National Immunisation Advisory Committee

UPDATED RECOMMENDATIONS FOR PRIMARY SERIES COVID-19 VACCINATION

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About NIAC

NIAC membership includes nominees from the Royal College of Physicians in Ireland, its Faculties and Institutes, the Royal College of Surgeons in 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 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 considers the evidence about vaccines and provides 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 Health Service Executive.

UPDATED RECOMMENDATIONS FOR PRIMARY SERIES COVID-19 VACCINATION

1. Recommendations regarding eligibility for primary series COVID-19 vaccination are unchanged.
2. For those aged 5 years and above the recommended primary series consists of a single dose of age-appropriate COVID-19 mRNA vaccine.
3. For those aged 6 months to 4 years the recommended primary series consists of:
    a. two doses of age-appropriate COVID-19 mRNA vaccine for those with no prior history of SARS-CoV-2 infection.
    b. a single dose of age-appropriate COVID-19 mRNA vaccine for those with a prior history* of SARS-CoV-2 infection.
4. For those with immunocompromising conditions aged 6 months and above, the recommended primary series consists of two doses of an age-appropriate COVID-19 vaccine. A third dose may be administered following instruction from a relevant specialist physician.
5. Comirnaty Omicron XBB.1.5 mRNA COVID-19 vaccine is the preferable vaccine, where available, for all those eligible for primary series vaccination, and should be given as follows:
    a. aged 6 months-4 years: Comirnaty Omicron XBB.1.5 (3 micrograms) with an interval of four weeks between doses if two doses are required.
    b. aged 5-11 years: Comirnaty Omicron XBB.1.5 (10 micrograms) one dose.
    c. aged 12 years and older: Comirnaty Omicron XBB.1.5 (30 micrograms) one dose.
    d. Immunocompromised: Comirnaty Omicron XBB.1.5 two age-appropriate doses with a four-week interval between dose one and two. If a third dose is required there should be an interval of eight weeks between dose two and three.
6. Nuvaxovid XBB.1.5 can be offered for primary series in adults and children aged 12 years and above with a contraindication to a mRNA vaccine, or in those who choose not to receive a mRNA vaccine.
    a. For immunocompetent adults and children aged 12 years and above, a single dose is recommended.
    b. For those with immunocompromising conditions, 2 doses should be administered with a four-week interval between dose one and dose two. If a third dose is required, there should be an interval of eight weeks between dose two and three.
7. NIAC no longer recommends a shorter interval first booster dose. Subsequent doses should be administered as per seasonal recommendations.

Recommendations may be updated when more information becomes available.

*Prior history of COVID-19 can be confirmed by any of; positive PCR test, antigen test or clinical diagnosis. For example, a single dose primary series could be considered in a child who had symptoms consistent with COVID-19 at a time when household contacts tested positive.

1. EXECUTIVE SUMMARY

- International organisations such as the European Medicines Agency (EMA), European Centre for Disease Prevention and Control (ECDC), and World Health Organization (WHO) have recently recommended that a single dose primary series is sufficient for most children and adults given the background population immunity at this time.
- As of 12 Oct 2023, 80% of the Irish population aged over 6 months have completed primary series COVID-19 vaccination, that figure increases to 90% in those aged 40 years and above.
- The numbers of individuals coming forward for primary series vaccination is now relatively small. Over the past ten weeks in Ireland less than 30 people per week have completed primary series vaccination.
- Since the introduction of COVID-19 vaccination the background population natural immunity to SARS-CoV-2 has increased.
- Latest figures estimate that 69-95% of the adult population in Ireland have been previously infected with SARS-CoV-2, with higher levels of natural immunity noted in younger adults.
- Seroprevalence data on children in Ireland are limited. The most recent data are from July 2022 at which point 82% of children aged 5-17 years, and 61% of children aged 0-4 years had evidence of previous infection.
- It is now well established that neutralising antibody levels are higher and more durable following vaccination in those who have had prior infection.
- Internationally a single dose primary series for those aged 5 years and above has been adopted by the EMA, the UK and the US.
- For those aged 6 months to four years of age, and for those who are immunocompromised, international practice regarding primary series vaccination varies.
- The initial three dose regimen of Comirnaty mRNA vaccines for those aged 6 months to 4 years was based on trial data that suggested that, possibly due to the lower dose used in this age group, three doses were required for primary series vaccination.
- In subgroup analysis, those aged 6 months to less than 2 years were found to have adequate immune responses following two doses, whereas those aged 2-4 years required three doses.
- A study including 120 children aged 6 months to 4 years reported that antibody levels after one and two doses of Comirnaty in those with prior SARS-CoV-2 infection were significantly higher than after three doses of Comirnaty in those who were infection naïve.
- Individuals with immunocompromise may have an impaired response to vaccination and hence require extra doses compared to the general population.
- Comirnaty (Pfizer) is currently the only mRNA vaccine available for use in Ireland. Comirnaty Omicron XBB.1.5, is the most recently updated version of the vaccine which will likely provide the best protection against currently circulating variants.
- Nuvaxovid XBB.1.5 (Novavax) may be offered to adults and children aged 12 years and over with a contraindication to an mRNA vaccine, or who have chosen not to receive an mRNA vaccine.

