ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

MEDIUM TERM STRATEGY FOR THE COVID-19 VACCINATION PROGRAMME

- RECOMMENDATIONS FOR SECOND BOOSTER DOSE
- FUTURE CONSIDERATIONS

NIAC | 05.04.2022

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 (DOH). The Department and the Minister for Health make policy decisions on vaccines which are implemented by the HSE.

RECOMMENDATIONS

These recommendations are made recognising the uncertainties regarding the trajectory of SARS-CoV-2 infections and on a precautionary basis to protect those most at risk of a severe outcome. They are based on current evidence and will be reviewed when more information becomes available. See the prior recommendations for primary and first booster vaccination.

1. Efforts to increase primary and first booster vaccination uptake should remain a public health priority. mRNA vaccines (Comirnaty and Spikevax) are the preferred vaccines for use in Ireland.
   - Those aged 12 years and older, including those pregnant or breastfeeding, should complete a primary course and receive a booster vaccine (total of three doses)
   - Those aged 5-11 years should complete a primary course (total of two doses)
   - Those with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or booster vaccination:
     a) aged 12 years and older should complete a primary course, an additional dose and a booster vaccine (total of four doses)
     b) aged 5-11 years should complete a primary course and an additional dose (total of three vaccine doses)
2. Those who have a contraindication to or who decline a primary course or booster dose of an mRNA vaccine should be offered a non-mRNA vaccine.
3. Those who have had previous SARS-CoV-2 infection should complete their primary and booster vaccination to optimise their protection.

Second Booster Vaccine

1. To maintain high levels of immunity in those most at risk of severe disease, a second booster dose of an mRNA vaccine is recommended for the following:
   a) those aged 65 years and older
   b) those aged 12 years and older with immunocompromise associated with a sub optimal response to vaccines
2. The second booster vaccine is recommended at least six months after the first booster. A minimum interval of four months may be used for operational reasons.
   a) For those aged 12-29 years, Comirnaty (0.3ml/30 micrograms) should be given
   b) For those aged 30 years and older, Comirnaty (0.3ml/30 micrograms) or Spikevax (0.25ml/50 micrograms) should be given
3. For those who have had a breakthrough infection following a first booster vaccine, it is recommended to defer the second booster vaccine for six months following infection onset. A minimum interval of four months may be used for operational reasons.
4. If an mRNA vaccine is contraindicated or declined, consideration may be given to using a non-mRNA vaccine as the second booster vaccine, following an individual benefit-risk assessment.

1.0 EXECUTIVE SUMMARY

When developing recommendations and advice, NIAC weighs the benefits and potential risks of vaccination against disease related risks, both to the individual and the community.

- The primary focus of the COVID-19 vaccination programme is to prevent hospitalisation, severe illness and death.
- In the Omicron era, completion of the primary series and booster vaccination, is essential to minimise the risk of infection and importantly, preventing hospitalisation and severe disease.
- Over 90% of the adult population in Ireland have received a primary vaccine series. Those who are unvaccinated or incompletely vaccinated are disproportionally represented in hospitalisations, accounting for one third of hospitalised COVID-19 cases.
- Vaccination has a limited short-term impact on infection with the Delta variant, protection declining from 12-20 weeks following the primary series. The decline with the Omicron variant is even more rapid. Protection against hospitalisation and severe illness is more durable.
- A first booster dose increases antibody levels up to 37 times the pre-booster level. Antibody levels peak at 2-4 weeks after booster vaccination and can fall by up to 50% by 90 days.
- The Omicron BA.2 sublineage is more readily transmitted than previous variants. It is associated with an increase in case numbers but not with increased disease severity.
- In the Omicron period in the US, vaccine effectiveness (VE) against hospitalisation in those aged 18 years and older peaked two months after the third dose at 91% and declined to 78% at four months or more. VE against urgent care/emergency department visits declined from 87% within two months to 66% by four months after the third dose.
- In the UK VE against symptomatic disease with 2 doses of mRNA vaccine was lower against Omicron that Delta and declined from around 65 to 70% to around 15% by 25 weeks after the second dose. Two to four weeks after a booster dose VE ranges from around 60 to 75%, dropping to 25 to 40% from 15+ weeks after the booster. VE estimates for the booster dose are very similar, irrespective of the primary course received and were slightly higher in younger compared to older age groups.
- While breakthrough infection in those vaccinated and boosted is generally mild and of short duration, in those at risk, e.g., older persons and those with immunocompromise, breakthrough infection can result in hospitalisation and severe illness. In Ireland, the number of people in hospital with confirmed PCR positive COVID-19 has doubled since early March 2022. Of those in hospital just under half were admitted because of COVID-19. The remainder were asymptomatic but potentially infectious.
- The age profile of COVID-19 hospitalisations has changed in Wave 5 compared to Wave 4. Between 1 February and 27 March 2022, those aged 65 years and older accounted for 50% of hospitalisations, 58% of ICU admissions, and 89% of deaths. This is increasing week on week and is likely associated with greater socialisation and time since first booster vaccination.

- Almost 95% of those aged 65 years and older have received their first booster. Age related immunosenescence and longer interval since first booster are likely factors contributing to the increase of hospitalisation and risk for severe illness in this cohort.
- Age and immune status, e.g., those aged 65 years and older and those aged 12 years and older with immunocompromise associated with a sub optimal response to vaccines, remain the most important determinants of risk of severe breakthrough infection.
- The aim of offering a second booster is to protect those most at risk of hospitalisation and severe breakthrough infection.
- In Israel, studies in those aged over 60 years have shown that a second booster dose provides considerable additional protection against infection, severe disease and death relative to three doses of the vaccine.
- A second booster vaccine programme will not affect outbreak management. Boosting immunity optimises protection for those at risk of severe disease and may protect against future variants.
- First booster doses of mRNA vaccines have not shown any unexpected short term 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 and the risk appears to be comparatively lower following a first booster dose. Data on second booster doses is more limited but preliminary experience from Israel has not revealed any new safety concerns.
- There is uncertainty about the trajectory of the COVID-19 pandemic including virus evolution, endemicity, seasonality, and the ultimate durability of current vaccines. A number of new vaccines are in development including Omicron specific, multivalent and intranasal vaccines. The characteristics of these vaccines and the timelines for availability are unknown. Knowledge gaps lead to significant uncertainty in future planning and will require adaptability and agility in any planned response.
- It is likely that a third booster dose will be required for the cohorts detailed in the current advice later this year.
- The need for a second booster for those other than detailed in the current advice is being kept under review. It would be prudent to have contingency plans in place to facilitate rapid rollout of booster vaccination for the general population. The cohorts to be vaccinated, choice of vaccine, optimal timing and duration of protection from further boosters remain to be determined.

