National Immunisation Advisory Committee (NIAC)

INTERIM RECOMMENDATIONS REGARDING
BOOSTER DOSES OF COVID-19 VACCINE FOR

- THOSE AGED 80 YEARS AND OLDER
- THOSE AGED 65 AND OLDER IN LONG TERM CARE FACILITIES

NIAC | 07.09.2021

1. About NIAC

NIAC membership includes representatives 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 meets to consider new evidence about vaccines and provide advice to the Chief Medical Officer (CMO) 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 unvaccinated or incompletely vaccinated people of any age, particularly those aged 80 and older, those living in long term care facilities (LTCFs) aged 65 and older and those living with and/or caring for them are strongly encouraged to complete the primary vaccination course.

2. A booster dose of an mRNA vaccine should be given to all those aged 80 and older and those living in LTCFs aged 65 and older who have completed their primary course with any vaccine type. The booster dose should be given after an interval of six months following the last dose of an authorised COVID-19 vaccine and can be given at the same time or at any interval before or after seasonal influenza vaccine.

3. All those aged 80 and older, those living in long term care facilities aged 65 and older and those living with and/or caring for them should observe all recommended non-pharmaceutical interventions (public health and social measures) to limit COVID-19 exposure.

2. Executive summary

These interim recommendations reflect current evidence. Scientific evidence about COVID-19 vaccines is continuously evolving and being refined. The recommendations will be reviewed when more information becomes available.

- The most effective way to prevent hospitalisations, severe illness and death related to COVID-19 is to ensure that all eligible people are fully vaccinated.
- Access to and completion of a primary vaccine series by all countries is an essential prerequisite to controlling the SARS-CoV-2 pandemic on a global basis. Until global control is achieved, all countries remain at risk, and full return to normality will be compromised.
- High levels of vaccine effectiveness (VE) against hospitalisation, severe disease and death have been sustained throughout the Alpha and the Delta periods. There is some attenuation of protection against infection with time from primary vaccination, but good protection against severe disease is retained for at least six months.
- However, declines in VE with an increase in breakthrough infections in those aged 65 and older have been reported from Israel and the US. This decline may be due to waning immunity in older persons coupled with relaxation of non-pharmaceutical interventions and the emergence of the Delta variant.

- While the absolute numbers were small, the proportion of breakthrough cases increased with age and were highest in those aged 80 years and older. This supports the need for a booster dose for this age group.
- High levels of SARS-CoV-2 community transmission increase the risk of outbreaks in long term care facilities (LTCFs) for those aged 65 and older. Furthermore, residents of LTCFs may also have altered vaccine protection due to their age and underlying conditions. Although direct VE data in this population is limited, VE against infection with the Delta variant in the general population is reduced compared to that against other variants.
- Consideration regarding booster COVID-19 vaccination of LTCF residents must include the effect on reduction of transmission, hospitalisation, severe disease, and death resulting in less outbreaks and restrictions. Most LTCF residents and many older people in the community have suffered severe disruption to their quality of life, and a negative impact on their psychological, and social wellbeing over the past 18 months.
- NIAC and the Centers for Disease Control and Prevention (CDC) have recommended that COVID-19 vaccines and seasonal influenza vaccine may be administered at the same time or at any interval from each other. This will allow the uptake of both vaccines to be optimised in these groups.
- NIAC continues to examine evidence regarding waning immunity and reduced VE in other groups. These groups include those at increased risk of severe COVID-19 disease e.g., other older persons, and those with underlying medical conditions, as well as healthcare workers because of their vital role in providing essential health services.
- Consideration for boosters in other groups will take account of the impact of the high vaccination uptake in Ireland, and the continued VE of the primary series of vaccinations in the general population.

3. Background

On 22 June 2021, NIAC received a request from the Department of Health (DOH) for advice on the need for booster vaccines in the National COVID-19 Vaccination Programme

On 19 July 2021, NIAC advised the CMO that COVID-19 booster vaccines were likely to be required by some people. Groups mentioned for priority consideration were:

- Those aged 16 years and older with immunocompromise associated with a suboptimal response to vaccines (as listed in Chapter 5a, Table 5.2)
- Residents of long-term care facilities (LTCFs) aged 65 and older
- Those aged 80 years and older
- Frontline healthcare workers

On 25 August 2021, the CMO asked if NIAC had "*any further advice in relation to the requirement for additional doses of vaccine, with particular reference to the priority groups identified in your previous advice".*

On 30 August 2021, NIAC issued recommendations regarding an additional COVID-19 vaccine dose for those with immunocompromise associated with a suboptimal response to vaccines.

This document considers booster vaccines for the other priority groups listed above.

4. Global and national equity

In developing these recommendations, NIAC is conscious of the global demands on vaccine supplies and recognises that facilitating vaccination on a global level is not only important on a humanitarian and global equity basis, but essential to limit the threat of COVID-19 to our own population.

Vaccines are a global public good for the benefit of all. As NIAC considers if and to whom a booster vaccine should be offered, it is mindful that low and middle income countries (LMIC) have insufficient doses to protect those most at risk, such as older people and frontline healthcare workers. Less than 2% of people in LMICs have received a first dose of vaccine; it is estimated that many will not have received even one vaccine be until late 2023.

Ending the global pandemic is a universal goal and vaccination is a collective project. Failure to mitigate high community transmission of SARS-CoV-2 in any country through vaccination and other non-pharmaceutical interventions can create selection pressure for vaccine-resistant variants, prolonging the threat of the virus in Ireland and globally.

