National Immunisation Advisory Committee

RECOMMENDATIONS FOR COVID-19 VACCINATION OF CHILDREN AGED 6 MONTHS TO 4 YEARS

NIAC | 16.01.2023, Version 1.1

About NIAC

NIAC membership includes nominees 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 considers new 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 HSE.

Amendment for clarification

Version 1.1, 16 January 2023

Page 14: Comirnaty (3 micrograms/dose) is administered intramuscularly as a primary course of three 0.2ml doses with an interval of three weeks between dose one and two and at least eight weeks between dose two and three.

Version 1.0, 24 November 2022

Page 14: Comirnaty (3 micrograms/dose) is administered intramuscularly as a primary course of three 0.2ml doses at zero, three and at least eight weeks.

RECOMMENDATIONS FOR CHILDREN AGED 6 MONTHS TO 4 YEARS

1. COVID-19 vaccination is recommended for those:
   - with underlying conditions that place them at higher risk of severe COVID-19.

2. COVID-19 vaccination should be offered to all others in this age group based on:
   - the safety profile of the vaccine
   - comparable immunogenicity to that in older children and adolescents
   - the protection provided against severe COVID-19 and MIS-C
   - the enhanced protection vaccination gives to those who have had COVID-19 infection
   - the modest benefit in reducing household transmission to those immunocompromised or too young for vaccination.

3. Comirnaty 3 micrograms/dose is the only COVID-19 vaccine available in Ireland for this age group. The schedule is three doses with an interval of three weeks between dose one and two and at least eight weeks between dose two and three.

4. For those previously infected with SARS-CoV-2, Comirnaty may be given after an interval of at least four weeks following symptom onset or a positive SARS-CoV-2 test. As increasing the time between infection and vaccination can enhance the immune response, vaccination may be deferred for up to six months.

5. Priority should be given to the routine childhood immunisation schedule.

6. Until there is evidence for safe co-administration in this age group, Comirnaty should be separated from other vaccines by 14 days.

7. Consideration should be given to establishing separate vaccination sessions for this age group to reduce the risk of vaccine administration errors.

Recommendations may be updated when more information becomes available.

1. EXECUTIVE SUMMARY

- SARS-CoV-2 infection in those aged 6 months to 4 years is often asymptomatic or mild. However, although epidemiological evidence shows that while risk of hospitalisation and severe disease in this age group is very low, it is higher than in older children.
- Since the beginning of the pandemic over 3,500 children were hospitalised with COVID-19 in Ireland. Of that number, 1,075 were aged 6 months to 4 years; they accounted for over a third of paediatric ICU (PICU) admissions, 72% (18/25) of which occurred during the Omicron wave.
- Since 1 September 2022 there has been a downward trend in COVID-19 cases, hospitalisations and ICU admissions in all age groups. Of those aged 6 months to 4 years, 90 were hospitalised, less than five required ICU admission and there were no deaths.
- In the US, there was a significant increase in paediatric cases of COVID-19 and associated hospitalisations in 2022, mostly due to Omicron. Of paediatric COVID-19 hospitalisations, 86% were due to COVID-19. The rate of hospitalisation and severe disease was highest in those aged 6 months to 4 years compared to older children and adolescents.
- Although the risk of hospitalisation is higher in those with underlying conditions, internationally 50-97% of hospitalised children in this age group had no known risk factor for severe disease. In Ireland, 53% of COVID-19 PICU admissions had no underlying condition.
- Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare complication after symptomatic or asymptomatic SARS-CoV-2 infection that affects children as young as three months of age. COVID-19 vaccination has been shown to reduce the risk of MIS-C in older children and adolescents and similar benefit is expected in this age group.
- On 19 October 2022 the European Medicines Agency (EMA) approved formulations of Comirnaty and Spikevax mRNA vaccines for use in those aged 6 months to 4 years and 5 years respectively. Paediatric formulations of Spikevax are not available in Ireland.
- In clinical trials the immune response of children aged 6 months to 4 years to the recommended lower doses of the vaccines was comparable to that in adolescents and young adults who received higher doses.
- Post-marketing evidence shows that mRNA vaccines in older age groups are highly effective at preventing COVID-19 related hospitalisation, severe illness and death.
- High SARS-CoV-2 seroprevalence rates have been reported in all children in the UK, Sweden and Finland. Of 171 children aged 0-4 years attending Irish hospitals, SARS-CoV-2 seroprevalence was 73% and thus they are expected to have some immunity.
- Evidence in older age groups shows that vaccination of those previously infected confers additional protection.
- Vaccine benefit is most evident for children with underlying conditions for whom the risk of severe COVID-19 is greatest.
- In the context of the current epidemiology, high seroprevalence and declining infection rates, the benefits of COVID-19 vaccination for the healthy child are more nuanced and are influenced by history and timing of previous infection as well as the need to minimise risks of COVID-19 within a household.

2. BACKGROUND

On 19 October 2022, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended extending the indication for Comirnaty and Spikevax mRNA vaccines to include use in those aged 6 months to 4 years and 5 years respectively. Paediatric formulations of Spikevax are not available in Ireland.

In December 2021, just prior to the Omicron wave, NIAC made recommendations regarding COVID-19 vaccination for those aged 5-11 years. This paper provides recommendations regarding COVID-19 vaccination for children aged 6 months to 4 years, taking account of the benefits and risks in the context of current SARS-CoV-2 epidemiology and the direct and indirect impacts of COVID-19 on children and their families. Consideration was also given to ethical principles underpinning vaccine use.