2.0 INTRODUCTION

We are now over two years into the COVID-19 pandemic and have learned much about the SARS-CoV-2 virus, COVID-19 disease and preventive measures including vaccination. The primary focus of the COVID-19 vaccination programme is to prevent hospitalisation, severe illness and death. COVID-19 vaccines have excellent safety profiles and are highly effective in preventing severe COVID-19 disease while protection against infection is limited and wanes over time.

This paper reviews the current situation regarding COVID-19 vaccines, evidence pertaining to second booster doses, outlines recommendations for a second booster dose and reviews some of the considerations that inform the next steps for the COVID-19 vaccination programme. However, there are important knowledge gaps that lead to significant uncertainty when it comes to future planning. These will necessitate adaptability and agility in any planned response.

3.0 SARS-CoV-2

The SARS-CoV2 virus has a high replication rate, with a large number of distinct lineages reported to date. Mutations have occurred that either enhance replication facilitating transmission, or that result in immune evasion compromising protection afforded by infection or vaccination.

The highly transmissible Omicron BA.2 is now the predominant variant in Ireland. The fact that Omicron dates back to pre-vaccine times in 2020 means that the evolution of SARS-CoV-2 variants have not yet reached the stage of gradual stepwise progression traditionally associated with seasonal human coronaviruses.

On 25 March 2022, the UK Health Security Agency reported three new recombinant lineages of interest. Two are a combination of Delta and BA1 (XD and XF) and the third, XE, is a BA.1/BA.2 recombinant. XE is estimated to have a growth advantage of 9.8% above BA.2 and BA.2 a 75% growth advantage over BA.1.[1] As yet it is too soon to determine their impact on disease severity or VE.

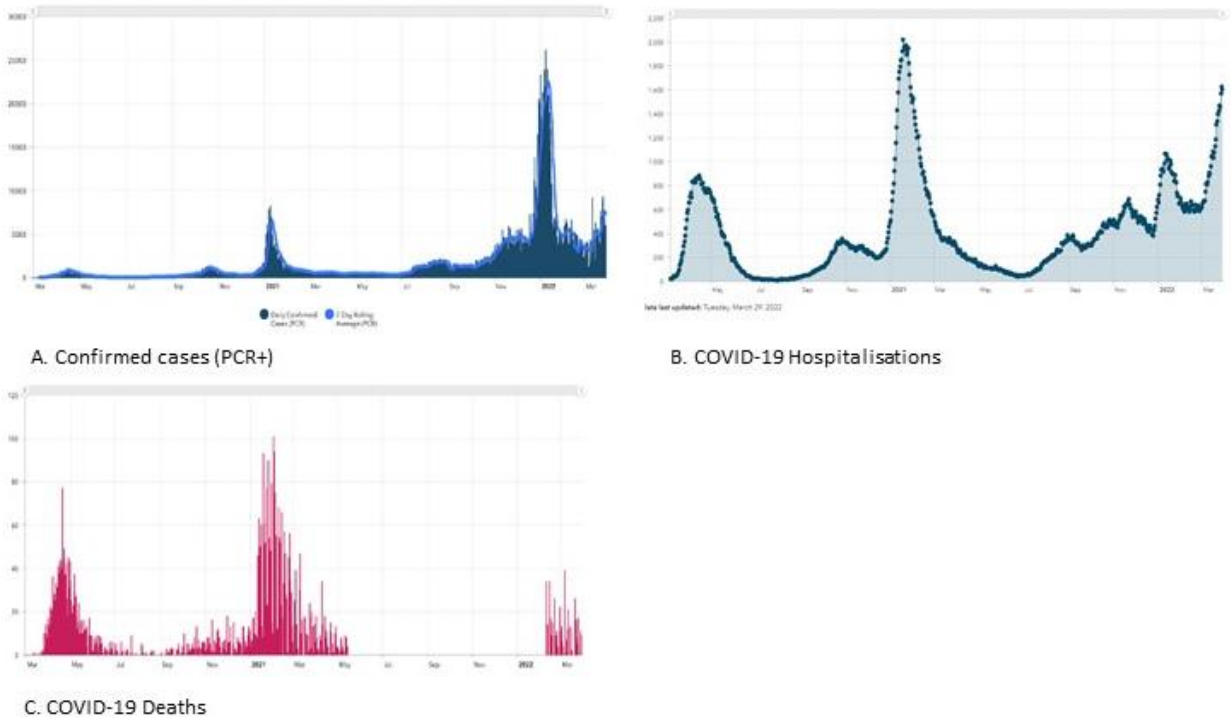
While currently available vaccines remain very effective against severe disease, they may not be able to reduce transmission of these strains. As noted by the World Health Organization (WHO) *"it is too early to declare victory against the coronavirus".*

4.0 COVID-19 EPIDEMIOLOGY IN IRELAND

In January 2022, the Omicron BA.1 wave slowly ebbed, COVID-19 case numbers declined and public health measures were relaxed on 28 February 2022.

The arrival of Omicron BA.2 reversed some of those gains. Case numbers increased, although there is no evidence that BA.2 is associated with greater disease severity than BA.1. Inevitably as case numbers increase, hospitalisations also rise, although the numbers who have died are markedly reduced compared to previous waves. (Figure 1)

Figure 1: A) PCR confirmed cases of SARS-COV-2 infection to 29 March 2022 B) COVID-19 hospitalisations C) COVID-19 deaths. Source: COVID-19 data hub, Accessed 29 March 2022.

