National Immunisation Advisory Committee

ADDITIONAL COVID-19 BOOSTER VACCINATION

NIAC | 22.07.2022

About NIAC

NIAC membership includes nominees from the RCPI, its Faculties and Institutes, the RCSI, the ICGP, 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 new evidence about vaccines 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.

RECOMMENDATIONS*

1. All those who are unvaccinated or incompletely vaccinated are strongly recommended to complete a primary COVID-19 vaccination course and booster vaccination as outlined in Table 2. Access for hard to reach populations and new arrivals should be facilitated.

2. All those aged 65 years and older and those with immunocompromise at the time of their primary or first booster vaccination and who have not yet availed of the recommended second booster vaccine are strongly recommended to do so.

3. A first mRNA COVID-19 booster vaccine is now recommended for
   - those aged 5 – 11 years with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or additional vaccination

4. A second mRNA COVID-19 booster vaccine is now recommended for
   - those aged 50-64 years
   - those aged 12–49 years who
     - have underlying medical conditions associated with a higher risk of severe COVID-19
     - are residents of long term care facilities

5. A second mRNA COVID-19 booster vaccine is recommended for
   - healthcare workers, and when practicable, should be given at the same time as seasonal influenza vaccine.

6. A third mRNA COVID-19 booster vaccine is recommended for
   - those aged 65 years and older
   - those aged 12 – 64 years with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or booster vaccination

   When practicable, it should be given at the same time as seasonal influenza vaccine.

7. To enhance maternal protection and provide optimal benefit to the infant, an additional mRNA COVID-19 booster vaccine is recommended in pregnancy at 16 weeks gestation or later for those who have not received a booster vaccine in the current pregnancy.

8. mRNA booster vaccines should be given as follows:
   - aged 30 years and older: Comirnaty (0.3ml/30 mcg) or Spikevax (0.25ml/50 mcg)
   - aged 12-29 years: Comirnaty (0.3ml/30 mcg)
   - aged 5-11 years: Comirnaty (0.2ml/10mcg)

9. Following the primary vaccine series or confirmed SARS-CoV-2 infection, a four month interval is recommended for any subsequent COVID-19 vaccine doses. A minimum interval of three months may be exceptionally used.

10. COVID-19 vaccines may be given at the same time or at any interval before or after any vaccine. This includes seasonal influenza and pertussis vaccines.

11. If an mRNA booster vaccine is contraindicated or declined, a non-mRNA vaccine may be given.

These recommendations reflect a dynamic vaccination programme. Scientific evidence is emerging and being refined. Recommendations may be updated when more information becomes available.

*See Table 1

Table 1: NIAC recommendations for COVID-19 vaccines by age and immune status July 2022.

Group		Primary course*	Additional dose	1st booster	2nd booster	3rd booster
65 years and older		√√		√	√	√
50-64 years		√√		√	√	
12-49 years	*Underlying medical conditions*	√√		√	√	
	Residents of long term care facilities	√√		√	√	
	Healthcare workers	√√		√	√	
	Others	√√		√		
Pregnancy		√√		√	√**	
5-11 years		√√				
12 years and older	*Immunocompromise associated with a sub optimal response to vaccines*	√√	√	√	√	√
5-11 years		√√	√	√		

*two dose primary course (one dose if COVID-19 vaccine Janssen)

**at 16 weeks gestation or later if not already boosted in this pregnancy

1. EXECUTIVE SUMMARY

- In Ireland the numbers of confirmed PCR and positive antigen tests have more than trebled since 1 June 2022. By 20 July 2022, the 14-day incidence rate of confirmed COVID-19 cases was 524/100,000. Incidence rates are underestimated.
- Seroprevalence studies in Ireland in 2022 show that, in those aged 50 years and older, seropositivity is predominantly related to vaccination. In those aged 18-49 years, seropositivity is mainly the result of a combination of vaccination and infection (i.e., hybrid immunity).
- Over 65% of COVID-19 hospitalisations are in those aged 55 years and older.
- Of COVID-19 hospitalisations, as of 19 July 2022, 43% were admitted because of COVID-19 disease.
- There is no evidence of increased disease severity, although limited preclinical data suggests this may be the case. However, as case numbers have increased, more severe disease is seen in older age cohorts and those with risk factors for severe COVID-19.
- While pregnancy is a risk factor for severe outcomes, the risk for severe maternal COVID-19 due to Omicron has been less in those vaccinated; however, hospitalisations of infants have increased. Vaccination in pregnancy can enhance maternal protection and optimise protection of the infant.
- In Ireland, 72% of those aged 12 years and older have received one booster (99% of those aged 65 years and older, 77% of those 18 years and older and 25% of those aged 12-17 years). However, only 58% of those aged 65 years and older have received a second booster.
- Those who are unvaccinated or have not completed their primary vaccination course are disproportionally represented in hospitalisations, accounting for over one third of those hospitalised because of COVID-19. Over half of those hospitalised because of COVID-19 have not received a first booster vaccine.
- COVID-19 vaccines effectively reduce COVID-19 hospitalisations, severe disease and death.
- Waning protection and emergence of immune evasive variants resulted in the need for a first booster to increase protection against severe disease and death. However waning protection against infection and symptomatic disease occurs quite rapidly, with some reduction in protection against severe disease. Data on vaccine effectiveness (VE) beyond six months following boosters are not available.
- First booster doses of mRNA vaccines have not shown any unexpected safety concerns. Myocarditis and pericarditis are very rare risks of mRNA vaccination, predominantly in males aged under 30 years after the second dose of the primary vaccination course. The risk is comparatively lower following a first booster dose and in children aged 5-11 years. Data on additional boosters is limited but no unanticipated safety concerns have been identified.
- Omicron BA.4 and BA.5 are less efficiently neutralised by sera from those vaccinated with three doses of COVID-19 vaccine or by sera from those with breakthrough BA.1 or BA.2 infection.
- Immunity following infection may be more durable than after vaccination. However, waning occurs and is boosted by vaccination.

- Hybrid immunity resulting from infection and booster vaccination confers stronger protection than infection alone.
- The World Health Organization (WHO) has stated that an increase in SARS-CoV-2 infections in autumn/winter is likely, due to the combination of waning immunity, seasonality, increase in travel and social mixing. This, together with an anticipated increase in influenza as seen in Australia, poses a significant threat to both individuals and to health care systems.
- An additional booster now may enhance protection of those most at risk of severe disease outcomes. For those receiving their second booster now, the need for a third booster during the winter will be reviewed.
- For healthy people aged 12 to 49 years, evidence indicates that a second booster is not yet needed to sustain protection against severe disease outcomes. The need for a second booster during the winter will be reviewed.
- There is some evidence that a second booster dose may reduce infection rates. This could benefit healthcare workers (HCWs) and help sustain the healthcare system.
- Authorised vaccines are effective against severe disease including that caused by Omicron.
- Variant-adapted booster vaccines which may induce a higher and broader immune response against SARS-CoV-2 are under evaluation.

NIAC will continue to examine new evidence regarding booster vaccination and the role of adapted vaccines.