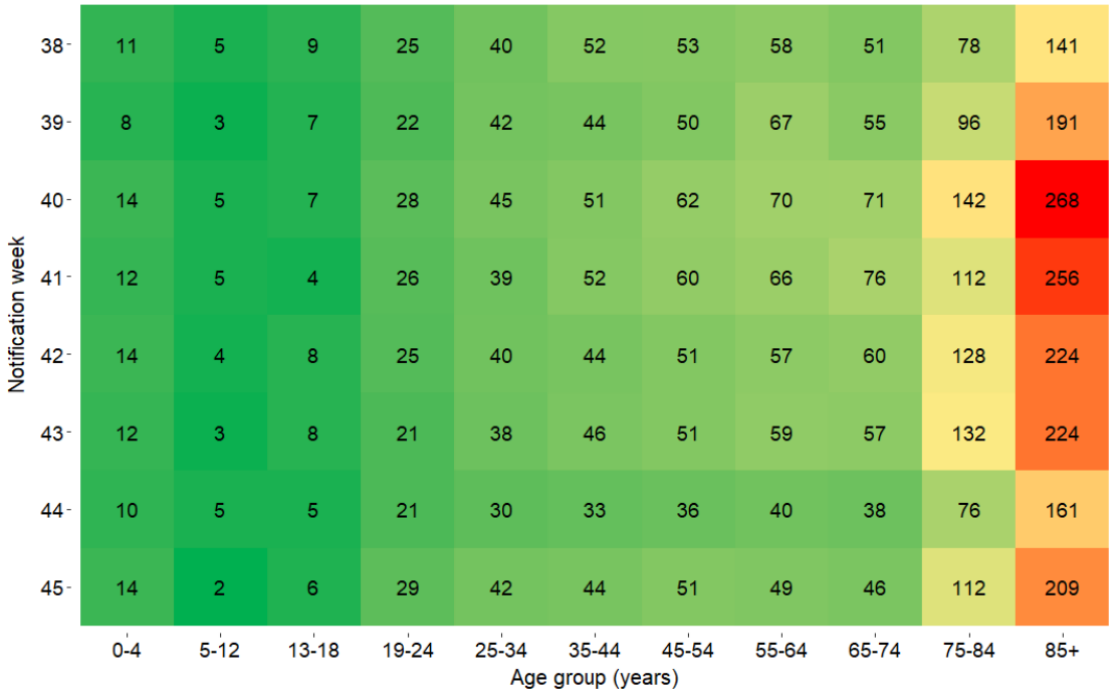
3. EPIDEMIOLOGY OF COVID-19 IN CHILDREN AGED 6 MONTHS TO 4 YEARS

Overall COVID-19 case notifications have been decreasing in Ireland since June 2022. Between 6-12 November 2022, 1,876 new PCR confirmed cases were reported compared with 16,792 in the week 3-9 July 2022.[1] These numbers are very likely a significant underestimate, as community testing is only recommended for higher risk groups and community testing of healthy children is no longer routinely recommended.

In the week beginning 9 October 2022, the National SARS-CoV-2 Wastewater Surveillance Programme reported the detection of SARS-CoV-2 RNA in 100% of tested wastewater samples.[2] Even though the detection rate decreased slightly to 94% in the week beginning 30 October 2022, it is still indicative of persistently high circulation in the community.[3]

For most age cohorts there has been a downward trend in the incidence of confirmed COVID-19 cases. Compared with adults, the incidence rate of PCR confirmed COVID-19 cases in those aged 0-4 years is low although consistently higher than that in those aged 5-18 years. (Figure 1)

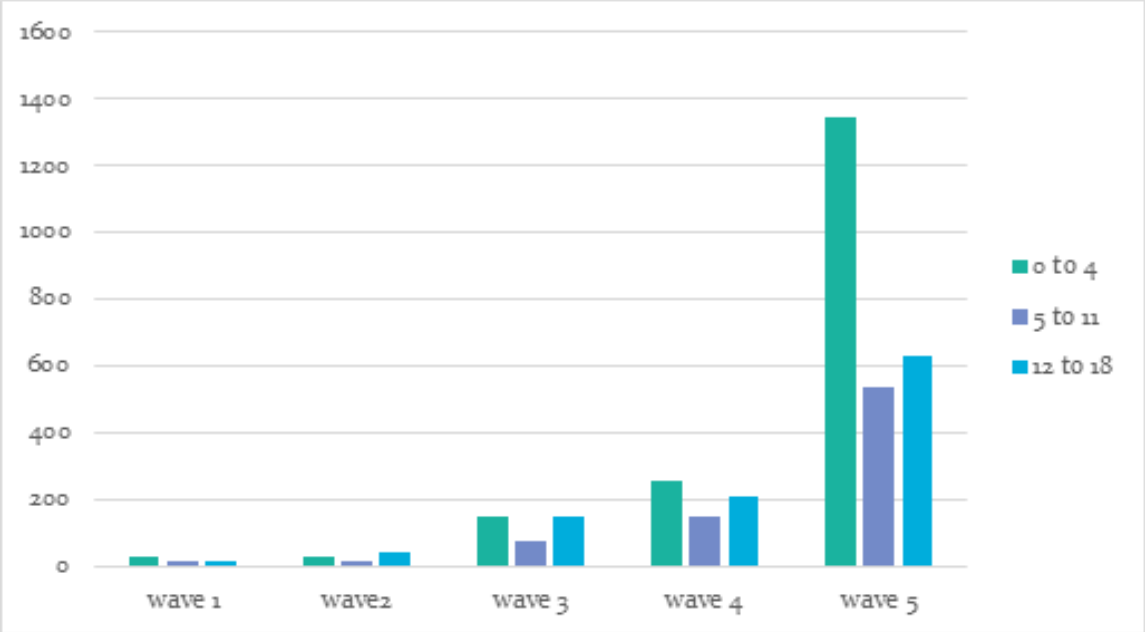
Figure 1: Heat map of weekly age-specific incidence rates of confirmed COVID-19 cases per 100,000 population in Ireland from 18 September 2022 to 12 November 2022. Source: HPSC.



In 2022, Omicron and its sublineages have remained predominant, causing infection surges that constitute the fifth wave. The increased transmissibility and immune evasiveness which characterise Omicron lineages increased infection rates even in those vaccinated and also led to large increases in incidence among children compared to previous waves.

While Omicron disease severity has been less than that of Delta, the increased incidence of infection in children has resulted in many more being hospitalised, with the youngest age cohort most affected.[4 5] Since the beginning of the fifth wave in Ireland, twice as many children aged 0-4 years have been hospitalised with COVID-19 compared to those aged 5-11 years and 12-18 years. (Figure 2)

Figure 2: Numbers of COVID-19 hospitalisations in those aged 0-18 years in Ireland, 1 March 2020 to 1 September 2022. Source: Department of Health.



