Memo

Third primary dose of the paediatric Pfizer mRNA COVID-19 vaccine for immunocompromised 5–11-year-olds: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	22 March 2022
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For your:	Consideration

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) recommendations on the use of a third primary dose of the paediatric Pfizer mRNA COVID-19 vaccine in severely immunocompromised 5–11-year-olds.

Background and context

2. On 21 September 2021, CV TAG issued recommendations for a third primary Pfizer mRNA COVID-19 vaccine dose in adults who are immunocompromised. CV TAG recommended that those with severe immunocompromise be offered an additional dose of the Pfizer vaccine. These recommendations were updated on 17 November 2021 to include all individuals aged 12 years and over who are severely immunocompromised to be offered a third primary dose of the Pfizer vaccine.
3. Children aged 5–11 years became eligible to receive the paediatric Pfizer vaccine in January 2022, with CV TAG recommending at the time that a safety review be conducted before second doses were given. On 16 February 2022, CV TAG recommended that a second dose be given with a minimum 8-week interval after the first dose. Given that the paediatric rollout is now underway, there will be a small group of children aged 5–11 years who are severely immunocompromised who will have completed their primary course (2 doses).
4. Some immunocompromised people do not mount an immune response following vaccination that is sufficient to provide protection from COVID-19.[1] Immunocompromised individuals are also at higher risk of severe outcomes from COVID-19 compared to the general population. Several underlying medical conditions, including diabetes, asplenia, and chronic lung and kidney disease, are also associated with increased risk of severe outcomes from COVID-19.[2, 3]

5. Immunocompromised individuals tend to have prolonged infection and viral shedding, are at higher risk of developing a new variant during infection, and are more likely to transmit the virus to household contacts than non-immunocompromised groups.[4] They are also more likely to have a breakthrough infection after being vaccinated, with studies in the US and Israel having estimated that 40-44% of hospitalised breakthrough cases are immunocompromised.[5, 6] Consequently, an additional vaccine dose may deliver better protection in immunocompromised individuals.

6. Furthermore, currently available data suggests that Omicron has significantly reduced the effectiveness of two doses against infection, highlighting the need for extra protection in those vulnerable to severe disease.

7. Some international jurisdictions are now recommending that severely immunocompromised children aged 5–11 years receive a third primary dose of the COVID-19 vaccine, in line with other severely immunocompromised age cohorts. Accordingly, guidance is being sought on the use and timing of a third primary dose for this age group in Aotearoa New Zealand.

COVID-19 vaccine in paediatric populations who are immunocompromised

8. There are currently no safety, reactogenicity, immunogenicity or efficacy data available for a third dose in the 5–11 year age group. However, data currently available for a primary course (2 doses) in older immunocompromised adolescents can be reviewed to understand the impact of vaccination.

9. A rapid review of the available evidence identified five studies with small cohort sizes that have reported on the immunogenicity and/or safety after a primary course (2 doses) in adolescents with immunocompromising conditions:

    a. *Inflammatory bowel disease (IBD) treated with anti-TNF therapy (n=68, age 14–16 years) [7]:* Paediatric IBD patients on infliximab (IFX) monotherapy and those on IFX in combination with methotrexate or azathioprine had comparable antibody responses to healthy adults after the second dose of Pfizer (when measured at 3 months after the first dose). However, a significantly lower neutralising capacity was observed for IBD patients on combination therapy when compared to adults and paediatric IBD patients on IFX monotherapy.

    b. *Solid organ transplant recipients (n=57, median age 14 years) [8]:* Overall, 73.3% of paediatric recipients had a positive antibody response after the second dose of Pfizer. This rate is much higher than previously reported rates for adult recipients, which ranges from 5–58.8%. Shorter time from transplantation, use of multiple immunosuppressive agents, and maintenance anti-metabolite immunosuppression were associated with a negative antibody response. The most commonly reported vaccine side effects were mild to moderate injection site pain (83.5%) and fatigue (39.5%). No patients developed allergic reactions or organ rejection.

    c. *Heart transplant recipients (n=40, median age 17.1 years) [9]:* Similar to the study above, 70% of recipients developed an antibody response following two doses of mRNA vaccine (Pfizer or Moderna). Neutropenia, diabetes mellitus, and previous use of rituximab were associated with absence of a detectable antibody. There were no cases of myocarditis detected in the study.

d. *Solid tumors (n=13, median age 17 years) [10]:* Overall, 90% of patients seroconverted one month after the second dose of Pfizer and all patients who seroconverted showed COVID-19 neutralising capacity. Mild pain at the injection site and fatigue were the most commonly reported local and systemic reactions, respectively. Aside from transient local and systemic reactions, no safety concerns were identified.

e. *Extremely vulnerable children (n=27, age 12–15 years) [11]:* This study provided an initial outlook on the safety and tolerability of the Pfizer vaccine in adolescents with various immunocompromising conditions, including neurological disorders, cardiac impairments, and immunodeficiencies. Overall, adverse reactions were mild to moderate. Redness, discomfort, fever, and fatigue were reported after both doses, with slightly higher severity after the second dose, however paracetamol use was lower with the second dose.

