ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee (NIAC)

RECOMMENDATIONS

BOOSTER DOSES OF COVID-19 VACCINE FOR

- HEALTHCARE WORKERS
- THOSE AGED 16-59 YEARS WITH UNDERLYING CONDITIONS
- THOSE AGED 50-59 YEARS

NIAC |15.11.2021

About NIAC

NIAC membership includes representatives from the Royal College of Physicians of Ireland, its Faculties and Institutes, the Royal College of Surgeons of Ireland the Irish College of General Practitioners, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory, and lay members. Meetings are attended by observers from the Department of Health, the Health Service Executive. 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 (CMO) 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

1. All those who are unvaccinated or incompletely vaccinated are strongly recommended to complete a primary COVID-19 vaccination course. Seasonal influenza vaccine can be given at the same time, to those for whom it is recommended.

2. All must continue to observe all recommended public health and social measures. The use of masks, physical distancing, hand hygiene, and ventilation of indoor spaces are key to reducing transmission of SARS-CoV-2.

   Booster vaccines will not immediately contribute to outbreak management and do not take the place of public health and social measures.

3. In addition to prior recommendations, a booster dose of an mRNA vaccine is recommended in order of priority for
   - Healthcare workers, including those pregnant (priority for frontline HCWs)
   - Those aged 16-59 years with underlying conditions as listed in Table 5a.2 of Chapter 5a COVID-19 in the Immunisation Guidelines for Ireland and all residents in long term healthcare facilities
   - Those aged 50-59 years

   For those aged 16-29 years, a full dose of Comirnaty (0.3ml/30 micrograms) should be given six months or longer following completion of a primary two dose course of any COVID-19 vaccine.

   For those aged 30 years and older, a full dose of Comirnaty (0.3ml/30 micrograms) or a half dose of Spikevax (0.25ml/50 micrograms) should be given six months or longer following completion of a primary two dose course of any COVID-19 vaccine.

   A minimum interval of five months may be used when necessary for operational reasons. Recipients of COVID-19 vaccine Janssen should receive an mRNA booster dose after an interval of three months.

4. Those who have a breakthrough infection following a primary vaccination course should defer booster vaccination for at least six months following infection onset.

5. If an mRNA vaccine is contraindicated, consideration can be given to boosting with an authorised non-mRNA vaccine following an individual benefit-risk assessment.

These recommendations reflect current evidence and will be reviewed when more information becomes available.

1. Executive summary

- Access to and completion of a primary COVID-19 vaccine series in all countries is an essential prerequisite to control the global SARS-CoV-2 pandemic. Until worldwide control is achieved, all countries remain at risk.
- In Ireland, COVID-19 vaccine uptake is very high, yet numbers of infection, hospitalisation, severe disease and death have increased. Most of those hospitalised with COVID-19 have been unvaccinated. However, as vaccination rates are so high, the proportion of those vaccinated who are admitted to hospital is increasing.
- The high transmissibility of the Delta variant, waning of immunity following vaccination, increasing socialisation and the time lapse since vaccination have contributed to the surge in new infections and increased the risk of severe disease in those with underlying conditions.
- Age, immune status, and the presence of underlying conditions are the main factors in determining the severity of breakthrough disease.
- Of fully vaccinated patients admitted to ICU In Ireland between 1 April and 30 October 2021, 98% had an underlying condition and 35% died.
- Booster doses given to those aged 80 years and older have been followed by a sharp decline in case numbers in that age group.
- Vaccine effectiveness (VE) in preventing symptomatic disease is similar in healthcare workers (HCWs) and the general population.
- HCWs accounted for less than 5% of confirmed cases reported between 15 and 28 October 2021. The most likely source of transmission was known in about 60% of cases. Of these, less than 2% were acquired in a healthcare setting.
- Booster doses for HCWs will reduce their incidence of breakthrough infection, provide additional protection for patients, and help support continuity of healthcare services.
- The risk of COVID-19 related hospitalisation in those aged 16-59 years is higher for those with underlying conditions.
- The risk of vaccinated people aged 50-59 years requiring hospitalisation and becoming seriously ill and dying is higher than in younger age groups.
- Booster doses for those aged 16-59 years with an underlying condition, residents of long-term healthcare facilities, and others aged 50-59 years will reduce their risk of severe breakthrough infection.
- Booster doses of mRNA vaccines have not shown any unexpected short term safety concerns. The risk of myocarditis or other rare adverse reaction following an mRNA booster dose has yet to be characterised and will be closely monitored. As a precaution, Comirnaty is the recommended booster vaccine for those aged 16-29 years.
- NIAC continues to examine new evidence regarding the durability of protection of the primary vaccine series in other groups, e.g., younger age groups who received adenoviral vector vaccines.

2. Background

On 19 July 2021, NIAC advised the CMO that COVID-19 booster vaccination was 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 5a.2)
- Residents of long-term healthcare facilities aged 65 years and older
- Those aged 80 years and older
- Frontline healthcare workers

On 30 August 2021, NIAC issued recommendations regarding an additional COVID-19 vaccine dose for those aged 12 years and older with immunocompromise associated with a suboptimal response to vaccines.

On 7 September 2021, NIAC issued recommendations regarding a booster dose of COVID-19 vaccine for those aged 80 years and older and those aged 65 and older in long term healthcare facilities.

On 18 October 2021, NIAC issued an overview of recommendations regarding a booster dose of COVID-19 vaccine for those aged 60 to 79 years. The evidence and rationale for these recommendations was issued on 22 October and updated on 29 October 2021.

On 1 November 2021, NIAC issued an overview of recommendations regarding a booster dose of COVID-19 vaccine for healthcare workers (HCWs).

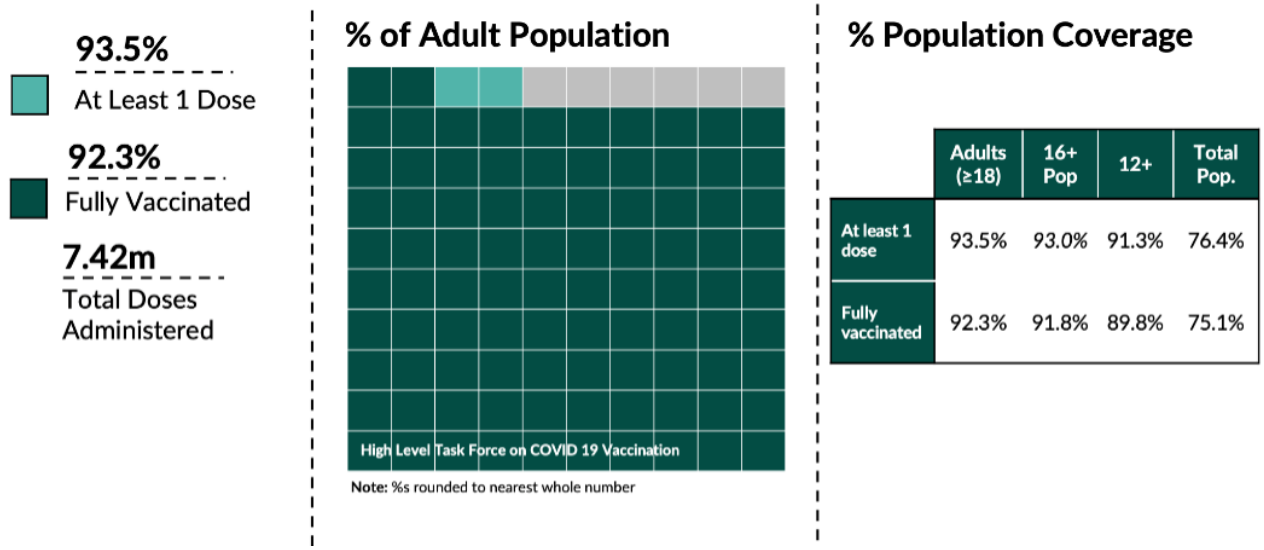
On 3 November 2021, NIAC updated recommendations regarding selection, dose and timing of booster doses of COVID-19 vaccine.

This document provides the evidence and rationale for recommending booster doses of COVID-19 vaccine for HCWs, those aged 16-59 years with underlying conditions, residents of long-term healthcare facilities under 65 and all others aged 50-59 years.

3. COVID-19 situation in Ireland

Vaccination is the most effective way to prevent hospitalisations, severe illness and death related to COVID-19. Thus, it is important to ensure that all eligible people are fully vaccinated. In Ireland, more than 75% of the total population and 92% of those aged 16 years and older are fully vaccinated. (Figure 1)

Figure 1: COVID-19 vaccine uptake Ireland 19 October 2021 (Source: High Level Task Force)



	Adults (≥18)	16+ Pop	12+	Total Pop.
At least 1 dose	93.5%	93.0%	91.3%	76.4%
Fully vaccinated	92.3%	91.8%	89.8%	75.1%