2. INTRODUCTION

The landscape of COVID-19 in Ireland and internationally has changed dramatically over the past three years. While COVID-19 remains a significant threat to those who are more vulnerable in society, the overall burden on healthcare and society has reduced compared with the beginning of the pandemic. This is due to both evolution of the virus, and increased population immunity secondary to natural infection and vaccination. With this in mind, international organisations such as the EMA, ECDC, and WHO have recently recommended that a single dose primary series is sufficient for most children and adults given the background population immunity at this time.

Until this point, NIAC recommendations for primary series COVID-19 vaccination with mRNA vaccines involved:

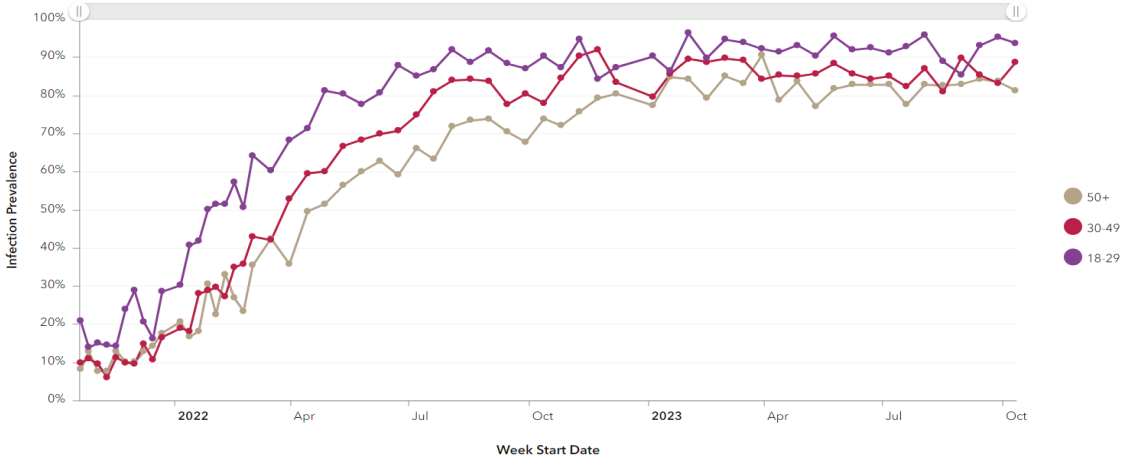
- two doses for all those aged 5 years and above
- three doses for those aged 6 months to 4 years, and those aged 5 years and above with immunocompromising conditions.

A shorter interval 'First booster' was recommended four months after the primary series was completed.

3. SEROEPIDEMIOLOGY

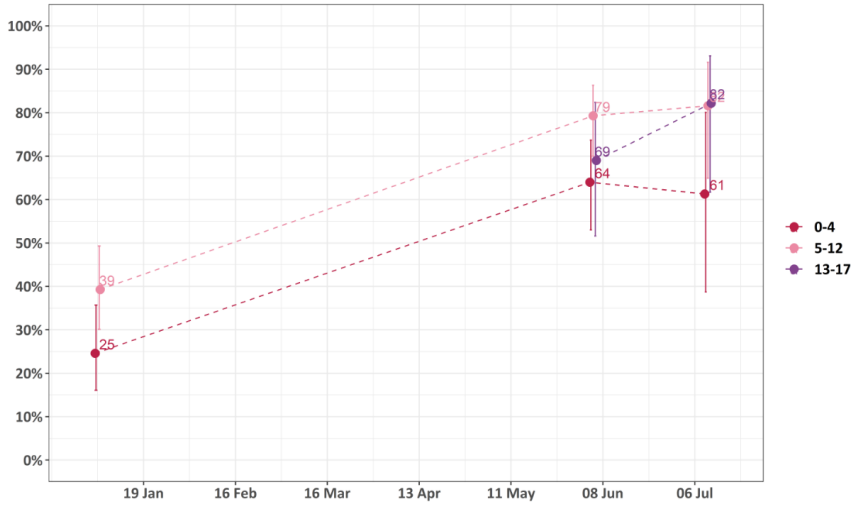
Latest figures estimate that 69-95% of the adult population in Ireland have been previously infected with SARS-CoV-2, with higher levels of natural immunity noted in younger adults compared to older adults. The levels of natural immunity have been relatively stable since the beginning of 2023 from data collected via the Irish blood Transfusion Service and the Laboratory Surveillance Network.[1 2] (Figure 1)