10. There remain limited data from paediatric and adolescent populations who are immunocompromised. Currently available data indicates that vaccination is generally well-tolerated in immunocompromised children. However, some severely immunocompromised groups may not develop antibody responses that are as robust as healthy individuals. Moreover, up to 30% of specific populations may not seroconvert following a primary course (2 doses). While this data is from older children and adolescents, the general trend is in keeping with that observed for adults and is expected to be similar for children aged 5–11 years. Accordingly, a third primary dose may be warranted in severely immunocompromised 5–11-year-olds.

Status of other jurisdictions – third dose for severely immunocompromised 5-11-year-olds

11. Currently, Australia, the United States, Canada, and the United Kingdom all recommend a third dose of COVID-19 vaccine for severely immunocompromised 5–11-year-olds following a 2-dose primary course.

    a. The **Australian Technical Advisory Group on Immunisation (ATAGI)** has advised that a third primary dose be offered to severely immunocompromised children aged 5–11 years. The recommended interval for a third primary dose is 2 months after the second dose.[12]

    b. The **US Centers for Disease Control and Prevention (CDC)** recommend that moderately or severely immunocompromised children aged 5–11 years receive a third primary dose of COVID-19 vaccine, to be given at least 4 weeks after the second dose. [13]

    c. In Canada, the **National Advisory Committee on Immunization (NACI)** recommends that moderately to severely immunocompromised children aged 5–11 years should be offered a third dose after a 2-dose primary series, and that this be given 4 to 8 weeks after the second dose.[14]

    d. The **UK Joint Committee on Vaccination and Immunisation (JCVI)** recommend a third primary dose be given to severely immunosuppressed 5–11-year-olds at least 8 weeks after their second dose, however with special attention paid to current or planned immunosuppressive therapies. Where possible the third dose should be delayed until two weeks after the period of immunosuppression, in addition to the

time period for clearance of the therapeutic agent. If not possible, consideration should be given to vaccination during a treatment 'holiday' or when the degree of immunosuppression is at a minimum.[15]

Recommendations

12. CV TAG met on 8 and 22 March 2022 to discuss recommendations on the use of a third primary dose of the paediatric Pfizer vaccine in severely immunocompromised 5–11-year-olds.

13. **CV TAG noted that:**

    a. Children 5–11 years of age who are severely immunocompromised may be at increased risk of severe outcomes from COVID-19 compared to children who are not severely immunocompromised.

    b. A third primary dose offers extra protection to severely immunocompromised people and may help to reduce transmission from immunocompromised individuals who become infected. A third primary dose is also likely to be well-tolerated in severely immunocompromised children.

    c. Based on recommendations of international jurisdictions to date, it would be reasonable to offer severely immunocompromised 5–11-year-olds a third primary dose.

14. **CV TAG recommend that:**

    a. Those aged 5–11 years who are severely immunocompromised should be offered a third primary dose of the paediatric Pfizer vaccine.

        i. The preliminary guidance for children who should be offered a third primary dose of the paediatric Pfizer COVID-19 vaccine is provided in Appendix 1. The list is not exhaustive but provides guidance on scenarios where a consumer should receive a third primary dose. **Note**: The list may expand or be modified over time as more evidence emerges. Advice for clinicians on the guidance is available through the Immunisation Advisory Centre, and this information will be updated periodically through the Immunisation Handbook.

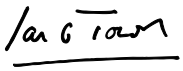
        ii. Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required for conditions or medicines that are not listed that are associated with severe immunocompromise.

    b. The third primary dose should be administered from 8 weeks after the second dose but can be administered from 4 weeks after the second dose after consideration of current or planned immunosuppressive therapies.

        i. For time limited immunosuppressive treatment, where possible the dose should be delayed until 2 weeks after the period of immunosuppression, in addition to the time period for clearance of the therapeutic agent.

        ii. For long term immunosuppressive treatment, consideration should be given to vaccination during a treatment 'holiday'.

15. CV TAG will continue to monitor all relevant information and will update their recommendations as further evidence becomes available.