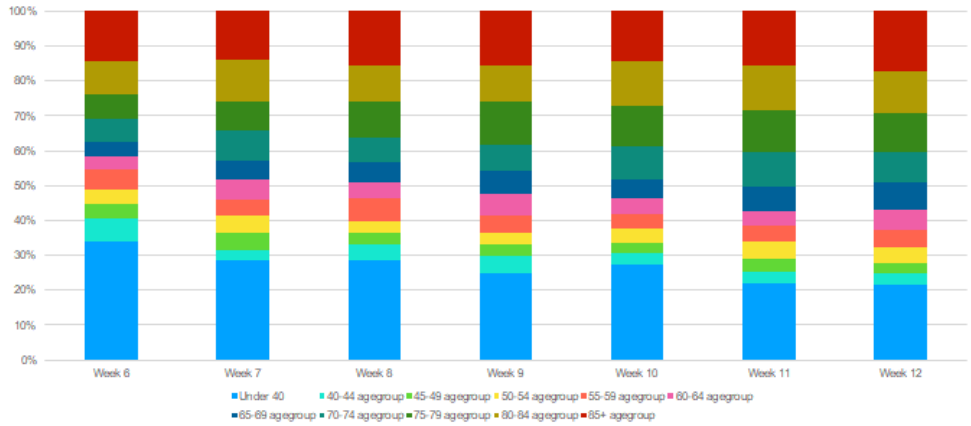


The number of confirmed COVID-19 cases in hospital increased from 378 on 25 December 2021 to 1624 cases on 28 March 2022. Between 15-29 March 2022 the number of COVID-19 hospitalisations increased by 53% (N 553).

The age profile of those admitted to hospital has changed in Wave 5 compared to Wave 4. Between 1 February and 27 March 2022, those aged 65 years and older accounted for 50% of hospitalisations, 58% of ICU admissions, and 89% of deaths. This is increasing week on week and is associated with the force of infection in the community, greater socialisation and longer time since first booster vaccination.

Between 1 February and 27 March 2022, the proportion of those hospitalised aged 65 years and older increased from 43% to 62%. (Figure 2)

Figure 2: Proportion of those hospitalised by age group from week 6 (week ending 13 February 2022) to week 12 (week ending 27 March 2022). Source: DOH.



Of those in hospital, just under half were admitted because of COVID-19. The remainder were asymptomatic but potentially infectious.

ICU admissions remain low and many COVID-19 cases are now admitted because of other conditions. In early January 2022, COVID-19 was the primary reason for ICU admission in 78% of COVID-19 cases. This figure reduced to 36% by 29 March 2022. Although numbers are low, the rate of ICU admissions in those aged 65 years and older has increased from 37.3% (272/729) in wave 4 (27 June-18 December 2021) to 58% (36/62) between 1 February and 27 March 2022.[2,3]

Omicron infections and the number of outbreaks in congregate settings has increased. Although case numbers have increased, hospitalisation rates remain low. In the fifth wave up to 19 March 2022, the overall death rate for those with confirmed COVID-19 linked to an outbreak was 1.8% compared with rates of 7.6 to 14.1% in earlier waves. (Table 1)

Table 1: Comparison of disease severity among cases linked to COVID-19 outbreaks in Nursing Homes and Community Hospitals by wave and age group. Source: CIDR 22 March 2022. Data to midnight 19 March 2022.

Age group	Wave	Number	Number hospitalised	% hospitalised	Number admitted to ICU	% ICU	Number who died	% died
<65 yrs	Wave 1	2672	88	3.3%	5	0.2%	20	0.7%
	Wave 2	779	15	1.9%	0	0.0%	1	0.1%
	Wave 3	4032	101	2.5%	8	0.2%	18	0.4%
	Wave 4	1173	16	1.4%	2	0.2%	7	0.6%
	Wave 5	2693	49	1.8%	0	0.0%	3	0.1%
65+ yrs	Wave 1	3577	388	10.8%	11	0.3%	864	24.2%
	Wave 2	776	75	9.7%	1	0.1%	133	17.1%
	Wave 3	4296	476	11.1%	4	0.1%	1009	23.5%
	Wave 4	1530	174	11.4%	1	0.1%	198	12.9%
	Wave 5	3659	195	5.3%	1	0.0%	111	3.0%
All ages	Wave 1	6251	476	7.6%	16	0.3%	884	14.1%
	Wave 2	1555	90	5.8%	1	0.1%	134	8.6%
	Wave 3	8328	577	6.9%	12	0.1%	1027	12.3%
	Wave 4	2703	190	7.0%	3	0.1%	205	7.6%
	Wave 5	6352	244	3.8%	1	0.0%	114	1.8%

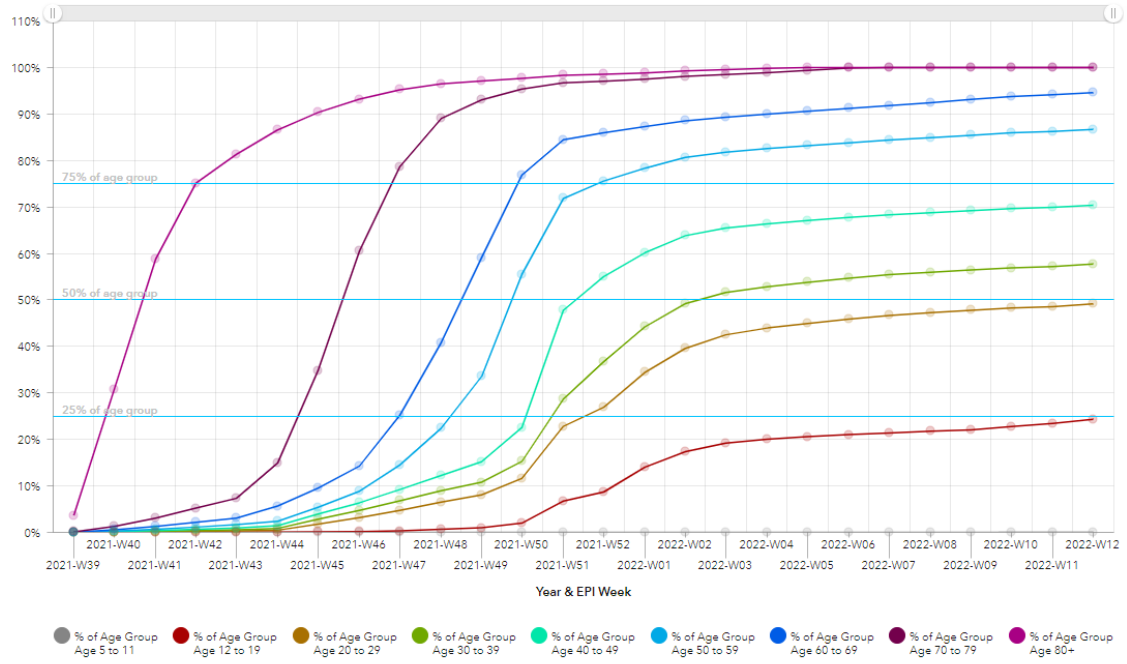
The situation in Ireland is reflective of what has been seen in other European countries. The European Centre for Disease Control has reported that a proportionally higher increase continued to be observed among people aged 65 years and older (14% increase, reaching 1,282 cases per 100,000), among whom testing is likely to have remained more constant.[4] This rate among 65 years and older is now as high as the January 2022 peak observed in this age group.