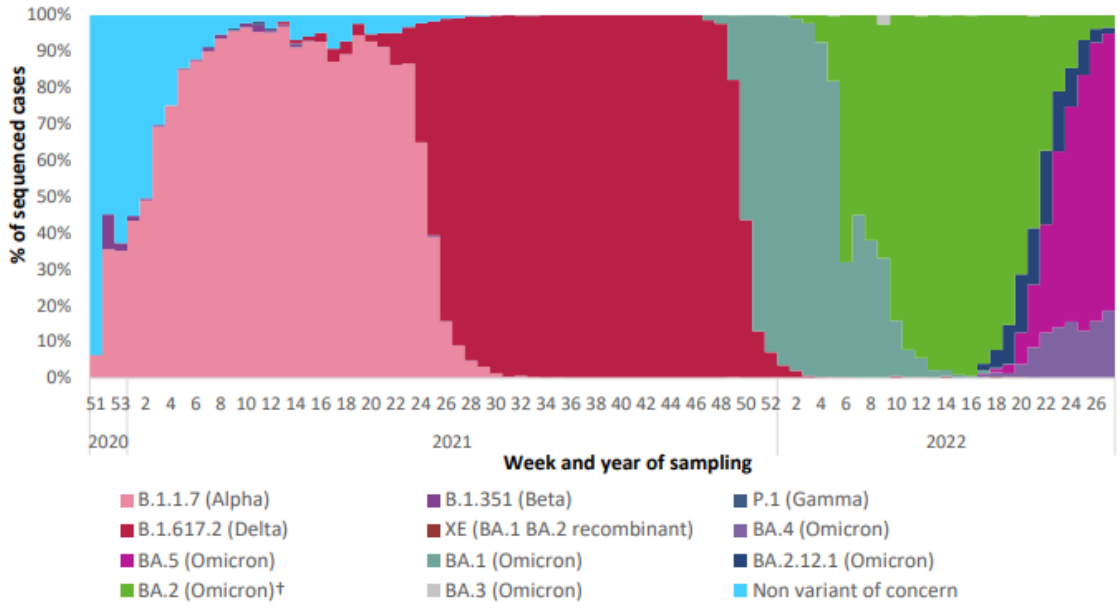
2. INTRODUCTION

Ireland entered its fifth COVID-19 pandemic wave in December 2021, despite a high uptake of the primary vaccine series and first booster. The arrival of further Omicron variants BA 2.12.1, BA.4 and BA.5 is aggravating the current situation as they are readily transmissible and are the most immune variants evasive to-date. An autumn/winter surge in infections is anticipated and although the majority of infections are likely to be mild, consideration must be given to the use of additional booster vaccination to protect the most vulnerable and the health care system. It is not known if SARS-CoV-2 will ultimately behave like other seasonal respiratory viruses, with need for a regular autumn booster as for influenza virus.

3. COVID-19 EPIDEMIOLOGY IN IRELAND

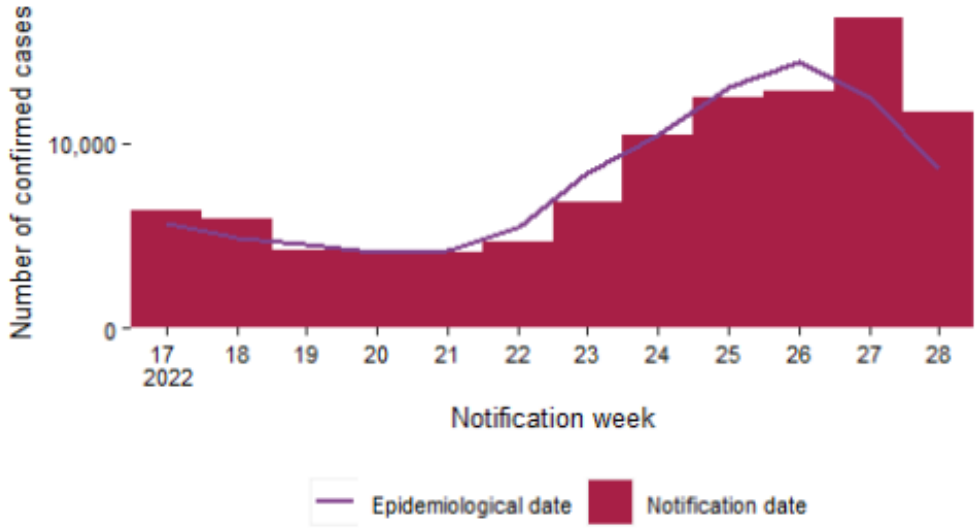
At the start of 2022, BA.1 was the dominant Omicron sublineage. It was replaced by BA.2. Since mid April the number of cases of BA.5, BA.4 and BA2.12.1 has increased rapidly with BA.5 and BA.4 now causing 95% of all cases. (Figure 1)[1]

Figure 1: Percentage of sequenced specimens by variant of concern or interest, specimen collection dates from 13 December 2021 to 4 July 2022. Source: HPSC.[1]



Between 10-16 July 2022, there were 11,675 new confirmed COVID-19 cases, a decrease of 30.5% from the previous week. (Figure 2)[2] Test positivity was 33% compared to 37% the previous week. The 14 day rate increased to 587/100,000 by 5 July.[3]

Figure 2: Number of confirmed COVID-19 cases by notification week and epidemiological date week 17 (25 April-1 May) – week 28 (10-16 July) 2022. Source: HPSC.[2]



A total of 13,689 were registered between 10-16 July 2022, a decrease of 32% from the previous week. The number of cases is likely to be underestimated due to the change in testing policy.

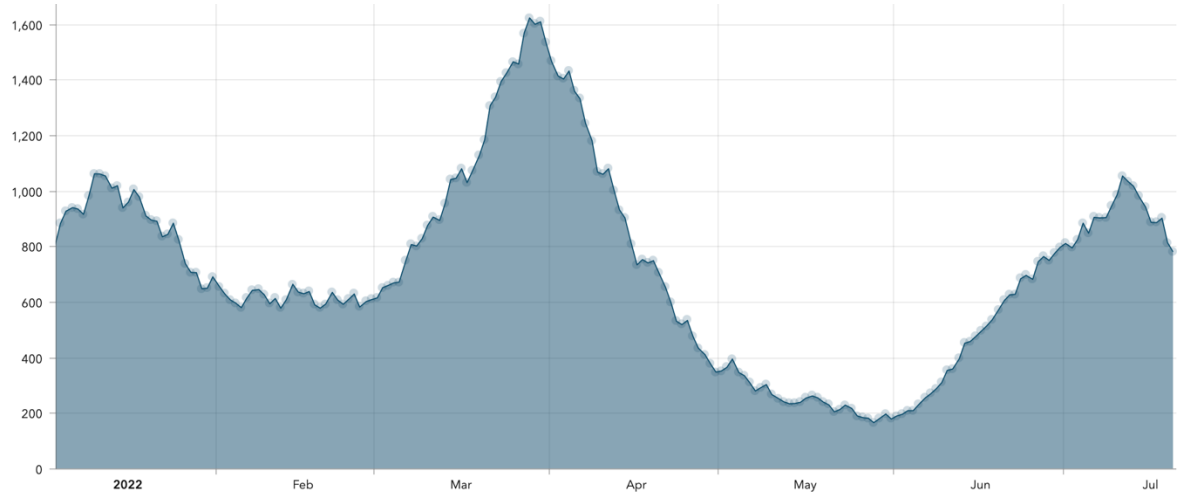
Since the start of wave 5, the National Surveillance Programme has detected SARS-CoV-2 in almost all specimens from 68 wastewater catchment areas across the country which cover 80% of the population connected to public wastewater treatment facilities, indicating high levels of community infection.[4]

In addition, the overall seroprevalence of SARS-CoV-2 from specimens collected between 30 January – 19 February 2022 in those aged 18 years and older was 96.5% (95% CI 95.2-97.5).[5] Serological results indicative of previous infection showed a seropositivity rate of 34% (95% CI 31.8-36.8). This was highest in the 18-29 year age group at 51% (95% CI 44.7-57.3), and lowest in the 70-79 age group at 14% (95% CI 8.8-1.1). National COVID-19 vaccination uptake rates show that adults aged 18-49 years had higher seroprevalence rates than vaccination uptake rates. Adults aged over 50 years had seroprevalence rates equal to or lower than vaccination rates.