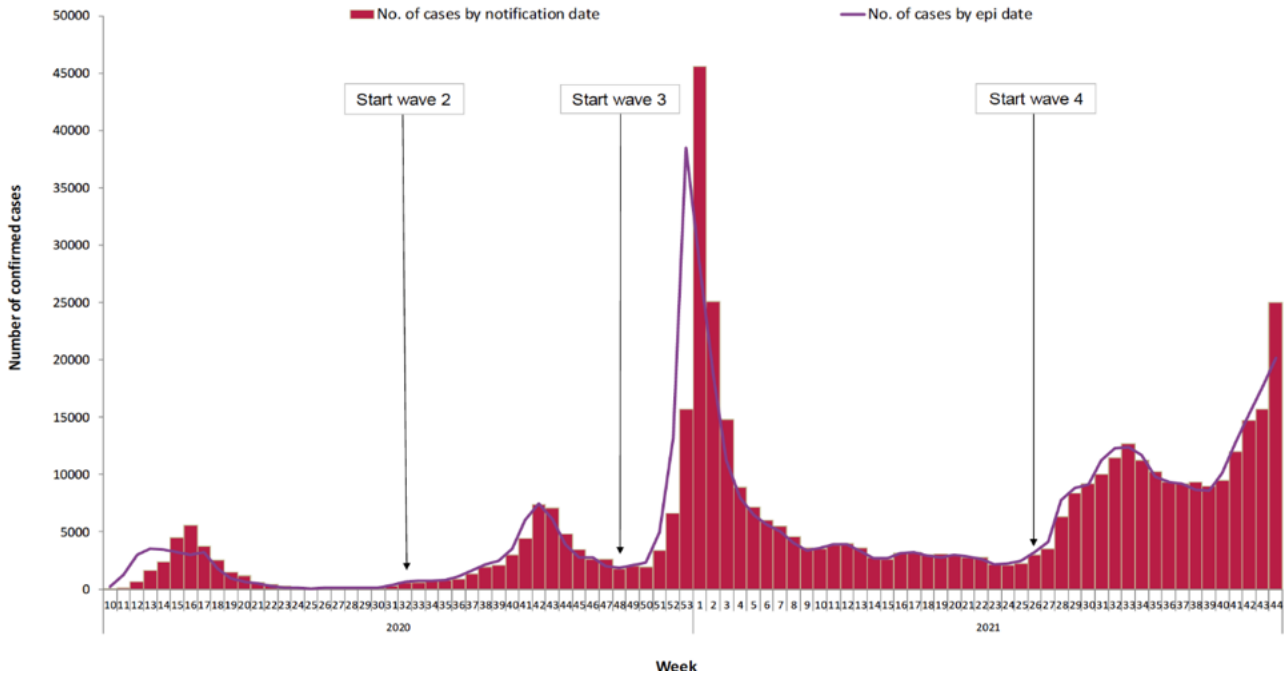
Vaccine uptake increases with age, with more than 97% of those aged 50 years and older fully vaccinated (Table 1).

Table 1: COVID-19 Vaccine uptake by age group Ireland 19 October 2021.) Source: DOH

Age Group	50-59	60-69	70-79	80+
Fully Vaccinated	96%	97%	100%	100%

Ireland is currently undergoing a surge in case numbers despite the high vaccine uptake (Figure 2). This is likely due to a number of factors, including the highly transmissible Delta variant, waning of immunity over time and the opening up of society with an increase in socialisation. These factors increase the risk of breakthrough infections and the risk of severe COVID-19 in those aged 50 and older and those with underlying conditions.

Figure 2: Number of confirmed cases of COVID-19 by notification week from March 2020 8 November 2021. Source: HPSC



Between 19 October and 1 November 2021, there were 33,095 cases, an incidence of 695 per 100,000. The benefit of vaccination can be seen when comparing these figures with a time of similar incidence at the beginning of the vaccine rollout. (Table 2)

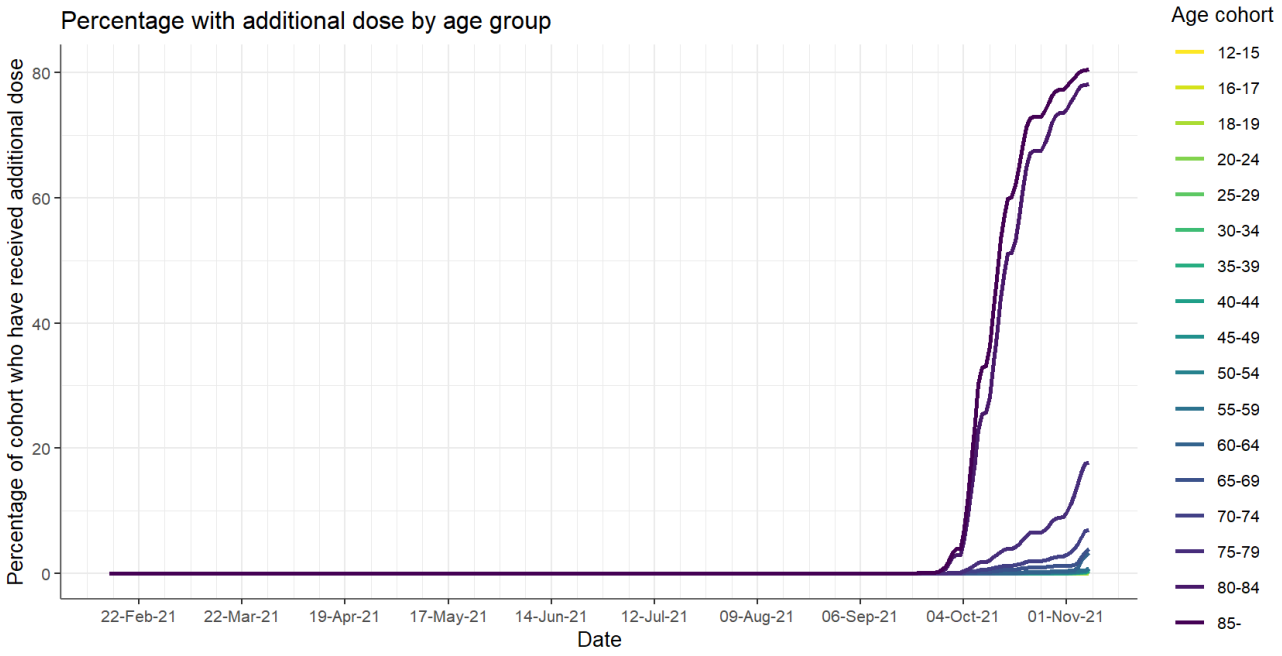
Nonetheless as we continue to have infections, those most at risk will still require hospitalisation and ICU admission and some will die.

Table 2: Comparison of vaccine uptake, hospitalisations and ICU admissions between January and October 2021 Source: HPSC

Characteristics	13 - 26 January 2021	19 October - 1 November 2021
Fully vaccinated	<1%	76%
Confirmed cases	32,103	33,095
Incidence/100,000	674	695
Hospitalisations (%)	1,986 (6.2%)	501 (1.5%)
ICU admissions (%)	99 (0.3%)	31 (0.1%)

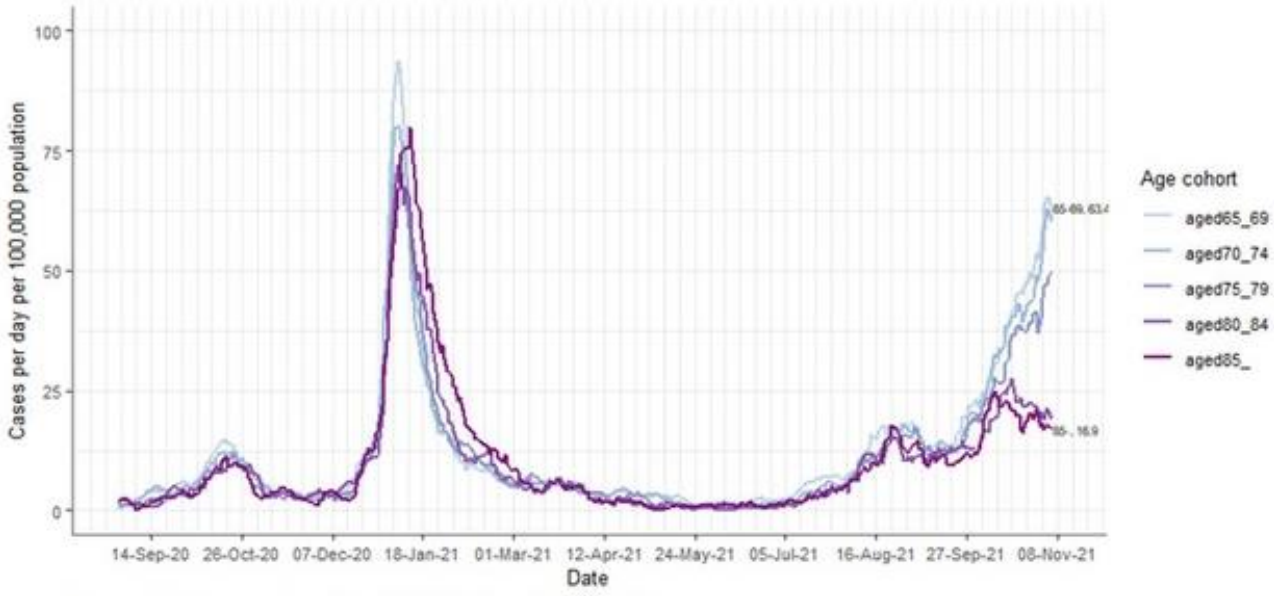
The booster vaccination programme began in early October 2021 and by 7 November 2021 almost 80% of those aged 80 and older had received a booster dose. (Figure 3).

