National Immunisation Advisory Committee

RECOMMENDATIONS FOR THE SECOND COVID-19 VACCINE DOSE FOR THOSE WHO HAVE ALREADY HAD A FIRST DOSE OF VAXZEVRIA®

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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

These recommendations reflect a dynamic vaccination programme strategy. Scientific evidence about COVID-19 vaccines is continuously evolving and being refined. Recommendations may be updated when more information becomes available.

NIAC reviews available evidence and international practices, and engages with the HPRA, DOH, and other stakeholders as necessary.

In forming recommendations and advice, NIAC weighs the potential risks of vaccine- associated harm against disease related risks, both to the individual and the community. NIAC also considers other disease mitigation strategies including availability of other vaccines. NIAC's overall priority for the COVID-19 vaccination programme continues to be prevention of severe disease and death in the most vulnerable.

Thrombosis Thrombocytopenia Syndrome (TTS) is a very rare side effect after either the first or second doses of the adenoviral vector vaccine Vaxzevria®. As the rates of TTS are reported to be higher in younger adults, NIAC has previously recommended the use of Covid-19 mRNA vaccines for those aged under 50 years who have not yet commenced a COVID-19 vaccination schedule.

On 27 May 2021, the UK reported a rate of TTS of 1.6/1,000,000 after the second dose of Vaxzevria®, and 13/1,000,000 after the first or unknown dose. On 28 April 2021 the respective rates were 1/1,000,000 and 8.6/1,000,000.

While there has been some increase in the UK reporting rates after the first and second doses, TTS remains a very rare event that appears to be even lower after a second dose.

There is insufficient evidence to recommend a change from the authorised two-dose Vaxzevria® schedule or to support giving a mRNA vaccine instead of a second dose of Vaxzevria®. There is a need for further evidence on safety and effectiveness of mixed (heterologous) vaccine schedules. Further information is expected in the coming months which may warrant an update of these recommendations.

The current NIAC recommendation for an interval of 8-12 weeks between the two doses of Vaxzevria® is based on enhanced immunogenicity and no drop off in protection during that interval. However, there is concern at the rate of rise in numbers of the more transmissible B.1617.1 and B1.617.2 variants which are now the predominant strains in the UK. Evidence of suboptimal protection against these variants after one dose of Vaxzevria® means that the shorter 8-week interval is preferable to ensure earlier protection, if that interval is practicable.

All those who have had a previously confirmed laboratory COVID-19 infection in the nine months prior to their first dose of Vaxzevria® have full protection 15 days after this dose and do not need a second dose of Vaxzevria®.

This advice may be revised as more information becomes available or if the epidemiological situation changes.

Recommendations for a second dose of Vaxzevria® for those who have received one dose

• Those who HAVE NOT had laboratory confirmed COVID-19 infection within the previous nine months
  ○ Should receive their second dose 8 - 12 weeks later. An 8-week interval is preferable if practicable
  ○ A shorter interval of 4 - < 8 weeks may be used in certain circumstances (e.g. pregnancy, imminent immunotherapy)
• Those who HAD laboratory confirmed COVID-19 infection and received one dose of vaccine within nine months following infection)
  ○ Aged **50 years and older** should receive a second dose of Vaxzevria®
  ○ Aged **under 50 years** and immunocompromised should receive a second dose of Vaxzevria®
  ○ Age **under 50 years and immunocompetent**: a single dose of Vaxzevria® is sufficient. They should be considered fully vaccinated and are protected 15 days following their vaccine dose
All other current recommendations remain in place

DOH request for advice

On 28 May 2021, NIAC received a request from the Department of Health (DOH) for advice regarding the safety and efficacy of a heterologous vaccination schedule and, "whether those under 50 years for whom the risk-benefit ratio is less favourable in terms of Thrombosis Thrombocytopenia Syndrome should continue to receive a second dose of Vaxzevria® or should be offered a mRNA vaccine as an alternative."

Background

Thrombosis Thrombocytopenia Syndrome (TTS) is a very rare side effect after either dose of the adenoviral vector vaccine Vaxzevria®. Previous NIAC recommendations were published on 13 May 2021.

The benefit/risk of Vaxzevria® is favourable in all ages and has been very clearly demonstrated in those aged 50 years and older. The benefit/risk of Vaxzevria® in those aged 18-49 years is more favourable when the 14-day rate of SARS-CoV-2 infection is above 500/100,000 or the rate of change is significantly increasing compared to low or stable rates of infection.

As the risks of TTS are reported to be higher in younger adults, NIAC has previously recommended the use of mRNA vaccines for those aged under 50 years who have not yet commenced a COVID-19 vaccination schedule.

