The most regularly reported include headache, fever, and tiredness.[14]

Myocarditis and pericarditis are recognised as very rare risks of mRNA vaccination, predominantly in males aged under 30 years after the second vaccine dose. The recommended interval between dose one and dose two of the primary vaccination schedule for Comirnaty is three weeks. For operational reasons and when vaccines supplies were constrained some countries elected to prioritise distribution of the first dose and extend the interdose interval. In Ireland a four week interval has been recommended to date.

In Denmark where the median interval between dose one and two was five weeks. The absolute rate of myocarditis and pericarditis in males aged 12-39 years following dose two of Comirnaty was 1.8 per 100 000 and was not significantly increased over the baseline risk.[15] In Israel with a three week interval, the rates of myocarditis per 100,000 males were 3.19, 13.73, and 8.95 for those aged 16-19, 20-24 and 25-29 years respectively.[16] Subsequently studies in Canada and France have confirmed the association between dosing interval and myocarditis risk.[17-19] In Ontario, a nationwide population based cohort study found higher rates of myocarditis across all ages and sexes when the interdose interval was less than 30 days.[17 18] In France, in a matched case control study of those aged 12 years and older the risk of myocarditis following each vaccine dose was increased however the risk decreased as the interdose intervals lengthened.[19]

Deciding on the appropriate dose interval involves an assessment of potential benefits and risks. The overall risks of myocarditis and pericarditis are higher from SARS-CoV-2 infection than from vaccinations and outweigh the vaccine associated risk. Where there is urgency to achieve protection, the shorter interval may be used. When SARS-CoV-2 risks are lower, extending the dosing interval may allow for further reduction of this rare vaccine side effect. An extended interval has been selected by some countries (Table 2) to optimise the benefits of vaccination while mitigating any potential adverse risk.

Table 2. International recommendations regarding optimal interval between first and second dose of mRNA COVID-19 primary series vaccination for adolescents and young adults aged 12-30 years.

Country	Recommended optimal interval
UK[20]	8-12 weeks
Germany[21]	3-6 weeks
Norway[22]	8-12 weeks (≥18 years 3-4 weeks)
USA[23]	8 weeks
Canada[24]	8 weeks
Australia[25]	8 weeks

6. VACCINE EFFECTIVENESS

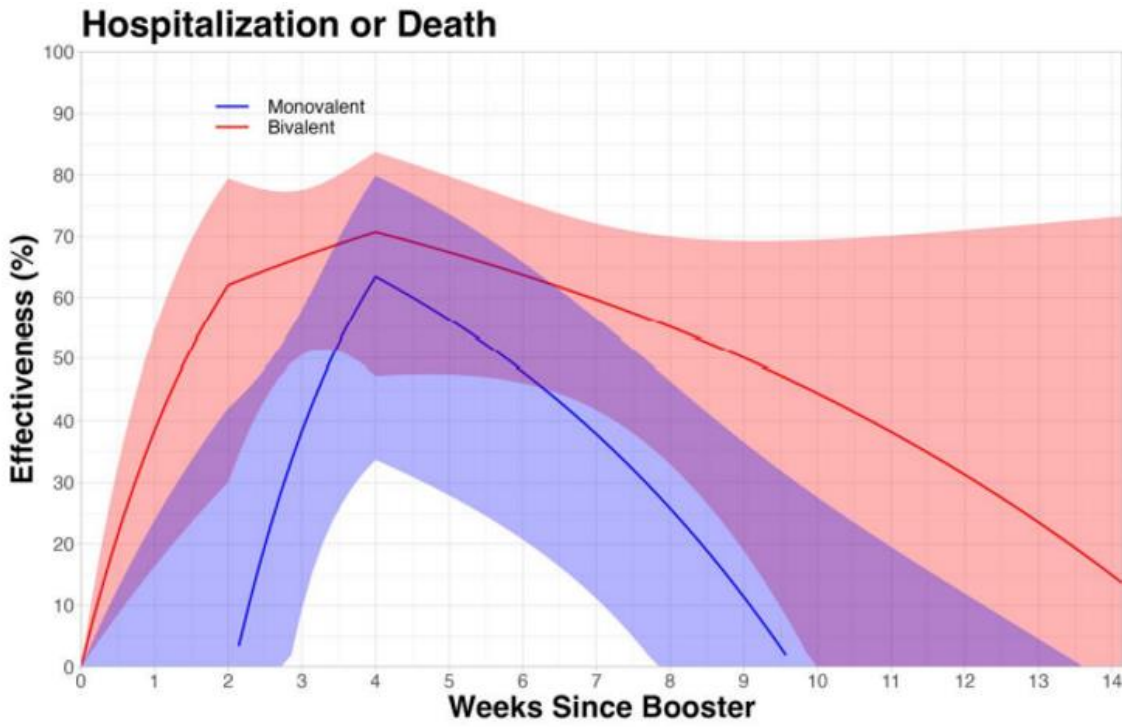
COVID-19 vaccines are effective in preventing hospitalisations, severe disease, and death secondary to SARS-CoV-2 infection. The protection they afford against infection and mild disease is limited.[26] Protection against more severe disease is more durable but also wanes gradually over time increasing the risk for those susceptible to severe disease as time from their last vaccine lapses.