Figure 3: Booster vaccine uptake by age group 7 November 2021 Source: DOH



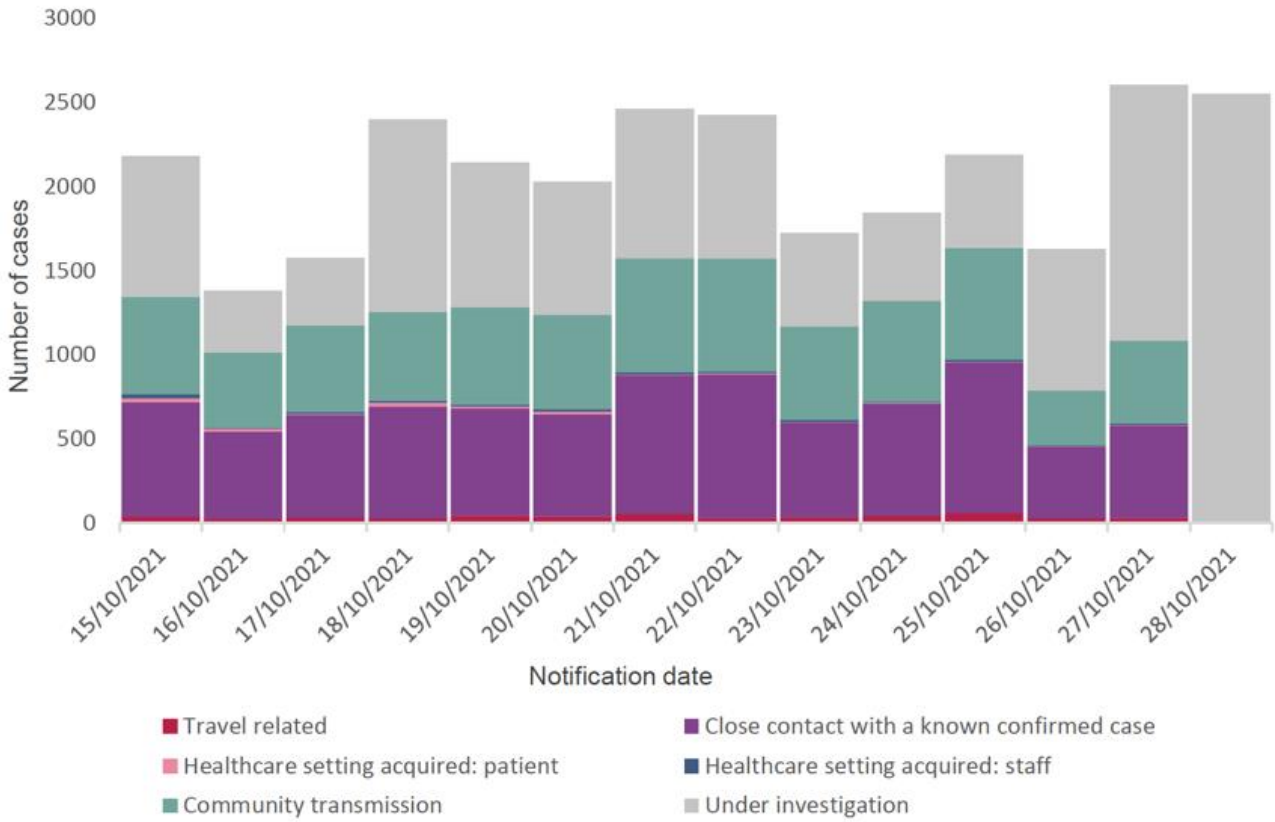
Since early October 2021, the rate of COVID-19 infections has decreased in those aged 80 years and older. There is early evidence that the infection rate is slowing down in those aged 75-79 years of age. (Figure 4)

Figure 4: Age specific incidence by age group in people aged 65 and older Source: DOH



HCWs accounted for less than 5% of confirmed cases reported between 15 and 28 October 2021. When the most likely source of transmission was known (about 60% of cases), less than 2% were acquired in a healthcare setting. (Figure 5)

Figure 5: Number of confirmed COVID-19 cases notified in Ireland by date/week of notification and most likely transmission source, 15 to 28 October 2021 Source: HPSC



Infections among HCWs were common during the pre-vaccination phase of the pandemic. In most countries, including Ireland, frontline HCWs were among the first to be vaccinated, with the remainder of the HCW workforce following shortly thereafter. Infection rates decreased dramatically following rollout of the vaccination programme.

Encouragingly, between 18-31 October 2021 the number of cases in HCWs declined to 672, representing 2% of all cases and 4.8% of cases, where the HCW status was known.

Between 27 June and 30 October 2021, 400 people aged 15 years and older with confirmed COVID-19 were reported to HPSC as being admitted to ICU. Their mean age was 55 years (range: 17-91 years). An underlying condition was present in 80%. Only 35% were fully vaccinated (breakthrough infections).

Of the 400 cases, aged 15 years and over admitted to ICU, 24% died and 24% were still in ICU. While the highest infection rates have been in the younger age cohorts between 27 June and 9 November 2021, there is an incremental increase in rates of ICU admissions and deaths by 10-year age cohort. Of those yet to be offered a booster vaccination, the rates of severe infection (ICU admission and death) are highest in those aged 50-59 years. (Table 3)

Table 3: Risk ratio of ICU admission and death by age group. 27 June to 9 November 2021 Source: DoH

Age group	ICU admission		Death	
	Rate/100,000	Risk Ratio*	Rate/100,000	Risk Ratio*
0-19	1.21	0.1	0.15	0.1
20-29	2.34	0.2	0.17	0.1
30-39	8.44	1.0	0.99	1.0
40-49	9.84	1.4	1.73	2.2
50-59	12.49	2.1	4.27	6.0
60-69	22.36	4.1	14.49	22.9
70 and over	19.36	4.7	78.04	162.4

*Using 30-39 as index

Delta variant

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 against hospitalisation and severe disease is sustained for at least six months in the general population. The Delta sublineage AY.4.2 is increasing in the UK and has been identified in Ireland. While it may be associated with slightly increased transmissibility, currently there is no evidence for an increase in severity or in reduction in VE.

Delta breakthrough infections are associated with a similar viral burden in both vaccinated and unvaccinated people. Most studies show that levels of culturable virus and duration of viral shedding are reduced in the vaccinated with breakthrough infection. Vaccination reduces transmission from vaccinated people, although less with Delta than with Alpha infection.

A household transmission study in a largely unvaccinated population found that the odds of subsequent transmission from a Delta variant was 70% higher than from Alpha cases. In the Netherlands, De Gier et al. found the effectiveness of full vaccination of the index case in preventing transmission to unvaccinated household contacts was 63%, lower than that with Alpha infection at 73%.

4. Global and national equity

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.

While ensuring that recommendations for booster COVID-19 vaccine doses are evidence based, as articulated by Dr Tedros Ghebreyesus, Director General of the World Health Organization, NIAC agrees that "the key is to make sure that the vulnerable will be protected and the key is to make sure that the number of cases will not overwhelm the healthcare capacity".

In Ireland, healthcare capacity is threatened on two fronts: an increase in community case numbers resulting in a surge of severe COVID-19, ICU admissions and deaths in the unvaccinated and in fully vaccinated vulnerable people and also by an increase in asymptomatic or mildly symptomatic HCW infection.

5. COVID-19 vaccine effectiveness

Duration of protection following infection

Neutralising antibodies are detectable within seven to 15 days of disease onset, and levels increase until days 14-22, before plateauing and then decreasing. Lower antibody titres have been observed in those with asymptomatic or clinically mild disease.

Immunity generally lasts for at least nine months following infection (HIQA report on duration of immunity, October 2021). Reinfection is uncommon within that timeframe, with rates ranging from 0 - 5.9%. The risks of reinfection are highest in those with immunocompromise, those aged 65 years and older and those who are seronegative at baseline.

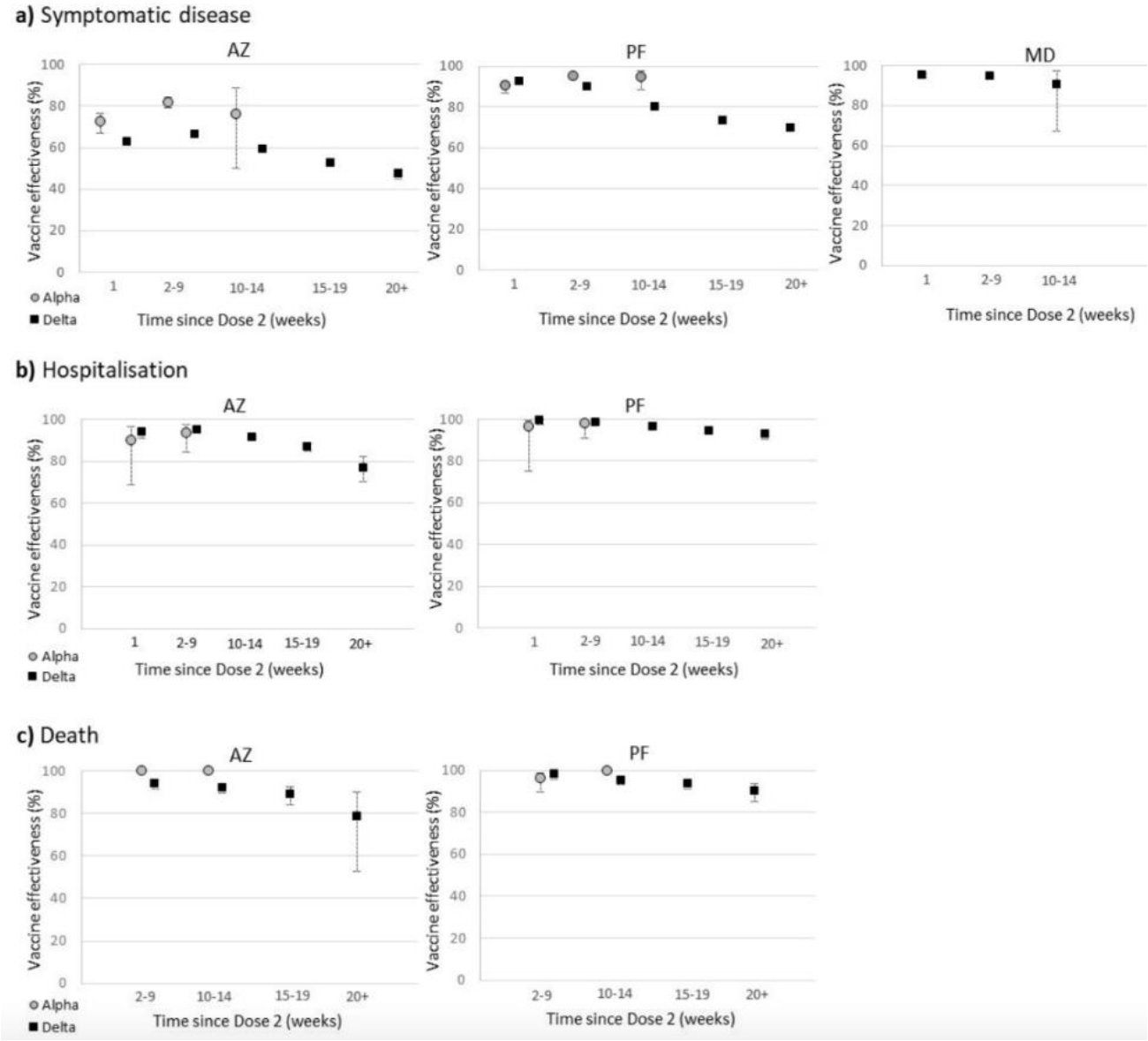
As protection following infection or vaccination wanes over time, booster vaccination can increase antibody levels and enhance protection, it is important to prioritise those who are most at risk of severe disease in the event of a breakthrough infection.

