ROYAL COLLEGE OF PHYSICIANS OF IRELAND

National Immunisation Advisory Committee

RECOMMENDATIONS FOR THE ROLE OF COVID-19 HETEROLOGOUS VACCINATION IN THE NATIONAL PROGRAMME

NIAC | 15.07.2021

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

In forming its recommendations and advice, NIAC weighs the potential benefits and risks of vaccines, 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 vaccination programme continues to be prevention of severe disease and death in the most vulnerable.

DOH request for advice

On 22 June 2021, NIAC received a request from the Department of Health (DOH) to review "the potential role of heterologous vaccination and the potential ongoing role of adenoviral vector vaccines as part of the COVID-19 vaccination programme in Ireland" in the context of the Delta variant.

A response was sent to the DOH by NIAC on 28 June 2021. The background document followed on 6 July 2021 stating that there was insufficient evidence to recommend the routine use of heterologous vaccination schedules in the National Programme. This document reviews additional evidence regarding the potential role of heterologous vaccination as part of the COVID-19 vaccination programme in the context of the Delta variant.

Executive Summary

Current homologous vaccine schedules including Vaxzevria® are proven highly effective against COVID-19 hospitalisation and severe disease including that caused by the Alpha and Delta variants.

While there are no immediate serious safety concerns with heterologous vaccine schedules, accumulating data indicates that the rates of side effects following the second dose may be higher, particularly when administered with the shorter four-week interval between doses. The longer-term safety profile remains to be assessed. Further monitoring is required to determine the overall safety profile of these schedules.

Early studies indicated that these heterologous combinations are highly immunogenic. A heterologous vaccine schedule is more immunogenic that homologous Vaxzevria® but not more immunogenic that a homologous Comirnaty® schedule. For those primed with Vaxzevria®, an mRNA vaccine as the second vaccine dose can result in excellent humoral and enhanced cellular immunity. Given that all the tested homologous schedules, including Vaxzevria®, are proven to be highly effective against severe COVID-19, it is likely that the heterologous schedule will also prove to be effective. However, as yet clinical effectiveness data is lacking. It remains to be proven that the augmented immunogenicity translates into better effectiveness against COVID-19.

Given the impact of the Delta variant and the rapidly rising case numbers there is an urgency to get everyone vaccinated as safely and as quickly as possible. Available evidence supports the selective use of heterologous vaccination schedules to maximise vaccine uptake.

Recommendations

1. Given the proven real-world effectiveness of the currently authorised homologous schedules, including effectiveness against the Delta variant, NIAC continues to preferentially recommend homologous schedules for all age groups.
2. Homologous mRNA vaccine schedules are preferred for those under 50 years of age.
3. Where a second vaccine dose of a homologous schedules is contraindicated, a heterologous vaccine schedule can be used, irrespective of whether the first dose was an mRNA or adenoviral vector vaccine.
4. For those who have already had a first dose of Vaxzevria® and who did not complete the vaccination schedule as recommended, an mRNA vaccine should be offered in line with their priority grouping or age cohort.
5. Those 18 - 34 years of age who opt for Vaxzevria® as a sooner alternative to an mRNA vaccine are recommended to complete that vaccine course with Vaxzevria®.
   5.1. If they decline the offer of a second dose of Vaxzevria®, they should be afforded the option of completing vaccination with an mRNA vaccine along with their age cohort. They should be informed that this may delay optimising their protection.
   5.2. If there are sufficient supplies of mRNA vaccines, individuals who receive a first dose of Vaxzevria® should be offered the option of a second vaccine of either Vaxzevria® or an mRNA vaccine.
6. Those who have received a heterologous schedule should be considered fully vaccinated after their second vaccine (7 days after Comirnaty®, 14 days after Spikevax® and 15 days after Vaxzevria®).