5.0 COVID-19 VACCINATION PROGRAMME IN IRELAND

Ireland has a highly vaccinated population. By 28 March 2022, 7.8 million COVID-19 vaccine doses had been administered, with 85% of the population aged five and older fully vaccinated, including over 90% of adults. Vaccination uptake rates increase with age with almost 100% of those aged 70 and older fully vaccinated and boosted. (Figure 3)

Those who are not fully vaccinated continue to be disproportionately affected and accounted for around 35% of hospitalisations during February 2022 and 30% of ICU admissions on 29 March 2022. In review of COVID-19 ICU admissions 12 October 2021 to 22 March 2022, none of those pregnant, or recently pregnant, had completed their primary vaccination.[5]

Figure 3: Booster and additional doses by age group 28 March 2022. Source: https://covid-19.geohive.ie/pages/vaccinations



It is three to five months since the first booster was received by those aged 70 years and older, those aged 65 years and older in long term care facilities and those aged 16 years and older with immunocompromise associated with a sub optimal response to vaccines.

Whilst 95% of those aged 16 years and older with immunocompromise associated with a sub optimal response to vaccines have received a primary course and an additional vaccine, only 33% have received a booster dose i.e., a total of four doses. This leaves many in this group at risk of severe COVID-19 disease. (Table 2)

Table 2: Vaccine uptake in those who are immunocompromised aged 16 years and older. 20 March 2022. Source: HSE.

	Number immunocompromised	Percent of immunocompromised cohort
Dose 1	120,933	99%
Dose 2	120,271	98%
Single Dose	1,410	1%
Additional Dose	116,268	95%
Booster	40,784	33%

Only 20.5% of children aged 5-11 years have completed their primary vaccination course. (Table 3) This may in part be because of the high rates of infection in this age group. Nonetheless, these children should complete their primary vaccination course.

Table 3: COVID-19 vaccination uptake of eligible population by age group and vaccination status week ending 20 March 2022. Source adapted from: HPSC.[6]

Age group	Partially vaccinated	Fully vaccinated
18+ years	0.8%	95.1%
12-17 years	2.0%	77.0%
5-11 years	4.6%	20.5%

6.0 COVID-19 VACCINES

COVID-19 was first recognised in December 2019 and SARS-CoV-2 identified in January 2020. Vaccines were authorised within a year and the first person in Ireland received a COVID-19 vaccine on 29 December 2020.

COVID-19 vaccines have been extremely effective in the main aim of the vaccination programme, i.e., protecting against serious disease, hospitalisation, and death. They are less effective in eliciting sustained protection against infection. The duration of VE against infection has declined progressively with each of the common variants, most notably with Omicron.

mRNA vaccines (Comirnaty and Spikevax) are the preferred vaccines for use in Ireland. They are both safe and effective. Although short term VE against symptomatic infection is lower with adenoviral vector vaccines than mRNA vaccines, they were similarly effective in protecting against severe disease and death in the Alpha and Delta time periods.[7]

Nuvaxovid, a protein sub-unit vaccine, is recently authorised. It may be offered to those with a contraindication to, or who decline an mRNA vaccine. While high efficacy levels have been reported in clinical trials,[8,9] data regarding efficacy against Omicron and the antibody decline following its primary course or boosting are awaited.

COVID-19 vaccine Janssen, authorised as a single dose, is associated with lower initial antibody levels. A second dose, two to six months after the first dose is associated with greater efficacy. [10,11]

Other COVID-19 vaccines are authorised for administration as a two dose (Comirnaty, Spikevax, Vaxzevria, Nuvaxovid) primary schedule with doses given at either a three or four week interval.

Early in the pandemic, given the urgency to provide protection to as many people as possible as quickly as possible, intervals of up to 12 weeks in the primary schedule were used in the UK and in Canada.[12-14] Evidence suggests a benefit to extending the interval of the primary series where epidemiology permits. Extended intervals of at least eight weeks have been recommended for children to enhance the immune response and to minimise the risk of myocarditis.

In Ireland, there are varying intervals recommended between primary doses and additional or booster doses, depending on age and associated conditions. These differences may need to be rationalised.

Booster doses have been recommended after intervals of two to six months following a primary schedule, depending on the local epidemiology. A longer interval could enhance the vaccine response.[12-14]

Valneva, an inactivated adjuvanted vaccine, is under review by the European Medicines Agency (EMA). Trials this far include those aged 18 to 55 years and may possibly be the first inactivated vaccine authorised for use in Ireland. In phase 1/2 clinical trial of adults aged 18-55 years, Valneva was well tolerated.[15] In company press release, the vaccine is reported to be less reactogenic and more immunogenic than its comparator Vaxzevria.[16] Details of the results are awaited. In a company press release Valneva was reported to induce neutralising antibodies against Delta and Omicron in 100% (30/30) and 87% (26/30) of samples tested.[17]

The emergence of SARS-CoV-2 variants challenges the ability to produce a stable vaccine with durable immunity which is also seen with influenza. Monovalent vaccines are unlikely to represent the ultimate answer to maintaining protection against COVID-19. Multivalent vaccines and intranasal vaccines are in development. Emerging data suggests that multivalent combinations incorporating the Wuhan and Omicron strains could provide wider protection against existing and future variants.[18,19] Preliminary animal model data suggest that intranasal vaccines could be more effective than intramuscular vaccines in protecting against infection and transmission.