Vaccine effectiveness (VE)

Vaccine specific outcomes

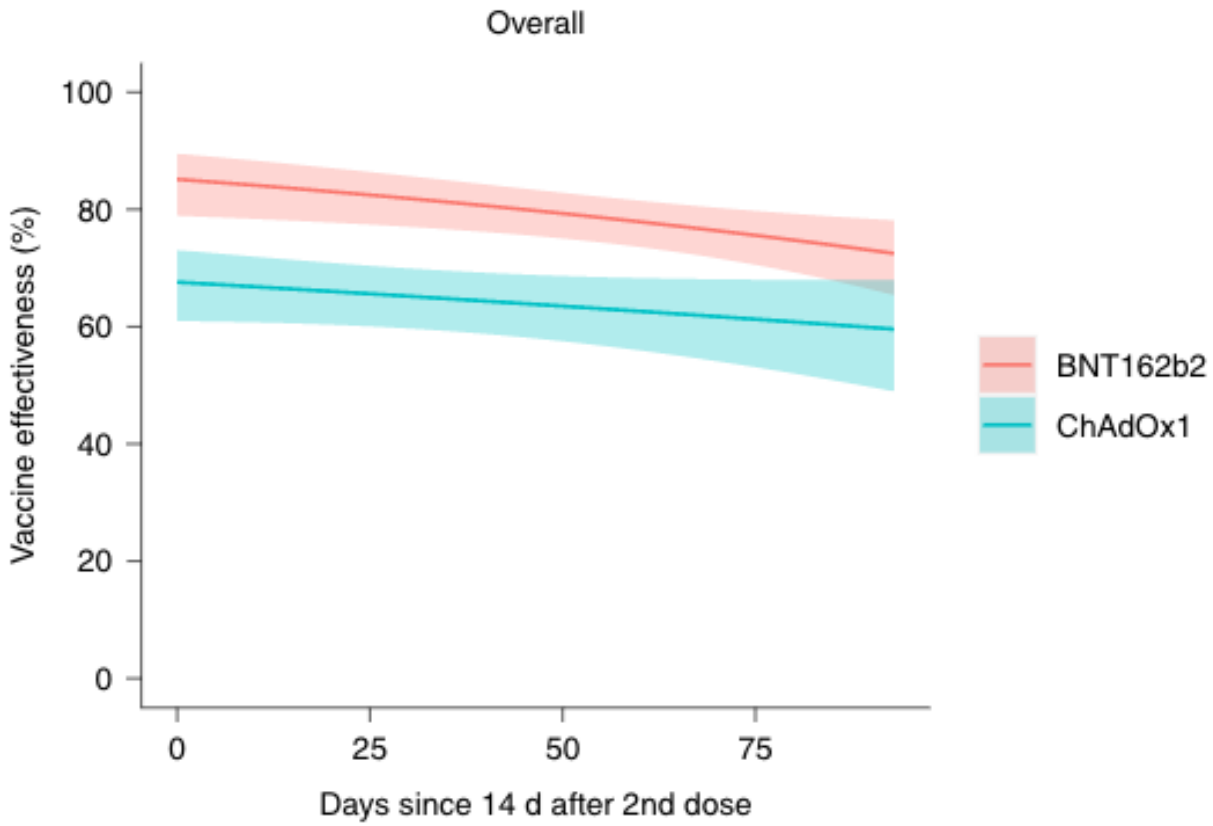
In an observational study, Andrews et al. noted a general decline in VE over time that was more apparent with Delta infections. Follow up was limited to 20+ weeks at which time there was some early indication of a VE decline from a lower baseline in Vaxzevria recipients compared to Comirnaty. (Figure 6)

Figure 6: VE against Delta symptomatic disease, hospitalisation and death among those aged 19 and older with two doses of Vaxzevria (AZ), Comirnaty (PF) or Spikevax (MD) in England (with 95% confidence intervals) Source: Andrews at al



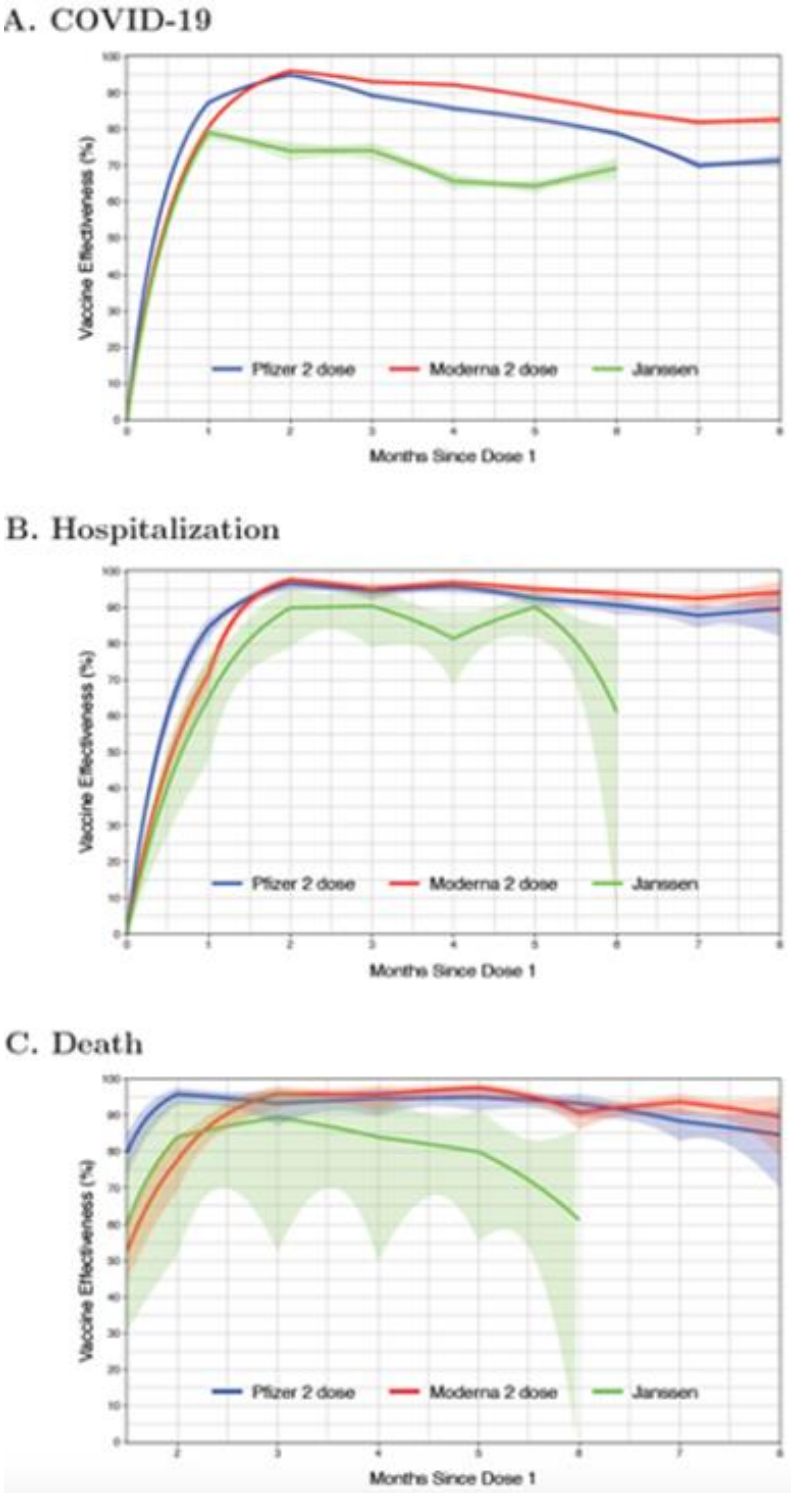
Pouwels et al. reported a decline of protection with a reduction in VE to less than 60% for Vaxzevria recipients. (Figure 7)

Figure 7: Protection against new PCR positive cases since second doses by vaccine and age group Source: Pouwels et al.



Lin et al. showed that the VE of COVID-19 vaccine Janssen was similar to that of the two mRNA vaccines one month after vaccination and then starts to decline. (Figure 8)

Figure 8: Vaccine Effectiveness of Comirnaty (Pfizer–BioNTech), Spikevax (Moderna), and COVID-19 vaccine Janssen (Janssen) in reducing the risks of COVID-19 disease (A), hospitalization (B), and death (C) in North Carolina, 13 December 2020 – 8 September 8, 2021. Source: Lin et al.



COVID-19 vaccine Janssen has a lower initial VE against infection compared with mRNA vaccines and there is some evidence of waning VE over time. (Table 4) (Source Self et al.)

Table 4: COVID-19 vaccine effectiveness* against COVID-19–associated hospitalisation among adults without immunocompromising conditions, by vaccine product — 21 hospitals in 18 U.S. States, March–August 2021. Source: Self et al.