Figure 1. Seroprevalence indicating previous infection by age group in adults donating to the Irish Blood Transfusion Service. Source: HPSC National Serosurveillance Programme.[1]



Seroprevalence data on children in Ireland are more limited. The most recent data are from July 2022 at which point 82% of children aged 5-17 years (n=278), and 61% of children aged 0-4 years (n=171) had evidence of previous infection.[3] (Figure 2)

Figure 2. Infection seroprevalence among children in Ireland age 0-17 years from January 2022 to July 2022. Source: HPSC Seroepidemiology Unit.[3]

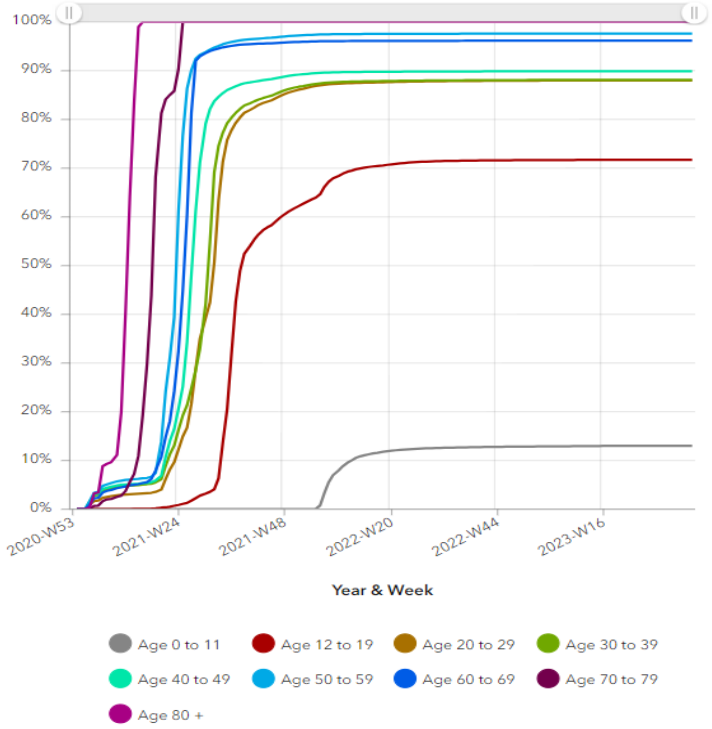


While seroprevalence data in children is limited, data from the National SARS-CoV-2 Wastewater surveillance programme, highlights the ongoing population exposure to SARS-CoV-2. The programme analyses samples from 30 catchment areas covering approximately 70% of the population. SARS-CoV-2 continues to be detected in wastewater samples from all catchment areas.[4]