Background

An effective vaccine often requires more than one dose to elicit an effective immune response. Traditionally the same (*homologous)* vaccines are given multiple times as homologous boosts. *Heterologous COVID-19* vaccination refers to the delivery of the same SARS-CoV-2 spike protein antigen using different delivery systems, e.g., Vaxzevria®, an adenoviral vector vaccine for the first (priming) dose followed by boosting with an mRNA vaccine for the second dose. Homologous vaccination refers to use of the same vaccine for all doses. Although data are limited, preliminary results strongly suggest that a heterologous schedule elicits

both humoral and cell-mediated immune responses that are higher or comparable in magnitude to the homologous mRNA schedules although with greater systemic reactogenicity.

There are three main reasons why heterologous vaccination schedules are being considered: -

1. **To increase flexibility of vaccine delivery within national programmes**
   Heterologous vaccination schedules were initially conceptualised as a way to mitigate logistical problems inherent in global mass vaccination programmes. The principle has been demonstrated with a number of vaccines e.g., hepatitis B. Such schedules, if safe and effective, could be used if a second dose is contraindicated or where vaccine supply chain issues prevent completion of the vaccination schedule with the same vaccine. If successful, it could add flexibility to national programmes. To inform this, recruitment in the Com-COV randomised trial of heterologous COVID-19 vaccination schedules began in February 2021.

2. **To minimise adenoviral vector vaccination in cohorts where Thrombocytopenia with Thrombosis Syndrome (TTS) is a higher risk**
   In March/April 2021, reports of the novel Thrombosis Thrombocytopenia Syndrome (TTS) as a rare side effect of both Vaxzevria® and COVID-19 Vaccine Janssen® prompted some countries to recommend a heterologous vaccination schedule using an mRNA vaccine, in place of the second dose of Vaxzevria® for those considered at higher risk of TTS (e.g., those aged less than 50 years). Canada recommends an mRNA vaccine for any adult who had received a first dose of Vaxzevria®.

3. **To enhance immunogenicity and increase protection against variants of concern**
   The SARS-CoV-2 Alpha (B.1.1.7) variant has been displaced in many countries by the Delta (B1.617.2) variant. In the UK, this has been associated with a rise in case numbers. As yet there remains a disconnect between the rise in case numbers and hospital admissions. However, modelling suggests that cases, hospitalisations, and deaths will increase over the coming months. In vitro studies have shown variable levels of reductions in neutralising activity by the vaccines against these variants, most notably the Beta (B1.351) variant, giving rise to the concern that that this could translate into clinically significant reduction in vaccine effectiveness. Preliminary results from observational studies indicating enhanced immunogenicity of heterologous vaccination schedules have led to suggestions that a heterologous vaccine schedule can be used.

These factors must be considered in light of available evidence on immunogenicity, efficacy, and clinical effectiveness of all the vaccines used in homologous and heterologous schedules, vaccine availability, the remaining target population, and the need to safely vaccinate as many people as possible in as short a time as possible, given the threat of the Delta variant.

On 14 July 2021, an EMA and ECDC update on COVID-19 stated “There are good scientific grounds to expect this strategy to be safe and effective when applied to vaccination against COVID-19. The use of a heterologous vaccination strategy may allow populations to be protected more quickly and make better use of available vaccine supplies.”

All individuals should continue to practise recommended public health and social measures for prevention and control of COVID-19 infection and transmission, whether vaccinated or not.

COVID-19 Vaccine Rollout in Ireland

In Ireland, more than 90% of those aged 70 years and older are fully vaccinated with mRNA vaccine. It is anticipated that the majority of those aged 60 – 69 years of age will be vaccinated with Vaxzevria® by 19 July 2021. Almost 70% of those aged 50-59 years of age are fully vaccinated. Vaccination of those aged less than 50 years is proceeding, with mRNA vaccines recommended.

The choice of an adenoviral vector vaccine on an "opt-in" basis has been approved for those aged 18 - 34 years who, rather than waiting for an mRNA vaccine, choose an earlier adenoviral vector vaccine.

An mRNA vaccine is recommended as a second dose if Vaxzevria® is contraindicated and vice versa.

It is likely that some people who have received one dose of Vaxzevria® have deferred or declined a second dose.

