An Roinn Sláinte
Department of Health
Office of the Chief Medical Officer

5th April 2022

Mr Stephen Donnelly TD
Minister for Health
Department of Health
Block 1, Miesian Plaza
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Via email to Private Secretary to the Minister for Health

Dear Minister

COVID-19 vaccination has been a central pillar of the public health response to the pandemic and remains an important component of the multifaceted approach in the ongoing management of the pandemic. On 10th January 2022, I sought advice from the National Immunisation Advisory Committee (NIAC) in respect of potential future requirements for COVID-19 vaccination in this calendar year, including if recommended, the optimal schedule for additional booster doses for some or all of the population. As you will be aware, work is ongoing between the Department and the HSE regarding the COVID-19 mid-term vaccination strategy, and this evening I received advice from NIAC which should greatly assist in informing and guiding the operational planning required for the COVID-19 immunisation programme.

In its advice, NIAC point out that considerable uncertainty remains regarding the future trajectory of the disease. It is not possible at this juncture to confidently predict the evolution of the virus, including the emergence of new variants of concern, if and when a regular seasonal wave of infection will be established, or how vaccine-mediated protective immunity will evolve over time. I note that in its third strategic preparedness and response plan published on 30th March, the World Health Organisation (WHO) current working model is that the COVID-19 virus will continue to evolve, but the severity of the disease it causes will reduce over time as immunity increases due to vaccination and infection. Advances in COVID-19 vaccines are ongoing; intranasal, Omicron specific and multivalent vaccines (designed against a broad collection of changes in the virus) are currently under development, although their effectiveness and when they may be available is, as yet, unclear. It is also difficult to know how well-matched available vaccines will be to any future variant of concern. In this context, NIAC point out the importance of building in flexibility and responsiveness to the COVID-19 vaccination programme to allow for a rapid and dynamic response to changes in viral transmission and disease severity.

As pointed out by NIAC, COVID-19 vaccines have achieved extraordinary success in preventing severe disease, hospitalisation, and death; yet some limitations exist, namely their more modest impact on disease transmission and the waning of protection against infection over a period of several months. COVID-19 vaccines have a very good safety profile with a very rare risk of myocarditis with mRNA vaccines and very rare risks of thrombosis with thrombocytopenia with adenoviral vector vaccines. Hundreds of millions of doses have now been administrated globally with no additional severe events being clearly associated with these vaccines.

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Since the original NIAC recommendations of 26th April and 2nd September 2021 regarding vaccination during pregnancy, a substantial body of additional evidence has accrued which demonstrates the safety and efficacy of mRNA vaccines during pregnancy and post-partum, with no increase in any adverse or neonatal outcomes. On that basis and given that pregnancy itself is associated with an increased risk of severe infection, **NIAC has reiterated its previous recommendation that pregnant women and adolescents from 12 years of age should be offered mRNA COVID-19 primary and booster vaccination at any stage of pregnancy.**

Ireland has one of the highest COVID-19 vaccine uptake rates in Europe, with just over 95% of the adult population being fully vaccinated, while 72% of the adult population had received a booster dose by the end of March 2022. Although COVID-19 vaccine effectiveness (VE) against symptomatic disease decreased with emergence of the Delta variant and waning of vaccine-induced immunity, protection against hospitalisation and death remained high. However, with the emergence of the Omicron variant with its ability to escape vaccine-induced immunity, it has become increasingly clear that two doses of an mRNA or adenoviral-vector vaccine do not provide adequate protection against infection or severe disease. Studies have shown that a first booster dose significantly increases the levels of antibodies, above that elicited by two doses. Antibody levels are a correlate of protection against infection, albeit there is currently no protective level defined. All studies which have evaluated the vaccine effectiveness of a first booster dose have documented higher vaccine effectiveness against onward viral transmission, infection, hospitalisation and death compared to two doses. **On that basis, NIAC continue to recommend that people get their primary vaccine course and booster shot if they haven't already done so, with mRNA vaccines remaining the vaccine of choice. Those who have a contraindication to or who decline an mRNA vaccine should be offered a non-mRNA vaccine**. **Notwithstanding the fact that an unvaccinated person may have had a previous infection or a fully vaccinated person has experienced a breakthrough infection, NIAC recommend they complete their primary and booster vaccination to optimise protection**.