4. PRIMARY SERIES VACCINATION UPTAKE

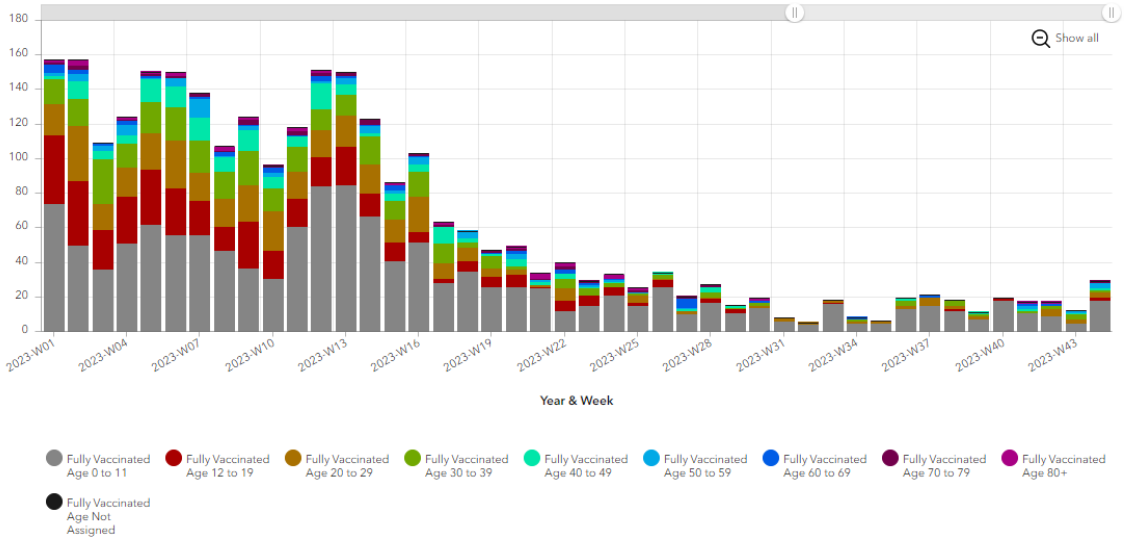
There has been high uptake of the COVID-19 primary series by adults in Ireland. As of 12 Oct 2023, 80% of the Irish population aged over 6 months have completed primary series COVID-19 vaccination. The percentage uptake increases with age. Ninety percent of those aged 40-49 years and 100% of those aged 70 and above have completed a primary series.[5] (Figure 3)

Figure 3. Percentage of population by age fully vaccinated with a primary course of COVID-19 vaccination by week, December 2022 to October 2023. Source: Ireland's COVID-19 Data Hub.[5]



The numbers of individuals coming forward for primary series vaccination is now relatively small. Over the past ten weeks in Ireland less than 30 people per week have received primary series vaccination. The majority of those now coming forward are children and adolescents.[5] (Figure 4)

Figure 4. The number of those fully vaccinated with a primary course from week one 2023 to week 44 2023 by age group per week. Source: Ireland's COVID-19 Data Hub.[5]



5. EVIDENCE FOR REDUCING PRIMARY SERIES VACCINATION DOSES

Hybrid immunity, the combination of protection from infection and vaccination, offers higher and more sustained protection against severe COVID-19 than infection induced immunity or vaccine induced immunity alone. A 2023 systematic review reported that, against the Omicron variant, the protection afforded by previous infection alone against hospital admission or severe disease was 75% at 12 months, whereas for hybrid immunity it was 97% at 12 months following primary series vaccination.[6] Most people in Ireland, especially those aged over 5 years of age have had at least one SARS-CoV-2 infection. Hence the need for multiple doses to confer robust immunity has decreased. This has led to recommendations internationally to reduce primary series mRNA vaccination from two doses to one dose in many jurisdictions in those aged five years and above.

Immune imprinting is the process by which prior antigenic exposures in the form of either infection or vaccination can impact on an individual's immune response to subsequent infections with novel variants. In some circumstances the memory B cells induced by the initial exposure can block the development of B cells to subsequent infection of novel but related virus variants. The clinical implications of imprinting are not clearly established in COVID-19. It remains the case that recent vaccination boosts protection against severe COVID-19 disease. However, some immunogenicity studies have reported that variant specific antibody response may be relatively limited by exposure to infection with variants, or vaccination with variant-specific vaccines. Similarly, a shorter interval since last antigenic exposure may relatively limit immune response to variant specific booster vaccination.[7 8] This has led to concern regarding repeated vaccination with one strain of vaccine, or of vaccinating more frequently than is necessary. In the setting of increased background population immunity, and the circulation of less pathogenic variants, vaccinating only as frequently as required and with antigenically updated vaccines, may mitigate the impact of immune imprinting while maintaining protection against severe disease in the long term.