NIAC welcomes Ireland's participation in the COVAX Facility as part of Team Europe, which supports LMICs in accessing COVID-19 vaccines. NIAC encourages the Government to continue and expand upon its commitment to the global coordinated effort, based on the principle of solidarity, to foster equitable access to COVID-19 vaccines.

As advised by the World Health Organization (WHO) in their interim statement on COVID-19 vaccine booster doses, NIAC has taken into account evidence regarding the need for additional doses for the elderly and the global availability of vaccines in recommending a booster dose of an mRNA COVID-19 vaccine for those aged 80 years and older in the community and those aged 65 years and older living in LTCFs.

Further, the National Allocation Framework for Equitable Access to COVID-19 Vaccine(s) sets out a number of ethical principles, namely moral equality, minimising harm, fairness and reciprocity, which should guide the stewardship of scarce resources to ensure equitable access to vaccines, with prioritisation for those most in need.

In upholding the principles of moral equality minimising harm and fairness, NIAC is seeking to protect those who are most at risk from severe disease should they contract SARS-CoV-2 while recognising that access to a lifesaving vaccine by those most at risk should not depend on country of origin or residency.

In restricting booster doses to those for whom the evidence indicates that it will be safe, effective and is required to protect them from severe disease, the principle of fairness (which is related to distributive justice and equity), is realised, as priority is given to those worst off. As stated by the European Group on Ethics in Science and Technologies, *"It is more important than ever in this difficult time to uphold a form of solidarity that is inclusive of everyone, which recognises that respect is due to everyone, and not exclusive to those that live in our own town, region, or country".*

5. Rationale for additional doses

Additional COVID-19 vaccine doses may be needed because of:

i. Inadequate response to primary vaccine series
ii. Waning immunity following vaccination
iii. Reduced protection against variant(s) of concern

The rationale for additional doses may differ by vaccine product, epidemiological setting, risk group, and vaccine coverage rates.

i. Inadequate response to primary vaccine series

Because of underlying conditions or treatment, some individuals may be incapable of mounting an adequate protective response with a one or two dose primary series. An additional dose may be necessary to improve protection **(i.e., an extended primary vaccination course)** as recommended by NIAC on 30 August 2021.

ii. Waning immunity

There is no agreed immune correlate of protection. It is unclear if declining neutralising antibody (NA) titres correlate with declining effectiveness of COVID-19 vaccines against disease. Data on the immunogenicity of some COVID-19 vaccines shows that NAs persist for at least six to eight

months but waning of NAs is reported. While there may be some attenuation of protection against infection, protection against severe disease may be retained due to cell mediated immunity and rapid mobilisation of memory responses. If evidence of reduced effectiveness against moderate or severe disease of a full vaccine course emerges, an additional reinforcing dose (**booster dose**) may be needed.

iii. Reduced protection against variants of concern

Although evidence to date shows that current vaccines maintain high effectiveness against severe infection and hospitalisation against the Alpha and Delta variants, it is possible that a new vaccine-resistant variant may emerge which could result in need for a **booster** dose, possibly with a modified vaccine.

6. COVID-19 Vaccination

Duration of immunity

Immunity following natural infection lasts for at least six to nine months. The immunogenicity of COVID-19 vaccines is at least as good as that following infection. However, questions remain as to the duration of protection against disease.

In the six-month efficacy data for Comirnaty®, VE declined over time, but was maintained at 83.7% for four to six months after the second dose. A study of healthy adults showed that Spikevax® elicited binding and neutralising antibodies which persisted through six months after the second dose.

In a large US cohort study, Tartof et al reported that protection against COVID-19-related hospitalisation did not wane over time, with overall adjusted VE estimates of 87% at less than one month after being fully vaccinated, and 88% at five or more months after full vaccination.

While antibody levels decline over time, the clinical impact of this decline remains uncertain as protection is also influenced by cellular immunity and affinity maturation. Pouwels et al, found that Comirnaty® and Vaxzevria® VE against infection waned over time, with this decline more marked in those aged 35 – 64 years compared with those aged 18 –34 years. This study also reported that the decline in VE over time is more gradual with Vaxzevria® compared to Comirnaty®, with both vaccines having similar effectiveness against symptomatic infections by 3.8 months following vaccination. However, across all age groups and during the Delta period, high levels of protection against symptomatic disease were maintained. The authors speculated that *"whilst protection against hospitalisation and death is maintained, "booster" vaccinations may not be needed, particularly since infection post vaccination may provide a natural antibody boost. However, declines in immunity against infection demonstrate this needs to be monitored closely".*

Conversely, the Israeli Ministry of Health reported a rise in infection rates over time following initiation of their vaccination rollout and noted an associated rise in rates of severe disease with 60% of severe cases fully vaccinated.

Mizrahi et al conducted a retrospective cohort study comparing the incidence rates of breakthrough infections between early and late vaccinated HCWs, aged 16 years and older. They reported a significant correlation between time from vaccine and protection afforded against SARS-CoV-2 infection. The study had a number of limitations e.g., those who were first vaccinated were those most at risk of infection, which may have contributed to the higher infection rate.

Goldberg et al reported data from all SARS-CoV-2 infections between July 11 to July 31, 2021, in Israel. People aged 60 years or older who were fully vaccinated in March 2021 were 1.7 times more protected against severe COVID-19 compared to those who were fully vaccinated in January 2021.

HIQA is currently undertaking review of the evidence regarding duration of immunity post vaccination which may inform future recommendations.