In Ireland, data regarding the number of children hospitalised because of COVID-19 rather than with SARS-CoV-2 infection as an incidental finding are not available. However, 75% of COVID-19 related PICU admissions of children aged 6 months to 4 years were due to COVID-19.[6] In the US, COVID-19 was responsible for over 85% of such admissions both before and during the Omicron waves.[7]

During April-November 2022 hospitalisation rates in the 0-4 year age group were higher than those aged 5-55 years for every week except one.[8 9] Since the beginning of the pandemic over 3,500 children have been hospitalised with COVID-19 in Ireland, 1,075 of these were aged between 6 months and 4 years. Those aged 6 months to 4 years also accounted for over a third of all PICU admissions, 72% (18/25) of which occurred during the Omicron wave. Since 1 September 2022 there has been a downward trend in COVID-19 cases, hospitalisations and ICU admissions in all age groups. Of those aged 6 months to 4 years, 90 were hospitalised, less than five required ICU admission, and there were no deaths. (Table 1)

Table 1: Confirmed COVID-19 cases, hospitalisations, ICU admissions and deaths in those aged 6 months to 18 years, March 2020 to 15 November 2022. Source: Department of Health.

	Confirmed SARS-CoV-2		Hospitalisations		ICU		Deaths
Age (years)	N	Rate/ 100,000 population	N	Rate/ 100,000 population	N	Rate/ 100,000 population	N
01/03/20 – 15/11/22 (Total since onset of pandemic)							
6 months-4 years	65,698	23,902	1075	391	25	9.1	<5
5-11	142,362	29,604	778	162	12	2.5	<5
12-18	139,634	29,535	1035	219	19	4.0	5
19/12/21 – 15/11/22 (Wave 5)							
6 months-4 years	38,241	13,915	793	290	18	6.6	<5
5-11	71,050	14,775	524	109	6	1.3	<5
12-18	80,135	16,950	628	133	5	1.1	<5
1/9/22 – 15/11/22 (Wave 5 Autumn 2022)							
6 months-4 years	267	97	90	33	<5	n/a	0
5-11	223	46	38	7.9	0	0	0
12-18	318	67	43	9.1	0	0	0

Seroprevalence studies in Ireland suggest that most children are likely to have been infected with COVID-19. A small study that included 171 residual samples from those age 0-4 years who were attending children's hospitals found that seropositivity increased from 29% in January 2022 to 73% in June 2022. As the samples were from children attending hospital the results may be an overestimate, with lower seroprevalence in those not attending a hospital.[10] High SARS-CoV-2 seroprevalence rates have also been reported in children in the UK, Sweden and Finland.[11]

Evidence in older age groups shows that vaccination of those previously infected confers additional protection.

In the EU/EEA countries similar trends in reported cases have been seen with recent marked decline in case numbers. Although hospital and ICU admission rates in those aged under five years are currently very low, they continue to exceed those aged 5-14 years but there is very low mortality in either age cohort. However, it is not possible to determine the proportion of cases in those aged under six months and thus ineligible for vaccination from these data.[11]

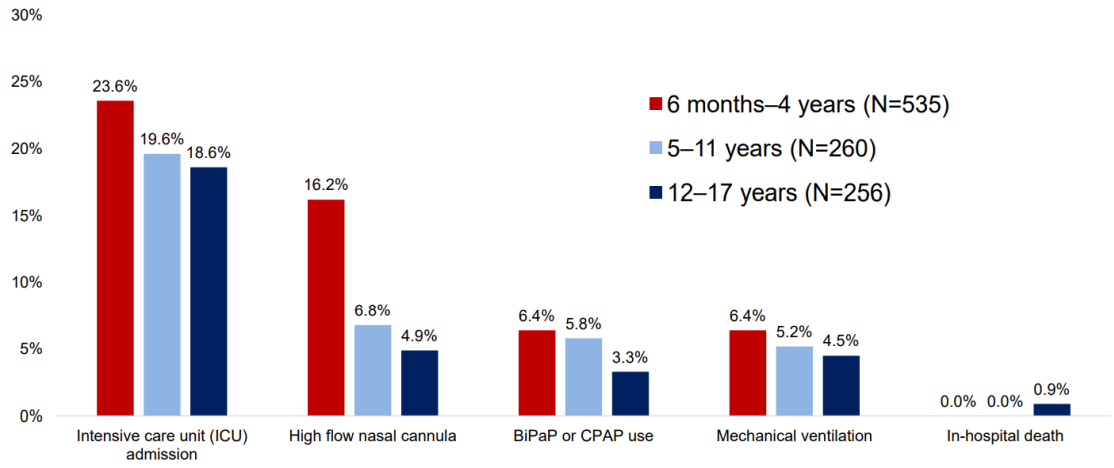
In updated US data, the hospitalisation rates for those 6 months to 4 years of age, while exceeding those for older children, are also decreasing.[11] In the US vaccination has been offered to children aged 6 months to 4 years beginning 22 June 2022. The uptake has been slow, with 10% of the population in that age group having received one dose so far.[12]

New variants continue to emerge, with attention in Europe currently focused on Omicron BQ.1.1 and its sublineages, with the potential to evolve into more immune evasive variants with higher growth rates than those preceding it. In Asia, the Omicron XBB variant may outpace Omicron BQ.1.1. As we enter the winter season COVID-19 case numbers and associated hospitalisations may increase. To date these variants do not appear to be associated with increased disease severity.