Heterologous vaccination

Evidence supports the use of heterologous vaccination in primary and booster schedules. The combination of adenoviral vector vaccines and mRNA vaccines produces good levels of antibodies and higher T-cell responses than homologous vaccination.[11,20,21] In the COV-BOOST study, Comirnaty, Spikevax, Vaxzevria, COVID-19 vaccine Janssen and Nuvaxovid were highly immunogenic as heterologous boosters. Valneva was less immunogenic as a heterologous booster.[20]

6.1 Vaccine Safety

The EMA closely monitors COVID-19 vaccines and assessing relevant data from all sources to draw robust conclusions on the safety of the vaccines. The Health Products Regulatory Authority[22]

monitors vaccine safety in Ireland, reporting nationally occurring adverse reactions to the EMA. While the vast majority of adverse reactions to COVID-19 vaccines are mild to moderate and of short duration, some very rare but important adverse reactions have emerged, resulting in updates to the product information warnings and advice. These include thrombosis with thrombocytopenia syndrome (TTS) with adenoviral vector vaccines and myocarditis and pericarditis with mRNA vaccines.

mRNA vaccines have higher effectiveness than adenoviral vaccines and remain are the preferred vaccines. The preference for mRNA vaccines in Ireland was also influenced by the associated risk of TTS initially associated with a very high mortality after adenoviral vector vaccines. Now with alertness for early TTS symptoms, interventions have proven effective with reduction in the associated mortality.

Very rare cases of vaccine associated myocarditis have been reported after mRNA vaccines predominantly in males aged under 30 years. Most cases are of short duration and resolve with symptomatic treatment.

By 28 February 2022, almost 620 million doses of Comirnaty, over 150 million doses of Spikevax, 69 million doses of Vaxzevria and over 19 million doses of COVID-19 vaccine Janssen had been administered in the EU/EEA area. The EMA and HPRA stated that the benefits of COVID-19 vaccines continue to outweigh the risks.[22]

The large amount of data on pregnant women given an mRNA COVID-19 vaccine has not shown any increase in adverse pregnancy or neonatal outcomes and supports the safe use of these vaccines in pregnancy and during breastfeeding.[23-25] [26,27]

Booster vaccine safety

First and second booster doses of mRNA vaccines have not shown any unexpected short term 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 and the risk appears to be comparatively lower following a first booster dose. Data on second booster doses is more limited but preliminary experience from Israel has not revealed any new safety concerns.[28]

6.2 Immunogenicity

Both SARS-CoV-2 infection and vaccination elicit humoral (antibody) and cellular immune responses. Antibody levels are correlates of protection against infection although there is no defined protective level. High antibody levels are necessary for protection against initial infection, whereas cellular immunity even when coupled with lower antibody levels, appears to be more important for protection against severe disease.

Persistence of antibodies does not always equate with immunity and reinfections can occur. Protection following infection is less robust against heterologous strains.

The levels of antibodies detected following natural infection are generally lower than those following vaccination. Up to 99% of unvaccinated adults with a history of confirmed infection have detectable SARS-CoV-2 antibodies that can persist without waning for up to 20 months.[29]

Vaccination elicits initial robust antibody response with decline over some 12 to 20+ weeks.

6.3 Vaccine impact

Unvaccinated

In unvaccinated individuals, infection with Omicron may not elicit protection against other variants.[19] Vaccination has been associated with increased protection against hospitalisation compared to prior infection in those who are unvaccinated. Vaccination is essential even in those with history of prior infection.

Following primary vaccination

Vaccine protection against hospitalisation and severe disease is more sustained than protection against infection. This may be because mucosal immunity, heavily reliant on IgA antibodies, is poorly induced by COVID-19 vaccines. Very high IgG antibodies, as present in the short term following vaccination provide some protection. For protection against more severe disease involving the lower respiratory tract, lower antibody levels coupled with a robust cellular immune response likely suffice. Persistence of cellular immunity is likely a significant factor in the reduced severity of breakthrough infection in otherwise healthy vaccinated individuals.

VE against infection declines within 10-12 weeks following primary vaccination. Similar declines can occur following first booster vaccination and decline may be more rapid than after primary vaccination. However, effectiveness against severe disease, hospitalisation and death is more durable.

Pregnancy has been associated with a higher risk of severe disease and COVID-19 vaccines are as effective at reducing the risk of hospitalisation and deaths in pregnant women as they are in non-pregnant women and may help prevent COVID-19 hospitalisation among infants under six months of age.[30]

Effectiveness against Omicron

mRNA and adenoviral vector vaccines are highly immunogenic with antibody levels higher than those following natural infection. Antibody levels decline as early as 12-20+ weeks after primary vaccination: the decline correlates with an increase in risk of breakthrough infection, particularly with Omicron. There is conflicting evidence as to the relative importance of declining antibody

levels versus the inherent immune evasiveness of Omicron in contributing to the susceptibility of those fully vaccinated to breakthrough infection.

A Swedish study compared the risk of severe COVID-19 during two periods in 2021 and 2022 when Delta and Omicron, respectively, were the dominating virus variants.[31] Markedly lower risks of severe disease were observed among those who had received at least two doses of any COVID-19 vaccine, during the period when Omicron dominated. VE remained high but changed in nature from protection against both infection and severe disease from Delta to protection mainly against severe disease from Omicron.

In the Omicron period in the US, VE against hospitalisation in those aged 18 years and older peaked two months after the third dose at 91% and declined to 78% at four months or more. VE against urgent care/emergency department visits declined from 87% within two months to 66% by four months after the third dose.[32]

In the UK with two doses of mRNA vaccine, VE against symptomatic disease was lower against Omicron that Delta and declined from around 65 to 70% to around 15% by 25 weeks after the second dose. Two to four weeks after a booster dose VE ranges from around 60 to 75%, dropping to 25 to 40% from 15+ weeks after the booster. VE estimates for the booster dose are very similar, irrespective of the primary course received and were slightly higher in younger compared to older age groups.[33]

Neutralising antibodies in vaccinated individuals without prior infection are lower against Omicron BA.1 than against other variants.[34] Based on routine testing data in the UK, VE appears similar between BA.1 and BA.2, both for symptomatic disease and hospitalisation.[35]

In the first pandemic wave the susceptibility of children to infection and risk of onwards transmission was reportedly less than adults. In the Omicron wave, children appear to be equally susceptible to infection and their capacity for transmission is increased without however any increase in disease severity.

Among adolescents 12-18 years, VE against hospitalisation in the Delta period was higher than 90% up to 44 weeks. In the Omicron period this declined to 40% against hospitalisation and 20% against non critical COVID-19,[36] underscoring the need for booster vaccination in this age group.