Vaccine effectiveness

COVID-19 vaccines are highly effective in protecting against symptomatic disease and severe illness caused by the Alpha and preceding variants. Protection is less reliably achieved in the immunosuppressed.

In most EU/EEA countries, including Ireland, the Delta variant is the predominant circulating strain. In the UK, data show that one dose of Comirnaty® or Vaxzevria® is insufficient to protect against symptomatic infection with the Delta variant, but two doses of either vaccine 12 weeks apart increased effectiveness to 88% and 67% respectively.

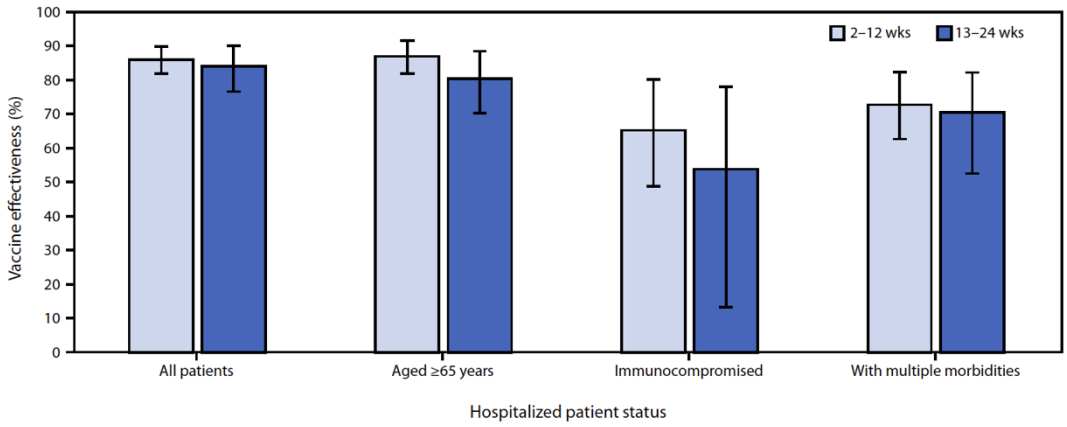
Data from South Africa showed that COVID-19 vaccine Janssen® was 71% effective in preventing hospitalisation and 96% effective in preventing death from the Delta variant, with durable protection up to 8 months.

Two studies from the US reported on mRNA VE from March to July 2021. In one, Delta caused 94% of all COVID-19 cases, with a significantly higher rate of breakthrough infections (17.4% Delta compared with 5.8% for all other variants), although only 8.4% of all COVID-19 cases occurred in fully vaccinated individuals and few required hospitalisation. Delta breakthrough infection in vaccinated cases had a high viral load, similar to that observed in unvaccinated patients with COVID-19.

The second US study showed that overall VE against COVID-19 associated hospitalisation during the same period was 86%. VE was 90% in immunocompetent persons, but only 63% in the immunocompromised. VE among patients with illness onset during March–May 2021 was 87%, and was 84% among those with illness onset during June–July 2021 (the time when Delta became

dominant). Reductions in VE between 2-12 weeks and 13-24 weeks after receiving a second dose were not significant (Figure 1). Longer follow up is required as the duration of monitoring during the Delta period was short.

Figure 1: Sustained vaccine effectiveness against COVID-19, by patient status and interval since vaccination in 21 medical centres in 18 US States March – July 2021. Source: CDC



A preprint of data from a UK community surveillance study reported the impact on VE of the Delta variant. Overall VE for those fully vaccinated remained high. In the Alpha and Delta dominant periods, VE for Comirnaty® was 78% and 80% respectively, and for Vaxzevria® was 79% and 67%. When restricting the analysis to new PCR positive cases with higher viral burden, VE was higher against Alpha than Delta - Comirnaty®, 94% down to 84% and Vaxzevria®, 86% down to 70%. There was no evidence that VE varied by dosing interval, but protection was higher among those vaccinated following a prior infection and in younger adults. Delta variant infections occurring following two vaccinations had similar peak viral burden to those unvaccinated. Both vaccines reduced the number of new Delta infections, but effectiveness and attenuation of peak viral burden was reduced compared with the Alpha period.

Data from Qatar in a population in which a large proportion of fully vaccinated persons had received their second dose several months earlier, showed VE of Comirnaty® against symptomatic or asymptomatic Delta infection was 64.2%, 14 days or more after one dose but was only 53.5%, 14 days or more after the second dose. Corresponding VE for Spikevax® was 79.0% and 84.8% respectively. Effectiveness against any severe, critical, or fatal COVID-19 disease due to Delta was 89.7% for Comirnaty® and 100% for Spikevax® 14 days or more after the second dose.

The Delta variant is characterised by very high transmissibility with an estimated basic reproduction rate of between five and eight. While antibody levels can decline over time, VE is sustained for at least six to eight months and remains high in the general population, particularly against hospitalisation and severe disease. Delta breakthrough infections have been reported to be associated with similar viral burden in both vaccinated and unvaccinated, however levels of culturable virus and duration of viral shedding are reduced in the vaccinated with breakthrough

infection. This suggests that transmission is reduced from vaccinated persons who have breakthrough infection.

The relative contributions of waning immunity, circulation of the Delta variant, and relaxation of non-pharmaceutical measures to community transmission and the increase in case numbers remains to be clarified.

Risk factors for breakthrough infections

Since the Delta variant became the predominant circulation strain, reports of breakthrough infections have increased primarily in the immunocompromised, residents of LTCFs and older persons. some resulting in hospitalisation, ICU admission and death.

