National Immunisation Advisory Committee

RECOMMENDATIONS REGARDING AN ADDITIONAL COVID-19 VACCINE DOSE FOR THOSE WITH IMMUNOCOMPROMISE ASSOCIATED WITH A SUBOPTIMAL RESPONSE TO VACCINES

NIAC | 30.08.2021

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

Executive summary

Interim recommendations reflect the current evidence. Scientific evidence about COVID-19 vaccines is continuously evolving and being refined. These recommendations will be reviewed as more information becomes available in the coming days to weeks.

On 19 July 2021, NIAC advised the CMO that COVID-19 booster vaccines were likely to be required by some vulnerable people. Groups mentioned for priority consideration included: the immunocompromised, residents of long-term care facilities (LTCFs) aged 65 and older, those aged 80 years and older and 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."

This paper focuses on the need for an additional COVID-19 vaccine dose for those with an inadequate response to the primary vaccination course.

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. All eligible unvaccinated or incompletely vaccinated people are strongly encouraged and should be facilitated to complete the vaccination course. It is also critical to the protection of any vulnerable contact (e.g., an immunocompromised or older person) that they might have.

Additional COVID-19 vaccines doses may be required either because of an inadequate response to the primary vaccination course or due to waning immunity and vaccine effectiveness over time. The former represents an extended primary vaccination course and the latter booster vaccination.

Data indicates that those with severe immunocompromise do not have adequate protection following a primary COVID-19 vaccine course. There is evidence that protection can be enhanced by an additional mRNA vaccine dose, representing an extension of the primary vaccination series.

NIAC continues to actively examine evidence regarding booster vaccines for those with waning immunity and reduced effectiveness in particular groups. These groups include those at increased risk of severe COVID-19 disease e.g., residents of LTCFs, older persons, and those with underlying medical conditions, as well as healthcare workers because of their vital role in providing essential health services. More information regarding the safety and effectiveness of homologous or heterologous booster vaccines in these groups is expected in the coming days and weeks which will allow NIAC to update these recommendations. Recommendations with respect to these groups will follow.

Efforts to minimise the risk of other respiratory infections in the coming months should be made. The 2021/22 seasonal influenza vaccination programme should proceed, with efforts enhanced to optimise uptake.

Recommendations

1. All eligible unvaccinated or incompletely vaccinated people are strongly encouraged to complete the vaccination course.

2. An additional mRNA vaccine dose should be given to those aged 12 and older with immunocompromise associated with a suboptimal response to vaccines who have completed their primary course, regardless of whether the primary course was of an mRNA or an adenoviral vector vaccine. This is an extended primary vaccination course. The additional vaccine should be given after a minimum interval of two months following the last dose of an authorised COVID-19 vaccine.

3. Those with immunocompromise associated with a suboptimal response to vaccines and those living with and/or caring for them should observe all recommended public health and social measures to limit their COVID-19 exposure.

4. Efforts to minimise the risk of other respiratory infections should be made. The 2021/22 seasonal influenza vaccination programme should proceed as planned, and efforts enhanced to optimise uptake.

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 vulnerable people. It was noted that there were information gaps and further evidence was awaited pertaining to the evolving disease epidemiology, clinical data, and booster vaccine effect.

Groups mentioned for priority consideration included:

- 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".

In developing this advice, 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.

Rationale for additional doses

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

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

The rationale for additional doses may differ by vaccine product, epidemiological setting, risk group, and vaccine coverage rates. This paper is focused on those who may have an inadequate response to their primary vaccine course

Inadequate response to primary vaccine series

Because of underlying conditions or treatment, some individuals may be incapable of mounting a 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).**

Vaccine effectiveness in the immunocompromised

COVID-19 vaccines are highly effective in protecting against symptomatic disease and severe illness caused by the Alpha and preceding variants. In the UK, data shows that one dose of Comirnaty® or Vaxzevria® is insufficient to protect against symptomatic infection with the Delta variant, but two doses of either vaccine increased effectiveness to 88% and 67% respectively. Protection is less reliably achieved in the immunosuppressed.

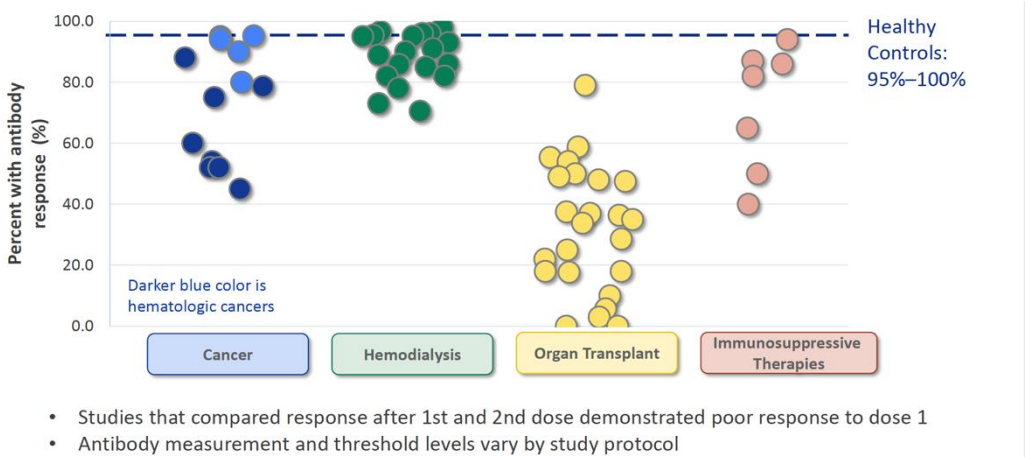
Those with immunocompromise associated with a suboptimal response to vaccines (as outlined in the Appendix) represent a particular vulnerability in terms of control of SARS-CoV-2 infections. They are more likely to get severely ill from COVID-19 and are at risk for prolonged viral shedding.