For the period 3-10 July 2022, the overall seroprevalence in residual blood samples from the Irish Blood Transfusion Board, generally representing a select healthy younger population, was 100%. In 78%, serological results were indicative of prior infection, with or without vaccination.[6]

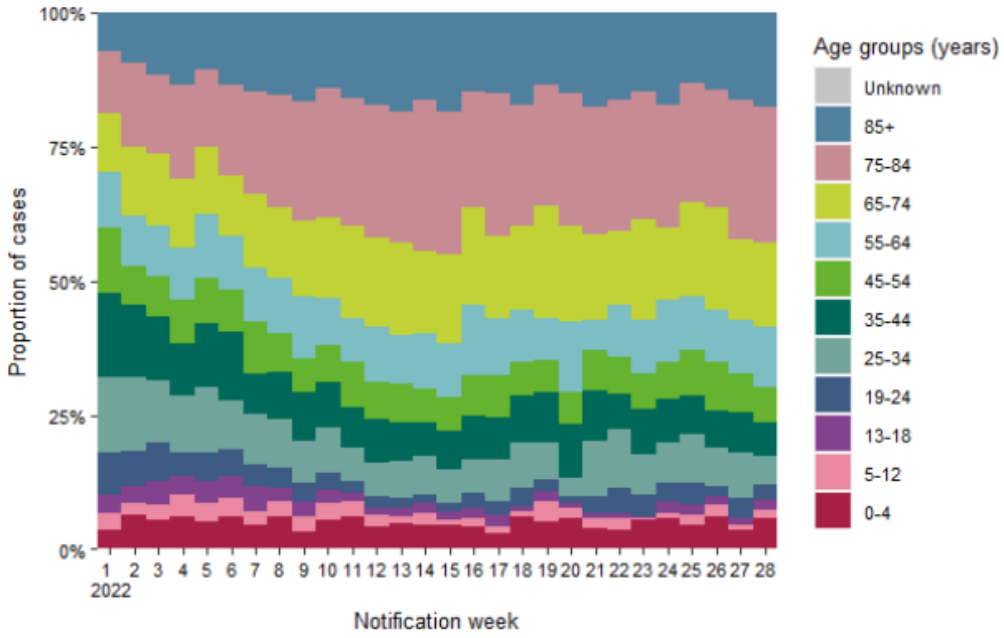
Approximately 1 in 15 confirmed COVID-19 cases were hospitalised from 1 April to 12 July 2022. (Figure 3)

Figure 3: Number of confirmed cases in hospital Wave 5, updated 14 July 2022. Source: COVID data hub, accessed 20 July 2022.



Most hospitalised cases are in those aged 55 years and older (88%). (Figure 4)

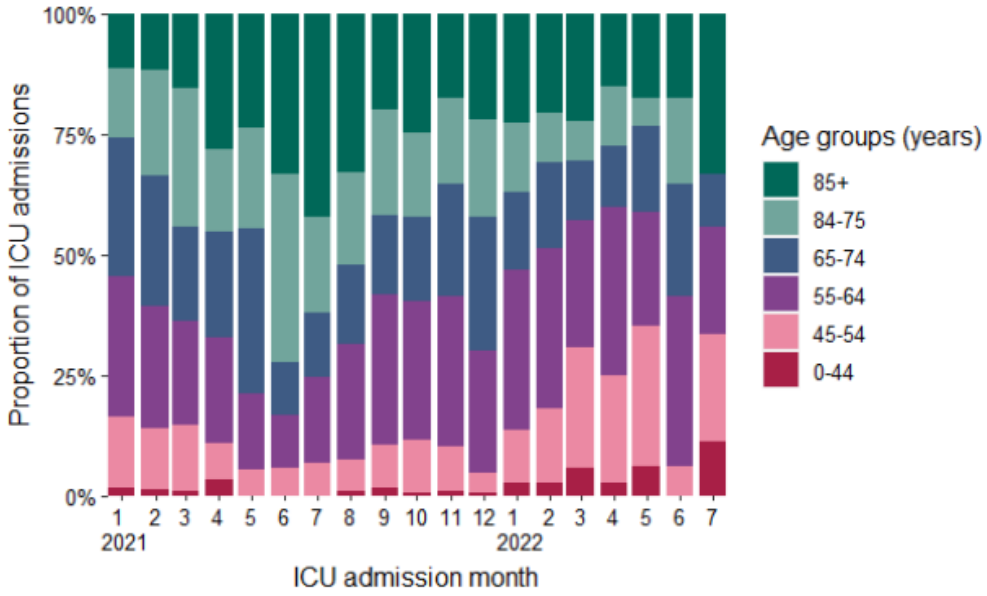
Figure 4: Age distribution of those in hospital with COVID-19* notified on CIDR in Ireland between week 1 (3-9 January) and week 28 (10-16 July), 2022. Source: HPSC.[2]



*The number of cases includes those admitted *with* COVID-19 and those admitted *because of* COVID-19 disease.

Although the numbers admitted to ICU remain low (0.05% of confirmed cases), the age profile in this wave has changed with a large majority aged 55 years and older (Figure 5), and with 85% having one or more underlying medical condition.

Figure 5: Age distribution of those with COVID-19 admitted to ICU by month of admission January 2021 – July 2022. Source: HPSC.[2]



4. CLINICAL FEATURES

Omicron BA.1 infection was generally associated with a lower risk of severe disease than infection with earlier variants. Some differences in the symptoms of Omicron compared with earlier variants have been reported. Loss of taste and smell were less commonly reported with Omicron BA.1/BA.2 and some reduction in reported shortness of breath, myalgia and fatigue while sore throat was more commonly reported.[8,9]

Omicron BA.4 and BA.5 were first reported from South Africa in April 2022 and have since been detected in many more countries, replacing BA.2 as the dominant strain. This has been associated with an increase in COVID-19 related hospitalisations.[10]

Portugal saw the first surge in cases of BA.4 and BA.5 in Europe and reported an increase in hospitalisations and ICU admissions mainly in those aged 60 years and older.[11] The European Centre for Disease Prevention and Control (ECDC) has noted many countries reporting an increasing trend in hospitalisations and anticipate that this may result in more ICU admissions and deaths.[12] The age distribution may vary depending on the demographics in each country.

On 12 May 2022, ECDC reclassified Omicron sub-lineages BA.4 and BA.5 from variants of interest to variants of concern.

Preclinical data suggest that Omicron BA.5 may have greater potential for invasion of alveolar cells with more severe disease than BA1 or BA.2.[13] There is however no evidence of increased infection severity of BA.4 and BA.5 compared to BA.1 and BA.2. Higher hospitalisations rates are likely due to the increased case numbers but increasing infection rates in older age cohorts and those at higher risk can be anticipated.

Omicron and its sublineages continues to pose the biggest risk to those aged 50 years and older, those with immunocompromise associated with a sub optimal response to vaccines, and those with underlying medical conditions that place them at high risk for severe COVID-19. Age remains the dominant risk factor for hospitalisation with COVID-19.

Underlying medical conditions

Patients with immunocompromise have a weaker initial immune response to vaccination and more rapid waning of vaccine associated protection against severe outcomes than other patients.[14,15]

Antibody levels decline more rapidly in those who have severe obesity (BMI > 40 kg/m^2). Levels are increased following a booster dose but decline more rapidly compared with normal weight controls.[16]

While there is no evidence the antibody levels wane more rapidly in patients with other comorbidities, their risk for severe disease in the event of developing a breakthrough infection is likely greater. In one Swedish study comorbidity increased the risk of severe disease in those vaccinated aged 40 years and older.[17] There is little information regarding risks of severe disease in vaccinated younger patients with comorbidities however booster vaccination may provide additional protection.

Pregnancy and the newborn

Pregnancy is a risk factor for severe outcomes related to COVID-19. Omicron has been associated with increased rates of infection, with most of the severe disease occurring in the unvaccinated population.

Infants aged under one year are at increased risk of hospitalisation and severe outcomes with COVID-19.[18] Most neonatal infections occur in infants of unvaccinated mothers. The long term risks of neonatal infection are unknown.

5. COVID-19 VACCINATION PROGRAMME IN IRELAND

The recommended number of doses of COVID-19 vaccine depends on age and immune status. (Table 2)

Table 2: Number of COVID-19 vaccine doses currently recommended by age group and immune status since April 2022. Source: Immunisation Guidelines for Ireland.