Vaccine	14- 120 days after full vaccination (95% CI)	>120 days after full vaccination (95% CI)
Spikevax	93 (90-95)	92 (87-96)
Comirnaty	91 (88-93)	77 (67-84)
COVID-19 vaccine Janssen	71* (56-81)	68** (49-80)

*full surveillance period and **more than 28 days

Healthcare workers

The high uptake of COVID-19 vaccines by HCWs from January 2021 resulted in a dramatic reduction of HCW infections.

In England, a large prospective cohort study of HCWs by 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.

In the months following introduction of COVID-19 vaccination, high levels of VE in HCWs were widely reported. Coincident with the rise in dominance of the Delta variant, relaxation of a mask wearing mandate and increasing time since vaccination, there was a resurgence of infections in HCWs in California. While infections rates increased, with 84% of those with breakthrough infection experiencing some symptoms, effectiveness against severe disease and hospitalisation was maintained. VE against symptomatic disease exceeded 90% from March to June 2021 but fell to 66% in July. The attack rate in fully vaccinated HCWs at 5.7 per 1,000 remained significantly lower than that in the unvaccinated (16.4 per 1,000).

In the Netherlands, Shamier et al., identified 161 breakthrough infections in a population of 24,706 HCWs immunised with mRNA or adenoviral vector vaccines. The Delta variant was identified in most cases. While there was a lower probability of infectious virus detection in vaccinated HCWs, infectious virus was found in 69% of breakthrough infections. 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 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.

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 (Fowlkes A, at al) VE exceeded 90% between March and June 2021, preceeding Delta predominance, but fell to 65.5% in July 2021. This decline occurred coincident with the rapid increase in the Delta variant infections as well as at the end of the mask mandate in mid-June 2021.

Eyre et al. in a prospective observational cohort study reported that transmission reductions declined over time after the second vaccination, reaching similar levels to unvaccinated individuals for Delta by 12 weeks following Vaxzevria vaccination and attenuating substantially for Comirnaty. Protection from vaccination in contacts also declined in the months after second vaccination.

The main aim of the vaccination programme is to prevent severe COVID-19 disease and death in the vaccinee and HCWs work in an environment with potentially vulnerable patients. The greatest risk of transmission within the healthcare setting is from infected individuals who are unvaccinated. However, vaccinated HCWs with breakthrough infections can unwittingly be a source of hospital or residential outbreaks involving both patients and other HCWs.

Preserving continuity of services, and the wellbeing of healthcare staff, are important factors in making recommendations regarding vaccination of HCWs.

Booster doses for HCWs will reduce their incidence of breakthrough infection, provide additional protection for patients and may also help support continuity of healthcare services.

Underlying conditions in those aged 16 to 59 years

A US population-based surveillance system, (COVID-NET), collects data on laboratory-confirmed COVID-19-associated hospitalisations among children and adults inf over 250 acute-care hospitals in 14 States. Data show that 67% of people hospitalised with COVID-19 had underlying conditions.

In Ireland, between 27 June and 30 October 2021, 81% of those aged 15 and over admitted to ICU with COVID-19 had an underlying condition. Of 136 fully vaccinated individuals admitted to ICU between 1 April and 30 October 2021, 98% had an underlying condition.

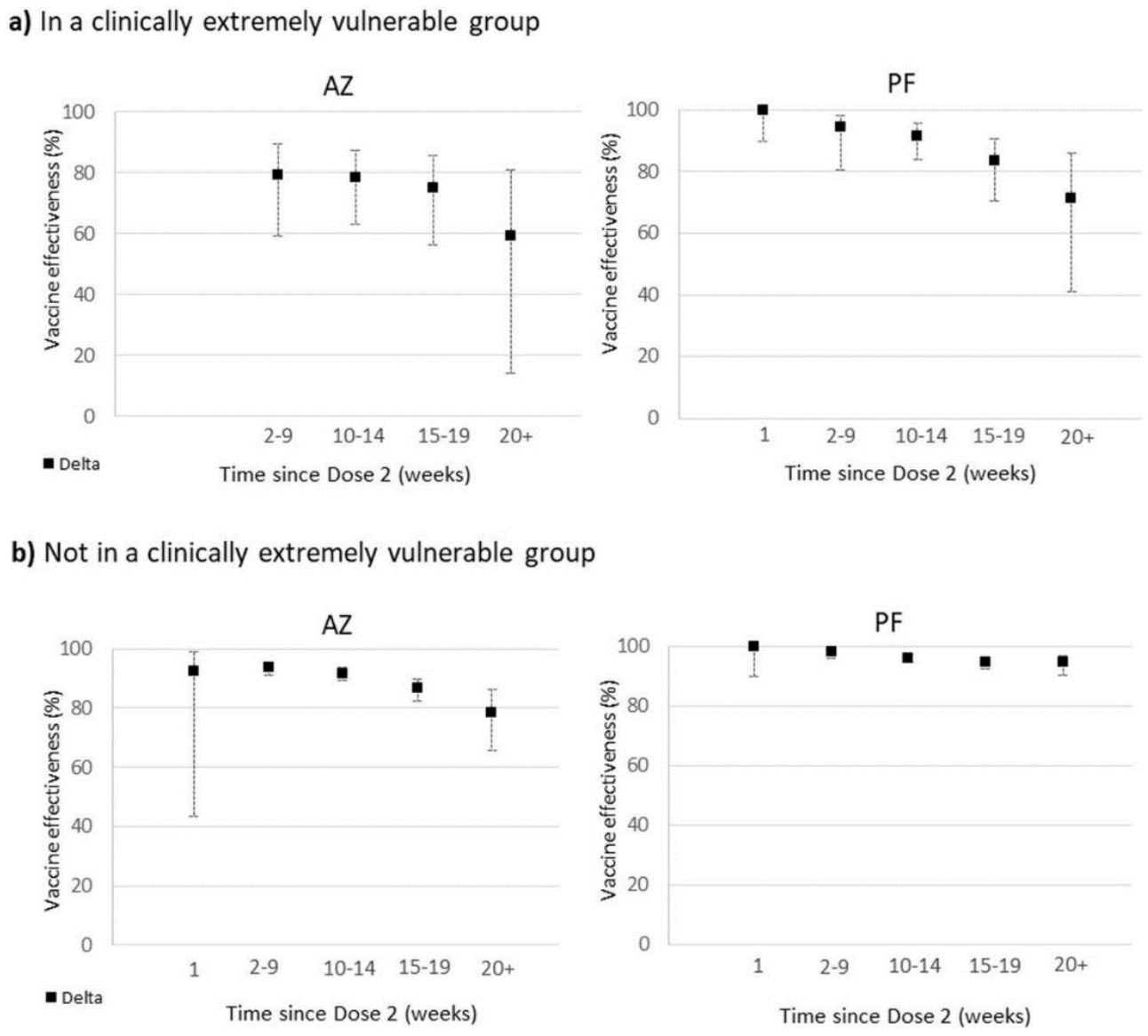
HIQA reviewed evidence on the duration of protective immunity following COVID-19 vaccination in people with an underlying condition. There was limited and inconsistent evidence regarding vaccine efficacy and effectiveness in this group and uncertainties remain. Most observational studies of effectiveness focussed on those aged 60 years and older or across the age spectrum, with an absence of robust data in those 16-65 with underlying conditions.

In pre-authorisation efficacy studies, vaccine protection was the same for those with or without underlying conditions, although those with immunocompromise were excluded.

Early VE studies carried out when the Alpha strain was dominant provided reassurance of the protection afforded within six months of vaccination, including for those with comorbidities. (Dagan et al., Pilishvili et al.)

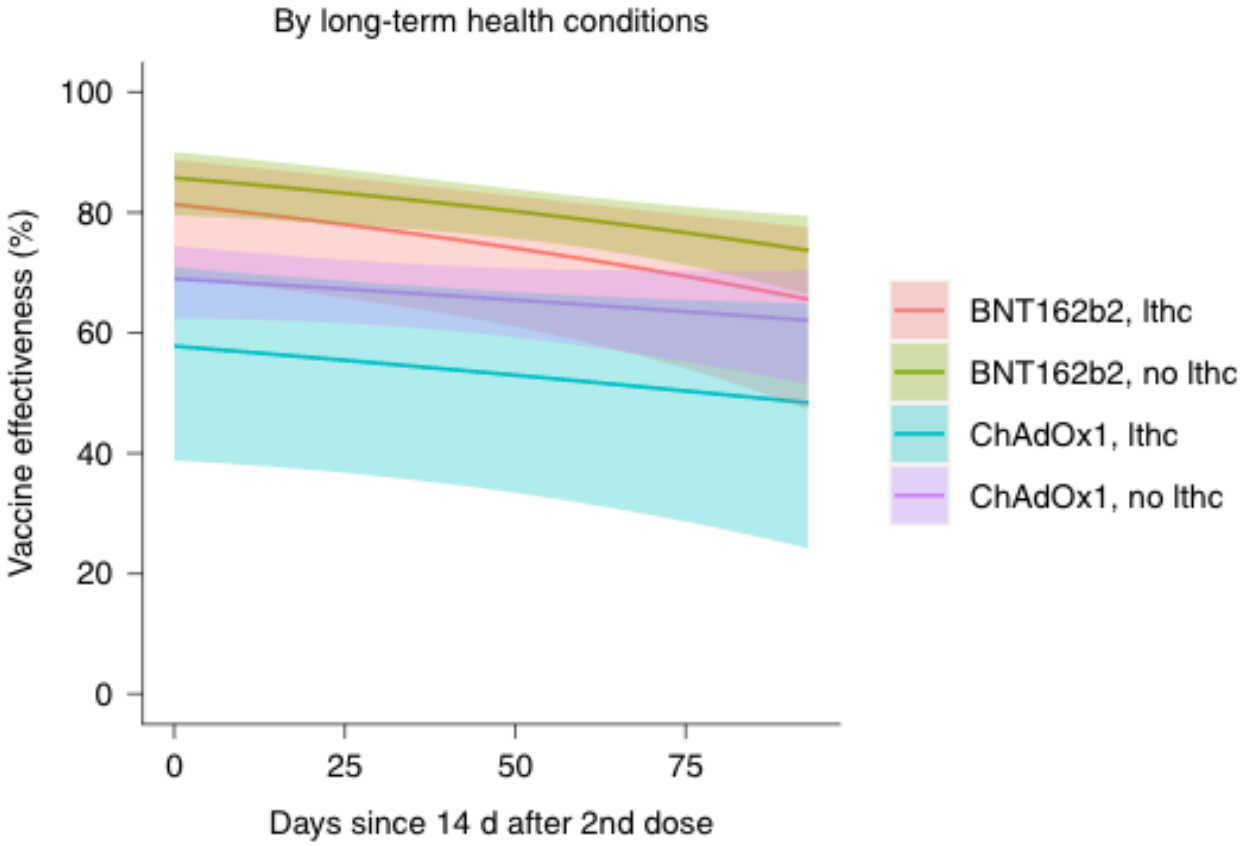
In an UK observational study, Andrews et al. noted a general decline in VE over time that was more apparent with Delta infections. Decline in protection against hospitalisation was greater in clinically extremely vulnerable groups aged 65 years and older. This was not observed in younger age cohorts. However, follow up was limited to 20+ weeks. (Figure 9)