Children aged less than five years

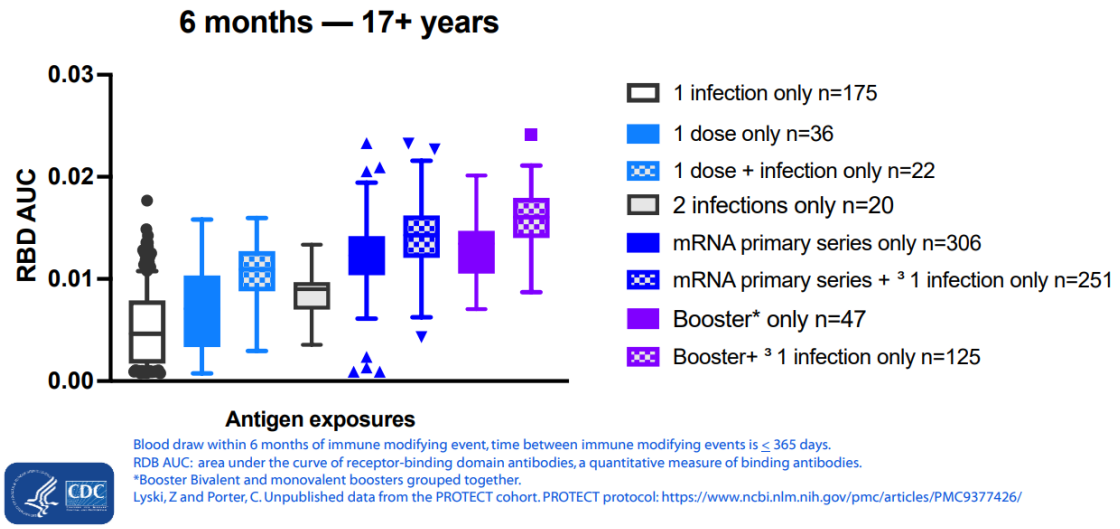
Children less than five years of age may be less likely to have had a prior infection than older age groups. While US data demonstrated that by the end of 2022 over 80% of those aged 12-23 months had infection induced immunity on serological testing, only 63% of those aged 6-11 months had previous infection. Paediatric seroprevalence data from 2023 are limited, and it should be noted that in 2022 the number of COVID-19 cases reported both in Europe and the US was high due to the Delta wave. As new entrants come into this younger age cohort all the time, they are less likely to have prior infection and therefore less likely to have hybrid immunity following primary series vaccination.

The initial three dose regimen of Pfizer's Comirnaty mRNA vaccine for those aged 6 months to 4 years was based on trial data which suggested that, possibly due to the lower dose (3 micrograms)

used in this age group, a third dose was required to complete a primary series vaccination.[9] Interestingly within the trial, after two vaccine doses the younger cohort aged 6 months to less than 2 years of age met immunobridging success criteria for both for seroresponse rate and geometric mean ratios (GMR) which compared to those aged 16-25 years. However, after two vaccine doses in those aged 2-4 years, success criteria were met for seroresponse rate but not GMR.[9] Moderna achieved adequate immune response in those aged 6 months to five years with two doses of Spikevax, possibly due to the higher dose (25 micrograms) of mRNA used, however differences in their technology platform may also have contributed.[10]

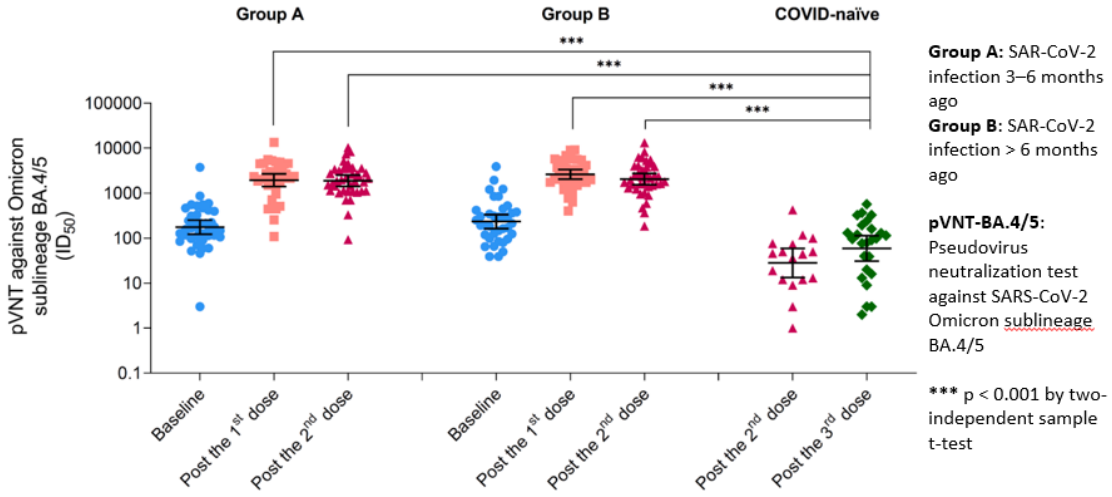
A US based study investigating the antibody response of children following infection and vaccination reported that one dose of mRNA vaccination in a child with prior infection produced a similar antibody response to a complete primary series of mRNA vaccination (2 or three doses depending on mRNA vaccine used) in a child with no prior infection.[11 12] (Figure 5)