Age group	Immunocompetent	Immunocompromise associated with a sub optimal response to vaccines
65 years and older	4 doses (Primary course +1st booster + 2nd booster)	5 doses (Primary course + additional dose + 1st booster + 2nd booster)
12-64 years	3 doses* (Primary course + 1st booster)	
5-11 years	2 doses (Primary course)	3 doses (Primary course + additional dose)

*2 doses if COVID-19 vaccine Janssen given as the primary vaccine

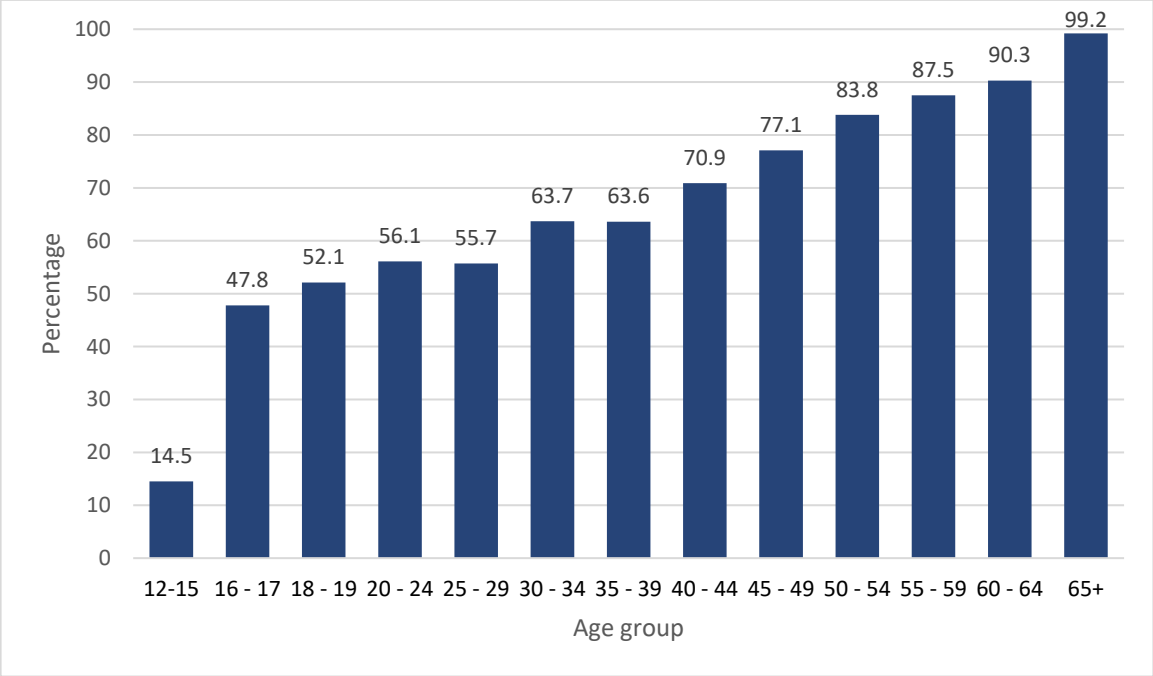
By 26 June 2022, over 95% of adults had completed a primary vaccination course. (Table 3)

Table 3: Percentage of completed primary course of COVID-19 vaccine by age group. Source: HPSC.

Age (years)	Vaccine uptake
18 and older	95.7%
12-17	74.3%
5-11	23.1%

Almost 72% of those aged 12 years and older have received one booster, 77% of those 18 years and older and 25% of those aged 12-17 years. Vaccination uptake rates increase with age, with over 99% of those aged 65 and older having completed a primary course and first booster vaccination. (Figure 6)

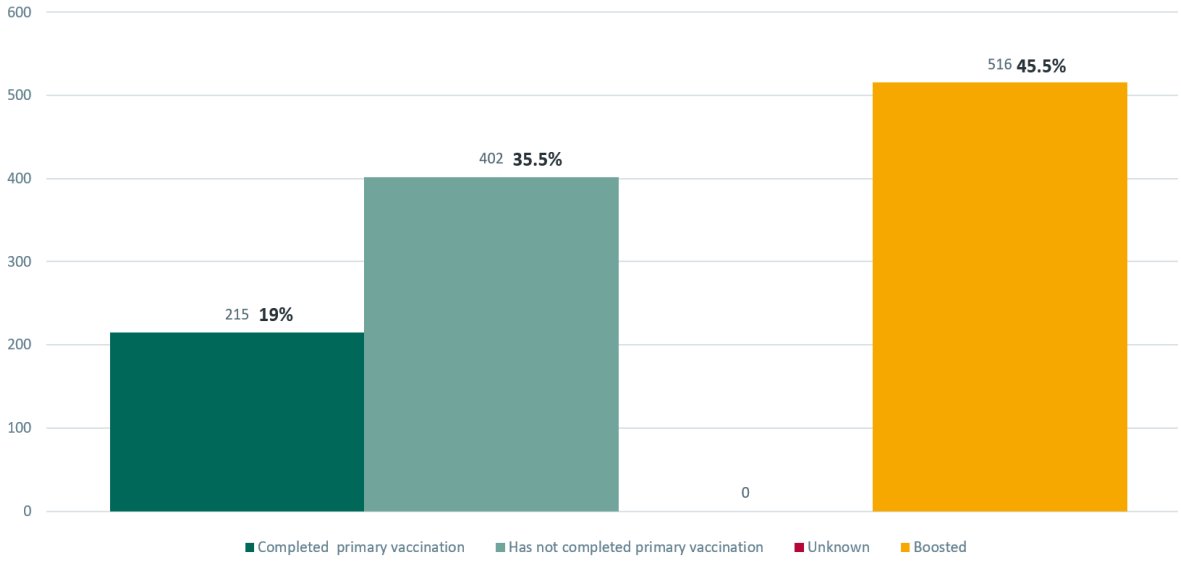
Figure 6: Percentage COVID-19 first booster vaccination uptake of eligible population by age group. 11 July 2022. Source: HPSC.



However, only 58% of those aged 65 years and older have availed of a second booster.[19]

Those who are unvaccinated or have not completed their primary vaccination course continue to be disproportionally represented in hospitalisations and account for over one third of those hospitalised because of COVID-19. More than half of COVID-19 hospitalisations have not received a first booster vaccine. (Figure 7)

Figure 7: Vaccination status of COVID-19 hospitalisations 19 July 2022. Source: HSE.



6. COVID-19 mRNA BOOSTER VACCINATION

Authorised COVID-19 vaccines are very effective in protecting against serious outcomes of COVID-19. The mRNA vaccines have been the backbone of the COVID-19 vaccination programme. They are effective both in primary vaccination and when used as a booster vaccine in both homologous and heterologous schedules[20,21] and following either an adenoviral vector or mRNA vaccine in the primary series.[22]

Vaccine safety

First booster doses of mRNA vaccines have not shown any unexpected short term safety concerns.[21] Myocarditis and pericarditis are very rare risks of mRNA vaccination, predominantly in males aged under 30 years after the second dose of the primary vaccination course. The risk is comparatively lower following a first booster dose and in children aged 5-11 years.

Data on second booster doses is more limited, but no unanticipated safety concerns have been identified.[23,24] In a COV-Boost sub study focussed on the safety and reactogenicity of a fourth dose given 6.8 months after the third dose, the fourth dose was well tolerated and no new concerns identified.[25] Pain, fatigue, malaise and headache, generally mild to moderate in severity were the most commonly reported local side effect. In other studies the safety profiles of Comirnaty[23] and Spikevax as a second booster dose were similar to those following a first booster dose.[26] There is no data yet pertaining to subsequent boosters.

Immunogenicity of vaccines

The mRNA vaccines are highly immunogenic against the ancestral SARS-CoV-2 strain and early variants. Protection against infection correlates with levels of neutralising antibody. Other immune responses, including cellular immunity, are important in preventing progression from asymptomatic to severe disease. CD4 and CD8 T-cell responses do not correlate well with neutralising activity but are better preserved and more durable.[27,28] This may in part explain why protection is best preserved for the most severe outcomes, even when protection against infection is reduced.