While overall VE against hospitalisation for COVID-19 was 86% in the US, it was 90% among the immunocompetent compared with 63% in the immunocompromised. Forty to 44% of hospitalised breakthrough infections were in the immunocompromised.

Depending on the level of immunocompromise, response to vaccines may be poor e.g., solid organ transplant (SOT) recipients and those with haematologic malignancy. Similar poor responses to primary immunisation have been reported in recipients of anti CD20-B-cell depleting therapy (Figure 1). Those who are immunocompromised are also at risk for prolonged infection,

during which emergence of variants can occur and could serve as a reservoir of escape variants that could spread to the general population.

Figure 1: Percentage of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63) Source: Oliver S. Data and clinical considerations for additional doses in immunocompromised people. ACIP meeting July 22, 2021



The OCTAVE trial is a multi-centre, multi-disease, prospective cohort that assessed COVID-19 vaccine responses across a range of conditions in potentially vulnerable groups, some of whom were immunocompromised, and compared them to those of healthy individuals. Approximately 11% of patients across all disease cohorts fail to generate antibodies that react to SARS-CoV-2 spike four weeks after two vaccines.

Those with immunocompromise associated with a suboptimal response to vaccines and those living with and/or caring for them should observe all recommended public health and social measures to limit their COVID-19 exposure.

Safety and effectiveness of additional doses of COVID-19 vaccines

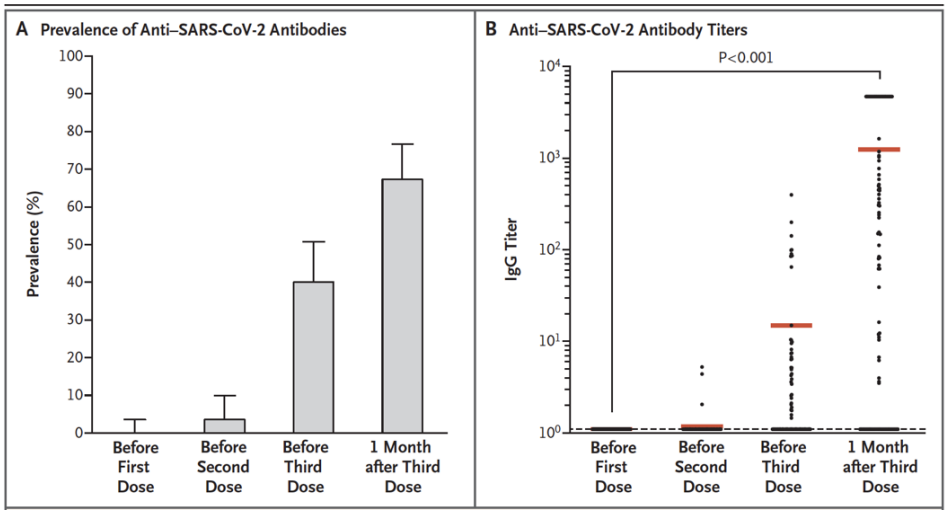
There is limited data available on the effectiveness of additional dose of COVID-19 vaccines. In a company press release Pfizer reported that data in individuals who received a third dose of Comirnaty® show a favourable safety profile and robust immune responses. The additional dose elicited significantly higher neutralising antibody (NA) 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 NA titres against wild type exceeding those following the primary immunisation.

Two reports of successful enhancement of immune response in solid organ transplant recipients have been reported. In a randomised controlled trial with 120 organ transplant recipients, median age 66 years, an additional dose of Spikevax® was given two months after the second dose and resulted in significant increases in antibody levels and neutralising activity.

In a separate study, Kamar reported on the results of 101 solid organ transplant recipients who received three doses of Comirnaty®, the third given two months after the second dose. These investigators also documented improved responses with seroconversion increasing from 40% to 68% recipients before, and four weeks after the third dose, respectively (Figure 2).