In Israel, a decline in VE with an increase in breakthrough infections in those aged 65 and older has been reported and prompted initiation of a booster vaccine campaign. Details on age specific risk and outcomes are not yet available.

In the UK, despite some increase in numbers infected, with attenuation of protection against infection in the Delta period, VE against hospitalisation has been maintained across the ages including for those aged 65 and older.

In Ireland, the current increase of viral transmission in the community is echoed in a rise in the 7-day age specific incidence of COVID-19 in those aged 65 and older, with highest rates in those 80 years and older. Overall, VE has been maintained with the majority of breakthrough infections associated with mild illness.

i. Older persons

In the US, Nace et al found while older adults (mean age 84.8 years) responded to COVID-19 vaccines, the strength and duration of the response may be shortened by age, sex, and other co-morbidities.

Whitaker et al in a large UK cohort study, did not report the same decline in VE by age. The study period was from December 2020 to June 2021. VE was maintained across all age groups with similar VE in the 16-64 year group (84.3%) and those aged 65 years and older (84.7%).

Among fully vaccinated persons in a large US cohort study, VE against infection was lowest for those aged 65 years and older (61%); VE against hospitalisations was 92% for those 16-44 years, and 86% for those aged 65 years and older.

In Ontario, Canada, 14 December to 7 August 2021, only 0.03% of fully vaccinated individuals became infected. Breakthrough cases accounted for 0.8% of hospitalisations and 1.2% of deaths (Figure 2). While the absolute numbers were small, the proportion of breakthrough cases increased with age and were highest in those aged 80 years and older (see Figures 3 and 4 and Table 1).

Figure 2. Proportion of confirmed COVID-19 cases, hospitalisations (including ICU admissions), and deaths among unvaccinated, partially vaccinated, and breakthrough cases: Ontario, 14 December 2020 to 7 August 7, 2021. Source: Public Health Ontario

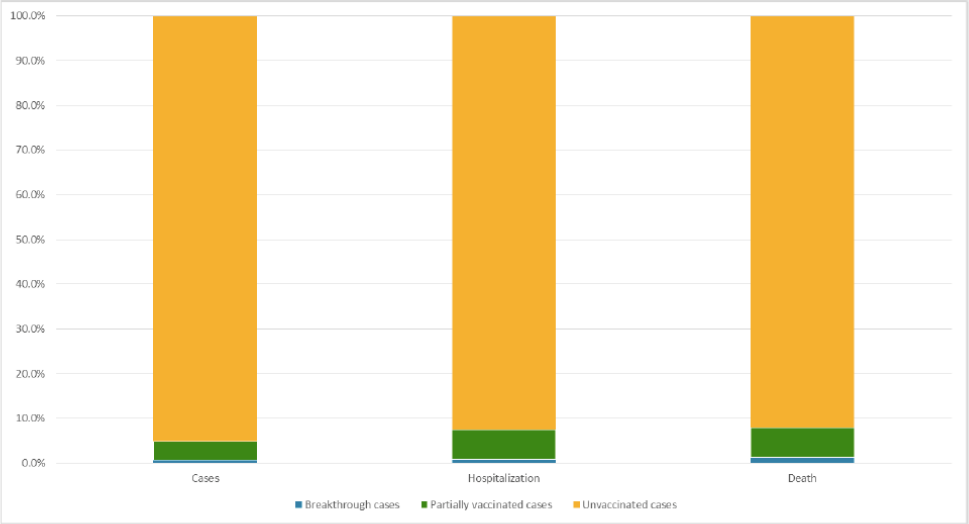


Figure 3: Hospitalisations (including ICU admissions) among partially vaccinated and breakthrough confirmed cases of COVID-19, Ontario: December 14, 2020, to August 7, 2021. Source: Public Health Ontario.

Note: The denominators used to calculate the age-specific proportions for hospitalisations is the total number of unvaccinated, partially vaccinated and breakthrough cases in each age group (see Table 1).

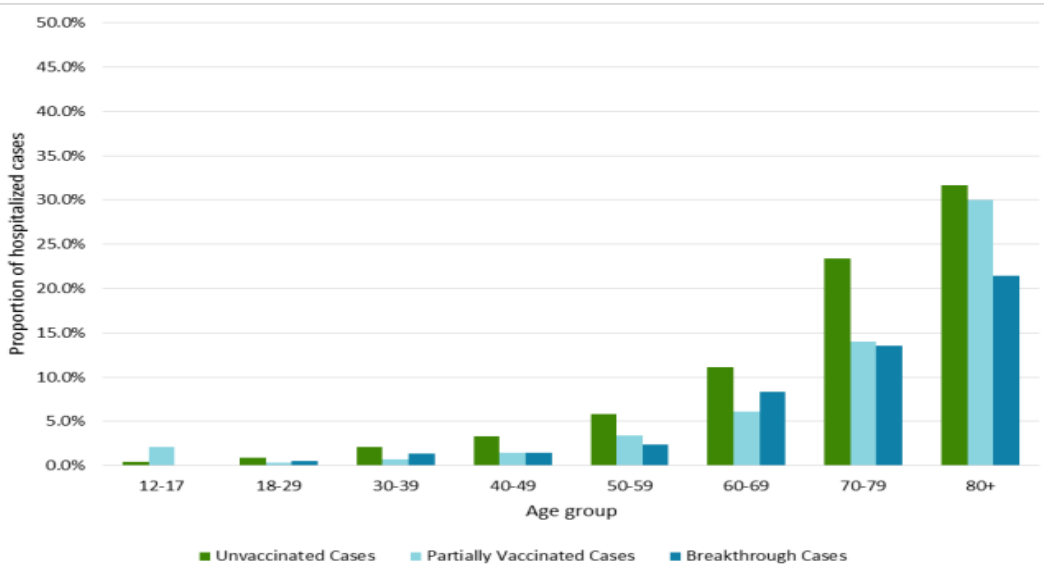


Figure 4: Fatalities among unvaccinated, partially vaccinated and breakthrough confirmed cases of COVID-19: Ontario, December 14, 2020, to August 21, 2021. Source: Public Health Ontario.