As the Delta variant dominates, given its increased transmissibility and the anticipated increase in hospitalisations, there is urgency to complete vaccination and optimise protection against severe disease for the population as safely and as rapidly as possible.

Vaccine Effectiveness and Impact of Variants

Data from the UK has confirmed the comparable effectiveness against hospitalisation and severe disease of two doses of either an mRNA vaccine or Vaxzevria® against the Delta and Alpha variants (Table 1). Encouraging results were reported by Nasreen et al. in assessing the effectiveness of COVID-19 vaccines against variants of concern in Canada. Vaccine effectiveness against hospitalisation or death caused by all studied variants of concern was generally higher than effectiveness against symptomatic infection after one dose of the three vaccines (Table 1). Vaccine effectiveness against the Delta variant after one dose of Comirnaty®, Spikevax® (formerly COVID-19 vaccine Moderna®), or Vaxzevria® was 78% (95% CI, 65–86%), 96% (95% CI, 72–99%), and 88% (95% CI, 60–96%), respectively. Inadequate sample size prevented assessment of protection after two doses of Vaxzevria®. However, most studies have indicated higher protection after two doses.

Table 1: Vaccine Effectiveness (%) against Symptomatic Disease & Hospitalisation with Variants of Concern

Vaccine	Symptomatic Disease				Hospitalisation			
	Alpha		Delta		Alpha		Delta	
	UK[1]	CA[3]	UK[1]	CA[3]	UK [2]	CA[3]	UK [2]	CA[3]
Comirnaty®								
Dose 1	49 (43 - 55)	66 (64-68)	33 (38– 51)	56 (45-64)	83 (62-93)	77 (69-83)	94 (46-99)	78 (65-86)
Dose 2	93 (90- 96)	89 (86 -91)	88 (78 – 93)	87 (64-95)	95 (78– 99)	95 (81-99)	96 (86 – 99)	N/A[4]
Vaxzevria®								
Dose 1	51 (47- 55)	67 (38-82)	33 (19 - 44)	64 (60-68)	76 (61 – 85)	85 (81-88)	71 (51 – 83)	88 (60-96)
Dose 2	66 (54- 75)	N/A	60 (29 - 77)	N/A	86 (53 – 96)	N/A	92 (75 – 97)	N/A
Spikevax®								
Dose 1	N/A	83 (80-86)	N/A	72 (57-82)	N/A	79 (74-83)	N/A	96 (72-99)
Dose 2	N/A	92 (86-96)	N/A	94 (89-97)	N/A	N/A	N/A	N/A

[1]Lopez Bernal J et al.. [2] Stowe J et al.. [3] Nasreen S et al.. [4]**N/A: Not Assessed**

The immunogenicity of COVID-19 Vaccine Janssen® against variants Alpha, Beta, Gamma, and CAL.20C (a Californian variant) has been reported. Results suggest that while neutralising antibody responses induced by the vaccine against Beta and Gamma were reduced, functional non-neutralising antibody responses and T cell responses were largely preserved against all the tested variants.

On1 July 2021, Jongeneelen et al. reported that all tested variants demonstrated susceptibility to COVID-19 Vaccine Janssen®. When compared with Alpha, reductions in neutralising activity were observed for the Beta (3.6-fold), Gamma (3.4-fold) and Delta (1.6-fold) variants. These results are consistent with studies in those who received Comirnaty®, Spikevax®, or Vaxzevria®.

For all the vaccines, the reduction in neutralisation titres was greater for the Beta than the Delta variant. One dose of COVID-19 Vaccine Janssen® elicited higher neutralizing antibody activity against the Delta than the Beta variant in South Africa, where high efficacy against severe/critical disease was demonstrated. In South Africa, Moore et al. found a disconnect between the reduction in neutralising activity following COVID-19 Vaccine Janssen® and clinical effectiveness. They postulated that, while even very low levels of neutralising antibodies might contribute to protection, other antibodies and cellular immune responses were likely important in protection. Early reports suggest that humoral and cellular immune responses generated by COVID-19 Vaccine Janssen® persisted for at least eight months indicating durability of protection.

mRNA Vaccines

Comirnaty® and Spikevax® are authorised for use in a two-dose, three or four-week schedule, respectively. For pragmatic reasons NIAC has recommended that both vaccines be administered at a four-week interval. A two-dose schedule of either vaccine has proved highly effective against the Delta variant.