Figure 5. Antibody levels by history of infection and vaccination status in children 6 months to 17 years. Source: ACIP meeting material June 2023.[11 12]



A Thai study of 120 children aged 6 months to four years compared the immunogenicity of one or two doses of Comirnaty in those with previous Omicron infection, to three doses in those who were COVID-19 naïve. Antibody levels after one and two doses of Comirnaty in children with past infection were significantly higher than after three doses of Comirnaty in children without a prior history of COVID-19 infection.[13] (Figure 6)

Figure 6. Geometric means (95% CI) of pseudovirus neutralisation test against SARS-CoV-2 Omicron BA.5/5 sublineage after Comirnaty vaccination in healthy children 6 months to under 5 years of age with and without a history of SARS-CoV-2 infection. Source: Nantanee et al.[13]



Immunocompromised

The immunocompromised population is heterogenous, both in terms of varied immune responses to COVID-19 vaccination and in terms of the risk of severe disease outcomes following infection with SARS-CoV-2. Even patients with the same condition can present with varied risk based on their mode of treatment, their response to treatment and their co-morbidities. Those with moderate to severe immunocompromise who are likely to have impaired response to vaccines such as those on B-cell depleting therapies, or those following solid organ or stem cell transplant are likely to benefit from a three dose primary series.[14] However, for individuals living with HIV that is well controlled on antiretroviral therapy, with CD4 counts greater than 500 cells/mm^3, the immune response to a two dose primary series has been found to be comparable with HIV-negative two dose vaccine recipients.[15] Hence it is prudent at this time to allow specialist physicians managing immunocompromised individuals to decide whether or not additional doses of COVID-19 vaccines are required for each individual patient based on their risk and predicted immune response.

First booster doses

In the past NIAC recommended a shorter interval 'first booster' be administered four months after completion of primary series vaccination in all adults aged over 18 years old, and in children aged 5-17 years with immunocompromise. The evidence regarding hybrid immunity and virus evolution as outlined above no longer supports this recommendation.

6. NUVAXOVID XBB.1.5 FOR PRIMARY SERIES COVID-19 VACCINATION

Nuvaxovid XBB.1.5 (Novavax), the most recently updated protein subunit COVID-19 vaccine, has been authorised by the EMA for use as a single dose in individuals 12 years of age and older regardless of previous vaccination status.[16] Aligning with the approach taken for mRNA vaccines, the decision to adopt a single-dose primary series for this vaccine was based on the high levels of natural immunity in the community, as detailed above.

For those with immunocompromising conditions aged 12 years and above, the recommended primary series consists of two doses. A third dose may be administered following instruction from a relevant specialist physician. The rationale for a two or three dose primary series in immunocompromised populations is outlined above.

Consistent with prior NIAC recommendations regarding Novavax vaccines, mRNA vaccines remain the preferred choice for COVID-19 vaccination because of the extensive safety and effectiveness data.[17] [18] Safety and effectiveness data is more limited for Nuvaxovid owing to the administration of fewer doses; as of June 2022, 649 million doses of Comirnaty had been administered in the EU/EEA compared to only 216,000 doses of Nuvaxovid.[19] It is anticipated that the safety profile of Nuvaxovid XBB.1.5 will be similar to the original Nuvaxovid. Post marketing safety data for Nuvaxovid has demonstrated it to have an acceptable safety profile consistent to data from preauthorisation clinical trials.[20] [21]

Nuvaxovid XBB.1.5 may be offered to those aged 12 years and over with a contraindication to mRNA vaccines, or those who have chosen not to receive an mRNA vaccine. Administration in pregnancy can be considered when the benefits of vaccination outweigh the potential risks to the mother or the fetus.

7. INTERNATIONAL POSITIONS

Table 1: International recommendations regarding number of doses required for primary series mRNA COVID-19 vaccination when indicated.