4. IMPACT OF COVID-19 ON CHILDREN 6 MONTHS TO 4 YEARS

As in the US and UK, in Ireland COVID-19 is more severe in this age group compared to older children and adolescents. In the US, from December 2021 to March 2022, disease severity was greater in those aged 6 months to 4 years, with a higher requirement for ICU admission and ventilation support than for older children.[7] (Figure 3)

Figure 3: Severity of COVID-19-associated hospitalisations among children and adolescents 6 months to 17 years, COVID-NET, 19 December 2021 – 31 March 2022 (Omicron period). Source ACIP presentation.[7]



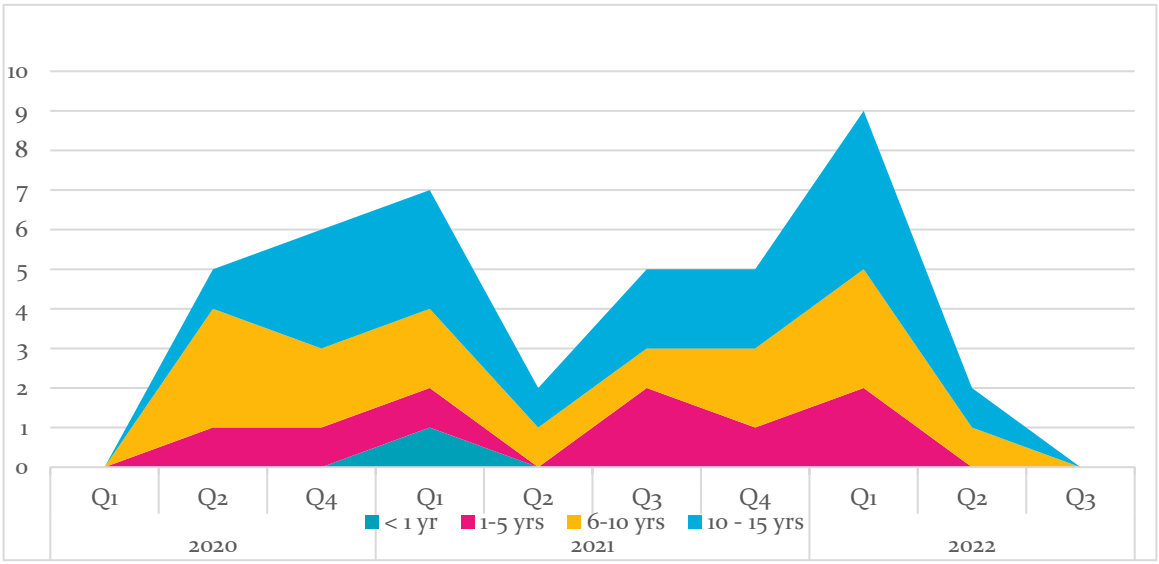
In the UK, between January 2020 and January 2022 there were 1,915 COVID-19 hospital admissions in infants aged less than one year; 12% were admitted to ICUs and 21 died. Over the same time period there were 1,049 hospital admissions among those aged 1-4 years, 15% of whom were admitted to ICU and seven died. The average length of hospital stay was approximately four days, ranging from 6.6 days during the Alpha predominant period to 1.9 days for infants and 1.5 days for those aged 1-4 years during Omicron predominance.[13]

In recently presented data from Belgium, of 1,631 children aged 0-4 years hospitalised with COVID-19 during the Omicron wave, 97% had no underlying medical conditions. A large number of the cases were in infants aged under 6 months.[14]

Multisystem Inflammatory Syndrome in Children (MIS-C)

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare event occurring in less than 1% of COVID-19 cases in children. The incidence and severity of MIS-C are lower after infection with Omicron compared to Alpha or Delta. However, as the number of infections with Omicron is much greater, the absolute number of MIS-C cases remains a concern.[15] In Ireland, those aged 5-11 years are the age group most affected; however, cases occur in children aged as young as three months.[16] [17] While the overall numbers are small, those aged 0-4 years accounted for 37% of all MIS-C cases in Ireland in the first year of the pandemic. MIS-C is often severe, requiring ICU admission, but outcomes are good with low mortality.[16] (Figure 4)

Figure 4: MIS-C admissions to Paediatric ICU in Ireland, March 2020-July 2022. Source: Beirne et al presentation at European Societies of Paediatrics, Barcelona, October 2022.[18]



While data in younger children are not available, evidence suggests that vaccination reduces the risk of MIS-C in adolescents.[16] [17]

Long COVID

Evidence regarding the prevalence and nature of long COVID in this age group is limited. A US retrospective cohort study of long COVID was carried out in those aged under 21 years from 1 March 2020 to 31 October 2021, with a median follow-up time of 4.6 months. Features were similar to those reported in adults (changes in taste or smell, chest pain, fatigue or malaise, cardiorespiratory signs or symptoms and fever or chills). Myocarditis was the most commonly diagnosed long COVID condition. Other features, such as abnormal liver enzymes, hair loss, skin rashes and diarrhoea occurred more commonly in children 1-6 months after infection compared with uninfected patients. The incidence of symptoms associated with long COVID was 42% among viral test-positive children vs 38% among viral test-negative children, with an incidence proportion difference of 4%. This indicates that the overall incidence of long COVID in this age group is low.

Another US study reported post–COVID-19 symptoms and conditions among children and adolescents 1-12 months following diagnosis between 1 March 2020 and 31 January 2022. Among children aged 2-4 years with COVID-19, compared with uninfected children of the same age, the relative risk was greatest for myocarditis and cardiomyopathy (aHR 2.39) and was also increased for acute and unspecified renal failure, and for coagulation and haemorrhagic disorders.[19]

Risk factors

In children less than two years of age, risk factors for severe COVID-19 include prematurity, cardiovascular conditions, respiratory conditions, abnormality of airways, neurological disorders, feeding tube dependence and hypertension. In those aged 2-5 years, risk factors include neurodevelopmental disorders, epilepsy and/or convulsions, obesity, chronic metabolic disease and immunosuppression.[7 20]

However, approximately 50-97% of hospitalised children aged 6 months to 4 years had no underlying condition.[7 11 14] Socioeconomic deprivation is associated with a higher risk of SARS-CoV-2 infection and disease severity.[21-24] Ensuring equity of access to vaccination, health care and health information to those from the most deprived areas is crucial in protecting children from severe COVID-19 disease.