Omicron BA.1 and BA.2 are associated with increased transmissibility and reduction in vaccine induced neutralising activity, but protection against severe outcomes was preserved.[29] The BA.4 and BA.5 variants have an even greater capacity for escape from vaccine induced neutralising activity, even in those boosted by vaccine or prior infection.[30-32] Booster vaccination increases neutralising activity in the short term.[24,33,34] However waning antibody levels post booster vaccination occurs.[35]

Peak responses after a second booster (fourth dose) were similar or higher than peak responses after the third dose.[24,25] Fourth doses given 201 to 212 days (median 209 days) following a third

dose were well tolerated and boosted cellular and humoral immunity.[25] Giving a booster with an authorised vaccine markedly increases neutralising antibody titres against BA.1, BA.2, BA.2.12.1, and to a lesser degree against BA.4/5.[32,36] Compared with the ancestral strain, reduction in potency against the BA 4/5 strains was markedly less following a booster dose than following the primary vaccine series.[36] Boosting with currently authorised vaccines will likely provide sufficient protection against Omicron-induced severe disease.[36]

Administration of booster vaccines in pregnancy is associated with an increase in antibody titres both in maternal and cord blood and can provide heightened protection for both mother and infant.[37] COVID-19 mRNA boosters are well tolerated and boost cellular and humoral immunity.[25] Neutralising antibody titres against Omicron are significantly higher following boosting, although reduced compared to those against earlier variants.[37,38]

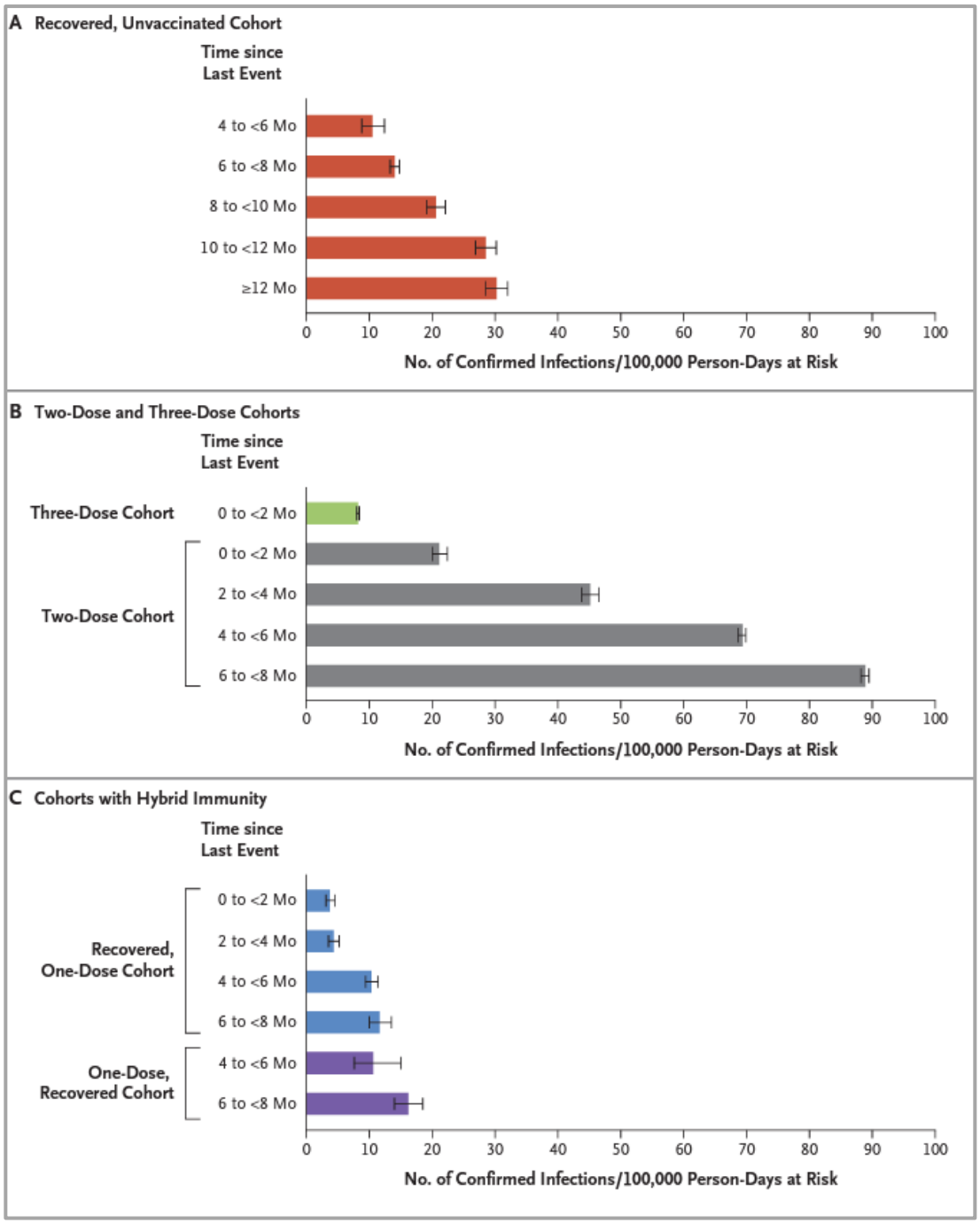
Hybrid immunity

The combination of vaccination and infection can result in greater immunogenicity with higher antibody levels with greater durability and wider breadth of protection than that afforded by either alone.[39-42]

A Qatari study reported similar levels of protection against symptomatic BA.1 and BA.2 following prior infection, vaccination or hybrid immunity. Vaccination enhanced protection in those who had a previous infection. Hybrid immunity resulting from previous infection and then booster vaccination conferred the strongest protection. High protection against severe or fatal COVID-19 was maintained even in two dose recipients, most of whom received the vaccine up to eight months earlier. However, the study cohort was young (median age 32 years (IQR 22-42)) so this may not be generalisable to other age groups or where BA.5 is dominant.[41]

Although protection from hybrid immunity may be more durable than that following vaccination alone, waning also occurs and can be boosted by a further vaccine dose. (Figure 8)[39,40]

Figure 8: Estimated Covariate adjusted rates of infection/100,000 persons days at risk. Source: Goldberg et al.[40]



Vaccine effectiveness

The level of protection afforded by vaccination is influenced by host factors (e.g., age, immune status, underlying medical conditions), time since vaccination, and the circulation of immune evasive variants. Recommendations regarding the frequency and timing of boosters depend on local epidemiology, host factors, circulating strain characteristics and booster effectiveness.

Waning protection following the primary vaccine series and emergence of immune evasive variants resulted in the need for a first booster vaccine. This provided additional strong protection against serious disease and death[29,41,43,44] at least in the short term. Data on booster vaccine effectiveness beyond six months are not available.

Immunity following SARS-CoV-2 infection also wanes over time and can be boosted by vaccination.[39,40]

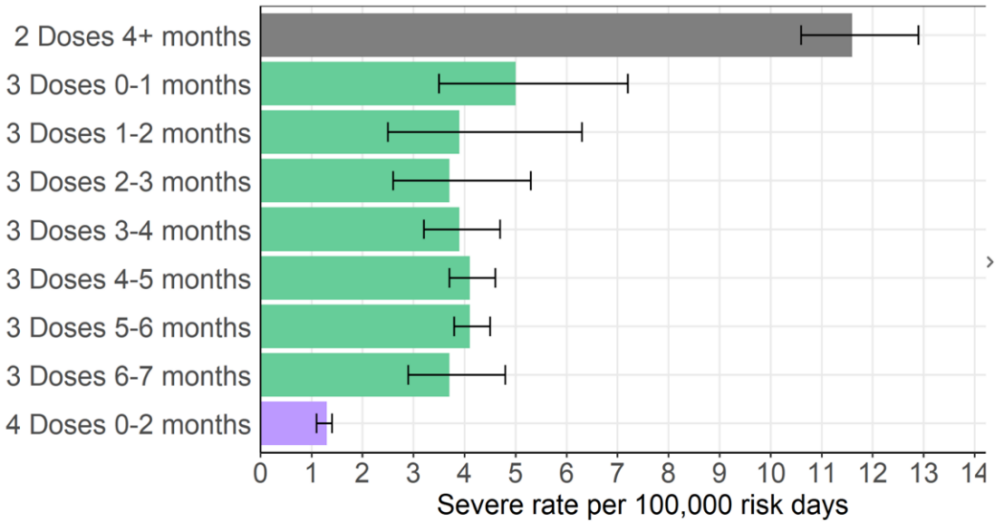
Although vaccination induced neutralising activity is significantly reduced against Omicron compared with earlier variants and protection against infection and symptomatic disease wanes rapidly, protection against hospitalisation, serious disease and death is sustained in most immunocompetent people.[15] However, there is some evidence of waning protection against severe disease particularly in higher risk groups. Restoration of high levels of protection can be achieved by booster vaccination.[45]

Booster vaccination with mRNA vaccines provides significant protection against hospitalisation and death in breakthrough Omicron infections.[46] However, rapid and significant rates of decline of antibodies against Omicron following booster vaccination have been reported.[47,48] At 120 days following a first booster, median anti-spike IgG levels declined by 45% for antibodies against the Wuhan strain, 59% against Delta and 65% against Omicron compared to day 7 post-booster IgG levels,[49] indicating a lower level of protection against infection.[49]

Analysis of outcomes among COVID-19 cases who had received a first booster dose showed hospitalisation and death were rare (0.6% and 0.1% respectively).[50] However, these risks are higher in those who received the first booster dose more than three months previously, those aged 60 years and older, and males.