Note: The denominators used to calculate the age-specific proportions for deaths is the total number of unvaccinated, partially vaccinated and breakthrough cases in each age group (see Table 1).

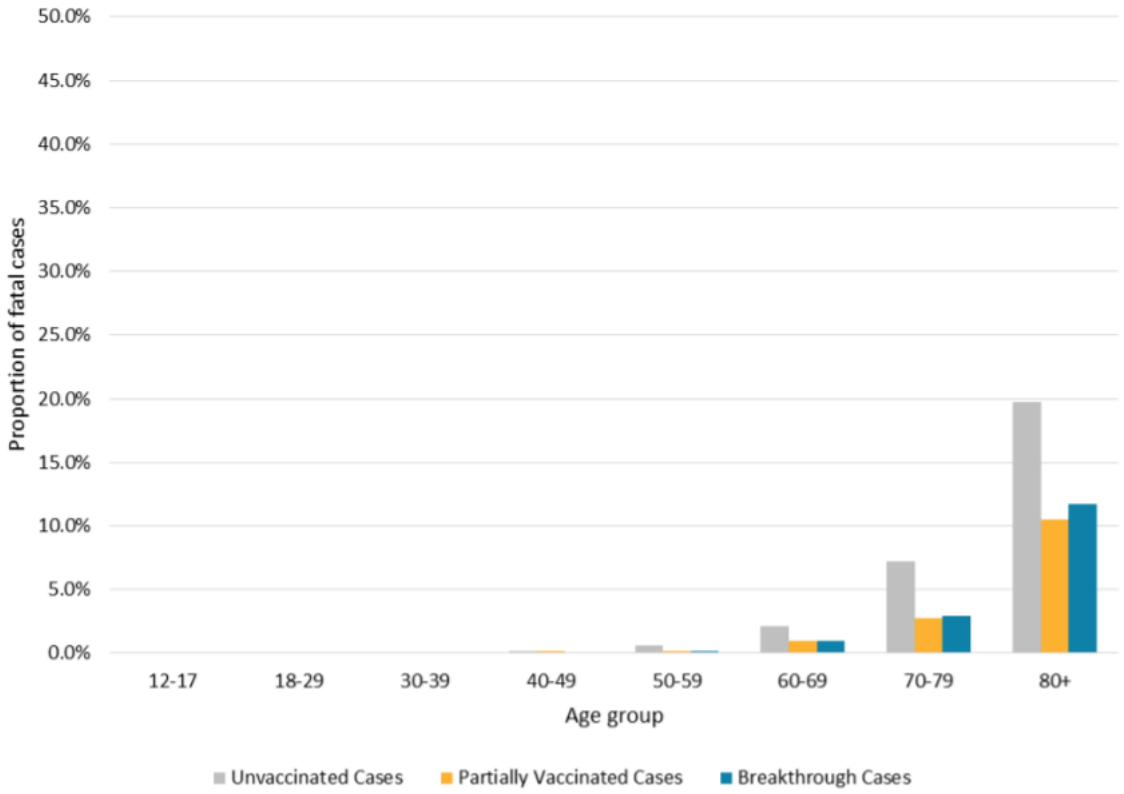


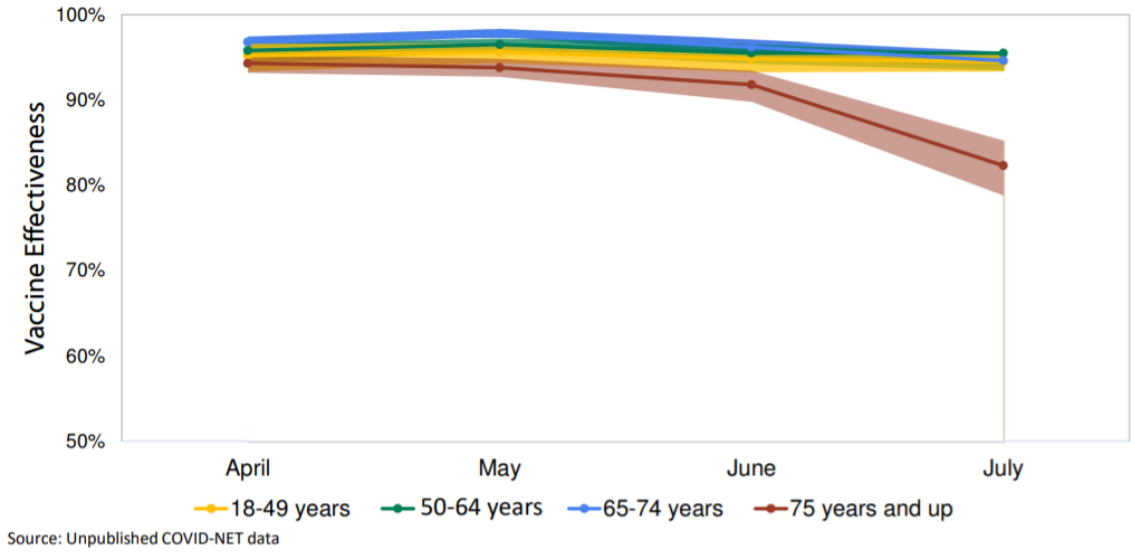
Table 1: Deaths among partially vaccinated breakthrough and confirmed cases of COVID-19: Ontario, December 14, 2020, to August 21, 2021, Source: Public Health Ontario.