Figure 9: Vaccine effectiveness against hospitalisation (aged 65 and older) by clinically extremely vulnerable group status for Vaxzevria (AZ) and Comirnaty (PF) Source: Andrews et al.



Pouwels et al. reported a reduced initial response and more marked decline of protection in those with underlying conditions in those who received Vaxzevria and Comirnaty. (Figure 10)

Figure 10: Protection against new PCR positive cases since second doses by vaccine and age group Source: Pouwels et al.



In Israel, a retrospective cohort study of 152 hospitalised fully vaccinated people (half of the hospitalised fully vaccinated people) noted a poor outcome in 38 patients and 22% died. The cohort was characterised by a high rate of underlying conditions including hypertension (71%), diabetes (48%), congestive heart failure (27%), chronic kidney and lung diseases (24% each), dementia (19%) and cancer (24%). Only 4% had no comorbidities. Forty percent of the patients were immunocompromised. (Brosh-Nissimov et al.)

A UK study showed that the absolute risk of severe COVID-19 was higher in those with risk conditions. Over a maximum follow-up of 26 weeks, while the vaccines were very effective overall, the rate ratios for severe COVID-19 were higher for those with moderate risk conditions and highest for the clinically extremely vulnerable. Results were not stratified by age. Vaccine efficacy after two doses was 94% for those without risk conditions, 89% for those with moderate risk and 73% for those considered clinically extremely vulnerable. (McKeigue et al.)

A US study of 4,440 unvaccinated and 292 fully vaccinated adults aged 18 years and older found that in addition to age and immunocompromise, those with multiple underlying medical conditions were more likely to be hospitalised. In those under 65 years of age, immunosuppression, neurological disease, and

cardiovascular disease were at significantly increased risk, where chronic lung disease (P=0.08) and renal disease (P=0.05) were not statistically significant. (Havers et al.)

There is little evidence specifically addressing the impact of underlying health conditions on those aged 16 to 59 years. However, the overall consistency of evidence indicates the presence of underlying conditions (Chapter 5a Table 5a.2) increase the risk of hospitalisation. A booster COVID-19 vaccination can mitigate this risk. This also applies to residents of long-term healthcare facilities, most if not all of whom have an underlying condition and all of whom require additional care.

Those aged 50 – 59 years

Age, immune status, and the presence of underlying conditions are the main factors in determining the severity of breakthrough disease. Neutralising antibodies have been identified as an important correlate of protection against SARS-CoV2 infection. As age increases, the strength and durability of NA decreases. This may contribute to the increase in case numbers occurring older vaccinated individuals. (Bates et al.) In a study of 167 vaccinees median age 42 years), Comirnaty recipients aged 50 years and older had lower pre-boost antibody responses than younger recipients. Differences were less marked for Spikevax recipients. (Richards et al.)

In some studies, younger age has been associated with increased risk of breakthrough infection (Uschner et al.), however the risk of adverse outcome increases with age.

In UK data, while the beneficial impact of vaccination in reducing hospitalisation and death is evident in the fully vaccinated, there is a gradual increase in hospitalisation and death by age (Table 5).

Table 5: Unadjusted rates of COVID-19 infection, hospitalisation and death in vaccinated and unvaccinated populations Source: UK Health Security Agency

Age group	Hospitalisation rate/100,000		Death rate/100,000	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Under 18	0.4	4.6	0.0	0.1
18-29	1.3	6.2	0.1	0.3
30-39	3.2	14.7	0.2	0.8
40-49	7.6	28.0	0.7	3.3
50-59	9.7	46.4	1.8	10.2
60-69	16.7	59.0	6.2	29.1
70-79	33.8	80.5	17.7	53.3
80 and older	62.3	133.7	64.2	144.1

Rationale for booster doses

Although COVID-19 antibody levels wane over time, VE against severe disease and death is generally sustained. However, protection against infection and mild disease declines.

The rationale for booster doses has been outlined in a previous recommendation. Older age and the presence of underlying conditions are associated with reduced strength and duration of immune response, increasing risk for breakthrough infection, and increased risk of severe illness and death. (Levin et al., Naaber et al., Richards et al., Green et al., Liu et al.)

Booster COVID-19 vaccine doses for HCWs are needed because waning immunity is associated with loss of protection against infection, although protection against severe disease is sustained. HCWs were among the first to be vaccinated, generally between six and ten months ago. As infection rates in the community rise, an increase in HCW infection rates can be anticipated even though the rate acquisition of infection in the health care environment remains very low (<1.0%). Providing booster doses for HCWs will reduce their infection rates. This will not only afford protection to the HCWs but importantly will be an added protection for vulnerable patients in their care. Reduction in infection rates among HCWs will also contribute to the sustainability of the health service.

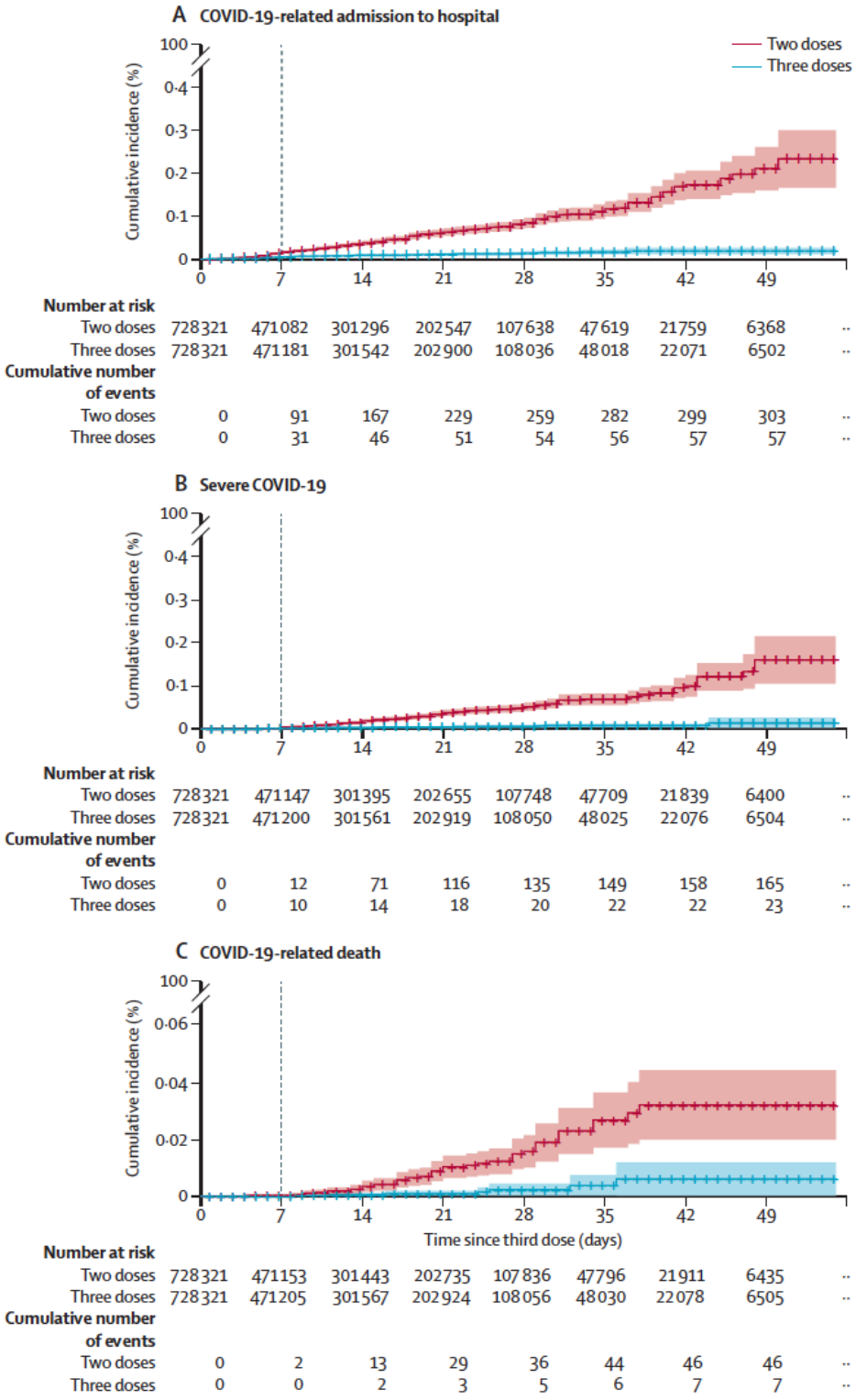
Homologous and heterologous booster vaccines have been shown to be highly immunogenic. Boosting antibody responses with an additional vaccine dose can be anticipated to further reduce the incidence of breakthrough infections in the fully vaccinated. (Bar-On et al.) The duration of protection that a booster dose affords is uncertain. However, given the high levels of antibodies achieved and based on experience with other vaccines, it is reasonable to expect that it might extend longer than that following a primary vaccine series.