Effectiveness of bivalent mRNA booster vaccination

Since their introduction in September 2022, bivalent mRNA booster vaccines have been shown to boost protection against COVID-19 related severe disease in adults aged 50 years and over. Studies from the UK, the Nordic Countries, the US and Israel have demonstrated additional protection from vaccination with mRNA bivalent booster vaccines in those previously vaccinated with at least the primary series. Protection ranged from 43-81% against hospitalisation and 78-86% against death. Protection peaked at 4-8 weeks and waned gradually thereafter.[27-31] As bivalent vaccines were only recently introduced the data on duration of effectiveness do not extend beyond three to four months.

While monovalent mRNA booster vaccines continue to provide protection against severe disease, bivalent mRNA vaccination is anticipated to modestly enhance protection. In a US study comparing the two, bivalent vaccines were found to provide superior protection. The estimated bivalent booster effectiveness against hospitalisation or death at 15-99 days post dose was 62%, whereas for the monovalent vaccine it was 25%.[29] (Figure 6)

Figure 6. Effectiveness of a monovalent or bivalent booster dose against hospitalisation or death due to Omicron infection. Source: Lin et al.[29]

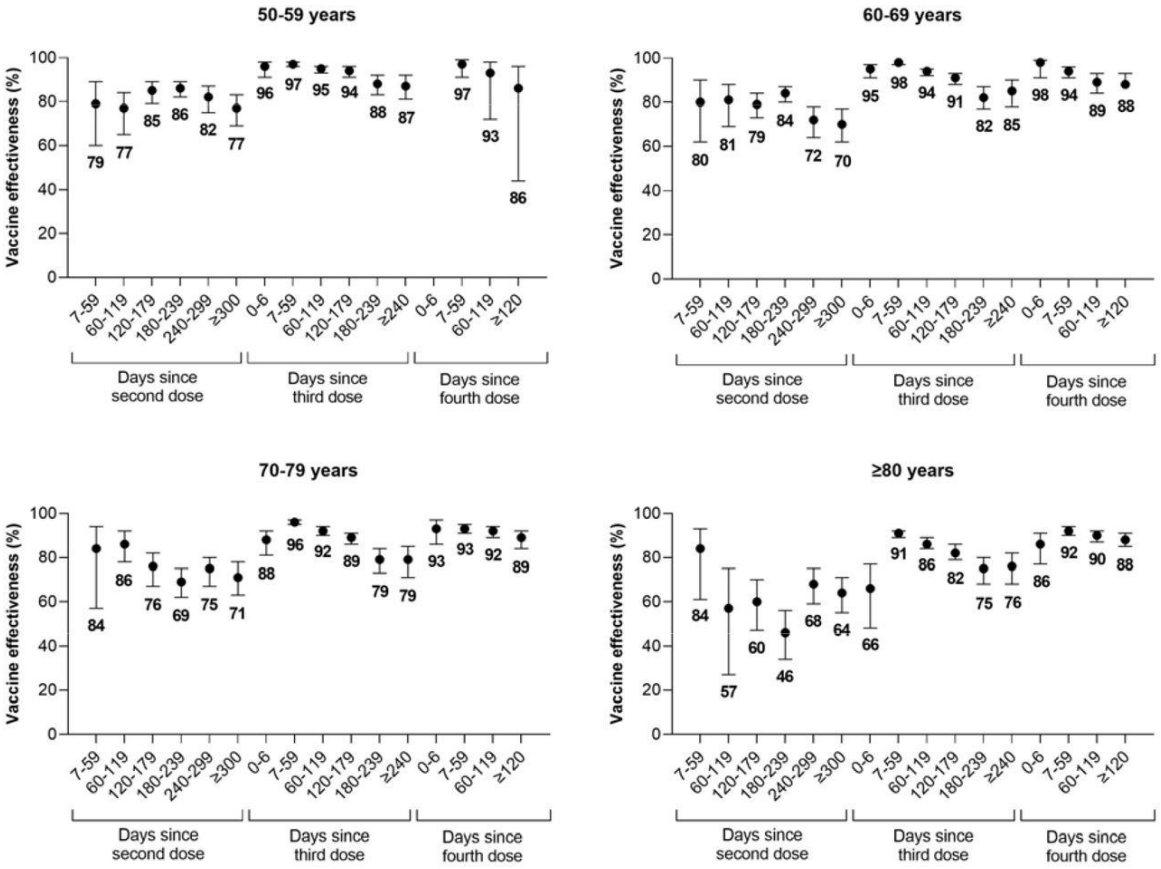


Determinants of protection

Age, sex and time since vaccination

Those of advanced age need more frequent booster vaccination to maintain adequate levels of protection against COVID-19 related severe disease than those of younger age. A Canadian study, in those aged 50 years and older, found that vaccine effectiveness (VE) was generally lower with increasing age. In all age groups, VE increased shortly after receipt of an mRNA monovalent vaccine dose, then declined gradually over time, with subsequent booster doses restoring protection.[32] (Figure 7)

Figure 7. Vaccine effectiveness of 2, 3 or 4 doses of monovalent mRNA COVID-19 vaccines against Omicron-associated severe outcomes in adults aged ≥50 years by age and time since vaccination. Source: Grewal et al.[32]



There are less data available regarding bivalent booster vaccination in those aged under 50 years. Younger cohorts may have good baseline protection due to previous monovalent vaccination and higher levels of natural immunity limiting the potential additional benefit of further booster doses.