As observed by NIAC, those who are unvaccinated or incompletely vaccinated continue to be disproportionality affected and account for approximately a third of hospitalisations for COVID-19. In general, vaccination induces higher levels of antibodies than natural infection and there is a growing body of evidence showing that vaccinating those with a history of previous infection significantly enhances their immune response and effectively reduces their risk of subsequent infection and hospitalisation. Moreover, infection with the Omicron variant in unvaccinated individuals may not offer adequate protection against other variants of SARS-CoV-2. Thus, given the variability of immune response to infection, likelihood of waning immunity and ongoing high levels of infection circulating in the community, it is important that all who are eligible, including those with a history of SARS-CoV-2 infection, be vaccinated. The Department will continue to engage with colleagues in the HSE to maximise primary and booster vaccine uptake through targeted outreach, including to those recently arrived in Ireland from Ukraine.

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As distinct from the first waves, NIAC observe that children appear to be equally susceptible as adults to infection with the Omicron variant. The efficacy and immunogenicity of mRNA vaccines for children and adolescents aged five years and older are as high or indeed higher than that seen in adults. The individual benefit of COVID-19 vaccination in young children may be somewhat less than in adults as the disease course is typically milder in children. However, some children do experience severe disease and require hospitalisation. Data from the US indicates that vaccine effectiveness amongst adolescents aged 12-18 years against hospitalisation in the Delta period was over 90% but decreased to 40% when Omicron was the predominantly circulating variant**.** The mRNA vaccine Comirnaty© has been shown to reduce hospitalisations due to the Omicron variant in younger children aged 5-11 years**. As observed by NIAC, this underscores the importance of those aged 12 years and older completing their primary course and receiving a booster dose, while those aged 5-11 years should complete a primary course of two doses.** Further, it is also noted that the risk of the multisystem inflammatory syndrome in children (MIS-C) following acute infection, the potential for other sequelae of SARS-CoV-2 infection e.g, long-COVID-19, remain important reasons for vaccination of children and adolescents. To date, 21% of children aged 5-11 years have completed their primary vaccination course, while 18% of those aged 12-17 years have received a booster dose. It remains unclear at this juncture whether a booster dose will be required for children aged 5-11 years old and NIAC has indicated it will keep this matter under ongoing review. Paediatric formulations of the authorised mRNA vaccines for use in younger children and infants under five years are currently being evaluated in clinical trials, with results expected later in the year. Once this data becomes available, NIAC has undertaken to assess the safety and efficacy of COVID-19 vaccination in this age group.

Individuals who have an immunocompromising condition or are taking immunosuppressive agents generally mount a suboptimal immune response to COVID-19 vaccines which puts them at greater risk of infection and severe disease. On that basis, NIAC has previously recommended an extended three dose primary series for this group, and evidence shows that addition of a third vaccine dose provides additional protection and is associated with seroconversion in around 40% of non-responders. Seroconversion rates are further enhanced followed receipt of the first booster dose (fourth dose). **In the current advice, NIAC has clarified that those who are aged 12 years and older who are immunocompromised either at the time of the primary or booster dose should complete a primary course, an additional dose and a booster vaccine (total of four doses). Those aged 5-11 years should complete a primary course and an additional dose (total of three vaccine doses).** As NIAC point out, while 95% of those aged 16 and older who are immunocompromised have received an extended primary series, only 33% have received their first booster. There are likely several reasons for this including identification and contacting those who fall into this group as well as a lack of awareness around the requirement for both an additional third dose and a fourth booster dose. We shall continue to work with the HSE to address these issues to ensure maximal protection for this at-risk group.

There is accumulating evidence that a longer interval between vaccine doses is beneficial in terms of improving the level and breadth of immunity. Due to epidemiological circumstances prevailing at the time of previous recommendation, there are currently varying intervals recommended between primary doses and additional or booster doses. In its advice today, NIAC has indicated its intention to examine harmonisation and optimisation of dosing intervals between primary doses and additional or booster doses in the coming months.

The BA.2 subvariant of Omicron currently represents over 95% of all sequenced cases in Ireland and is more transmissible, although no more likely to cause severe disease, than the previously circulating BA.1. There is accumulating evidence that protection against infection and hospitalisation restored by a first booster becomes less effective over time, especially in older persons. Data from the UK indicates that protection afforded by a booster dose against symptomatic Omicron infection drops from 60-75% to 25-40% after 15 weeks.