Age (years)*	Fatal symptomatic and asymptomatic partially vaccinated cases: Number (%)	Fatal symptomatic and asymptomatic breakthrough cases: Number (%)	Fatal unvaccinated cases: Number (%)	Unvaccinated cases
12-17	0 (0.0%)	0 (0.0%)	1 (<0.1%)	24,662
18-29	0 (0.0%)	0 (0.0%)	23 (<0.1%)	100,148
30-39	0 (0.0%)	0 (0.0%)	49 (0.1%)	66,272
40-49	5 (0.2%)	0 (0.0%)	111 (0.2%)	56,762
50-59	7 (0.2%)	1 (0.2%)	315 (0.6%)	54,145
60-69	37 (1.0%)	5 (1.0%)	656 (2.1%)	31,643
70-79	60 (2.7%)	6 (2.9%)	1,059 (7.2%)	14,745
80+	217 (10.5%)	51 (11.7%)	2,295 (19.7%)	11,631

US data regarding hospitalisations among fully vaccinated patients shows that VE remained high for all age groups between April and July 2021, apart from those over 75 years of age who had reduced VE in July 2021 although VE remained above 80% for all groups (Figure 5). This trend is of concern and will be monitored.

Figure 5: Preliminary VE against COVID-19–associated hospitalisation among fully vaccinated patients aged 18 years and older, by age group and month. Source: ACIP

Note: Fully vaccinated patients received both doses of Comirnaty® or Spikevax® with second dose received 14 days or more before hospitalisation, or a single dose of COVID-19 vaccine Janssen 14 days or more before hospitalisation.



ii. Residents of LTCFs aged 65 and older

High levels of SARS-CoV-2 community transmission increase the risk of outbreaks in LTCFs for those aged 65 and older and increase the risk of infection for those unvaccinated or partially vaccinated. Furthermore, residents of LTCFs may also have reduced vaccine protection due to their age and underlying conditions, although direct VE data in this population is limited. VE against infection with Delta in the general population is reduced compared with that against other variants.

In Israel, a decline in VE with an increase in breakthrough infections in those aged 65 and older has been reported and prompted initiation of a booster vaccine campaign. Details on age specific risk and outcomes are expected.

In nursing homes in the US, mRNA VE against SARS CoV-2 infection for the fully vaccinated in the pre-Delta period was 75%, declining to 53% in the Delta period. This decline may have resulted from waning immunity in older persons coupled with relaxation of non-pharmaceutical measures and the emergence of the Delta variant.

In Ireland, the Health Protection Surveillance Centre has reported 46 COVID-19 outbreaks with 533 associated cases between 27 June and 30 August 2021. The number of outbreaks was highest between 9 and 23 August 2021, although five outbreaks have been reported in the first two days of the week of 30 August 2021. Approximately 95% of the associated cases were reported since the beginning of August 2021.

Data is available on 431 of the 533 cases. Ten of the 431 cases (2.3%) were hospitalised (age range 59-95, median age 88) and 8 (1.9%) cases died (age range 77-94, median age 85). The eight deaths were spread across five outbreaks. There is limited data on vaccination status; where known, 95% residents and 81% staff were vaccinated.

iii. Healthcare workers (HCWs)

Infections among HCWs were common during the pre-vaccination phase of the pandemic. It is thus important to evaluate the ongoing risks to HCWs following widespread vaccination in this group.

In a large prospective cohort study of HCWs in England, Hall et al. reported VE of 85% seven days after two doses of Comirnaty® with just four infections per 10,000 person-days in the vaccinated group. The Alpha variant was dominant at the time of this study.

Keehner et al. reported similar results in a US cohort across two healthcare facilities, monitored from December 2020 to February 2021. A SARS-CoV-2 positivity rate of 0.05% in vaccinated healthcare staff, was seen versus 2.6% in those not vaccinated.

A German study published in August 2021 reported a rate of breakthrough infections of 0.35% among 1,137 fully vaccinated HCWs in a healthcare centre. Only mild symptoms were reported in the four HCWs who tested positive for SARS-CoV-2.

A study from Ontario, Canada (Abe et al) reported vaccine responses among staff and residents of a LTCF. Residents demonstrated high rates of seroconversion following two doses of vaccine; 92.2% (106/130) of residents had seroconverted for both spike and its receptor binding domain. The staff also showed robust antibody responses to both the original SARS-CoV-2 virus and Beta and Gamma variants, with higher antibody responses in staff than in residents.

A large Italian cohort study showed that the risk of SARS-CoV-2 infection decreased significantly following vaccination, and that this decreased risk was maintained for up to 112 days following first vaccination dose (incidence risk ratio 0.21).

In a study of HCWs in a large health facility in the US, mRNA VE exceeded 90% between March and June 2021 but fell to 65.5% in July 2021. This decline occurred at the same time as the rapid increase in the Delta variant infections as well as at the end of the mask mandate in mid June 2021, highlighting the importance of rapidly re-instating non-pharmaceutical interventions.