Of interest, a register-based cohort study from Finland recently reported in preprint that in those aged 65-120 years a bivalent vaccine dose reduced the risk of hospitalisation and death, however in those aged 18-54 years with chronic conditions a similar reduction was not found. These results may be confounded by the low vaccination uptake (15%), and small overall numbers of hospitalisations and deaths in this cohort leading to imprecise estimates.[33]

SARS-CoV-2 evolution

Virus evolution can impact on VE. In England, preliminary estimates of incremental VE against hospitalisation with emerging sublineage CH.1.1 was 34.8% as compared to 47.2% with BQ.1 and 51.3% with BA.5. This suggests that VE against newly emerging sublineages may be less, although numbers in the included analysis are small.[34] (Table 3)

Table 3. Vaccine effectiveness against hospitalisation with CH1.1, BQ.1 and BA.5. Source: UK Health Security Agency.[34]

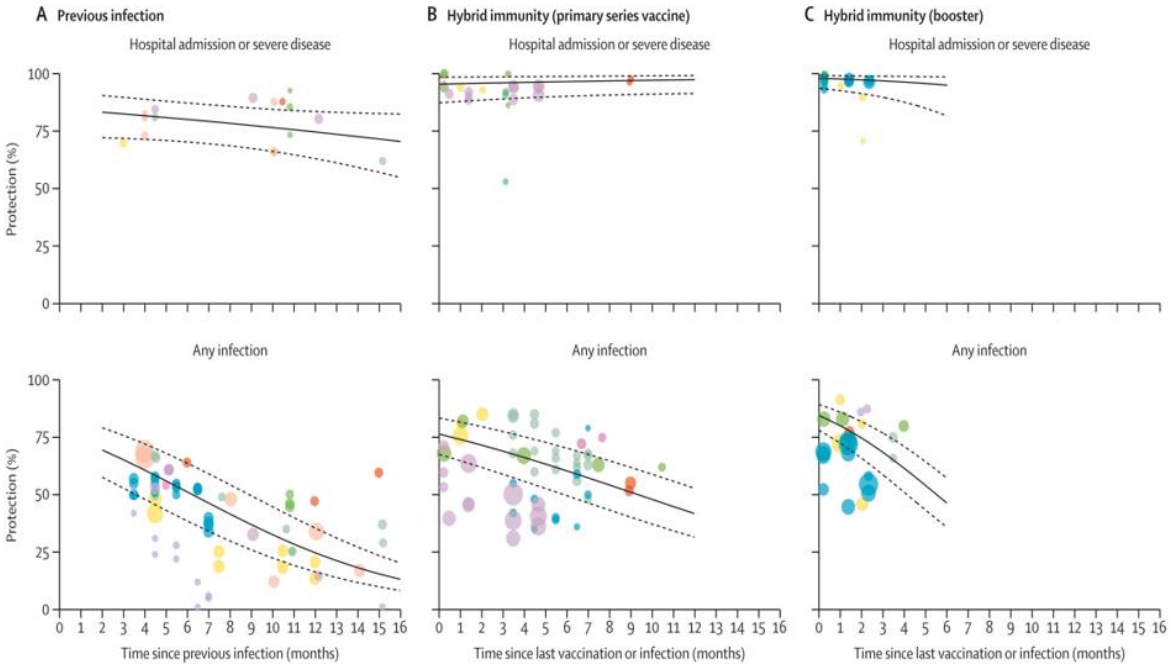
Variant	2 days stay with a respiratory diagnosis code			2 days stay with any diagnosis code		
	Controls	Cases	VE (95% CI)	Controls	Cases	VE (95% CI)
CH.1.1	16,829	66	34.3 (-0.3 to 57.0)	83,970	169	34.8 (14.9 to 50.0)
BQ.1	16,829	342	43.4 (32.7 to 52.5)	83,970	749	47.2 (40.7 to 53.0)
BA.5	16,829	166	56.8 (46.1 to 65.3)	83,970	371	51.3 (43.4 to 58.1)

7. PRIOR INFECTION AND HYBRID IMMUNITY

Prior infection offers some protection against reinfection and severe disease. In a 2023 metanalysis, protection from prior COVID-19 infection against reinfection was reported to wane to approximately 36% by nine months post infection.[35] In a Qatari nationwide study, protection afforded by prior infection against COVID-19 associated hospitalisation, severe disease and death remains strong (75-90%) extending at least beyond 12-14 months.[36]

Hybrid immunity, the combination of protection from infection and vaccination, offers more durable protection against severe COVID-19 than either natural infection or vaccination alone.[37] As with infection, the duration of protection of hybrid immunity against severe disease has been shown to persist for up to 12 months. (Figure 8)