Booster vaccine

Effectiveness

An Israeli case-control study was reported on 29 October 2021 which involved over 1.4 million people. Half received two doses of Comirnaty and half received three doses of Comirnaty. The median age was 52 years and the median follow-up time was 13 days. VE evaluated at least seven days after receipt of the third dose was estimated to be 93% for admission to hospital, 92% for severe disease, and 81% for COVID-19-related death. The conclusion was that a third dose of the Comirnaty is effective in protecting individuals against severe COVID-19-related outcomes, compared with receiving only two doses at least five months prior. (Barda et al.) (Figure 11)

Figure 11: Cumulative incidence curves comparing COVID-19-related admission to hospital (A), severe disease (B), and death (C) in individuals who received two versus three doses of Comirnaty. Source: Barda et al.



The main limitation of this study is the short duration of follow up.

In a clinical trial conducted at ten U.S. sites, adults who received one of three authorised COVID-19 vaccines at least 12 weeks prior to enrolment, received a booster with one of three vaccines (full dose Spikevax, COVID-19 vaccine Janssen, or Comirnaty) in nine different combinations. The results showed that heterologous or homologous booster vaccination was highly immunogenic and that reactogenicity was similar to the primary reported series. (Atmar et al.)

In the Netherlands, Salberolles et al. in randomised controlled trial in HCWs vaccinated with COVID-19 vaccine Janssen compared the reactogenicity and immunogenicity of homologous or heterologous boosting with either Comirnaty or Spikevax with no boosting. Homologous and heterologous booster vaccinations resulted in an increase in SARS-CoV-2-specific binding antibodies, neutralising antibodies and T-cell responses when compared to single COVID-19 vaccine Janssen vaccination. In comparison with the homologous boost, the increase was significantly larger in heterologous regimens with the mRNA-based vaccines. Spikevax boosting was most immunogenic and was associated with higher reactogenicity. Only mild to moderate local and systemic reactions were observed on the first two days following booster.

Safety

The Israeli Health Ministry shared findings of their population-based booster programme at the Vaccines and Related Biological Products Advisory Committee meeting of the US Federal Drug Administration on 14-15 October 2021. Overall, 3.7 million booster doses of Comirnaty have been administered to those aged 16 and older with 1.2 million doses given to those aged 60 years and older. No initial safety concerns have been identified with a similar profile but lower rate of systemic and local reactions than after first or second doses.

Booster doses of Comirnaty have not shown any unexpected patterns with regard to short term safety when administered at least five months after an mRNA primary vaccine course. Current data for Spikevax also indicate that the pattern of side effects after the booster is similar to what occurs after the second dose.

In Scandinavia and France, preliminary data indicate that the rate of myocarditis is higher in males aged 16-29 years of age receiving a full dose of Spikevax as a second dose, compared to those receiving Comirnaty. While the EMA assesses the data, as a precaution Comirnaty is recommended as a booster for all in this age group.

Age, timing and vaccine selection

On 4 October 2021, the EMA stated that a booster dose of Comirnaty (0.3ml, full dose) may be considered in those aged 18 years and older. The safety and immunogenicity of a booster dose of Comirnaty was based on data in those aged 18 to 55 years who showed a rise in antibody levels when a booster dose was given approximately six months (range 4.8 to 8.0 months) after the second dose. On 25 October 2021, the EMA stated that a booster dose of Spikevax (0.25ml, half the dose of the primary schedule) may be considered in those aged 18 years and older. The safety and immunogenicity of a booster dose of Spikevax was based on data in those aged 18 years and older who showed a rise in antibody levels when a booster dose was given at least six months (range 6 to 8 months) after the second dose. The EMA concluded that booster doses of Comirnaty and Spikevax may be considered at least six months after the second dose for those aged 18 years and older.

Real world evidence from Israel (Bar-On et al.) and preliminary data from a randomised control trial of participants aged 16 and over, supports the safety and effectiveness of Comirnaty booster vaccines in those 16 years and older. Boosters should be given to those eligible in this age group.

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. The results of heterologous studies carried out as primary or booster immunisation indicate that an adenoviral vector vaccine followed by an mRNA vaccine is safe and immunogenic.

Having reviewed this and additional data, NIAC recommends that a full dose of Comirnaty (0.3ml/30 micrograms) or half dose of Spikevax (0.25ml/50 micrograms) should be given after an interval of six months or longer following completion of the primary course of any two dose COVID-19 vaccine. A minimum interval of five months may be used when necessary for operational reasons.

If eligible, COVID-19 vaccine Janssen recipients should receive an mRNA booster dose after an interval of three months. This is because the VE of this single dose vaccine is less robust than the vaccines with a two dose schedule.

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.

This is consistent with recommendations from CDC and the UK and results from the UK ComFluCOV study which showed that administering an influenza vaccine at the same time as a second dose of a COVID-19 vaccine produced no safety concerns and preserved the immune response to both vaccines.

6. International recommendations

Table 6: COVID-19 booster vaccine recommendations by country [information accessed 11 November 2021]

Country	Healthcare workers	Underlying conditions	Age group
Austria	√	√	12 and older
Belgium	√	√	12 and older[1]
Bulgaria		Cancer patients	65 and older
Denmark	√		over 65
Estonia	√		65 and older
Finland		√	over 60
France	√	√	65 and older
Germany	√		70 and older
Hungary	√	√	18 and older[2]
Iceland	√		60 and older[3]
Israel	√	√	12 and older
Italy	√		60 and older[4]
Latvia	√	√	50 and older
Lithuania	√	√	18 and older
Norway	√	√	65 and older
Malta	√		60 and older[5]
Poland	√	√	18 and older
Romania	√	√	18 and older
Slovakia	√	√	55 and older
Slovenia		√	70 and older
Spain		√	over 65
Sweden	√		65 and older
Canada	√		80 and older[6]
UK	√	√	50 and older
US	√	√	65 and older

[1] to be discussed 27 November 2021
[2] everyone will receive a booster according to their registration
[3] everyone over 16 years will be offered a booster
[4] 40 and older from 1 December 2021
[5] will be offered to all of the population
[6] may be offered to those aged 70-79 years

7. Conclusions

COVID-19 related hospitalisation and severe illness can be prevented by optimising the protection afforded by vaccination. This can be achieved by strongly encouraging and facilitating unvaccinated or incompletely vaccinated people eligible for COVID-19 vaccine to complete a primary vaccination course.

Ireland is currently undergoing a surge in case numbers across all ages, despite high vaccination rates especially in those aged 50 years and older (97% or higher). This is likely due to a number of factors, including the highly transmissible Delta variant, waning of immunity over time and the opening up of society with an increase in socialisation. These factors increase the risk of breakthrough infections and the risk of severe COVID-19 in those aged 50 and older and those with underlying conditions.

While the highest infection rates since the end of June 2021 have been in the younger age cohorts, there is an incremental increase in rates of ICU admissions and deaths by 10-year age cohort. Of those yet to be offered a booster vaccination, the rates of severe infection (ICU admission and death) are highest in those aged 50-59 years. The vast majority of ICU COVID-19 admissions aged 15 years and older have an underlying medical condition.

VE for all COVID-19 vaccines has been shown to wane over time although VE against severe disease and death is generally sustained. VE waning is more marked in older people and those with underlying conditions. As the initial VE was lower for adenoviral vector vaccines the impact of further decline is uncertain.

VE in preventing symptomatic disease is similar in HCWs and the general population. HCWs accounted for less than 5% of confirmed cases reported between 15 and 28 October 2021. When the most likely source of transmission was known (about 60% of cases), less than 2% were acquired in a healthcare setting.

The main aim of the vaccination programme is to prevent severe COVID-19 disease and death in the vaccinee and decreasing the incidence of HCW infection will reduce the risk of transmission and help protect vulnerable patients.

The greatest risk of transmission within the healthcare setting is from infected individuals who are unvaccinated. However, vaccinated HCWs with breakthrough infections can unwittingly be a source of hospital or residential outbreaks involving both patients and other HCWs.

mRNA booster vaccination is safe and immunogenic. Booster doses for HCWs will reduce their incidence of breakthrough infection, reduce the risk of transmission, provide additional protection for patients, and may also help support continuity of healthcare services.

The impact of booster vaccination is already evident in other countries. Booster vaccination of older age groups has reduced hospitalisation and infection rates in Ireland. Booster vaccination of further groups at risk will contribute to mitigating their risk of a severe breakthrough infection, i.e., those aged 16-59 with underlying conditions. This also applies to residents of long-term healthcare facilities, most if not all of whom have an underlying condition and all of whom require additional care.

There is an incremental increase in COVID-19 hospitalisations in those aged 50-59 years of age compared to younger age groups and this age cohort may be at additional risk based on their primary COVID-19 vaccine. Extending the recommendations to all those aged 50-59 years includes those who by virtue of age have a less robust response to vaccines and those who received adenoviral vector vaccines in the primary series.

It is essential that all recommended public health and social measures to limit COVID-19 exposure are observed. Booster doses will not immediately contribute to outbreak management nor take the place of public health and social measures.

NIAC continues to examine new evidence regarding the durability of protection of the primary vaccine series in other groups, e.g., younger age groups who received adenoviral vector vaccines.