Pericarditis and myocarditis have recently reported following immunisation with mRNA vaccination. On 23 June 2021, after reviewing available evidence including that for risks of myocarditis, the US Advisory Committee on Immunization Practices (ACIP) determined that the benefits of using mRNA COVID-19 vaccines clearly outweigh the risks in all populations, including adolescents and young adults.

On 9 July 2021, the EMA completed a review and recommended that myocarditis and pericarditis be added to the product information of Comirnaty® and Spikevax® as very rare adverse reactions (actual frequency unknown). EMA concluded that the cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger adult men. For Comirnaty®, 145 cases of myocarditis were reported by 31 May 2021, by which time approximately 177 million doses had been administered in the EEA. For Spikevax® there were 19 cases of myocarditis reported in context of 20 million doses. While overall the observed rate of myocarditis was not greater than expected, the rate was higher than would be expected in younger adult males. Overall, for both mRNA vaccines the observed/expected analysis in the US and Israel, has also shown a higher rate than expected in younger adult males.

In the European case review, there were no fatal cases following Spikevax®. There were 5 fatal cases from 145 reports following Comirnaty®, all in adults aged over 50 and associated with advanced aged or with co-morbidity. Available data suggest that the myocarditis and pericarditis is similar to the typical course, usually improving with rest or treatment. However, follow up time has been short.

In Ireland, up to 9 June 2021, the HPRA had received nine reports of myocarditis and/or pericarditis following vaccination with mRNA vaccines, (5 male, 4 female, median age 56 years, range 38 to 81). There has been no trend in younger adults or following the second dose but exposure to mRNA vaccines has been very low to date in this cohort.

In conclusion, very rare cases of myocarditis and pericarditis have been reported following vaccination with mRNA vaccines, but the overall benefit risk remains favourable.

Heterologous Vaccination

Heterologous vaccination using different vaccines, first to prime and then to boost the immune system when inducing immunity against a pathogen, has been studied related to different viral pathogens including hepatitis B, HPV, influenza, and Ebola. In relation to SARS-CoV-2 the concept was first explored in a mouse model study using an adenovirus vector as primer and either an inactivated, recombinant protein subunit or mRNA vaccine as the booster. Improved levels of neutralising antibodies and cellular immune responses were found.

In the UK, the Com-COV study was conceived, in anticipation that flexibility in vaccine utilisation might be required in the event of supply issues. The recognition of TTS as a rare complication of the adenoviral vector vaccines Vaxzevria® and COVID-19 Vaccine Janssen® prompted some countries, including Spain and Germany, to recommend an mRNA vaccine, Comirnaty®, as the second vaccine dose for those aged 50 years and under who had received a first dose of Vaxzevria®.

A number of centres have now reported their observational experience of this strategy.

A multi-centre phase 2 randomised trial in Spain showed that a heterologous Vaxzevria®/Comirnaty® schedule (N=450) induced a robust immune response with an acceptable and manageable reactogenicity profile. The small sample size and short follow-up time does not allow for full assessment of the safety of the heterologous vaccination schedule.

A German study (Hillus et al.) reported that a heterologous Vaxzevria®/ Comirnaty® schedule with a 10 to 12-week interval was well tolerated and slightly more immunogenic than homologous vaccination given with a three-week interval. Three weeks after the second dose, antibody responses in Comirnaty®/Comirnaty® immunised participants were comparable to Vaxzevria®/Comirnaty® immunised participants. Of note, three weeks after Vaxzevria® prime immunisation, participants showed robust T cell responses, and T cell reactivity was significantly higher after Vaxzevria®/ Comirnaty® immunisation compared to Comirnaty® /Comirnaty®, suggesting that heterologous vaccination with viral vector priming could confer an immunologic advantage. However, confounding factors, such as differing time intervals of administration could account for the observed differences.