This document sets out current evidence-based recommendations for those awaiting their second dose of Vaxzevria®.

All individuals should continue to practice recommended public health measures for prevention and control of COVID-19 infection and transmission after COVID-19 vaccination.

THROMBOSIS THROMBOCYTOPENIA SYNDROME (TTS) UPDATE

On 13 May 2021 NIAC recommended that all those who had received one dose of Vaxzevria® should receive their second dose 12 weeks later. There was no evidence of a higher risk of TTS following a second dose of Vaxzevria® and based on the reporting rate, the risk of TTS appeared lower than after the first dose.

The latest weekly report from the Medicines & Healthcare products Regulatory Agency (MHRA) on 27 May 2021, including data up to 19 May 2021, states that 24.2 million doses of Vaxzevria® were administered in the UK, of which 10.7 million were second doses.

A total of 332 reports of TTS following vaccination with Vaxzevria® were received, 180 in women and 151 in men. Age ranged from 18 to 93 years with 58 deaths (case fatality rate CFR 17%). There were 120 cases of cerebral venous sinus thrombosis (average age 46 years) and 212 other major thromboembolic events (average age 55 years).

On 27 May 2021, the reporting rate after the second dose was 1.6/1,000,000, (1/1,000,000 on 28 April 2021). The overall reporting rate for first or unknown doses of Vaxzevria® was 13/1,000,000, (8.6/1,000,000 on 28 April 2021). (Table 1).

Table 1: TTS Reporting Rate per million doses following Vaxzevria®

MHRA (UK) TTS Reporting Rate per million doses following Vaxzevria®		
Date	Dose 1	Dose 2
28 April 2021	8.6	1
27 May 2021	13	1.6

This suggests that the risk following a second dose of vaccine is substantially less than following the first dose. However, the reporting rates are not directly comparable as follow-up time after the second doses is shorter and the majority of second doses have been received by older adults.

While there has been some increase in the UK reporting incidence following both first and second doses, TTS remains a very rare event that appears to be less likely after a second dose.

At an EMA Press Conference of 28 May 2021, it was stated that there has been no change to the overall published TTS reporting rate of 10/ 1,000,000 in the EU/EEA.

IMPACT OF THE B1.617.1 AND B1.617.2 (INDIA) VARIANTS

Those who have received one dose of Vaxzevria® gain considerable short-term benefit in terms of protection against hospitalisation, severe illness and death, although this benefit may be less in the case of the B1.617.1 and B1.617.2 variant strains.

Reduced effectiveness against symptomatic disease from the B.1617 variant strains following a single dose of Vaxzevria® was reported by Lopez Bernal. Effectiveness was restored following a second dose (Table 2). The estimates of effectiveness would likely have been higher if their analysis had been restricted to protection against severe disease and death, as is the case in all COVID-19 vaccine studies to date.

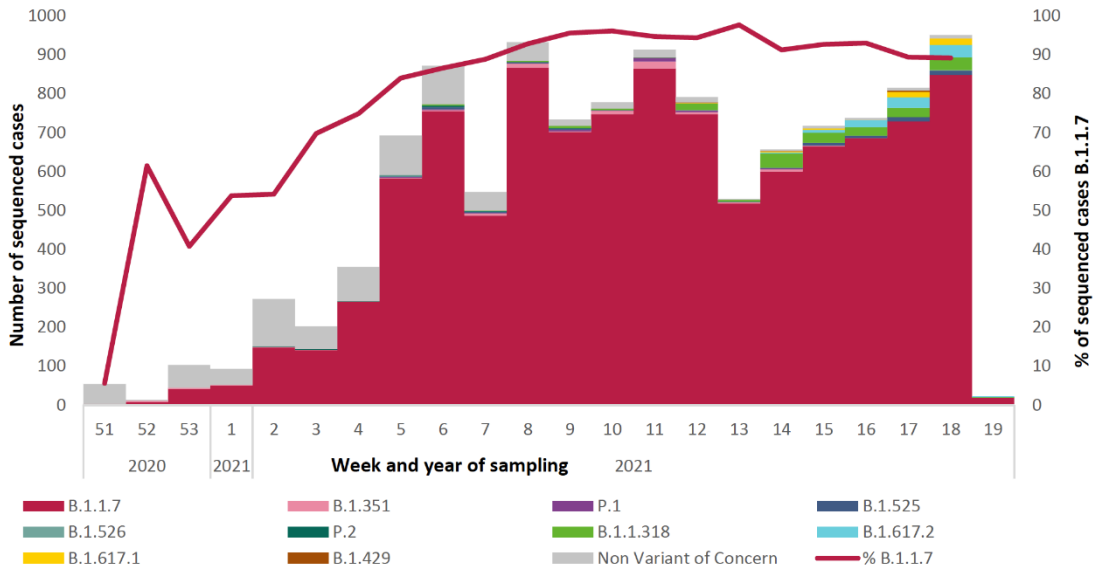
Table 2. Estimates of effectiveness of Vaxzevria® against B.1.1.7 and B.1.617.2 variants by dose