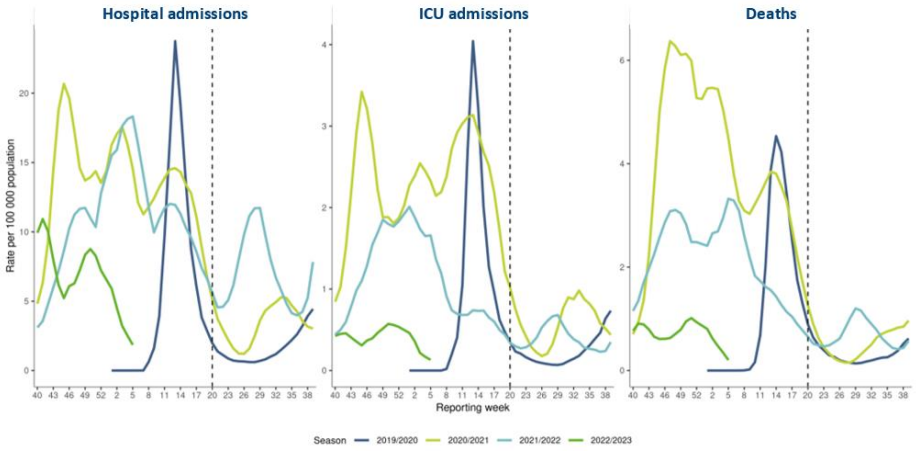
Figure 8. Protection against symptomatic COVID-19 infection and COVID-19 related hospital admission or severe disease over time from A. Previous infection, B. Hybrid immunity following primary series vaccination and C. Hybrid immunity following booster vaccination. Source: Bobrovitz et al.[37]



8. TIMING OF ADDITIONAL BOOSTER VACCINATION

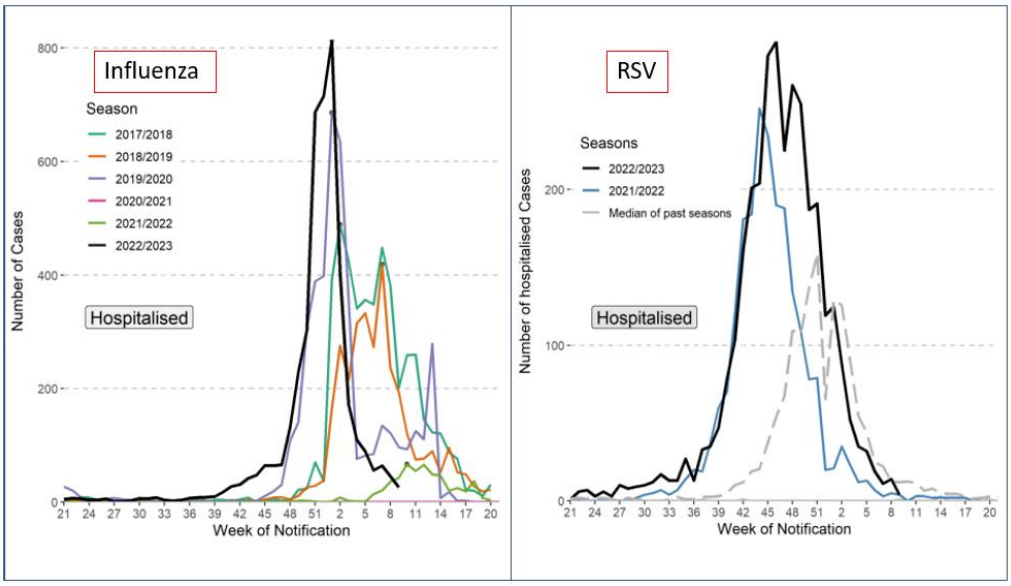
SARS-CoV-2 seasonality has not yet been clearly established as is the case for other viruses such as influenza. However, there has been a distinct winter wave, and a less pronounced summer wave each year since the arrival of SARS-CoV-2.[38] (Figure 9)

Figure 9. Hospital admission, ICU admission and death rates across Europe showing pronounced impact of COVID-19 during Winter (flu season = weeks 40-20) since 2020. Source: ECDC.[38]



Timing further doses of COVID-19 vaccination to occur in advance of the winter season could provide a number of advantages. Influenza, RSV and other respiratory viruses are known to surge during the winter season.[39] (Figure 10) Boosting population immunity against COVID-19 will minimise the impact of co-infection for individuals and reduce the burden of COVID-19 on health systems during peak times for other viral infections. Combining the roll out of influenza and COVID-19 vaccination is safe and may increase vaccine uptake and result in a more streamlined and efficient implementation and potentially reduce the burden on the health care system at a time of maximum stress to it.