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Appendix 1

Preliminary guidance for children who should be offered a third primary dose of the paediatric Pfizer COVID-19 vaccine

Note: *This list is not exhaustive but provides guidance on scenarios where a consumer should receive a third primary dose. Drug dose, disease activity, and co-morbidity can affect the severity of immunocompromise. The list may expand or be modified over time as more evidence emerges. Advice for clinicians on the guidance is available through the Immunisation Advisory Centre, and this information will be updated periodically through the Immunisation Handbook.*

- *Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required for conditions or medicines that are not listed below that are associated with severe immunocompromise.*
- *Conversely, clinicians may decide that individual patients with conditions or medicines listed below are at low risk of being severely immunocompromised and do not require a third primary vaccine dose.*

1. Individuals with primary or acquired immunodeficiency states at the time of vaccination due to conditions including but not limited to (see note above):
    a. acute and chronic leukaemias, and clinically aggressive lymphomas (including Hodgkin's lymphoma) who were under treatment or within 12 months of achieving cure.
    b. individuals under follow up for chronic lymphoproliferative disorders including haematological malignancies such as indolent lymphoma, chronic lymphoid leukaemia, myeloma, Waldenstrom's macroglobulinemia and other plasma cell dyscrasias.
    c. immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/µl.
    d. primary or acquired cellular and combined immune deficiencies – those with lymphopaenia ($<10^9$ lymphocytes/L) or with a functional lymphocyte disorder.
    e. those who had received an allogeneic (cells from a donor) or an autologous (using their own cells) stem cell transplant in the previous 24 months.
    f. those who had received a stem cell transplant more than 24 months ago but had ongoing immunosuppression or graft versus host disease (GVHD).
    g. persistent agammaglobulinaemia (IgG <3g/L) due to primary immunodeficiency (for example, common variable immunodeficiency) or secondary to disease/therapy.
2. Individuals on, or recently on, immunosuppressive therapy at the time of vaccination including but not limited to (see note above):
    a. receiving immunosuppressive therapy for a solid organ transplant.
    b. received within the previous 6 months rituximab or other B cell-depleting biologic therapy for autoimmune or autoinflammatory disease.
    c. received within the previous 3 months other biologics or targeted therapy for autoimmune or autoinflammatory disease. Examples are provided in **Table 1** and are based on the ATAGI list. Clinicians may use their judgement for medicines which are not listed.

d. received within the previous 6 months cytotoxic chemotherapy or immunosuppressive radiotherapy for any indication.

3. Individuals with chronic immune-mediated inflammatory disease who were receiving or had received immunosuppressive therapy prior to vaccination including but not limited to (see note above):
    a. high dose or long-term moderate dose corticosteroids. Indicative dosage thresholds are provided in **Table 2**.
    b. immunosuppressants:
        i. including mycophenolate, methotrexate, leflunomide, thiopurines (e.g., azathioprine), 6-mercaptopurine, alkylating agents (e.g., cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g., cyclosporin, tacrolimus). Clinical judgement should be applied by the prescriber to determine whether a third primary dose is required.
        ii. excluding hydroxychloroquine, sulfasalazine, or mesalazine, when used as monotherapy
    c. combinations of immunosuppressive therapy where the cumulative effect is considered to be severely immunosuppressive, as determined by clinical judgement.

4. Individuals receiving long-term haemodialysis or peritoneal dialysis should be offered a third primary dose of the Pfizer COVID-19 vaccine.

Table 1: Examples for biologics

A third primary dose **is recommended** for people taking the following biologics	
Class	Examples
Anti CD 20 antibodies	rituximab, obinutuzumab, ocrelizumab
BTK inhibitors	ibrutinib,
JAK inhibitors	ruxolitinib
Sphingosine 1-phosphate receptor modulators	fingolimod
Anti-CD52 antibodies	alemtuzumab
Anti-complement antibodies	eculizumab
Anti-thymocyte globulin	anti-thymocyte globulin
A third primary dose **is not routinely recommended** for people taking the following biologics*	
Anti-integrins	natalizumab
Anti-TNF-α antibodies	infliximab, adalimumab, etanercept
Anti-IL1 antibodies	anakinra
Anti-IL6 antibodies	tocilizumab
Anti-IL17 antibodies	secukinumab
Anti-IL4 antibodies	dupilumab
Anti-IL23 antibodies	ustekinumab
Immune checkpoint inhibitors	nivolumab, pembrolizumab, ipilimumab, atezolizumab

*A third primary dose is recommended for people taking multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.

Table 2: Indicative dosage thresholds for corticosteroids

A third primary dose **is recommended** for:
a. Individuals with chronic immune-mediated inflammatory disease: i. on high dose corticosteroids (equivalent to ≥20mg prednisone per day for more than 10 days, in the previous month) ii. on long-term moderate dose corticosteroids (equivalent to ≥10mg prednisone per day for more than 4 weeks, in the previous 3 months) b. Individuals who had received high-dose steroids (equivalent to >40mg prednisone per day for more than a week) for any reason, in the previous month
A third primary dose **is not routinely recommended** for:
a. Individuals who had received brief immunosuppression (equivalent to ≤40 mg prednisone per day), for example, asthma / chronic obstructive pulmonary disease / COVID-19) b. Individuals receiving low dose locally acting steroids (inhaled or topical) c. Individuals on replacement corticosteroids for adrenal insufficiency

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