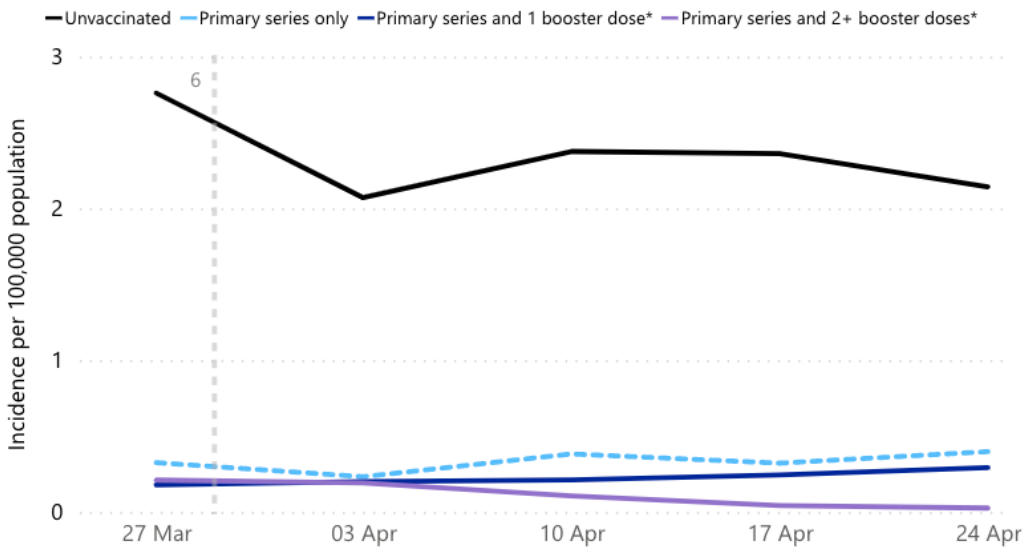
A second booster or fourth vaccine dose can enhance protection, at least in the short term. [43,51,52,53] For those aged 60 years and older there was a halving of the infection rate and a four fold reduction in severe COVID-19. Protection against infection waned, however protection against severe disease was sustained over the study period.[53] In a population based study of more than 500,000 people, 58% of whom received a second booster dose, VE against death over the 40 day study period was 88% compared to those with three doses only.[54] An observational study during Israel's fifth wave found that, in those aged 60 years and older protection against Omicron infection following a third vaccine dose was substantially lower than against Delta and waned quickly. Effectiveness against severe disease appeared to wane over a 7-month period. A fourth dose (second booster) provided additional protection. (Figure 9)[55]

Figure 9: Adjusted rates of severe illness per 100,000 risk days for the study period 1 January 2022 to 12 March 2022, adjusted for a category (60 – 69, 70 – 79, 80+), gender, sector and exposure (based on epidemiological week). Source: Amir et al.[55]



In the US in April 2022, in those aged 50 years and older, unvaccinated people had 42 times the risk of dying from COVID-19 compared to those fully vaccinated and up to date with recommended boosters (one or two doses); those fully vaccinated plus one booster had four times the risk of dying from COVID-19 compared to those fully vaccinated and with two or more booster doses. (Figure 10)[56]

Figure 10: Rate of COVID-19 deaths by vaccination status in those aged 50 years and older in 18 US jurisdictions, 27 March – 30 April 2022. Source: CDC.[56]



In the US in those aged 50 years and older the fourth vaccine dose given 120 days or more after the third dose improved VE during the BA.2/BA.2.12.1 period although follow-up time after dose four was limited. Vaccine effectiveness against COVID-19–associated hospitalisation was 55% more than 4 months after a booster (third dose) and increased to 80% more than a week after the fourth dose.[57]

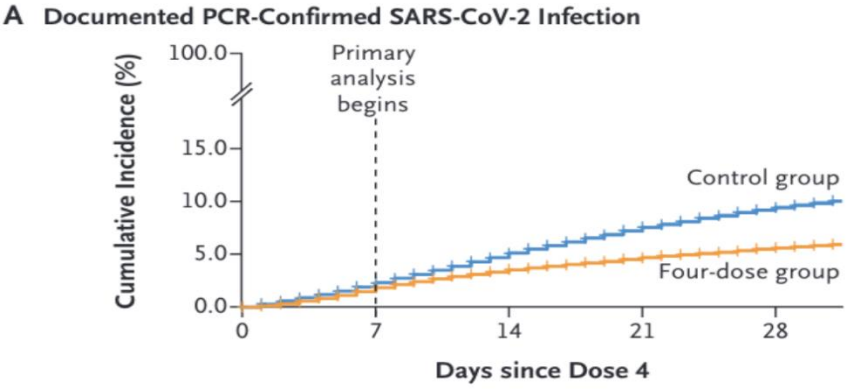
Some other countries including Ireland have introduced a second booster with age cut offs ranging from 50 to 80 years. There are early indications of waning of protection in older age cohorts even after that second booster dose. In Sweden in a population based study of all cause mortality in those aged 80 years an older during the Omicron period, there was significant benefit from a fourth compared to a third dose. There was some evidence of slight waning of protection from two months, indicating that further boosting might be necessary to sustain protection.[58]

Impact of second booster on infection

There is evidence on the short term benefit of a second booster in reducing infection rates. In recently boosted (median 20 days, IQR 14-31 days) healthy young adults (median 30 years, IQR 25-39 years) booster vaccination compared to the primary series was associated with a significant reduction in incident infections during the study period (45 days),[59] confirming the potential for vaccination to impact on infection rates at least in the short term.

In Israel, the impact of a second compared to a first booster given four months earlier was seen with almost halving of the risk of infection from around day 14 to day 30 following the second booster. Subsequent follow up data is not yet available. (Figure 11)[52]

Figure 11: Documented PCR-Confirmed SARS-CoV-2 Infection; Four dose (second booster) compared with Three dose (first booster). Source: Magen et al.[52]



No. at Risk					
Control group	182,122	138,003	113,810	99,706	87,330
Four-dose group	182,122	138,931	116,323	103,937	92,513
Cumulative No. of Events					
Control group	0	3,643	7,192	9,902	11,836
Four-dose group	0	2,838	5,008	6,323	7,269

In HCWs, a second booster or fourth mRNA vaccine dose increased neutralising antibody titres, slightly higher than those achieved after the previous dose and resulted in reduced infection rates compared to that observed after a first booster dose.[24]

For those aged under 50 years and healthy, evidence indicates that a second booster is not yet needed to sustain protection against severe disease outcomes, and that the benefit in reducing infection may be likely small and possibly short lived, however the short to medium term benefits in preventing infection warrants its consideration for HCWs.

Booster vaccination: interval

The optimal interval between first and second booster dose is influenced by the urgency to optimise protection maximising the immune response, and minimising risks.