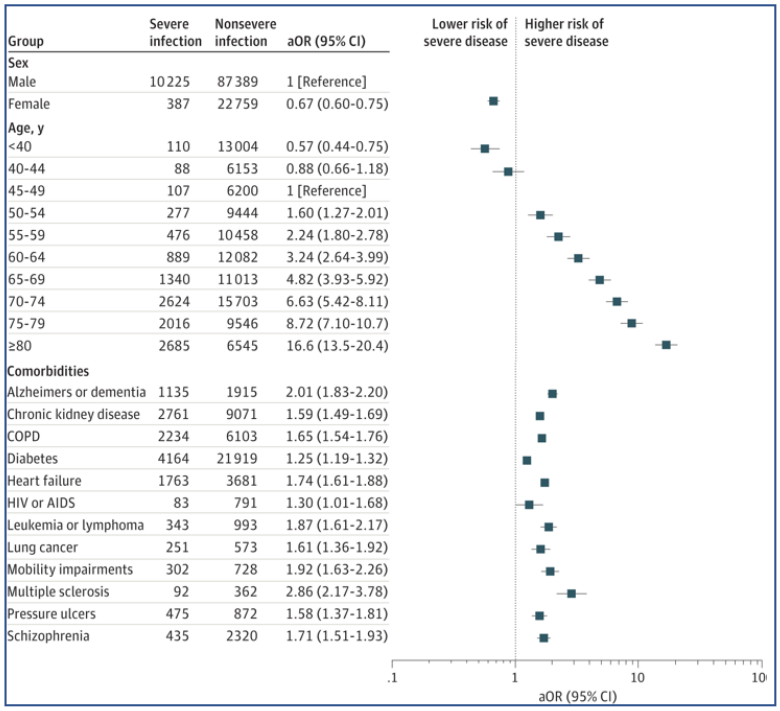
Figure 10: Influenza and RSV hospitalisation trends as of 4 March 2023. Source: HPSC.[39]



9. RISK FACTORS FOR SEVERE DISEASE

Age is the strongest risk factor for severe COVID-19 outcomes. The risk of severe outcomes increases markedly with increasing age. Data from the US reported in February 2023 showed that, compared to those age 18-29 years of age, the overall rate of death was 10 times higher in those aged 40-49 years and 350 times higher in those aged 85 years and above.[40] In a separate study involving over 110,000 veterans who tested positive for SARS-CoV-2 after being vaccinated, the strongest association with severe disease was age. Above the age of 50 the odds ratio for severe disease increased by 1.42 per five year age increase. The increased risk of severe disease associated with being aged 60-64 was higher than the risk associated with any individual co-morbidity investigated in this study.[41] (Figure 11)

Figure 11. Risk of severe COVID-19 disease in those previously vaccinated by age and co-morbidity. Source: Vo et al.[41]



Group	Severe infection	Nonsevere infection	aOR (95% CI)
Sex			
Male	10225	87389	1 [Reference]
Female	387	22759	0.67 (0.60-0.75)
Age, y			
<40	110	13004	0.57 (0.44-0.75)
40-44	88	6153	0.88 (0.66-1.18)
45-49	107	6200	1 [Reference]
50-54	277	9444	1.60 (1.27-2.01)
55-59	476	10458	2.24 (1.80-2.78)
60-64	889	12082	3.24 (2.64-3.99)
65-69	1340	11013	4.82 (3.93-5.92)
70-74	2624	15703	6.63 (5.42-8.11)
75-79	2016	9546	8.72 (7.10-10.7)
≥80	2685	6545	16.6 (13.5-20.4)
Comorbidities			
Alzheimers or dementia	1135	1915	2.01 (1.83-2.20)
Chronic kidney disease	2761	9071	1.59 (1.49-1.69)
COPD	2234	6103	1.65 (1.54-1.76)
Diabetes	4164	21919	1.25 (1.19-1.32)
Heart failure	1763	3681	1.74 (1.61-1.88)
HIV or AIDS	83	791	1.30 (1.01-1.68)
Leukemia or lymphoma	343	993	1.87 (1.61-2.17)
Lung cancer	251	573	1.61 (1.36-1.92)
Mobility impairments	302	728	1.92 (1.63-2.26)
Multiple sclerosis	92	362	2.86 (2.17-3.78)
Pressure ulcers	475	872	1.58 (1.37-1.81)
Schizophrenia	435	2320	1.71 (1.51-1.93)

Certain underlying medical conditions and the number of such conditions are associated with an increased risk of severe disease. Comorbidities reflecting end organ damage (such as heart failure and chronic kidney disease) are associated with a higher risk of severe disease compared to their predisposing conditions (such as hypertension and diabetes). Immunosuppressive therapies such as glucocorticoids and chemotherapy are also associated with significantly increased risk even in those who were vaccinated prior to starting these therapies.[41]

A list of conditions associated with an increased risk of severe COVID-19 is available in Chapter 5a. This list is not intended to be exhaustive or to replace individual risk-benefit assessment.

10. COVID-19 VACCINES

In Ireland, mRNA vaccines are preferred for COVID-19 primary and booster vaccination. The bivalent mRNA COVID-19 vaccines are the preferred choice for booster vaccination. Bivalent mRNA vaccines are authorised for use as boosters. The EMA's Emergency Task Force has stated that mRNA bivalent vaccines may be used for primary vaccination should it become necessary.[42] Protein based vaccines (Nuvaxovid and VidPrevtyn Beta) may be used as alternatives for those for whom an mRNA vaccine is contraindicated or declined. Nuvaxovid is the preferred alternate and

can be used for primary and booster vaccination. Data on VidPrevtyn Beta are more limited. It is only authorised as a booster.