	Vaxzevria® Effectiveness	
	B.1.1.7 (UK variant/alpha variant)	B.1.617.2 (India variants/delta variant)
Dose 1	51%	33%
Dose 2	66%	60%

The incidence of B1.617.1 and B1.617.2 infections is now higher than the incidence of B1.1.7 infections in the UK. There is concern at the rate of rise of the B1.617 strains which are more transmissible than the B1.1.7 strain, with an increase in UK case numbers in the last week, with most A&E visits and hospitalisations in the unvaccinated or partially vaccinated.

In Ireland, 58 cases of B1.617.1 and 97 cases of B1.617.2 infection have been identified mainly related to two clusters (Figure 1). The report relates to specimens received up to 15 May 2021 as there is a two-week lag time for the results of whole genome sequencing.

Figure 1. Whole genome sequencing results and percentage of sequenced specimens that were found to be the B.1.1.7 (UK) variant of concern, specimen collection rates from week 51 (13 Dec 2020) to week 19 (15 May 2021)



Source: Summary of COVID-19 virus variants in Ireland HPSC and NVRL 25/05/2021

While, as yet there has been no identified widespread community transmission in Ireland, there is no time for complacency, given the experience in the UK. The potential for rapid of spread of these variants represents a real threat and underscores the need to complete vaccination as soon as possible.

POTENTIAL IMMUNISATION STRATEGIES FOLLOWING A FIRST DOSE OF VAXZEVRIA®

The European Centre for Disease Control (ECDC) published an overview of EU/EEA country recommendations on COVID-19 vaccination with Vaxzevria®, on 18 May 2021.

- Twenty EU/EEA countries recommend a second dose of Vaxzevria®
- Five countries recommend giving a mRNA vaccine as the second dose
- Four countries were reviewing their recommendations

The decision to administer a second dose of Vaxzevria® was influenced by the low probability of TTS occurring after the second dose and the lack of evidence on the effectiveness of mixed vaccine schedules.

OPTION 1: VAXZEVRIA® AS A SECOND DOSE

Vaxzevria® is authorised for administration only as a two-dose schedule, with an interval of 4-12 weeks between doses. The second dose of Vaxzevria® is essential to enhance protection.

The EMA on 23 April 2021, acknowledging TTS as a very rare side effect, recommended no change to the authorised two-dose schedule with a 4-12 week interval, and have made no changes since then.

The current NIAC recommendation for an interval of 8-12 weeks is based on enhanced immunogenicity and no drop off in protection during that interval. However, the threat of new variants in circulation and evidence of suboptimal protection against B.1.617.1 and B.1.617.2 variants after one dose of Vaxzevria® means that the shorter 8-week interval is preferable to ensure earlier protection, if practicable.

The recommendation for those aged under 50 years who have already received one dose of Vaxzevria® differs from the recommendation for those aged under 50 years who are unvaccinated. This is because:

- Data on the safety and immunogenicity of an mRNA vaccine following Vaxzevria® are insufficient and data on efficacy and effectiveness are lacking.
- The risk posed by COVID-19 in Ireland persists. Incomplete vaccination gives suboptimal protection which is of particular importance given the B1.617.1 and B.1.617.2 variant threat.
- The reporting rate of TTS following a second dose of Vaxzevria® is lower than after the first dose. This suggests that the risk following a second dose of vaccine is substantially less that following the first dose.

OPTION 2: mRNA COVID-19 VACCINE AS A SECOND DOSE

There is some evidence from animal studies and other heterologous vaccination schedules. to support the use of a heterologous vaccination strategy (using a different vaccine for the first and subsequent doses of a multi-dose schedule)

Animal studies indicate a strengthened immune response, when using prime boost heterologous strategies using adenoviral vector and mRNA COVID-19 vaccines.

There is precedent for using a heterologous prime-boost strategy with other vaccines e.g.: Hepatitis B.

All COVID-19 vaccines target the same antigen (spike protein) and a combined vaccine schedule could potentially boost immune responses Several countries are studying heterologous vaccine schedules with trials planned or ongoing e.g., Denmark, France, Netherlands and Finland. Some results have been reported.