A longer interval between doses may enhance immunogenicity.[25,60,61] Extending the interval to maximise the immune response must be balanced against the need to restore waning protection. Booster doses have been recommended in different countries after minimum intervals of two to six months with most safety data relating to intervals of at least four months. Strong protection following a first booster vaccination is generally sustained for at least three months and longer in healthy young cohorts,[29] with some evidence of waning against infection after three to four months.

To minimise vaccine errors due to different intervals between the primary series and additional or booster vaccines, a four month interval is recommended for any subsequent COVID-19 vaccine doses. A minimum interval of three months may be exceptionally used.

A four month interval is also recommended for any subsequent COVID-19 vaccine doses after confirmed SARS-CoV-2 infection. A minimum interval of three months may be exceptionally used.

Booster vaccination: timing in pregnancy

Booster vaccination in pregnancy is associated with with a reduced risk of hospitalisation for the mother and infant under six months of age because of COVID-19, including for critical illness.[62] The importance of transplacental antibodies in protecting against severe disease with other pathogens e.g., pertussis, respiratory syncytial virus and varicella zoster virus is known. Vaccination in pregnancy can protect infants too young for vaccination.[38]

It is very important for any unvaccinated pregnant woman to receive the primary series and first booster at the earliest opportunity to ensure their own protection and reduce risks for their infant.

While the optimal timing of a COVID-19 booster in pregnancy has not been defined, the timing selected is a balance between aiming for peak antibody levels at the time of delivery and ensuring protective levels for infants born early. COVID-19 vaccines are safe at any time in pregnancy. The

addition of a further vaccine in pregnancy at 16 weeks gestation or later with a minimum interval of four months since their last booster vaccine or confirmed infection can significantly enhance protection of the mother and optimise protection for the infant.

Co-administration

A recent US study[63] of self reported adverse events indicated that respondents who received co-administration of an mRNA COVID-19 booster with an influenza vaccine were more likely to report systemic reactions in the week following vaccination than respondents who received COVID-19 mRNA booster alone. In both groups, most reactions reported in the week following vaccination were generally mild. The most frequently reported systemic reactions with vaccine co-administration were fatigue, headache, and myalgia. Local reactogenicity was predominantly pain at the injection site.

Results from the UK ComFluCOV study showed that administering an influenza vaccine at the same time as a second dose of a COVID-19 vaccine produced no safety concerns and preserved the immune response to both vaccines.

In keeping with international recommendations, NIAC continues to recommend co-administration of both vaccines to maximise uptake. Vaccinees should be informed there may be a slight increase in short term mild adverse events after co-administration.

Adapted vaccines

Preliminary data indicate that adapted bivalent mRNA vaccines, which incorporate an Omicron variant strain, when used as a booster could increase and extend the breadth of protection. The EMA has started a rolling review of adapted vaccines which may provide better protection against variants of SARS-CoV-2, including BA.4 and BA.5. It is unclear if the adapted vaccines based on BA.1 will show superior efficacy against current circulating variants. Boosting using currently authorised COVID-19 vaccines will provide sufficient protection against Omicron induced severe disease.

7. INTERNATIONAL RECOMMENDATIONS

WHO ETAGE[64]	Consider a second booster dose for
	
	• moderately and severely immunocompromised individuals aged 5 years and above and their close contacts
	• as a precautionary measure for
	  ○ residents and staff of long-term care facilities
	  ○ older adults (age specific cut-off should be defined by countries based on local COVID-19 epidemiology)
	  ○ health care workers
	  ○ pregnant women
	  ○ other patient groups at high risk of severe COVID-19 outcomes defined by countries based on local COVID-19 epidemiology
	
	Consider co-administration of COVID-19 vaccines and seasonal influenza vaccines, whenever feasible.

EU/EMA[50]	An early second booster rollout should now be considered to prevent severe disease and safeguard health system capacity, and countries should consider a rapid deployment for • those aged 80 years and above • adults between the ages of 60 and 79 years • medically vulnerable individuals regardless of age Early administration of a second booster dose in healthcare workers and people working in long-term care facilities is likely to offer only modest benefits in terms of limiting the risks of transmission to vulnerable people in their care, and be of limited duration. There is no clear epidemiological evidence to support a second booster dose in immunocompetent individuals below 60 years of age. Consider the need for rollout of further additional booster doses of mRNA vaccines for population groups at risk of severe disease later in the year, possibly combining campaigns for vaccination against COVID-19 and influenza e.g., • aged 60 years and older. • with underlying comorbidities, • immunocompromised individuals • pregnant women

	The boosting of HCW and LTCF personnel should also be considered for this later rollout.
Belgium[50]	An additional booster for • adults 65 years of age and older • any patient with immune suppression due to disease or treatment • any patient with at least one comorbidity • all pregnant women all 'persons active in the care sector' in and outside care institutions people living in the same household as people at high risk of severe disease
Denmark[50]	An autumn vaccination campaign for • residents in LTCF • other vulnerable elderly people. From 1 October 2022, • all individuals over 50 years of age • those who are severely immunocompromised (regardless of age) Final recommendations are expected in August.
France[50]	An autumn vaccination booster campaign combined with the influenza vaccination campaign for • those aged 65 years and older • those who are immunocompromised • those with comorbidities Consideration of vaccination of healthcare professionals.
Portugal[50]	A booster of COVID-19 vaccine will be given to: • nursing home residents • people aged 65 and over • people aged 18 years and over with comorbidities that have a risk for COVID-19 • healthcare and nursing home professionals. The inclusion of other priority groups is under discussion.
Sweden[50]	An additional booster is recommended • for adults aged 65 years or over • people aged 18 or over who are in an at-risk group including among others pregnant women, people with weakened immune systems, people with heart and lung disease

	For adults 18-64 years of age, the recommendation remains for one booster dose, however anyone can take a second booster in this age group if they request it.
UK[65]	A further dose is recommended for • all adults aged 50 years and over • those aged 5 to 49 years in a clinical risk group, including pregnant women • those aged 5 to 49 years who are household contacts of people with immunosuppression • those aged 16 to 49 years who are carers • residents in a care home for older adults and staff working in care homes for older adults • frontline health and social care workers
USA[66]	A second booster using an mRNA COVID-19 vaccine is recommended in the following populations: • People ages 50 years and older who received an initial COVID-19 booster dose (regardless of which vaccine was used) at least 4 months ago • People ages 12 years and older who are moderately or severely immunocompromised who received an initial COVID-19 booster dose (regardless of which vaccine was used) at least 4 months ago • People ages 18 years and older who received both a primary dose and an initial booster dose of J&J/Janssen COVID-19 vaccine at least 4 months ago
Canada[67]	A COVID-19 vaccine booster dose, regardless of the number of booster doses previously received) should be offered to: • Older adults (≥65 years of age) • Residents of long-term care facilities or congregate living settings for seniors • Individuals 12 years of age and older with an underlying medical condition that places them at high risk of severe COVID-19 • Adults in or from First Nations, Métis, or Inuit communities, where infection can have disproportionate consequences • Adults in racialised communities and marginalized communities (e.g., people living with disabilities) disproportionately affected by COVID-19, • Residents of other congregate living settings (e.g., quarters for migrant workers, shelters, correctional facilities, group homes) who are 12 years of age and older All other individuals 12 to 64 years of age may be offered a COVID-19 booster dose in Autumn 2022, regardless of the number of booster doses previously received

Australia[68]	A winter booster vaccine is recommended for • adults aged 65 years or older • adults aged 50 to 64 years (added July 2022) • residents of aged care or disability care facilities • Aboriginal and Torres Strait Islander people aged 50 years or older • people who are severely immunocompromised (this will be their fifth dose) • people aged 16 years or older with a medical condition that increases the risk of severe COVID-19 illness

8. DISCUSSION

As the Omicron BA.1 and BA.2 waves swept through Europe and abroad, notwithstanding evidence suggesting associated decrease in disease severity, the increase in case numbers and resultant increased hospitalisations for those in higher risk groups prompted a number of countries to recommend a second booster for those most at risk of severe infection. In Ireland a second booster was recommended for those aged 65 years and older and those with with immunocompromise associated with a suboptimal response to vaccines. Uptake of the second booster however has been relatively low compared to the first booster.