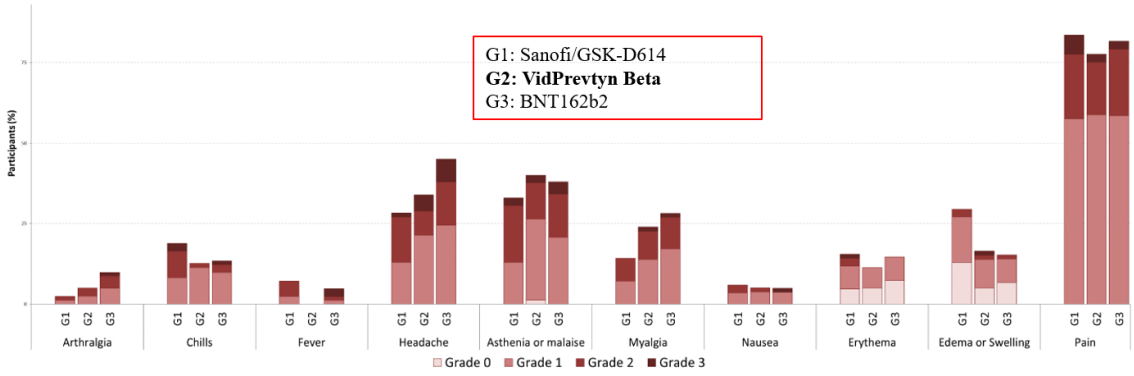
VidPrevtyn Beta

On 10 November 2022, the EMA recommended approval of VidPrevtyn Beta as a COVID-19 booster vaccine for adults previously vaccinated with an mRNA or adenoviral vector COVID-19 vaccine. VidPrevtyn Beta is a monovalent protein based vaccine which contains a version of the spike protein found on the surface of the Beta variant (B.1.351 strain) of SAR-CoV-2 virus, and the AS03 adjuvant.

Safety

The safety of VidPrevtyn Beta was assessed in 705 adults aged 18 years and older who were administered the vaccine as a first booster dose 4-10 months after receiving a primary series with an mRNA, adenoviral vector or protein based COVID-19 vaccine. The median duration of safety follow-up was 145 days, with 610 (86.5%) participants completing more than two months safety follow-up after booster injection. The most common adverse reactions were injection site pain, headache, myalgia, malaise, arthralgia and chills. Most occurred within three days of vaccination and were mild to moderate. The safety profile was similar to that of Comirnaty. (Figure 12) Due to the size and duration of the safety database for VidPrevtyn Beta, uncommon adverse reactions and longer term effects may not have been detected. Further supportive safety data were collected from trials in over 7,000 adults aged 18 years and older who received primary or booster vaccine formulations containing the same Beta antigen and AS03 adjuvant. Similar adverse event profiles were reported.[43] [44]

Figure 12. Rates and grades of severity of solicited adverse events. Source: Launay et al.[44]

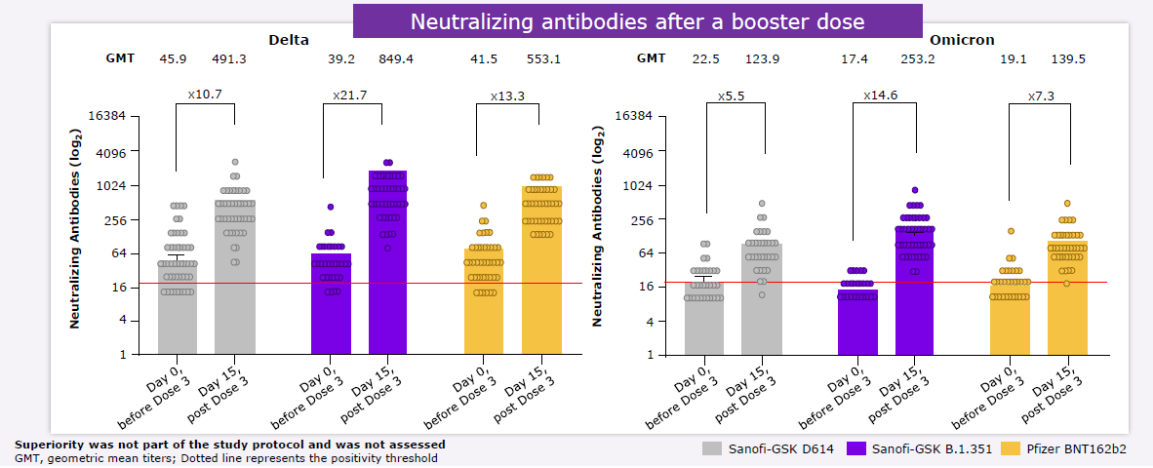


Immunogenicity

There are no post-marketing effectiveness data on VidPrevtyn Beta available to date. The efficacy has been inferred by immunobridging of immune responses to previously authorised COVID-19 vaccines to which vaccine efficacy has already been established.