Protection against hospitalisation remains much higher; in those aged 18 years and older in the US who received a booster dose peaked after two months at 91% and declined to 78% by four months or more. This is likely due to the more durable cellular response elicited by COVID-19 (compared to the humoral response), which appears to be of particular importance for protection against severe disease. The risk of breakthrough infection is higher with Omicron, although for most who have completed their primary course and have received a booster dose, such infections are generally mild and of short duration. However, in older persons and those who are immunocompromised, breakthrough infection can result in severe illness. In Ireland, between 1st February and 27th March 2022, those aged 65 years and older accounted for 50% of hospitalisations, 58% of ICU admissions, and 89% of deaths, despite over 95% of this cohort having received a first booster dose. Age-related immunosenescence and longer interval since first booster are likely factors contributing to the increase in hospitalisations in this age group. A similar pattern has been seen in other EU countries, with a proportionally higher increase in cases seen in those aged 65 years and older, and most of the burden of ICU admissions and mortality among people age 60 years and older, as documented by the European Centre of Disease Control at the end of March 2022.

A number of countries have recently announced plans for/started to administer second booster doses to particular population groups, most notably, older people and the immunocompromised. A second booster dose of Comirnaty® was authorised in Israel in January 2022 for individuals aged 60 years and older, and preliminary evidence indicates significant additional protection against infection and severe disease in this age group. In a study of those aged 60-100 years, a second booster dose resulted in a 78% reduction in mortality in those who had received two booster doses compared to those who had received a single booster. In a separate study, of those aged 60 years and older, the risk of infection was halved, and the rate of severe illness was lower by a factor of 4.3 in those who received a second booster compared to those who had not. In yet another Israeli study in those over 60 years, VE against severe disease was sustained at greater than 73% over a six-nine week follow-up period in those who had received a second booster. However, VE against infection rapidly declined from a peak of 64% to 29% after 10 weeks. In the same study, those who were immunocompromised and had received only one booster were twice as likely to develop severe disease as those who had received a second booster. The limitation of the aforementioned data is the relatively short duration of follow-up. Importantly, a pre-print reporting findings of a study on immunogenicity, efficacy and safety in Israeli healthcare workers who had received a second mRNA booster dose, recorded antibody levels similar to those seen after the first booster, however efficacy in preventing mild or asymptomatic Omicron infections or breakthrough infections was limited. Vaccine effectiveness against infection was 30% and 11% for Comirnaty and Spikevax respectively, while VE against symptomatic disease was higher at 43% and 31%. There have been no unexpected short-term safety concerns noted with the first booster doses of mRNA vaccines. Data on second booster doses is more limited but preliminary experience from Israel has not revealed any new safety concerns.

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While a second booster dose appears to be beneficial at preventing severe disease in older or immunocompromised individuals, it may only have marginal benefits for other groups at the current time. The key goal of the COVID-19 vaccination programme is to reduce severe disease. Taking into consideration that many older persons and immunocompromised individuals will have received their first booster dose three to five months ago, **in order to maintain high levels of immunity in those most at risk of severe disease, NIAC has recommended a second mRNA booster dose for those aged 65 years and older and those aged 12 years and older with immunocompromise associated with a sub optimal response to vaccines.** Offering a second booster to those most at risk of severe outcome at this time optimises their protection and may protect them against future variants.

The second booster vaccine is recommended at least six months after the first booster, with a minimum interval of four months permissible if required for operational reasons. Specifically, for those aged 12-29 years, Comirnaty (0.3ml/30 micrograms) should be given. For those aged 30 years and older, Comirnaty (0.3ml/30 micrograms) or Spikevax (0.25ml/50 micrograms) can be given. **For those who have had a breakthrough infection following a first booster vaccine, it is recommended to defer the second booster vaccine for six months (minimum interval of 4 months) following infection onset. If an mRNA vaccine is contraindicated or declined, consideration may be given to using a non-mRNA vaccine as the second booster vaccine, following an individual benefit-risk assessment.**

I note that on 29th March, the US Food and Drug Administration (FDA) issued an emergency use authorization for a second booster dose of Comirnaty and Spikevax for people 50 and older, and for those with immunocompromised conditions who received their first booster at least four months ago. As yet, no similar application has been received by the European Medicines Agency and, as such, administration of a second booster dose in line with the current NIAC advice will be on an off-label basis.

Notwithstanding the current uncertainties detailed by NIAC in its advice today, based on current evidence, NIAC consider that it is likely that a third booster dose will be required for older persons and the immunocompromised in Autumn 2022. It also considers it likely that additional groups may beyond those detailed in the current advice could benefit from a second booster dose in Autumn 2022. The Committee will continue to actively examine the evidence regarding the likely benefit of a second booster to other groups, vaccine choice and interval considering the likely predominant variant in order to make further recommendations in this regard.

I am endorsing the NIAC recommendations as set out above. In recognising the significant degree of uncertainty regarding the evolution of the virus and the immunological response to current and new vaccines, it is important that the COVID-19 immunisation programme remain flexible and capable of rapidly adapting to changes in viral transmission and disease severity.

Yours sincerely

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