5. COVID-19 VACCINES FOR CHILDREN AGED 6 MONTHS TO 4 YEARS

Comirnaty and Spikevax mRNA vaccines are authorised for use in children from 6 months of age.[25] The approved doses of both vaccines are lower than those recommended for older children. Both vaccines were authorised for this age group based on immunogenicity and safety data from clinical trials in children aged 6 months to 4 or 5 years. This is supported by post-marketing effectiveness and safety data available in older children and adults.

Paediatric formulations of Spikevax for those aged under 5 years are not available in Ireland.

Safety

In clinical trials in this age group, the safety profiles were similar for both vaccines and were comparable to those seen in older trial participants. In a clinical trial of Comirnaty 3 micrograms/dose, more than 4,500 children, aged 6 months to 4 years, were randomised to receive Comirnaty (n=3,013) or placebo (n=1,513). No new safety concerns were observed in the vaccine recipients. The most common side effects in children aged from 6 months to 4 or 5 years were irritability, sleepiness, loss of appetite, rash and tenderness at the injection site. These effects were usually mild or moderate and improved within a few days of vaccination.[26 27]

In the US, over one million children aged 6 months to 5 years have received at least one dose of either Comirnaty or Spikevax. The CDC reviewed adverse events during this time that were reported to v-safe* and VAERS (vaccine adverse event reporting system). Overall COVID-19 vaccines are very safe in this age group with most reactions reported as mild to moderate. The most commonly reported symptoms were irritability or crying, sleepiness, loss of appetite and fever. Almost all (98%) reports were for non-serious events. Of the serious events reported, two

*V-safe provides personalised health check-ins via text messages and web surveys to help CDC monitor the safety of COVID-19 vaccines.

were likely attributable to the vaccination, one febrile convulsion and one anaphylaxis associated with a dosing error. No cases of myocarditis were reported.[28]

In the US, following the first one million vaccinations in this age group, vaccination errors were among the most common (455; 44.7%) events reported to VAERS. Commonly reported errors included; incorrect dose administered, product administered to patient of inappropriate age, or product or preparation issue.[28] This highlights the potential risk of medication error in this population which should be considered in operational/roll-out planning. Given the lower doses advised in this age group, separate paediatric vaccination clinics for this age group are recommended to minimise vaccine errors.

Immunogenicity

In the Comirnaty clinical trial in those aged 6 months to 4 years, three doses were required to achieve antibody levels comparable to those seen following two doses in those aged 16-25 years. (Table 2)

Table 2: Immunogenicity of Comirnaty 3µg in children aged 6 months to 4 years compared with young adults. Adapted from: Pfizer Comirnaty Summary of Product Characteristics.[26]

	1 month after dose 3 (3µg dose)		1 month after dose 2 (30 µg dose)
	Children		Young adults
	6-23 months	2-4 years	16-25 years
SARS-CoV-2 GMTs at 1 month post vaccination course			
Number	82	143	170
GMT (95% CI)	1406 (1211-1633)	1535 (1388-1697)	1180 (1066-1305)
GMR versus young adults (95% CI)	1.19 (1.0-1.42)	1.3 (1.13-1.50)	
Serologic response at 1 month post vaccination course			
Serologic response	100%	100%	98.8%
Number	80	141	170
95% CI	95.5-100	97.4-100	95.8-99.9
Difference in serologic response % versus young adults	1.2 (3.4-4.2)	1.2 (1.5-4.2)	

In a clinical trial of Spikevax involving over 6,000 children aged 6 months to 5 years followed up for 70 days after the second injection, the immune response of those who received the vaccine was comparable to that seen in young adults (18-25 years) who had received Spikevax in previous trials.[27]

Efficacy

The efficacy of Comirnaty against COVID-19 illness was analysed during the Omicron period in 1,254 children aged 6 months to 4 years who received three doses of either Comirnaty (n=873) or placebo (n=381) and were SARS-CoV-2 negative at baseline. The median follow-up following dose three was 1.3 months. An estimated vaccine efficacy (VE) against SARS-CoV-2 infection of 73% in those 6 months to 4 years was observed. A total of 21 cases of SARS-CoV-2 were reported in the placebo group and 13 cases in the vaccinated group.[26]

The efficacy of Spikevax against COVID-19 (one respiratory symptom and a positive PCR test) was analysed during the Omicron period in 5,476 children aged 6 months to 5 years who received two doses of either Spikevax (n=4,105) or placebo (n=1,371) and were negative at baseline for SARS-CoV-2. The median length of follow-up was approximately 70 days. VE against infection was 37% (95% CI: 12.5, 54.0) for children aged 2-5 years and 51% (95% CI: 21.4, 68.6) for children aged 6-23 months. A total of 95 cases of SARS-CoV-2 were reported in the placebo group and 170 cases in the vaccinated group.[27 29]

Estimates of Spikevax vaccine efficacy against symptomatic disease during the Omicron wave in children aged 6 months to 5 years are consistent with VE reported for Comirnaty (10 micrograms/dose) vaccine among children 5 to 11 years of age during the Omicron wave.[30]

Of note, VE cannot be compared across these paediatric studies, as there were differences in study design and follow-up.

Post-marketing studies show that mRNA vaccines in older age groups are highly effective at preventing severe outcomes of COVID-19 including hospitalisation and death.[31 32] They are also highly effective against hospitalisation due to MIS-C in adolescents.[33] The clinical trials in those aged 6 months to 4 years were not powered to assess efficacy against these more severe outcomes. mRNA vaccines are less effective at preventing Omicron infection compared to previous variants.[34 35] Waning of immunity over time is well documented in older age groups and may also contribute to lower effectiveness estimates when calculated at longer intervals following vaccination or infection.

Vaccine dose and schedule for children aged 6 months to 4 years

Comirnaty (3 micrograms/dose) is administered intramuscularly as a primary course of three 0.2ml doses with an interval of three weeks between dose one and two and at least eight weeks between dose two and three.

If a child turns five years old between their doses in the vaccination course, the series should be completed with an age appropriate dose. If having received an initial 3 microgram dose they turn five years, they should complete the vaccine series with two 10 microgram doses.