The arrival of Omicron BA.4, BA.5 and associated sublineages has led to further increase in cases, hospitalisations and deaths. In Ireland the vast majority of cases (70-80%) are in those aged 50 years and older. Less than half of hospitalised cases have availed of a first booster, while one third have not completed their primary vaccination. The greatest beneficial impact on hospitalisations, severe disease and death is afforded by ensuring all those eligible are fully vaccinated and have received a first booster.

A key imperative to combat the negative impact of the Omicron and future SARS-CoV-2 waves is to maximise the uptake of the primary series and first booster, i.e., three doses for all and four doses for those with immunocompromise. The first booster has been recommended for all those aged 12 years and older and should be availed of. A second booster (dose 4 for the immunocompetent or dose 5 for those with immunocompromise) is recommended for those aged 65 years and older and those with immunocompromise since 5 April 2022. Those who have received an offer of a second booster should take it now without further delay.

SARS-CoV-2 infection induces some protection that can be more durable than that following vaccination. Immunity is not always cross protective e.g., prior infection with Omicron BA.1 or BA.2 provides little protection against Omicron BA.4 or BA.5 infection. Vaccination following infection resulting in hybrid immunity can significantly enhance protection.

BA.4 and BA.5 are the most immune evasive variants to date. Protection against infection even after a first booster can wane relatively rapidly. Waning against more severe outcomes is more nuanced. For older age cohorts and those with immunecompromise, a longer interval from a booster is associated with some increased risk of infection and severe disease. For younger healthy age groups protection against hospitalisation, severe disease, and death is sustained at least for many months. Most data relates to the initial phase of Omicron and before the arrival of BA.4 and BA.5. Data for more than six months following booster is not yet available.

In general, authorised COVID-19 vaccines do not afford sustained protection against infection. Some reduction in infection rates can be achieved by booster vaccination, at least in the short to medium term. Rates of infection in young healthy adults were decreased following booster vaccination compared to those unboosted. In HCWs, a second booster dose was immunogenic and afforded some added protection. Most who acquired infection were asymptomatic or had only mild symptoms.

There is no clinical evidence that Omicron BA.4 or BA.5 cause more severe disease although limited preclinical data raises this possibility. Omicron and its sublineages are currently predominant however whether or not this will be the case throughout the autumn/winter season is unknown. Even in the absence of any increased disease severity, the impact of these and future variants on the healthcare system may be very significant. As infection rates rise, an increase in hospitalisations and deaths can be anticipated in those with risk factors, e.g., age, obesity, comorbidities and immunocompromise.

SARS-CoV-2 infection can result in adverse pregnancy outcomes and neonatal infection. In the Omicron wave although the risk of adverse maternal outcomes was less than that during the Delta wave, hospitalisations rates for infants with COVID-19 increased significantly. Maternal vaccination in pregnancy is a safe strategy that can enhance maternal protection and mitigate risk to the infant. Timing additional booster vaccination from 16 weeks gestation can optimise protection for the infant.

Data has clearly shown that a second booster dose can confer significant benefit in the short to medium term. Additional booster doses have been well tolerated and no new safety concerns identified. Boosting with current vaccines is immunogenic and increases protection against all of the Omicron sublineages and enhances protection against the prior variants.

Appropriately timed booster vaccination can be used to help mitigate the negative impacts of COVID-19. Evidence supports extending the offer of a second booster now to those aged 50 years and older and those at higher risk of severe outcome.

Novel adapted vaccines may in the future provide even better protection against Omicron but are unlikely to be available before late autumn or winter. Ultimately the goal is to develop an effective vaccine that will stop infection. The hope lies in the development of either effective nasal vaccines

or a pancoronavirus vaccine. For now the challenge is to protect those at risk from severe COVID-19, to safeguard the health care system and in as far as possible to minimise societal disruption using the available vaccines.

COVID-19 has not gone away. The perception that Omicron is mild relates primarily to the high levels of partial immunity, from vaccination and from infection, in the community. Consequences of COVID-19 relate not just to the severity of the acute illness but also to potential long term consequences e.g, Long COVID and social disruption. Evidence increasingly suggests that the primary vaccine schedule (one or two doses) is limited in its ability to protect against SARS-CoV-2 and its variants. This is particularly evidenced in relation to Omicron BA.5. The combined attributes of immune evasiveness and growth advantage have made BA.5 a most successful pathogen, even in highly fully vaccinated populations. Susceptibility to reinfection has also increased progressively with each Omicron variant with limited protection against BA.5 afforded by prior infection with BA.1 or earlier variants.

There is strong evidence that protection for those who have their primary series and those who have had a prior infection can be strengthened by booster vaccination. It is important that people avail of booster doses when offered to reduce the risk of COVID-19 hospitalisation and mitigate other more long term consequences.

9. RECOMMENDATIONS

RECOMMENDATIONS*

1. All those who are unvaccinated or incompletely vaccinated are strongly recommended to complete a primary COVID-19 vaccination course and booster vaccination as outlined in Table 2. Access for hard to reach populations and new arrivals should be facilitated.

2. All those aged 65 years and older and those with immunocompromise at the time of their primary or first booster vaccination and who have not yet availed of the recommended second booster vaccine are strongly recommended to do so.

3. A first mRNA COVID-19 booster vaccine is now recommended for
   - those aged 5 – 11 years with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or additional vaccination

4. A second mRNA COVID-19 booster vaccine is now recommended for
   - those aged 50-64 years
   - those aged 12–49 years who
     - have underlying medical conditions associated with a higher risk of severe COVID-19
     - are residents of long term care facilities

5. A second mRNA COVID-19 booster vaccine is recommended for
   - healthcare workers, and when practicable, should be given at the same time as seasonal influenza vaccine.

6. A third mRNA COVID-19 booster vaccine is recommended for
   - those aged 65 years and older
   - those aged 12 – 64 years with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or booster vaccination

   When practicable, it should be given at the same time as seasonal influenza vaccine.

7. To enhance maternal protection and provide optimal benefit to the infant, an additional mRNA COVID-19 booster vaccine is recommended in pregnancy at 16 weeks gestation or later for those who have not received a booster vaccine in the current pregnancy.

8. mRNA booster vaccines should be given as follows:
   - aged 30 years and older: Comirnaty (0.3ml/30 mcg) or Spikevax (0.25ml/50 mcg)
   - aged 12-29 years: Comirnaty (0.3ml/30 mcg)
   - aged 5-11 years: Comirnaty (0.2ml/10mcg)

9. Following the primary vaccine series or confirmed SARS-CoV-2 infection, a four month interval is recommended for any subsequent COVID-19 vaccine doses. A minimum interval of three months may be exceptionally used.

10. COVID-19 vaccines may be given at the same time or at any interval before or after any vaccine. This includes seasonal influenza and pertussis vaccines.

11. If an mRNA booster vaccine is contraindicated or declined, a non-mRNA vaccine may be given.

These recommendations reflect a dynamic vaccination programme. Scientific evidence is emerging and being refined. Recommendations may be updated when more information becomes available.

*See Table 1

Table 1: NIAC recommendations for COVID-19 vaccines by age and immune status July 2022.

Group		Primary course*	Additional dose	1st booster	2nd booster	3rd booster
65 years and older		√√		√	√	√
50-64 years		√√		√	√	
12-49 years	*Underlying medical conditions*	√√		√	√	
	Residents of long term care facilities	√√		√	√	
	Healthcare workers	√√		√	√	
	Others	√√		√		
Pregnancy		√√		√	√**	
5-11 years		√√				
12 years and older	*Immunocompromise associated with a sub optimal response to vaccines*	√√	√	√	√	√
5-11 years		√√	√	√		

*two dose primary course (one dose if COVID-19 vaccine Janssen)

**at 16 weeks gestation or later if not already boosted in this pregnancy

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ACKNOWLEDGEMENTS

NIAC would like to thank all the individuals and organisations who provided data, time, advice and information in support of this work.

- HSE Libraries Team
- NIAC SpR Research Panel
- NIAC Members
- RCPI Communications Department