In the first study, trial participants who had previously received a primary series of a Comirnaty were randomised to receive a first booster of either VidPrevtyn Beta or Comirnaty (monovalent). Superiority of Geometric Mean Titres (GMT) of neutralising antibodies against Omicron BA.1 was demonstrated for VidPrevtyn Beta 28 days post dose. Neutralising antibody response against Delta was also found to be higher in those who received VidPrevtyn Beta.[43] [44] (Figure 13)

Figure 13. Neutralising antibody response against Delta and Omicron BA.1 of VidPrevtyn Beta (Sanofi-GSK B.1.351) compared to Comirnaty (Pfizer BNT162b2). Source adapted from Launay et al.[44]



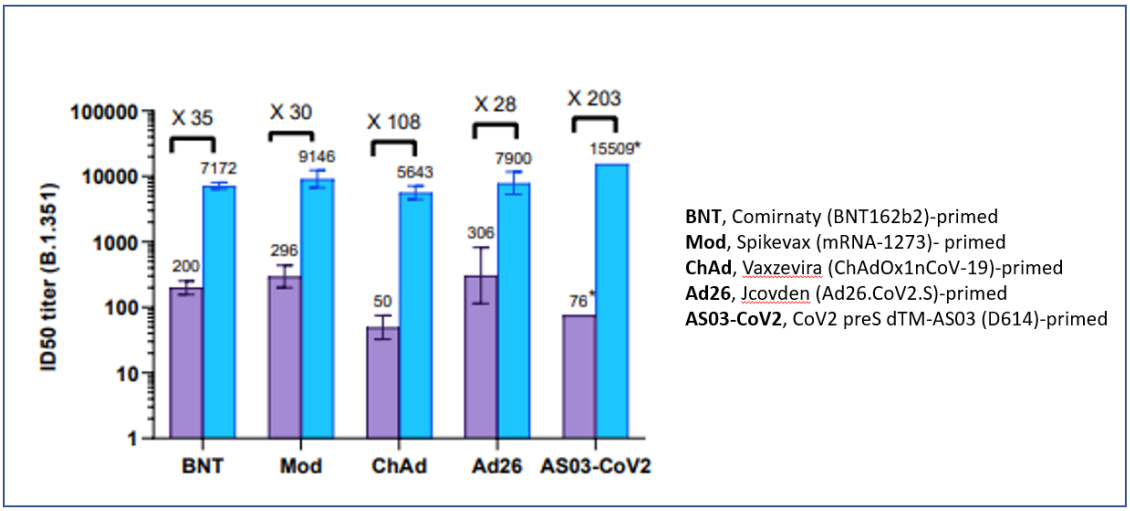
The seroresponse rate of Vidprevtyn Beta was found to be non-inferior against Omicron BA.1 and D614G strains. (Table 4)

Table 4. Seroresponse rate for VidPrevtyn Beta versus Comirnaty with individual neutralisation titre against Omicron BA.1 and D614G (28 days post-booster dose per-protocol analysis subset). Source: Adapted from Launay et al.[44]

	VidPrevtyn Beta (n=54)		Comirnaty (n=60)		VidPrevtyn Beta/ Comirnaty	
	Seroresponse rate	95% CI	Seroresponse rate	95% CI	Difference	Non inferiority demonstrated
D614G	96.2%	87-99.5	93.2%	83.5-98.1	3%	Yes
Omicron BA.1	100%	92.2-100	96.2%	87-99.5	3.8%	Yes

The second study included 543 participants aged 18 years and older, who had received a booster dose of VidPrevtyn Beta 4-10 months after receiving a primary course of either Comirnaty, Spikevax, Vaxzevria, JCOVDEN or adjuvanted protein (CoV2 preS dTM-AS03 [D614]) vaccine. A booster response to VidPrevtyn Beta was demonstrated regardless of the vaccine used for primary vaccination.[45] (Figure 14)

Figure 14. Booster pseudo virus neutralising antibody response against B.1.351 strain for VidPrevtyn Beta by priming vaccine. Source: De Bruyn et al.[45]



There are no data available from immunobridging studies comparing VidPrevtyn Beta to bivalent mRNA vaccine boosters which are currently in use, nor are there data available regarding the response to more recent Omicron variants such as BA.4, BA.5 and their sublineages.

11. 2023 INTERNATIONAL COVID-19 BOOSTER VACCINE RECOMMENDATIONS

Country	Spring	Autumn
France	Those aged ≥80 years Immunocompromised Those deemed high risk as part of a shared medical decision with health care team	Those aged ≥65 years Those aged ≥6 months with high risk co-morbidities or immunocompromise Pregnant women Those living with or in regular contact with high risk individuals such as HCWs Those deemed high risk as part of a shared medical decision with health care team
	Six month interval for all[1]	
Sweden[2]	**Recommended to:** Those aged ≥80 years Those living in care homes for the elderly **Available to:** Those aged 65-79 years Those aged 18-64 years with risk factors	**Recommended to:** Those aged ≥80 years Those living in care homes for the elderly Those aged 50-79 years Those aged 18-64 years with risk factors **Available to:** Those aged 18-49 years
	Nine month interval for those aged 18-64 years. Six month interval for those ≥65 years*	
UK	Adults aged ≥75 years Residents in a care home for older adults Individuals aged ≥5 years who are immunosuppressed	"Persons at higher risk of severe COVID-19 could be offered a booster vaccine dose in preparation for Winter 2023 to 2024"
Canada	Adults ≥80 years Adults 65-79 years – particularly if they do not have a history of COVID-19 infection Adult residents of long term care homes and other congregate living settings for seniors or those with complex medical care needs Adults ≥18 years with moderate-severe immunocompromise	Recommendations pending
Australia[3]		**Recommended for:** All adults ≥ aged 65 years 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. **Can be considered for**: Adults aged 18-64 years Children aged 5-17 years with severe disease risk factors **Boosters should occur prior to June 2023**[v]
	Six month interval for all*	
Netherlands	Spring booster programme not recommended	Recommendations pending
Denmark	Spring booster programme not recommended	Recommendations pending