Co-administration

No interaction studies in young children have been performed on coadministration of mRNA vaccines with childhood vaccines. Priority should be given to the routine childhood immunisation schedule. Until there is more evidence it is prudent to separate COVID-19 vaccination in children aged 6 months to 4 years from other vaccines for 14 days.

Vaccination after COVID-19

For those previously infected with SARS-CoV-2, Comirnaty may be given after an interval of at least four weeks following symptom onset or a positive SARS-CoV-2 test. Recent COVID-19 infection is not a contraindication to COVID-19 vaccination which should be deferred until clinical recovery. Those with persisting symptoms post COVID-19 may be vaccinated unless there is evidence of recent clinical deterioration.

Increasing the time between infection and vaccination may enhance the immune response to vaccination.[36] Delaying initiation of the primary series for up to six months after diagnosis of COVID-19 or onset of symptoms may be of benefit, taking into consideration the background epidemiological setting and urgency of vaccination, i.e., incidence of COVID-19, season, presence of underlying conditions and predominant circulating variants. Serological testing prior to vaccination is not recommended.

6. INTERNATIONAL RECOMMENDATIONS

International recommendations for primary series COVID-19 mRNA vaccination for children aged 6 months to 4 years		
Region	No underlying conditions	Have underlying conditions with high risk of severe disease
Belgium[14]	Not recommended	Both vaccines recommended
Finland[11]	Not recommended	Will be offered
Germany[37]	Recommended for those born prematurely under 2 years of age Those in contact with high risk individuals - decide on case by case basis	Both vaccines recommended however Spikevax is unavailable in Germany for this age.
Sweden[11]	Not recommended	May be vaccinated following advice from responsible physician
UK [38]	No recommendation	No recommendation
Canada[39]	Both vaccines recommended	Both vaccines recommended, Spikevax preferred
Australia [40]	No recommendation	Spikevax recommended
US [41]	Both vaccines recommended	Both vaccines recommended
New Zealand[42]	No recommendation	No recommendation
Israel[43]	Both vaccines “allowed”	Both vaccines recommended

7. ETHICAL CONSIDERATIONS

The recommendations to offer COVID-19 vaccination to children aged 6 months to 4 years have been made following careful consideration of the risks of SARS-CoV-2 infection and the potential benefits and risks of vaccination. The reported efficacy of the mRNA COVID-19 vaccines in this age group, the good safety profile of the vaccines, and the increased risk of severe disease for those with underlying conditions supports recommending COVID-19 vaccination for this group. From a beneficence perspective, it is appropriate to recommend the vaccine to those at higher risk of severe disease.

The situation is more finely balanced in relation to healthy children, many of whom have already experienced SARS-CoV-2 infection. Hospitalisations are highest in the youngest age groups compared to older children and adolescents. Most of those hospitalised did not have an underlying health condition. SARS-CoV-2 infection may lead to rare but serious health issues including MIS-C and long COVID, even after mild or asymptomatic infection. COVID-19 vaccination can be ethically justified in the child's own interests.

Even if individual children do not stand to benefit substantially from vaccination, it could be ethically justifiable to choose vaccination to mitigate the risk posed to family members and other close contacts who may be at increased risk of severe COVID-19. COVID-19 vaccines have a modest and transitory effect on transmission of the virus so any benefit conferred by vaccination to a vulnerable person should not displace non-pharmaceutical measures. Offering COVID-19 vaccination to healthy children in this age group recognises the autonomy of parents and guardians to make decisions for their own children and circumstances.

Before vaccination parents and guardians should be informed of the known benefits, risks and uncertainties of COVID-19 vaccination.

The potential impact on routine childhood vaccination was also considered in making these recommendations. A decline or delay in routine immunisations poses a serious risk of vaccine-preventable disease outbreaks. If COVID-19 vaccine is administered in dedicated vaccination clinics, NIAC is satisfied that there would be no opportunity cost to routine childhood vaccinations from these recommendations.

8. DISCUSSION

The primary aim of the vaccination programme is to prevent serious illness and death. When considering if COVID-19 vaccination should be offered to those aged 6 months to 4 years the key questions are whether the vaccine is needed, if the vaccine is safe, and will the vaccine be effective.

In assessing whether the vaccine is needed, a detailed review of the evidence relating to the threat posed by SARS-CoV-2 infection and the direct benefits and potential harms of vaccination was conducted. Incomplete information regarding the long-term effects of the vaccine was balanced with the known risks of COVID-19 and the uncertain long-term impact of SARS-CoV-2 and its variants.

Over the last 12 months, the epidemiology of COVID-19 has changed very significantly for young children. Omicron and its sublineages are now predominant but uncertainty regarding future evolution remains. Although the disease associated with Omicron is less severe with less risk of MIS-C, SARS-CoV-2 infection remains a threat especially for those with underlying conditions that increase their risk of severe disease. However, the risk to healthy children is not negligible.

The vaccine is safe and immunogenic in young children albeit three doses are required to achieve comparable immunogenicity to two doses in older cohorts. In clinical trials over 3,000 vaccine recipients aged 6 months to 4 years have received the vaccine with mild reactogenicity commonly observed. The safety of mRNA vaccines in this age group is further supported by post-marketing data with no increased risk of myocarditis identified after 1.7 million children had received at least one dose of vaccine, over 300,000 of whom are fully vaccinated.[11 12 28]

Vaccination reduces the risk of serious disease and its complications. The benefits of vaccination are most clearly evidenced for children with risk factors whereas the benefits for healthy children in this time of lower virus circulation are more nuanced.

An Irish study carried out between June and August 2021 assessed parental attitudes to COVID-19 vaccination. Of the 855 parents of children aged 0-2 years old interviewed, just over 50% intended to vaccinate their children and 20% were unsure. The belief that COVID-19 can be a serious illness in children was a strong predictor of parental intention to vaccinate.[44]

Although Omicron is generally associated with less severe infection than previous variants, the highly transmissible nature and large numbers of Omicron infections means that the absolute number of younger children requiring hospitalisation was very significant. For those already infected, vaccination affords added protection. Nonetheless the perception that Omicron poses less of a threat to children overall and the fact that most children have likely experienced infection may mean that parental attitudes towards vaccination could have changed since this survey was carried out.