8. Recommendations

1. All those who are unvaccinated or incompletely vaccinated are strongly recommended to complete a primary COVID-19 vaccination course. Seasonal influenza vaccine can be given at the same time, to those for whom it is recommended.

2. All must continue to observe all recommended public health and social measures. The use of masks, physical distancing, hand hygiene, and ventilation of indoor spaces are key to reducing transmission of SARS-CoV-2.

   Booster vaccines will not immediately contribute to outbreak management and do not take the place of public health and social measures.

3. In addition to prior recommendations, a booster dose of an mRNA vaccine is recommended in order of priority for
   - Healthcare workers, including those pregnant (priority for frontline HCWs)
   - Those aged 16-59 years with underlying conditions as listed in Table 5a.2 of Chapter 5a COVID-19 in the Immunisation Guidelines for Ireland and all residents in long term healthcare facilities
   - Those aged 50-59 years

   For those aged 16-29 years, a full dose of Comirnaty (0.3ml/30 micrograms) should be given six months or longer following completion of a primary two dose course of any COVID-19 vaccine.

   For those aged 30 years and older, a full dose of Comirnaty (0.3ml/30 micrograms) or a half dose of Spikevax (0.25ml/50 micrograms) should be given six months or longer following completion of a primary two dose course of any COVID-19 vaccine.

   A minimum interval of five months may be used when necessary for operational reasons. Recipients of COVID-19 vaccine Janssen should receive an mRNA booster dose after an interval of three months.

4. Those who have a breakthrough infection following a primary vaccination course should defer booster vaccination for at least six months following infection onset.

5. If an mRNA vaccine is contraindicated, consideration can be given to boosting with an authorised non-mRNA vaccine following an individual benefit-risk assessment.

These recommendations reflect current evidence and will be reviewed when more information becomes available.

References

Andrews N et al. (2021). Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. MedRxiv. Preprint https://www.medrxiv.org/content/10.1101/2021.09.15.21263583v2

Allen H et al. (2021). Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2): national case-control study. The Lancet Regional Health https://doi.org/10.1016/j.lanepe.2021.100252

Atmar RL et al. (2021). Heterologous SARS-CoV-2 Booster Vaccinations – Preliminary Report. MedRxiv. Preprint https://www.medrxiv.org/content/10.1101/2021.10.10.21264827v2

Barda N et al. (2021). Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet. DOI: https://doi.org/10.1016/S0140-6736(21)02249-2

Bar-On YM et al. (2021). Protection Across Age Groups of BNT162b2 Vaccine Booster against Covid-19. MedRxiv. Preprint https://www.medrxiv.org/content/10.1101/2021.10.07.21264626v1

Bar-On YM et al. (2021). Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. N Engl J Med 2021;385:1393-400. https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

Bates TA et al. (2021). Age-Dependent Neutralization of SARS-CoV-2 and P.1 Variant by Vaccine Immune Serum Samples. JAMA. 2021;326(9):868-869 https://jamanetwork.com/journals/jama/fullarticle/2782428

Bianchi FP et al. (2021). BNT162b2 mRNA COVID-19 Vaccine Effectiveness in the Prevention of SARS-CoV-2 Infection and Symptomatic Disease in Five-Month Follow-Up: A Retrospective Cohort Study Vaccines 2021, 9, 1143. https://doi.org/10.3390/vaccines9101143

Bouton TC et al. (2021). Vaccine impact on rates of SARS CoV-2 Cases and Postvaccination Strain Sequences Among Healthcare Workers at an Urban Academic Medical Center: A Prospective Cohort Study. Open Forum Infectious Diseases 2021 https://doi.org/10.1093/ofid/ofab465

Brosh- Nissimov T et al. (2021). BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. Clinical Microbiology and Infection. https://doi.org/10.1016/j.cmi.2021.06.036

Centers for Disease Control and Prevention (2021). ACIP Presentation Slides: October 20-21, 2021 Meeting. https://www.cdc.gov/vaccines/acip/meetings/slides-2021-10-20-21.html

Dagan N et al. (2021). BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021; 384:1412-1423 DOI: https://www.nejm.org/doi/full/10.1056/nejmoa2101765

de Gier B et al. (2021). Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), the Netherlands, August to September 2021. Euro Surveillence. 2021;26(44) https://doi.org/10.2807/1560-7917.ES.2021.26.44.2100977

Eyre D et al. (2021). The impact of SARS-CoV-2 vaccination on Alpha & Delta variant transmission. MedRxiv. Preprint https://www.medrxiv.org/content/10.1101/2021.09.28.21264260v2

Fowlkes A et al. (2021). Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep 2021; 70:1167-1169. DOI: https://doi.org/10.15585/mmwr.mm7034e4

Green A et al. (2021). Describing the population experiencing COVID-19 vaccine breakthrough following second vaccination in England: a cohort study from OpenSAFELY MedRxiv. https://www.medrxiv.org/content/10.1101/2021.11.08.21265380v1

Hall VJ et al. (2021). COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet 2021. https://pubmed.ncbi.nlm.nih.gov/33901423/

Havers F et al. (2021). COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years – COVID2 NET, 13 states, January 1 – July 24, 2021. MedRxiv. Preprint https://www.medrxiv.org/content/10.1101/2021.08.27.21262356v1

Health Information and Quality Authority. (2021). Duration of immunity following COVID-19 vaccination (efficacy and effectiveness). 18 October 2021 (*unpublished*).

Health Protection Surveillance Centre (2021). COVID-19 Cases in Ireland https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/casesinireland/

Health Security Agency UK (2021). COVID-19 vaccine surveillance report. Week 44. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1032671/Vaccine_surveillance_report_-_week_44.pdf

Katz MA et al. (2021). Covid-19 Vaccine Effectiveness in Healthcare Personnel in six Israeli Hospitals (CoVEHPI) https://doi.org/10.1101/2021.08.30.21262465

Keehner J et al. (2021). SARS-CoV-2 Infection after Vaccination in Healthcare Workers in California. N Engl J Med https://www.nejm.org/doi/full/10.1056/NEJMc2101927 https://www.nejm.org/doi/full/10.1056/NEJMc2101927

Keehner J et al. (2021) Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. N Engl J Med. 2021 Sep1. https://www.nejm.org/doi/pdf/10.1056/NEJMc2112981?articleTools=true

Lazarus R et al. (2021). The Safety and Immunogenicity of Concomitant Administration of COVID-19 Vaccines (ChAdOx1 or BNT162b2) with Seasonal Influenza Vaccines in Adults: A Phase IV, Multicentre Randomised Controlled Trial with Blinding (ComFluCOV). Preprint. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3931758

Levin et al. (2021). Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. N Engl J Med DOI: https://www.nejm.org/doi/full/10.1056/nejmoa2114583

Lin DY et al. (2021). Effectiveness of Covid-19 Vaccines in the United States Over 9 Months: Surveillance Data from the State of North Carolina. MedRxiv. Preprint. https://www.medrxiv.org/content/10.1101/2021.10.25.21265304v1.full.pdf

Liu C et al. (2021). A Retrospective Analysis of COVID-19 mRNA Vaccine Breakthrough Infections – Risk Factors and Vaccine Effectiveness. MedRxiv. Preprint. https://www.medrxiv.org/content/10.1101/2021.10.05.21264583v1

Mbaeyi S et al. (2021). The Advisory Committee on Immunization Practices' Interim Recommendations for Additional Primary and Booster Doses of COVID-19 Vaccines - United States, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1545-1552. DOI: https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e2.htm

McKeigue, P.M. et al. (2021) Efficacy of COVID-19 vaccination in individuals designated as clinically extremely vulnerable in Scotland [version 1; peer review: awaiting peer review] https://researchonline.gcu.ac.uk/en/publications/efficacy-of-covid-19-vaccination-in-individuals-designated-as-cli

Mizrahi B et al. (2021). Correlation of SARS-CoV-2 Breakthrough Infections to Time-from-vaccine; Preliminary Study. MedRxiv Preprint. https://www.medrxiv.org/content/10.1101/2021.07.29.21261317v1

Naaber P et al. (2021). Dynamics of antibody response to BNT162b2 vaccine after six months: a longitudinal prospective study. Lancet Reg Health Eur. 2021 Nov;10:100208. DOI: https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00185-X/fulltext

Pilishvili T et al. (2021). Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel N Engl J Med DOI: https://www.nejm.org/doi/full/10.1056/NEJMoa2106599

Poewels KB et al. (2021). Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. https://www.nejm.org/doi/full/10.1056/NEJMc2113090

Richards NE et al. (2021). Comparison of SARS-CoV-2 Antibody Response by Age Among Recipients of the BNT162b2 vs the mRNA-1273 Vaccine. JAMA Netw Open. 2021;4(9): e2124331. DOI: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2783685

Saberolles et al. (2021). Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming. MedRxiv. Preprint. https://www.medrxiv.org/content/10.1101/2021.10.18.21264979v1

Self WH, et al. (2021). Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March-August 2021. MMWR Morb Mortal Wkly Rep 2021; 70:1337-1343. https://www.cdc.gov/mmwr/volumes/70/wr/mm7038e1.htm

Shamier MC et al. (2021). Virological characteristics of SARS-CoV-2 vaccine breakthrough infections in healthcare workers. Medrxiv. Preprint. https://www.medrxiv.org/content/10.1101/2021.08.20.21262158v1

Uschner D et al. (2021). Breakthrough SARS-CoV-2 Infections after Vaccination in North Carolina. https://www.medrxiv.org/content/10.1101/2021.10.10.21264812v1

Vaccines and Related Biological Products Advisory Committee Meeting Presentation. (2021). Meeting Presentation. Israel Ministry of Health; 2021 October 14-15, 2021. https://www.fda.gov/media/153086/download

Acknowledgements

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

- HIQA
- HSE Libraries Team
- NIAC SpR Research Panel
- NIAC members
- RCPI Communications Department