HCW: Health and care workers
[1]Interval refers to time from last COVID-19 vaccine, or time since last confirmed SARS-CoV-2 infection, whichever is most recent
[2]Sweden offered either one or two booster vaccine doses during 2023 rather than spring and autumn doses
[3]Reminder that June is winter in southern hemisphere

11. DISCUSSION

The aim of the 2023 vaccination recommendations is to prevent COVID-19 hospitalisations, severe disease and death and to reduce the burden on the health care system. At this stage in the pandemic the majority of the population have a level of protection due to the vaccination, past infection or hybrid immunity i.e., immunity resulting from the combination of vaccination and infection.

Protection, whether from vaccination, infection, or both ultimately wanes. It can subsequently be boosted by either vaccination or infection. Repeated episodes of infection are not devoid of risk. The overall risks from infection with Omicron and its sublineages are lower than previously. They are not negligible. The risk of severe disease increases as time from last booster lengthens, especially for older persons and for those who are immunocompromised.

Older persons when infected have higher risks of hospitalisation, longer hospitalisation, and greater risk of death than younger individuals. While the overall risks are lower than during earlier stages in the pandemic, the trends remain with those aged 70 years and older most at risk of the severe consequences of COVID-19. Age is the dominant risk factor for severe COVID-19. The risks for those younger are not zero as development of long COVID can threaten even those with relatively mild infection and can occur following a reinfection.

In planning future vaccination, a number of uncertainties remain; how SARS-CoV-2 will evolve and whether more virulent variants, unrelated to Omicron and possibly resistant to neutralisation will emerge. COVID-19 seasonality is not clearly established. Time since the last vaccination or infection rather than season is more predictive of risk of severe COVID-19. However, the impact of COVID-19 on the health care system is highest during the winter months when health care resources are already stretched due to the co-circulation of respiratory viruses. As we enter the endemic phase of this infection and public health restrictions have been eased, the stress on the health care system is further exacerbated by the increased demand for hospitalisations relating to deferred treatments, delayed diagnoses and the late consequences of COVID-19 infection due to the pandemic. Concerted efforts are necessary to safeguard the health care system. Using COVID-19 vaccination to optimise population protection can confer individual benefit and reduce demands on the health care system.

Further COVID-19 vaccination in advance of the summer is not indicated for the majority of the population due to the high seroprevalence of SARS-CoV-2 antibodies in the community. Adolescents and young adults have the highest seroprevalence mainly due to hybrid immunity. For them, protection against severe disease can be anticipated to extend beyond 12 months and sooner boosting is not indicated. For those who may not have experienced SARS-CoV-2 infection, that protection is likely to extend to at least nine months.

Given the recent offer of a bivalent booster to all aged 18-49 years, further boosters are not indicated before autumn/winter 2023 at the earliest. For those in this age group who are up to date with their vaccines additional booster vaccination may only confer a modest benefit. However, for some within this age cohort this benefit could be important, especially for those without previous SARS-CoV-2 infection who do not have hybrid immunity and also for those wishing to temporarily reduce their risk of transmitting infection to protect others.

Those aged 70 years and older have experienced less infection, have less hybrid immunity and are more reliant on vaccination for protection than younger cohorts. Approximately 47% of those aged over 70-79 years have not received the most recently offered COVID-19 vaccine dose meaning that 9-12 months may have elapsed since they last received a vaccine dose. This cohort will benefit from the added protection of a vaccine dose in spring 2023.

The current recommendations aim to protect those most vulnerable to severe COVID-19 and take into account the existing offers of bivalent booster vaccination to all aged 18 years and older. Vaccination uptake for the primary and first booster dose has been excellent. Notwithstanding the fact that we have among the highest uptake rates in Europe for boosters, uptake rates have declined with each subsequent booster offered. This in part is due to the high levels of intercurrent SARS-CoV-2 infection that necessarily led to deferral of booster uptake but also due to levels of booster fatigue particularly evident in younger people.

This strategy targets spring booster vaccines for those who because of their age, immune status, and/or infection naïve status, are most likely to have suboptimal protection from severe disease. An autumn campaign targeting all at risk of severe COVID-19 is important to minimise the impact of SARS-CoV-2 infection as we enter the respiratory virus season.

The success of vaccination depends heavily on the level of uptake achieved among those for whom COVID-19 vaccines are recommended. A clear communication strategy will be needed. Efforts should be made to identify facilitators and barriers to vaccination so that uptake can be optimised. Concomitant administration of the influenza and COVID-19 vaccines, each vaccine in a separate arm, will reduce the number of health care visits and may facilitate uptake. For those who decline or have a contraindication to an mRNA vaccine, alternates, the protein subunit vaccines are available and access can be facilitated.

SARS-CoV-2 continues to circulate throughout our community. Hospitalisation rates are low in a very large part due to the success of the vaccination campaigns. The virus no longer represents the same threat to those young and healthy with high levels of durable protection from severe disease. For others, continued protection from severe COVID-19 is required and for this additional booster vaccinations are necessary.

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