A secondary benefit of vaccination of children may be reducing the likelihood of transmission by those vaccinated should they become infected, with an indirect benefit of protecting vulnerable household members, infants too young to be vaccinated, and those with immunocompromise who may not respond well to vaccine.

The decision for parents or guardians requires an assessment of a number of factors including the best interests of the health and wellbeing of their child in the context of their family

circumstances. Prior to offering vaccination, parents or guardians should be informed of benefits and risks of COVID-19 vaccination, the risks of COVID-19 to their age group and the remaining uncertainties. Any decision by parents should be respected.

9. CONCLUSION

The risks of COVID-19 in the healthy child are low but not negligible. Most children admitted to hospital have no underlying condition and their stay is short. Many children have had SARS-CoV-2 infection, mainly during the Omicron wave. However, there will be new entrants to this age cohort who will be more likely to be virus naive if virus circulation stabilises or further decreases. Some children, even among those not hospitalised, will develop MIS-C. Virtually all will recover from the acute episode but long term consequences are uncertain. Vaccination will protect these children from severe disease.

The vaccine is safe in young children. No new safety concerns have been identified and lower rates of adverse events have been reported than in other age cohorts. The vaccine is as immunogenic in young children as in the older cohorts, however three doses are required.

The benefits of vaccination for children with risk factors for severe COVID-19 are more evident than for healthy children. In the context of the current epidemiology, high seroprevalence rates and declining infection rates, additional considerations underlying a decision to vaccinate a healthy child are nuanced and influenced by factors including whether a child had prior infection, the interval since the infection, family circumstances and the need to minimise risks of COVID-19 infection within a household.

REFERENCES

1. Health Protection Surveillance Centre, HSE. Weekly report on the epidemiology of COVID-19 in Ireland. Week 45, 2022 2022 [Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/epidemiologyofcovid-19inirelandweeklyreports/2022-11-15_Weekly_report_v1.3.pdf.

2. COVID-19 Epidemiology Team H. National SARS-CoV-2 Wastewater Surveillance Programme Week 41, 2022 (09/10/2022 to 15/10/2022) www.hpsc.ie: HPSC; 2022 [Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/wastewatersurveillanceprogramme/nwsp_main_public_Wk%2041.html accessed 1 November 2022.

3. COVID-19 Epidemiology Team H. National SARS-CoV-2 Wastewater Surveillance Programme. Week 44, 2022 (30/10/2022 to 05/11/2022) 2022 [Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/wastewatersurveillanceprogramme/nwsp_main_public_Wk44.html accessed 21 November 2022.

4. Butt AA, Dargham SR, Loka S, et al. Coronavirus Disease 2019 Disease Severity in Children Infected With the Omicron Variant. *Clin Infect Dis* 2022;75(1):e361-e67. doi: 10.1093/cid/ciac275

5. Wang L, Berger NA, Kaelber DC, et al. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. *medRxiv* 2022 doi: 10.1101/2022.01.12.22269179 [published Online First: 20220113]

6. Paediatric ICU department Children's Health Ireland. COVID-19 Related Admissions to Paediatric Intensive Care in Ireland, unpublished data, 2022.

7. COVID-19 epidemiology in children ages 6 months–4 years. ACIP meeting June 17, 2022; 2022.

8. Health Protection Surveillance Centre. Epidemiology of COVID-19 in Ireland weekly reports - 2022 2022 [Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/epidemiologyofcovid-19inirelandweeklyreports/ accessed 21 Novemeber 2022.

9. Health Protection Surveillance Centre H. Weekly report on the epidemiology of COVID-19 in Ireland Week 43, 2022 2022 [Available from: https://www.hpsc.ie/a-z/respiratory/coronavirus/novelcoronavirus/surveillance/epidemiologyofcovid-19inirelandweeklyreports/2022-11-01_Weekly_report_v1.3.pdf.

10. Health Protection Surveillance Centre SU. Seroprevalence of SARS-CoV-2 antibodies in children. www.hpsc.ie, 2022.

11. COVID-19 vaccination in infants and children. EU-EEA NITAG Collaboration Webinar; 2022 15 November 2022.

12. American Academy of Pediatrics. Summary of data publicly reported by the Centers for Disease Control and Prevention Date: 11/9/22 2022 [Available from:

https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-vaccination-trends/#:~:text=At%2014%20weeks%20following%20vaccine,dose%20of%20COVID%2D19%20vaccine accessed 21 November 2022.

13. ISARIC4C CCCC, COVID-19 Clinical Information Network C-C. Co-Cin update January 2022, 2022.

14. Superior Health Council. Vaccination against COVID-19 with mRNA vaccines for children from 6 months of age in Belgium. Brussels: SHC; 2022. Report 9722. 2022 [Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/20221110_shc_9722_covid19_children_under_5_vweb.pdf accessed 21 November 2022.

15. Cohen JM, Carter MJ, Ronny Cheung C, et al. Lower Risk of Multisystem Inflammatory Syndrome in Children (MIS-C) with the Delta and Omicron variants of SARS-CoV-2. *Clin Infect Dis* 2022 doi: 10.1093/cid/ciac553 [published Online First: 20220705]

16. UpToDate. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis - UpToDate 2022 [Available from: https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and-diagnosis accessed 19 October 2022.

17. Kaushik A, Gupta S, Sood M, et al. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. *The Pediatric Infectious Disease Journal* 2020;39(11)

18. COVID-19 related admissions to paediatric intensive care in Ireland European Academy of Paediatric Societies; 2022 October 7-11, 2022; Barcelona, Spain.

19. Kompaniyets L, Bull-Otterson L, Boehmer T, et al. Post–COVID-19 Symptoms and Conditions Among Children and Adolescents — United States, March 1, 2020–January 31, 2022. MMWR Morb Mortal Wkly Rep 2022;71:993–999. , 2022.

20. The National Collaborating Centre for Methods and Tools. What are the risk factors associated with severe COVID-19 outcomes in children 5 years and under?, 2022.