Gross et al. investigated the immunogenicity of heterologous vaccine schedules against the virus variants. Neutralising effect against Alpha was 3.9-fold higher with heterologous than homologous vaccination, suggesting stronger humoral protection with a heterologous schedule. Alpha, Beta and Delta variants were potently neutralized following heterologous vaccination in participants primed with Vaxzevria®. The heterologous schedule was more reactogenic, but reactions were not severe and usually resolved in a few days. Additionally, an increase in CD4+ and CD8+ T cells 2 weeks after full vaccination was reported.

Overall, preliminary results indicated that heterologous vaccination could have the same or an enhancing effect on the innate and cellular immune response compared to homologous schedules.

There has been a small number of broadly similar studies of varying quality, all in preprint, from which a common theme emerges. Heterologous vaccination has been variably associated with some increase in local reactogenicity and early short-lived systemic symptoms. Overall, in these studies the humoral immune response was enhanced compared to that seen after homologous vaccination with vaccines given at a three-week interval. The reported enhanced cellular immunity with viral vector priming suggests that there may be an additional benefit from heterologous vaccination in terms of durability of responses.

The ongoing UK Com-COV randomised clinical trial aims to compare the tolerability and immunogenicity of homologous (Vaxzevria®/ Vaxzevria®, Comirnaty®/ Comirnaty®) and heterologous (Vaxzevria®/ Comirnaty®, Comirnaty®/ Vaxzevria®) schedules given at 4- or 12-week interval in individuals 50 years and older. Initial reactogenicity data on those who received the vaccine at a 4-week interval were published in May 2021. An increase in systemic reactogenicity after the second dose was found with the heterologous schedules but was short lived. Studies in in Spain and Germany using an 8-12 week interval did not show greater reactogenicity.

In a follow-up Com-COV publication (Liu at al) humoral immunogenicity of a Vaxzevria®/ Comirnaty® schedule was non inferior to that in those given a homologous Vaxzevria® schedule. In this group the heterologous schedule was statistically superior to a homologous Vaxzevria® schedule. Conversely, for individuals primed with an mRNA vaccine, the homologous schedule was superior to a heterologous schedule both for SARS COV-2 anti-spike IgG and in pseudoneutralisation assay. All the schedules studied induced concentrations of SARS-CoV-2 anti- spike IgG concentrations at least as high as those induced after a homologous Vaxzevria® schedule, which is effective in preventing symptomatic COVID-19 when administered at a 4-12 week prime-boost interval. Nevertheless, it is notable that the Comirnaty® containing schedules were more immunogenic than the homologous schedule, and none of the heterologous schedules generated binding or pseudovirus neutralising antibodies above those induced by homologous immunisation.

As part of an ongoing Swedish longitudinal study of immunogenicity of COVID-19 vaccines published on 14 July 2021, Normark et al. concluded that Spikevax® can efficiently stimulate the SARS-CoV-2–specific B-cell memory that has been generated by a prime dose of Vaxzevria® vaccine 9 to 12 weeks earlier and that this heterologous schedule may provide better protection against the Beta variant than a homologous Vaxzevria® schedule. The reported adverse events are in line with what has been published previously for homologous Comirnaty® or Vaxzevria® vaccination schedules.

The Com-COV study confirms that both the heterologous and the homologous schedules of Comirnaty® and Vaxzevria® can induce robust immune responses with a 4-week prime boost interval and the heterologous schedule is likely to be highly effective. Further data from the Com-COV study using a 12-week interval are awaited. Swedish data is consistent showing higher antibody levels using a heterologous schedule of

Vaxzevria® and Spikevax® with a 9-12 week interval. While there have been no early safety concerns with heterologous schedules, more long-term follow-up data are needed.