In the US, Comirnaty vaccination has been shown to reduce hospitalisations due to the Omicron variant by two thirds in children aged 5-11 years.[36]

There are currently no authorised COVID-19 vaccines for children younger than five years of age although clinical trials are ongoing. In the US, the incidence of SARS-CoV-2 infection in children under five years of age increased from 2.4 per thousand pre-Omicron to 8.6 per thousand in the

Omicron predominant period. The risk of severe infection was significantly lower than in those with Delta infection.[37]

Breakthrough infection

Fully vaccinated and boosted household members are over twice as likely to have a breakthrough infection with Omicron than with Delta and twice as likely to transmit it. The benefits of booster vaccination are evident as those who are boosted are 38% less likely to transmit Delta infection and 22% less likely to transmit Omicron infection than those with just two doses.[38]

Although there is significant cross protection between BA.1 and BA.2, reinfection can occur after several weeks. There is substantial immunological evidence and a growing body of epidemiological evidence which indicates that vaccination after infection significantly enhances protection and further reduces risk of reinfection so booster doses after breakthrough infection are still essential to optimise protection.[39] Booster vaccinations are needed to trigger recall immunity and maintain efficacy against new variants.[18,19]

Those who have had previous infection should complete their primary and booster vaccination to optimise protection.

Following first booster vaccination

Administration of a first booster vaccine raises the antibody levels above that of primary vaccination[40] and the rates of breakthrough infection decrease at least in the short term. However the trajectory of decline may be steeper than that after a second dose.[41] Reassuringly, protection against hospitalisation and severe disease is more durable.

In a UK study of adults aged 50 years and older, there were rapid serological responses to boosting with Comirnaty, irrespective of vaccine type used for primary immunisation, with higher post-booster responses with longer interval between primary immunisation and boosting.[42] The longer interval may allow more time for enhancing immune memory and greater waning of antibodies, both likely to enhance post-booster responses. Antibody levels peaked 2-4 weeks post booster and declined by up to 85% at 24-29 weeks depending on primary schedule and dose intervals.

In the UK, the VIVALDI study highlighted the importance of the first booster dose in protection against hospitalisation and death in residents of long term care facilities.[43] Protection following vaccination exceeded that from natural infection and for those previously infected, significant benefit was accrued with the third dose. Protection among staff was more durable than in residents likely reflecting age related immunesenescence.

Following second booster vaccination

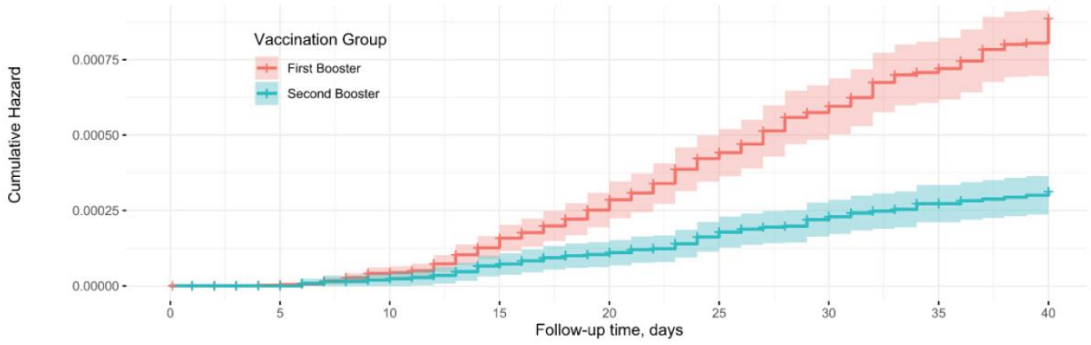
VE data of the second booster vaccine relates to the use of an mRNA vaccine in Israel introduced on 2 January 2022 for those aged 60 years and older and those at high risk and health care workers who had received their first booster more than four months previously.

In a study of those aged 60 years and older, the risk of infection was halved, and the rate of severe illness was lower by a factor of 4.3 (95% CI 2.4 to 7.6) in those who received a second booster compared to those who had not.[44] The limitations of this data include the very short duration of follow up, 12 days for infection and just seven days for severe cases.

Two further Israeli studies support the effectiveness of a second booster in older populations. In a study of those aged 60 years a second booster of Comirnaty provided considerable additional protection against both infection and severe disease compared to one booster dose. Although additional VE against infection waned rapidly, declining from a peak of 64% to 29% after 10 weeks, the additional protection against severe disease was sustained at greater than 73% over 6-9 weeks follow-up. Again in this study the duration of follow-up was limited.[45]

A separate study of those aged 60-100 years focused on the impact of a second Comirnaty booster dose on mortality. The median age of participants was 73 years. The second booster uptake rate in the eligible population was 58% and was higher in older age groups. Over the 40 day study period there were 92 COVID-19 related deaths among 328,597 second booster recipients compared to 232 in 233,847 first booster recipients giving an adjusted hazard ratio of 0.22 demonstrating a significant reduction in COVID-19 mortality from the second booster.[46] (Figure 4)

Figure 4: Cumulative COVID-19 mortality rates during the study period. Source: Adapted from Arbel R et al.[46]



Among Israeli health care workers who received a second booster (Comirnaty or Spikevax), each vaccine was similarly immunogenic, boosting antibody levels by a factor of nine, to levels similar or higher than those after the first booster.[28] In contrast antibody levels in age matched control

first booster recipients continued to wane. VE against infection was 30% and 11% for Comirnaty and Spikevax respectively but there were wide overlapping confidence intervals. VE against symptomatic disease was higher at 43% and 31%.

Thus, a second booster just four months after the first booster may have only marginal benefits in healthy young people as they may have already achieved peak responses from these vaccines.

Immunocompromised

In Ireland, whilst 95% of those aged 16 years and older with immunocompromise associated with a sub optimal response to vaccines have received a primary course and an additional vaccine, only 33% have received a booster dose i.e., a total of four doses. This leaves many in this group at risk of severe COVID-19 disease. This is likely due to a number of factors including the difficulty identifying those in this cohort of those in this group, the absence of a unique patient identifier and the lack of awareness around the requirement for both an additional dose and a first booster dose.

Individuals who are immunocompromised have significantly reduced COVID-19 vaccine responses with considerable heterogeneity in response compared to those who are not immunocompromised. Recent systematic reviews showed evidence that seroconversion rates after primary course COVID-19 were significantly lower in those with immunocompromise than in those who are not immunocompromised.[47,48] The addition of a third vaccine dose as part of an extended primary series provides additional protection and is associated with seroconversion in around 40% of non-responders.[49] [48] However, those who are immunocompromised have reduced levels of protection and are at greater risk of severe outcome with breakthrough infection and additional protective measures should continue to be used.