21. Broad J, Forman J, Brighouse J, et al. Post-COVID-19 paediatric inflammatory multisystem syndrome: association of ethnicity, key worker and socioeconomic status with risk and severity. *Arch Dis Child* 2021;106(12):1218-25. doi: 10.1136/archdischild-2020-320388 [published Online First: 20210316]

22. Dragano N, Dortmann O, Timm J, et al. Association of Household Deprivation, Comorbidities, and COVID-19 Hospitalization in Children in Germany, January 2020 to July 2021. *JAMA Netw Open* 2022;5(10):e2234319. doi: 10.1001/jamanetworkopen.2022.34319 [published Online First: 20221003]

23. Madden JM, More S, Teljeur C, et al. Population Mobility Trends, Deprivation Index and the Spatio-Temporal Spread of Coronavirus Disease 2019 in Ireland. *Int J Environ Res Public Health* 2021;18(12) doi: 10.3390/ijerph18126285 [published Online First: 20210610]

24. Mannheim J, Konda S, Logan LK. Racial, ethnic and socioeconomic disparities in SARS-CoV-2 infection amongst children. *Paediatr Perinat Epidemiol* 2022;36(3):337-46. doi: 10.1111/ppe.12865 [published Online First: 20220125]

25. European Medicines Agency E. EMA recommends approval of Comirnaty and Spikevax COVID-19 vaccines for children from 6 months of age 2022 [Available from: https://www.ema.europa.eu/en/news/ema-recommends-approval-comirnaty-spikevax-covid-19-vaccines-children-6-months-age#:~:text=Contacts-,EMA%20recommends%20approval%20of%20Comirnaty%20and%20Spikevax%20COVID%2D19%20vaccines,from%206%20months%20of%20age&text=EMA's%20human%20medicines%20committee%20(CHMP,of%20SARS%2DCoV%2D2. accessed 02 November 2022 2022.

26. Agency EM. Summary of Product Characteristics of Comirnaty, Comirnaty Original/Omicron BA.1, and Comirnaty Original/Omicron BA.4-5 www.ema.europa.eu2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf accessed 14 September 2022.

27. Anderson EJ, Creech CB, Berthaud V, et al. Evaluation of mRNA-1273 Vaccine in Children 6 Months to 5 Years of Age. *N Engl J Med* 2022 doi: 10.1056/NEJMoa2209367 [published Online First: 20221019]

28. Hause A, Marquez P, Zhang B, et al. COVID-19 mRNA Vaccine Safety Among Children Aged 6 Months–5 Years — United States, June 18, 2022–August 21, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1115–1120.

29. Agency EM. Summary of Product Characteristics for Spikevax and Spikevax bivalent Original/Omicron BA.1 www.ema.europa.eu2022 [Available from: https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf accessed 14 September 2022.

30. Fowlkes A, Yoon S, Lutrick K, et al. Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5-11 Years and Adolescents Aged 12-15 Years - PROTECT Cohort, July 2021-February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(11) doi: 10.15585/mmwr.mm7111e1

31. UK Health Security Agency. COVID-19 vaccine surveillance report Week 40 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1115372/vaccine-surveillance-report-week-40.pdf accessed 9 November 2022.

32. Watson OJ, Barnsley G, Toor J, et al. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022;22(9):1293-302. doi: 10.1016/S1473-3099(22)00320-6 [published Online First: 20220623]

33. Levy M, Recher M, Hubert H, et al. Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France. *JAMA* 2022;327(3):281-83. doi: 10.1001/jama.2021.23262

34. Buchan SA, Chung H, Brown KA, et al. Estimated Effectiveness of COVID-19 Vaccines Against Omicron or Delta Symptomatic Infection and Severe Outcomes. *JAMA Netw Open*

2022;5(9):e2232760. doi: 10.1001/jamanetworkopen.2022.32760 [published Online First: 20220901]

35. Gram MA, Emborg HD, Schelde AB, et al. Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the Alpha, Delta, or Omicron SARS-CoV-2 variant: A nationwide Danish cohort study. *PLoS Med* 2022;19(9):e1003992. doi: 10.1371/journal.pmed.1003992 [published Online First: 20220901]

36. Zhong D, Xiao S, Debes AK, et al. Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection. *JAMA* 2021;326(24):2524-26. doi: 10.1001/jama.2021.19996

37. Standing Committee on Vaccination. STIKO press release on the 23rd update of the COVID-19 vaccination recommendation 2022 [Available from: https://www.rki.de/DE/Content/Kommissionen/STIKO/Empfehlungen/PM_2022-11-17.html accessed 21 November 2022.

38. UKHSA UHSA. Coronavirus (COVID-19) vaccination information for public health professionals. The Green Book. www.gov.uk2022.

39. National Advisory Committee on Immunization N. Recommendations on the use of Pfizer-BioNTech Comirnaty (3 mcg) COVID-19 vaccine in children 6 months to 4 years of age 2022 [updated October 21 2022. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-pfizer-biontech-comirnaty-3-mcg-covid-19-vaccine-children-6-months-4-years.html#t1.

40. Australian Technical Advisory Group on Immunisation (ATAGI). Clinical recommendations for COVID-19 vaccines | Australian Government Department of Health and Aged Care 2022 [updated 2022-01-05T13:28+11:00. Available from: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-recommendations#primary-vaccination-course-recommendations.

41. Prevention CDC. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States 2022 [Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html accessed 19 October 2022.

42. New Zealand Ministry of Health. Immunisation Handbook, Coronavirus disease (COVID-19) 2022 [Available from: https://www.health.govt.nz/our-work/immunisation-handbook-2020/5-coronavirus-disease-covid-19#23-5 accessed 19 October 2022.

43. Health IMo. COVID-19 Vaccine for Toddlers 2022 [Available from: https://corona.health.gov.il/en/vaccine-for-covid/toddler-vaccinations/ accessed 9 November 2022.

44. Marron L, Ferenczi A, O'Brien KM, et al. Views on COVID-19 vaccination of young children in Ireland, results from a cross-sectional survey of parents. *Vaccine* 2022;40(39):5716-25. doi: https://doi.org/10.1016/j.vaccine.2022.08.030

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