The UK Com-Cov trial is studying heterologous vaccine schedules using four combinations of Vaxzevria® and Comirnaty®, given at 4- or 12-week intervals. A preliminary report of 29 May 2021 focused on those who received their vaccines at a 4-week interval. Heterologous vaccination induced greater systemic reactogenicity following the booster dose than their homologous counterparts. The data were obtained in participants aged 50 years and older, and the authors noted that reactogenicity might be higher in younger age groups.

In Germany, Hillus et al reported the reactogenicity of homologous Comirnaty® or heterologous Vaxzevria®/Comirnaty® prime-boost immunisations in a prospective observational cohort study of 326 healthcare workers. No major differences were observed in the frequency or severity of local reactions after either of the vaccinations. In contrast, notable differences were observed for systemic reactions, which were most frequent after prime immunisation with Vaxzevria® (86%), and less frequent after homologous Comirnaty®/Comirnaty®(65%), or heterologous Vaxzevria®/Comirnaty® boosters (48%). The authors speculated that the more favourable reactogenicity results in this study reflected the longer interval between doses (12 weeks) compared to the Com-Cov results

In Spain, preliminary results of the CombivacS study comparing homologous Vaxzevria® with Vaxzevria®/Comirnaty® were noted in the recent ECDC technical report. A press report noted that the regimen was highly immunogenic with a sevenfold rise in neutralising antibodies when the a second dose was Comirnaty®. Mild side effects were common, and similar to those seen in standard vaccination regimens. The report concluded that the combination is highly safe and effective. However, the results are preliminary and are not peer reviewed or published.

In summary, there is insufficient evidence regarding safety and efficacy to recommend heterologous schedule. Further results are expected in the coming months.

OPTION 3: FOR THOSE WITH LABORATORY CONFIRMED COVID-19 INFECTION WHO SUBSEQUENTLY RECEIVED ONE DOSE OF VAXZEVRIA®

NIAC has issued evidence-based recommendations for vaccination of those who have had prior laboratory confirmed COVID-19 infection up to six months before their first scheduled COVID-19 vaccination. For those aged under 50 years and immunocompetent and who have had a laboratory confirmed COVID-19 infection in the previous six months, a single dose of COVID-19 vaccine is sufficient, and they should then be considered fully vaccinated.

Based on the recent HIQA review of duration of immunity following natural infection the interval can now be extended to nine months. Thus, for those who had laboratory confirmed COVID-19 infection in the nine months preceding their first dose of Vaxzevria® a second dose is not indicated, and they can be considered fully protected 15 days after their first vaccine.

This does not apply to those who have had laboratory confirmed COVID-19 infection after a first dose of COVID-19 vaccine. They should be given a second dose of Vaxzevria®.

Conclusions

These conclusions reflect a review of available scientific evidence. Information about COVID-19 infection and COVID-19 vaccines is continuously evolving and being refined. The formation of recommendations is dynamic and iterative.

There is preliminary evidence of the safety of heterologous vaccine schedules, albeit with potential for increased reactogenicity. There is an unpublished report of the immunogenicity of such schedules. Efficacy and effectiveness data are lacking.

A single dose of Vaxzevria® affords inadequate protection against the B1.617.1 and B.1.617.2 variants. Effectiveness is restored following a second dose. Given the increased transmissibility of these strains and the potential for greater dissemination, the need for soonest protection remains.

There is insufficient evidence to recommend a change from the authorised two-dose Vaxzevria® schedule.

There is insufficient evidence to date to support giving a mRNA vaccine instead of a second dose of Vaxzevria®.

Those who have received one dose of Vaxzevria® should receive a second dose 8 - 12 weeks later with a preference for the shorter interval of 8 weeks to provide earlier protection.

Those who have had a previously confirmed laboratory COVID-19 infection in the nine months prior to their first dose of vaccine have full protection 15 days after this dose and do not need a second dose.

This advice may be revised as more information becomes available or if the epidemiological situation changes.

Recommendations for a second dose of Vaxzevria® for those who have received one dose

- Those who HAVE NOT had laboratory confirmed COVID-19 infection within the previous nine months
    - Should receive their second dose 8 - 12 weeks later. An 8-week interval is preferable if practicable
    - A shorter interval of 4 - < 8 weeks may be used in certain circumstances (e.g.: pregnancy, imminent immunotherapy)
- Those who HAD laboratory confirmed COVID-19 infection and received one dose of vaccine within nine months following infection)
    - Aged **50 years and older** should receive a second dose of Vaxzevria®
    - Aged **under 50 years** and immunocompromised should receive a second dose of Vaxzevria®
    - Age **under 50 years and immunocompetent**: a single dose of Vaxzevria® is sufficient. They should be considered fully vaccinated and are protected 15 days following their vaccine dose

All other current recommendations remain in place

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