Country	Primary course for those aged 6 months-4/5 years (Comirnaty, Pfizer)	Primary course for those aged ≥5 years	Primary course for immunocompromised
EU (EMA)[22]	No prior COVID: 3 doses Prior COVID: 1 dose	1 dose	May require additional doses
Austria[23]	No prior COVID: 3 doses Prior COVID: 1 dose	1 dose	3 doses
Germany[24]	3 'antigenic exposures' i.e., vaccine doses or infections	3 'antigenic exposures' i.e., vaccine doses or infections	May require additional doses Assessment of serological response to vaccination suggested
Netherlands[25]	3 doses	1 dose	May require additional doses
UK[26]	2 doses	1 dose	May require additional doses
US [27]	3 doses	1 dose	3 doses
Canada[28]	3 doses	1 dose	2 doses
WHO[29]	2 doses	1 dose	2 doses recommended 3 doses can be considered

8. CONCLUSION

The landscape of COVID-19 infection has changed considerably over the past three years, due to population immunity, vaccination, and changes in the pathogenicity of circulating strains. It is important that vaccine recommendations adapt accordingly. The current available evidence supports changing to a single dose primary series vaccination for all immunocompetent people aged five years and above. This recommendation is based on high levels of natural immunity in the population, and evidence that hybrid immunity confers improved protection against severe disease compared to vaccination alone.

In children under 5 years of age, as the likelihood of prior infection is lower, there is less evidence to support a change to a single dose for all children regardless of infection history. Immunogenicity data in this age group suggests that hybrid immunity with a single dose of mRNA vaccine and prior infection elicits similar antibody responses to a complete three dose series in those who are infection naïve. These data support the administration of a single dose primary series in those under 5 years of age with a known history of COVID-19 infection. However, in the era of decreased testing this will be more difficult to widely ascertain. The initial three dose regimen in this group was based on trial data that suggested that, possibly due to the lower dose used in this age group, three doses were required for primary series vaccination with Comirnaty mRNA vaccines. On subgroup analysis, two doses were sufficient in those aged under two years of age. These data were reassuring when a move to a two dose primary series was considered as this is the group most likely to be COVID-19 naïve. While a single dose primary series would be more acceptable to parents and their children, current evidence does not yet support this given a sizeable portion of children under 5, and particularly under 1, are likely to be COVID-19 naïve.

Taking into consideration uncertainty around immunogenicity and seroprevalence as well as acceptability of multiple dose regimens in this age group, NIAC recommends moving to a two dose primary series for immunocompetent children aged 6 months-5 years who are COVID-19 naïve or in whom history of infection is unknown. In those in this age group with a prior history of COVID-19 infection NIAC recommends a single dose primary series. Confirmation of a prior history of COVID-19 infection either by PCR or antigen testing will be challenging given the reduction in community testing, particularly in children. NIAC's recommendations allow for clinical judgement to be used in children in the absence of testing. For example, a single dose primary series could be considered in a child who had symptoms consistent with COVID-19 at a time when household contacts tested positive. As per previous NIAC recommendations, primary series is only recommended in those aged 6 months-5 years with underlying medical conditions, however it is available to all in this age group.

Immunocompromised children and adults continue to be at risk of severe infection and persisting infection from COVID-19. This risk is different according to distinct levels of immunosuppression. Similarly, responses to vaccines will be different in different immunocompromised groups. Due to hybrid immunity, for most immunocompromised people a two dose primary series should provide

sufficient protection from severe COVID-19 infection. However, a subset of patients with severe immunocompromise will require a third dose. The decision for a third dose needs evaluation of individual patient specific risk factors and thus will require the input of a specialist physician. NIAC recommends a two dose primary series for all immunocompromised patients with a third dose to be considered based on advice from the relevant specialist physician.

As COVID-19 vaccination advice adapts to the changing landscape, it is important that recommendations are simplified when clinically appropriate. In line with this goal, recommended dosing intervals are now the same for all patient groups in whom more than one dose of a vaccine is indicated for primary series. Additionally, NIAC no longer recommends a shorter interval first booster dose. All subsequent doses should follow seasonal recommendations.

Finally, as per recent recommendations regarding Autumn COVID-19 boosters, Comirnaty Omicron XBB.1.5 mRNA COVID-19 vaccine is the preferable vaccine for all those eligible for primary series vaccination if available, as it will likely provide the best protection against current circulating strains. Nuvaxovid XBB.1.5 can be offered to adults and children aged 12 years and above with a contraindication to mRNA vaccines, or who have chosen not to receive an mRNA vaccine.

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