In a large US cohort study, Fowlkes et al reported VE in frontline workers (including HCWs) in eight US locations. This study did not measure rates of severe disease or hospitalisations and included pre-Delta and Delta periods. While VE against infection declined over time (85% in those less than 120 days since vaccination compared with 73% in those more than 150 days post vaccination), differences in VE were not statistically significant. Preserving continuity of services, and the wellbeing of healthcare staff, are important factors in making recommendations regarding vaccination of HCWs.

There is insufficient evidence for booster vaccination of HCWs. However, any HCW who has not completed a primary vaccine schedule is strongly advised to do so.

Safety and effectiveness of booster vaccines

There is limited data on the safety and effectiveness of booster doses of COVID-19 vaccines. In a press release, Pfizer reported that data in individuals who received a third dose of Comirnaty® show a favourable safety profile and robust immune responses. The booster dose elicited significantly higher neutralising antibody titres against the initial SARS-CoV-2 virus (wild type), and the Beta and Delta variants, compared to the levels observed after the two-dose primary series.

Wu et al reported the results of a preliminary evaluation of Spikevax® and a mRNA-1723.351 modified vaccine assessing immunogenicity against the less sensitive Beta strain. In the study, a half dose (50 microgram) booster was given 5.9 to 7.5 months after receipt of the second vaccine dose to participants aged 27 -76 years. The vaccines were found to have a favourable safety profile consistent with the known safety profile of Spikevax® and to be immunogenic. There were significant increases in neutralising titres against wild-type, Beta and Gamma variants with neutralising titres against wild-type exceeding those following the primary immunisation.

Publication of real world effectiveness data of booster vaccines in specific risk groups, e.g., residents of LTCFs, older persons, and those with underlying medical conditions, as well as healthcare workers and the general population is awaited.

The Israeli Health Ministry shared preliminary findings of their population-based booster programme at the EU meeting for National Immunisation Technical Advisory Groups on 30 August 2021. Over one million booster doses of Comirnaty® have been given to those aged 60 years and older and about 500,000 doses to those aged 40 – 59 years. No safety concerns have been identified with a similar profile but lower rate of systemic and local reactions than after first or second doses. More detail on the rates of breakthrough hospitalisations and serious disease and of the effectiveness of the third dose of Comirnaty® in preventing adverse outcomes is awaited.

In the UK, Flaxman et al included data on administration of a third dose of Vaxzevria® 44 – 45 weeks after the primary series and found that antibodies were significantly higher following a

third dose compared with the response 28 days after a second dose. Neutralising activity was also increased against the Alpha, Beta and Delta variants. No safety concerns were identified.

Data pertaining to a second dose of COVID-19 Vaccine Janssen® is awaited with two current studies underway. A recent press release indicates that data will be made available soon.

On the 12 August 2021, the Food and Drug Administration in the US updated the emergency use authorisations for both Comirnaty® and Spikevax® to allow for the use of an additional dose in certain immunocompromised individuals i.e., solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

To date, the European Medicines Agency (EMA) has not authorised additional or booster doses for any COVID-19 vaccine so such use would currently be off label. However, the EMA is currently assessing data on an additional dose in the immunocompromised for both Comirnaty® and Spikevax® and has also begun assessing data on booster doses to be given six months after the second dose for Comirnaty® to consider whether updates to the licensed product information are appropriate.

The EMA has stated that *"Advice on how vaccinations should be given remains the prerogative of the national immunisation technical advisory groups (NITAGs) guiding the vaccination campaigns in each EU Member State. These bodies are best placed to take into account the local conditions, including the spread of the virus (especially any variants of concern), the availability of vaccines and the capacities of national health systems".*

Timing and selection of booster doses

Booster doses have been given from two to many months following completion of the primary course. The reason for administration of a booster dose will influence the recommended time interval.

When an additional dose is given as a reinforcing or a booster dose, then the optimal time interval will depend on the dynamics of the decline in VE and may vary depending on the vaccine first used. Overall, an interval of six months is reasonable and is in line with the booster interval that the EMA is currently assessing.

Most of the evidence regarding booster vaccination relates to the use of an mRNA vaccine. There are limited data on the use of adenoviral vector booster vaccines.

In the limited available data, booster doses have consisted of an homologous vaccine. Results of studies carried out in the primary immunisation series indicate that an mRNA vaccine following a viral vector vaccine is safe and immunogenic.

Co-administration

NIAC has previously advised that COVID-19 vaccines and other vaccines including seasonal influenza vaccine may be administered at the same time or at any interval. As it is not known if COVID-19 vaccine reactogenicity is increased with co-administration, vaccines should preferably be given in different limbs.

This is consistent with recommendations from CDC.

7. International recommendations

EU/EEA

The European Centre for Disease Control and Prevention published interim public health considerations for the provision of additional COVID-19 vaccine doses on 1 September 2021 which states

"Consideration could also be given to providing an additional dose as a precautionary measure to older frail individuals, in particular those living in closed settings (e.g. residents of long-term care facilities)."

and

"Close monitoring of vaccine effectiveness data and breakthrough infections, particularly among vulnerable groups at risk of severe COVID-19 and among those living in closed settings, should be continued, and decisions adapted accordingly, should a substantial decrease in effectiveness be noted in one or more population groups".

Austria has recommended booster vaccines for other groups such as older persons, LTCF residents, those with underlying medical conditions, those who received an adenoviral vector vaccine course and healthcare workers.