A first booster dose has been associated with increased seroconversion rates[50] including in some who are seronegative following the extended primary series.[51]

In Israel, those with immunocompromise who received a first booster dose (four doses) at least four months previously were twice as likely to develop severe COVID-19 disease compared those who had received two booster doses (five doses).[45]

7.0 INTERNATIONAL RECOMMENDATIONS FOR SECOND BOOSTERS

Table 4: Recommendations for second booster vaccination by country and age. Source: DOH

Country	Risk groups	Interval after first booster
Australia	Aged 65 years and older, LTRCF, 16 years and older who are severely immunocompromised, Aboriginal and Torres Strait Islander people aged 50 years and older	4-6 months
Canada	Aged 18 years and older who are severely immunocompromised, LTRCF	At least 3 months
Chile	Aged over 55 years, weakened immune system	At least 6 months
Finland	Aged over 80 years, LTRCF, 12 years and older with severely weakened immune defence	At least 3 months
France	Aged over 80 years, immunocompromised, cancer patients, obesity, diabetes, renal, cardiac or respiratory disease or hypertension	At least 3 months
Germany	Aged 70 years and older, vulnerable groups, HCWs	At least 6 months
Hungary	Aged 18 years and older provided the patient's primary care physician or vaccinator believes it is warranted	At least 3 months
Israel	Aged 18 years and older	At least 4 months
Netherlands	Aged 60 years and older, LTRCF, with Down syndrome, adults with severe immune disorders	At least 3 months
Sweden	Aged 80 years and older, LTRCF, housebound	At least 4 months
UK	Aged 75 years and older, LTRCF, aged 12 years and older with weakened immune systems	At least 6 months
US	Aged 50 years and older, severely immunocompromised aged 12 years and older (authorised by FDA and CDC)	At least 4 months

LTRCF: Long term residents of care facilities

FDA: Food and Drug Administration

CDC: Centers for Disease Control and Prevention

8.0 PLANNING FOR THE FUTURE

The spectrum of SARS-CoV-2 infection ranges from asymptomatic to very severe. Those at highest risk of severe illness and death include older persons, residents in long term care facilities and those with immunocompromise. SARS-CoV-2 infection is associated with sequelae. In adults hyperinflammation usually presents within days of onset of symptomatic disease. In children the inflammatory response generally occurs some weeks following asymptomatic or mild infection i.e., multisystem inflammatory syndrome in children.[52]

Those with severe illness and prolonged ICU stays may need lengthy rehabilitation related to severity of initial illness. Long term sequelae can also affect those with mild or moderate illness. Long COVID (symptoms lasting at least 12 weeks) appears to be very common in adults following confirmed infection, with 57% of patients experiencing least one long COVID-19 symptom in the six months after infection.[53,54] While less frequently reported, long COVID can also affect children. In the UK, 1% of primary school children and 2.7% of second level school pupils met the criteria for long COVID.[55]

There remain significant information gaps which hamper the real time response to planning for the future including the following:

a) The reasons for differing primary and booster vaccine uptake in different cohorts are incompletely understood. A more detailed understanding would facilitate targeted information campaigns.
b) Available modelling to inform future planning.
c) Lack of real-time data (e.g., linkage of infection and vaccination status for hospitalisations, ICU admissions, deaths by age and underlying condition, outbreaks).
d) The lack of a coordinated IT infrastructure that can rapidly link individual vaccination records and outcomes. Pertinent to this is the need for a unique patient identifier that crosses all platforms and would allow early identification and contact with individuals who stand to benefit most from vaccination.

In addition, there are significant knowledge gaps which hamper strategic planning regarding issues including:

a) Ongoing virus evolution – degree of immune evasion, more or less virulent, more or less transmissible, seasonal or perennial.
b) The definition of a correlate of protection against infection and severe disease.
c) The best protective strategies for those with immunocompromise including the value of regular antibody testing to determine their suitability for pre-exposure prophylaxis.

d) Further studies on the short and long term negative outcomes of COVID-19, e.g., long COVID, MIS-C.
e) The role of antivirals in breakthrough infection.
f) The requirement for COVID-19 vaccination in subsequent pregnancies to afford neonatal protection.
g) The effectiveness and timelines for availability of new vaccines against current and future variants.
h) The impact of coinfection of SARS-CoV-2 with respiratory viruses e.g., influenza.

On 30 March 2022, WHO published a Strategic Preparedness, Readiness and Response Plan to End the Global COVID-19 Emergency in 2022 outlining scenarios regarding evolution of the SARS-CoV-2 virus and immunity. (Table 5)[56]

Table 5: Best case, base case and worst case planning scenarios. Adapted from the WHO Strategic Plan.[56]

Scenario	Details
Best case	Significantly less severe future variants Protection against severe disease is maintained without the need for periodic boosting or significant alterations to current vaccines
Base case	Reduced severity from evolving variants due to sustained and sufficient immunity against severe disease and death Further decoupling between incidence of cases and severe disease leading to progressively less severe outbreaks May be periodic spikes in transmission due to increasing proportion of susceptible individuals over time if waning immunity is significant May require periodic boosting at least for high-priority populations A seasonal pattern of peaks in transmission in temperate zones may emerge
Worst case	Emergence of a more virulent and highly transmissible variant Less effective vaccines and/or rapid waning of immunity against severe disease and death especially in the most vulnerable groups Significant alterations to current vaccines required and full redeployment and/or broader boosting of all high-priority groups

WHO's working model uses the base case but acknowledges the high degree of uncertainty attached to all scenarios, and recommends flexibility is bult to adapt to rapid and dynamic changes in viral transmission, disease severity, and their impact on individual and population-level immunity.

Using the WHO approach, considerations for the COVID-19 vaccination programme in Ireland include:

- Enhanced surveillance that is critical to inform planning as we progress to the next phase.
- Based on current evidence, it is likely that a third booster dose will be required for the cohorts detailed in the current advice in autumn 2022.
- A second booster dose will likely be required in autumn 2022. However, the additional cohorts to be vaccinated, and vaccine choice considering the likely predominant variant, epidemiology, transmissibility and seasonality and schedules remain to be determined.
- If a variant that is more immune evasive, with increased transmission and virulence emerges, there will be a need to rapidly vaccinate the general population, likely in the same order of priority as for the initial vaccine rollout.