Figure 2: Prevalence of anti SARS-CoV-2 antibodies and anti SARS-CoV-2 antibody titres before and after vaccination in the study population. Source: Kamar N et al



An extended primary series using an additional third dose in the immunocompromised may not reliably induce protection for all; however, among those with no detectable antibody response to an initial mRNA vaccine series, 30 - 50% developed an antibody response to an additional dose. In patients with SOT a third dose of an mRNA vaccine, given 2 months after the second dose, was significantly more immunogenic (Virus neutralisation 71% in third dose recipients compared with 12% in two dose recipients).

Preliminary findings of a population based booster programme have been shared by the Israeli Health Ministry who, on 20 August 2021, reported that approximately one million booster doses of Comirnaty® have been given to those aged 60 years and older and about 250,000 doses to those aged 50 – 59 years. No safety concerns were identified with similar profile but lower rates of systemic and local reactions than following the first or second doses. More detail on the rates of breakthrough hospitalisations and serious disease and of the safety and effectiveness of the third dose of Comirnaty® in preventing adverse outcomes is awaited.

Flaxman et al in a small study 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.

There has been no such update from the European Medicines Agency so any use of an additional or booster dose would be off label.

Timing and selection of the additional dose

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

When an additional dose is being given as an extended primary vaccine course to those who are likely to have an impaired response to vaccines e.g., the immunocompromised, that dose should be given after a minimum interval of two months to achieve early protection.

In the limited available data, additional doses have been 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. All studies of a third dose for the immunocompromised have been with an mRNA vaccine.

International recommendations

EU/EEA

The European Centre for Disease Control and Prevention (ECDC) is due to publish interim considerations for additional doses of COVID-19 vaccine soon.

Based on the most recent available information from ECDC, eight EU/EEA countries (Austria, Belgium, France, Hungary, Liechtenstein, Lithuania, Luxembourg and Slovenia), are currently recommending the use of an additional vaccine dose for immunocompromised persons.

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 program in the UK would include adults aged 16 years and over who are immunosuppressed.

This advice has not yet been finalised.

US

On 20 August 2021, CDC recommended people who are moderately to severely immunocompromised should receive an additional dose of mRNA COVID-19 vaccine after the initial two doses.

Israel

Israel began a national booster vaccine programme at the end of July 2021, following an increase in COVID-19 Delta infections using Comirnaty® initially starting with older persons. Currently, a booster dose of vaccine is recommended for all those aged 30 years and older after a minimum of five months following their primary course.

Conclusions

Data indicate that those with severe immunocompromise do not have adequate protective responses following a primary COVID-19 vaccine course. There is evidence that protection can be enhanced by an additional mRNA vaccine dose. This in effect represents an extension of the primary vaccination course.

NIAC continues to actively examine evidence regarding booster vaccines for waning immunity and reduced effectiveness in particular groups. These groups include those at increased risk of severe COVID-19 disease e.g., residents of LTCFs, older persons, and those with underlying medical

conditions, as well as healthcare workers because of their vital role in providing essential health services. More information regarding the safety and effectiveness of homologous or heterologous additional vaccines in these groups is expected in the coming days and weeks which NIAC will consider.

The key focus must remain on completing vaccination of the unvaccinated.

Efforts to minimise the risk of other respiratory infections in the coming months should be made. The 2021/22 seasonal influenza vaccination programme should proceed, with efforts enhanced to optimise uptake.

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

Recommendations

1. All eligible unvaccinated or incompletely vaccinated people are strongly encouraged to complete the vaccination course.

2. An additional mRNA vaccine dose should be given to those aged 12 and older with immunocompromise associated with a suboptimal response to vaccines who have completed their primary course, regardless of whether the primary course was of an mRNA or an adenoviral vector vaccine. This is an extended primary vaccination course. The additional vaccine should be given after a minimum interval of two months following the last dose of an authorised COVID-19 vaccine.

3. Those with immunocompromise associated with a suboptimal response to vaccines and those living with and/or caring for them should observe all recommended public health and social measures to limit their COVID-19 exposure.

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Appendix

Extract from Table 5a.2 of Chapter 5a of the Immunisation Guidelines

Conditions associated with a suboptimal response to vaccines

Cancer:

- All cancer patients actively receiving (and/or within 6 weeks of receiving) systemic therapy with cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies and surgery or radical radiotherapy for lung or head and neck cancer
- All patients with advanced/ metastatic cancers
- Haematological cancers - within 1 year of diagnosis

Chronic kidney disease:

- On dialysis, or eGFR<30ml/min

Transplantation:

- Listed for solid organ or haematopoietic stem cell transplant (HSCT)
- Post solid organ transplant at any time
- Post HSCT within 12 months

Genetic diseases:

- APECED[1]
- Inborn errors in the interferon pathway

Treatment:

- including but not limited to Cyclophosphamide, Rituximab, Alemtuzumab, Cladribine or Ocrelizumab in the last 6 months

Other e.g.

- High dose systemic steroids[2]
- Persons living with HIV

[1] APECED - autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

[2] The following doses of prednisolone (or equivalent dose of other glucocorticoid) may increase the risk of severe COVID-19 disease:

- ≥10mg per day for more than 4 weeks with one other immunosuppressant
- ≥20mg per day for more than 4 weeks

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