France has announced plans to offer booster doses for those aged 65 and over commencing in October 2021.

Germany commenced a booster programme on 1 September 2021, offering an additional mRNA vaccine dose to *"those over 80 years; residents in nursing homes or other facilities with vulnerable individuals; residents in facilities of integration assistance, individuals in need of care in their own domesticity and individuals with a complete vector based vaccination".*

In Hungary, all those aged 18 years and older are eligible for an additional dose after at least four months since the completion of the primary vaccination series. The additional dose is particularly recommended for older persons, those with underlying medical conditions or immunosuppressed individuals.

A decision about booster vaccines is currently under discussion in thirteen EU/EEA countries.

UK

On 30 June 2021, the Joint Committee on Vaccination and Immunisation (JCVI) issued interim advice about a booster vaccine programme.

The first stage of the booster programme in the UK would include adults aged 16 years and over who are immunosuppressed, those living in residential care homes for older adults, all adults aged 70 years or over, adults aged 16 years and over who are considered clinically extremely vulnerable, and frontline health and social care workers. A second stage could follow as soon as practicable and would include all adults aged 50 years and over, adults aged 16 to 49 years who are in an influenza or COVID-19 at risk group, and adult household contacts of immunosuppressed individuals.

On 1 September 2021, JCVI advised that *"a third primary dose be offered to individuals aged 12 years and over with severe immunosuppression in proximity of their first or second COVID-19 vaccine doses in the primary schedule."*

Further details about the booster vaccination programme are awaited.

US

On 13 August 2021, the Advisory Committee on Immunization Practices approved "*the third dose of the Pfizer-BioNTech and Moderna COVID-19 vaccines for immunocompromised populations ≥12 years old and ≥18 years old, respectively."*

On 18 August 2021, a joint statement from Public Health and Medical Experts was released by the U.S. Department of Health and Human Services with a proposed plan for COVID-19 booster vaccines. The groups that "will likely be eligible for a booster vaccine" include older persons, LTCF residents and healthcare workers.

Further details are awaited.

Israel

Israel began a national booster vaccine programme at the end of July 2021 using Comirnaty®, following an increase in COVID-19 Delta infections. The programme initially targeted older persons. Currently, a booster dose of vaccine is recommended for anyone aged 12 years and older, after a minimum of five months following their primary course.

8. Conclusions

The focus must remain on completing vaccination of the unvaccinated or incompletely vaccinated.

NIAC agrees with the WHO that national vaccination programme policy decisions to add a booster dose should take into account both the strength of evidence regarding the need for these doses and global availability of vaccines. Offering booster doses to a large proportion of a population in

one country when many in low-resource countries have not yet received even a first dose undermines the principle of national and global equity. Prioritising booster doses over speed and breadth in initial dose coverage may also damage the prospects for global mitigation of the pandemic, with severe implications for the health, social and economic well-being of people globally.

There is some attenuation of protection against infection with time from primary vaccination, but good protection against severe disease is retained. However, declines in VE with an increase in breakthrough infections in those aged 65 and older have been reported from Israel and the US. This decline may have resulted from waning immunity in older persons coupled with relaxation of public health measures and the emergence of the Delta variant. While the absolute numbers were small, the proportion of breakthrough cases increased with age and are highest in those aged 80 years and older.

This evidence of reduced effectiveness supports the need for a booster dose in this age group.

High levels of SARS-CoV-2 community transmission increase the risk of outbreaks in LTCFs for those aged 65 and older. Furthermore, the population residing in LTCFs may also have altered vaccine protection due to their age and underlying conditions, although direct VE data in this population is limited. VE against infection with the Delta variant in the general population is reduced compared to that against other variants.

Consideration of booster COVID-19 vaccination for LTCF residents must include the effect on severe disease, hospitalisation and death, and the reduction in disease transmission resulting in less outbreaks and restrictions. Most LTCF residents and many older people in the community have suffered severe disruption to their quality of life and the consequent impact on their psychological and social wellbeing over the past 18 months.

NIAC and the CDC recommend that COVID-19 vaccines and seasonal influenza vaccine may be administered at the same time or at any interval. This will allow the uptake of both vaccines to be optimised in these groups.

NIAC continues to examine evidence regarding booster vaccines for those with waning immunity and reduced effectiveness in other groups. These groups include those at increased risk of severe COVID-19 disease e.g., other older persons and those with underlying medical conditions, as well as HCWs because of their vital role in providing essential health services.

Any consideration for boosters in other groups will take account of the impact of the high vaccination uptake in Ireland, and the continued VE of the primary series of vaccinations in the general population.

These interim recommendations reflect current evidence. Scientific evidence about COVID-19 vaccines is continuously evolving and being refined. These recommendations will be reviewed when more information becomes available.

9. Recommendations

1. All unvaccinated or incompletely vaccinated people of any age, particularly those aged 80 and older, those living in long term care facilities (LTCFs) aged 65 and older and those living with and/or caring for them are strongly encouraged to complete the primary vaccination course.

2. A booster dose of an mRNA vaccine should be given to all those aged 80 and older and those living in LTCFs aged 65 and older who have completed their primary course with any vaccine type. The booster dose should be given after an interval of six months following the last dose of an authorised COVID-19 vaccine and can be given at the same time or at any interval before or after seasonal influenza vaccine.

3. All those aged 80 and older, those living in long term care facilities and those living with and/or caring for them should observe all recommended non-pharmaceutical interventions (public health and social measures) to limit COVID-19 exposure.

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