Taking into account global vaccine equity, NIAC will consider the following issues over the coming months:

- Harmonisation and optimisation of dosing intervals between primary doses and additional or booster doses.
- Booster doses for children aged 5-11 years.
- Safety and efficacy of vaccination for children under 5 years of age.
- The role of hybrid immunity (from vaccination and infection) in contributing to population protection.
- New and updating existing recommendations for authorised COVID-19 vaccines.

9.0 DISCUSSION

The primary focus of the COVID-19 vaccination programme is to prevent hospitalisation, severe illness and death and completion of the primary series and booster vaccination is essential to reduce the risk of infection and importantly, prevent hospitalisation and severe disease. Over 90% of the adult population in Ireland have received a primary vaccine series. Those who are unvaccinated or incompletely vaccinated are disproportionally represented in hospitalisations, accounting for one third of hospitalised COVID-19 cases.

Outreach to those who remain unvaccinated, including to new arrivals from countries where vaccination rates are much lower than in Ireland, and efforts to remove any barriers to vaccination must continue.

The arrival of Omicron has presented significant challenges. Given the very high transmissibility of the BA.2 variant, and the limited short term impact of vaccination on protection against infection, continuing presence of the virus in the community can be anticipated. As this virus has not yet reached the end of its evolutionary journey, specific viral characteristics such as degree of immune evasion, seasonality and endemicity remain to be determined.

Reassuringly VE against hospitalisation and severe disease is much more durable than against infection. However, there is consistency in the evidence supporting the need for the first booster dose if that protection is to be robustly maintained. Booster doses after breakthrough infection are also essential to reduce the risk of reinfection and provide a greater breath of protection against variants.

While breakthrough infection in those vaccinated and boosted is generally mild and of short duration, in high risk, e.g., older persons and those with immunocompromise, breakthrough infection can result in severe illness. It is estimated that only a third of those with immunocompromise have received a booster dose i.e., a total of four doses. This leaves many at risk of severe COVID-19 disease. Factor contributing to the low uptake include the absence of a unique patient identifier, difficulties in identifying those who belong to this cohort and lack of awareness by those meeting criteria for a fourth dose booster about the requirement for both an additional (third) dose and a first booster (fourth) dose.

Preliminary evidence indicates that this cohort can also benefit from a second booster although the durability of the response remains to be determined. Those who were immunocompromised at the time of their first booster should also receive a second booster vaccine as the response to the first booster would have been compromised.

Age is one of the key determinants of outcome following COVID-19 infection. Vaccine responses are not as robust in the older age cohorts and durability of protection from infection can be compromised. In Israel, studies in those aged over 60 years have shown that a second booster dose provides considerable additional protection against infection, severe disease and death relative to three doses of the vaccine.

There is uncertainty about the trajectory of the COVID-19 pandemic. A number of new vaccines are in development including Omicron specific, multivalent and intranasal vaccines. The characteristics of these vaccines and the timelines for availability are unknown.

Offering a second booster to those most at risk of severe outcome at this time optimises their protection and may protect them against future variants. A second booster vaccine programme will not affect outbreak management.

It is likely that a third booster dose will be required for the cohorts detailed in the current advice later this year. However, as increasing numbers of the vaccinated population acquire infection, the presence of hybrid immunity (from vaccination and infection) in the population could impact the need for future booster doses.

To date, evidence does not support the need for a second booster for those other than detailed in the current advice. In healthy health care workers, only a marginal additional protective effect was seen. This is being kept under review. However, given the uncertainties, it would be prudent to have contingency plans in place to facilitate rapid rollout of booster vaccination for the general population. The cohorts to be vaccinated, choice of vaccine, optimal timing and duration of protection from further boosters remain to be determined.

Knowledge gaps lead to significant uncertainty in future planning and will require adaptability and agility in any planned response.

10.0 RECOMMENDATIONS

RECOMMENDATIONS

These recommendations are made recognising the uncertainties regarding the trajectory of SARS-CoV-2 infections and on a precautionary basis to protect those most at risk of a severe outcome. They are based on current evidence and will be reviewed when more information becomes available. See the prior recommendations for primary and first booster vaccination.

1. Efforts to increase primary and first booster vaccination uptake should remain a public health priority. mRNA vaccines (Comirnaty and Spikevax) are the preferred vaccines for use in Ireland.
   - Those aged 12 years and older, including those pregnant or breastfeeding, should complete a primary course and receive a booster vaccine (total of three doses)
   - Those aged 5-11 years should complete a primary course (total of two doses)
   - Those with immunocompromise associated with a sub optimal response to vaccines at the time of their primary or booster vaccination:
     a) aged 12 years and older should complete a primary course, an additional dose and a booster vaccine (total of four doses)
     b) aged 5-11 years should complete a primary course and an additional dose (total of three vaccine doses)
2. Those who have a contraindication to or who decline a primary course or booster dose of an mRNA vaccine should be offered a non-mRNA vaccine.
3. Those who have had previous SARS-CoV-2 infection should complete their primary and booster vaccination to optimise their protection.

Second Booster Vaccine

1. To maintain high levels of immunity in those most at risk of severe disease, a second booster dose of an mRNA vaccine is recommended for the following:
   a) those aged 65 years and older
   b) those aged 12 years and older with immunocompromise associated with a sub optimal response to vaccines
2. The second booster vaccine is recommended at least six months after the first booster. A minimum interval of four months may be used for operational reasons.
   a) For those aged 12-29 years, Comirnaty (0.3ml/30 micrograms) should be given
   b) For those aged 30 years and older, Comirnaty (0.3ml/30 micrograms) or Spikevax (0.25ml/50 micrograms) should be given
3. For those who have had a breakthrough infection following a first booster vaccine, it is recommended to defer the second booster vaccine for six months following infection onset. A minimum interval of four months may be used for operational reasons.
4. If an mRNA vaccine is contraindicated or declined, consideration may be given to using a non-mRNA vaccine as the second booster vaccine, following an individual benefit-risk assessment.

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- HPSC
- HSE Libraries Team
- NIAC SpR Research Panel
- NIAC members
- NPHET Modelling Team
- RCPI & DOH Communications Departments