These results support flexibility in deploying mRNA and adenoviral viral vector vaccines, subject to supply and logistical considerations, and emphasise the importance of obtaining information on other mixed schedules with different prime boost intervals. These data on heterologous vaccination will also inform COVID-19 booster immunisation programmes currently being considered in preparation for the Northern Hemisphere 2021/2022 winter.

Based on the overall results, those who have received a heterologous schedule should be considered fully vaccinated after their second vaccine (7 days after Comirnaty®, 14 days after Spikevax® and 15 days after Vaxzevria®).

International Practice

There is diversity in the approach of the EU member states to the use of heterologous COVID-19 vaccination schedules. Some countries, notably France, Germany and Spain were early adopters of the practice to minimise any potential risk related to TTS. Recommendations for substitution of the second scheduled Vaxzevria® dose with an mRNA vaccine have varied in different countries with respect to the age cut off chosen ranging from 40 to 65 years of age. Canada now recommends that anyone, irrespective of age, who has received Vaxzevria® should receive an mRNA vaccine to complete their vaccination course.

In the UK, given the effectiveness of the existing schedules and related to concerns regarding the potential increase in reactogenicity of the mixed schedules, it is recommended that every effort be made to complete the vaccination course with the same vaccine. A mixed schedule is recommended only for those with a contraindication to completing the homologous schedule. This approach has been adopted by a number of other countries who continue to recommend a homologous schedule as the preferred option.

In as far as can be ascertained, as of 12 July 2021, no country has adopted a planned strategy of routine heterologous vaccination for the unvaccinated.

Conclusions

Current homologous vaccine schedules including Vaxzevria® are proven highly effective against COVID-19 hospitalisation and severe disease including that caused by the Alpha and Delta variants.

While there are no immediate serious safety concerns with heterologous vaccine schedules, accumulating data indicates that the rates of side effects following the second dose may be higher, particularly when administered with the shorter 4-week interval between doses. The longer-term safety profile remains to be assessed. Further monitoring is required to determine the overall safety profile of these schedules.

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homologous Comirnaty® schedule. For those primed with Vaxzevria®, an mRNA vaccine as the second vaccine dose can result in excellent humoral and enhanced cellular immunity. Given that all the tested homologous schedules, including Vaxzevria®, are proven to be highly effective against severe COVID-19, it is likely that the heterologous schedules will also prove to be effective. However, clinical effectiveness data is lacking. It remains to be proven that the augmented immunogenicity translates into better effectiveness against COVID-19. While there have been no early safety concerns with heterologous schedules, more long-term follow-up data are needed.

Given the impact of the Delta variant and the rapidly rising case numbers there is an urgency to get everyone vaccinated as safely and as quickly as possible. Available evidence supports the selective use of heterologous vaccination schedules to maximise vaccine uptake.

Recommendations

1. Given the proven real-world effectiveness of the currently authorised homologous schedules, including effectiveness against the Delta variant, NIAC continues to preferentially recommend homologous schedules for all age groups.
2. Homologous mRNA vaccine schedules are preferred for those under 50 years of age.
3. Where a second vaccine dose of a homologous schedule is contraindicated, a heterologous vaccine schedule can be used, irrespective of whether the first dose was an mRNA or adenoviral vector vaccine.
4. For those who have already had a first dose of Vaxzevria® and who did not complete the vaccination schedule as recommended, an mRNA vaccine should be offered in line with their priority grouping or age cohort.
5. Those 18 - 34 years of age who opt for Vaxzevria® as a sooner alternative to an mRNA vaccine, are recommended to complete the vaccine course with Vaxzevria®.
    5.1. If they decline the offer of a second dose of Vaxzevria®, they should be afforded the option of completing vaccination with an mRNA vaccine along with their age cohort. They should be informed that this may delay optimising their protection.
    5.2. If there are sufficient supplies of mRNA vaccines, individuals who receive a first dose of Vaxzevria® should be offered the option of a second vaccine of either Vaxzevria® or an mRNA vaccine.
6. Those who have received a heterologous schedule should be considered fully vaccinated after their second vaccine (7 days after Comirnaty®, 14 days after Spikevax® and 15 days after Vaxzevria®).

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