Memo

Additional Pfizer mRNA COVID-19 vaccine dose in the immunocompromised: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	21 September 2021
To:	Joanne Gibbs, Director of National Operations, COVID Vaccine Immunisation Programme
From:	Dr Ian Town, Chief Science Advisor
For your:	Consideration

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) recommendations on the use of an additional Pfizer mRNA COVID-19 vaccine dose in those who are immunocompromised.

Background and context

2. 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]

3. 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.

4. Emerging evidence suggests that a third dose of the Pfizer COVID-19 vaccine may increase the antibody titres in immunocompromised individuals who developed low antibody titres to the original two-dose regimen and result in the detection of antibodies in some of the non-responders.[4] Among those who had no detectable antibody response to an initial 2-dose mRNA vaccine series, about 33-50% developed an antibody response to a third dose. So far, reactions reported after the third dose in small studies were similar to those after two doses, with fatigue and pain at injection site being the most commonly reported side effects, and overall, most side effects reported were mild to moderate.[7]

5. One study evaluated the humoral response to a third dose of the Pfizer vaccine in 101 solid organ transplant patients.[8] Patients were given two doses of Pfizer one month apart, followed by a third dose of Pfizer two months later. Among the 59 patients who had been seronegative before the third dose, 26 (44%) were seropositive one month after the third dose.

6. Another study found that among 82 hemodialysis patients, only a small proportion (15.9%) failed to seroconvert after two doses.[9] Of these, 12 patients were given a third dose one month later and five (41.6%) developed an immune response following the third dose.

7. The level of individual protection that a third dose confers on an immunocompromised person is unknown. However, based on the emerging data for the COVID vaccines, and principles of vaccinology and immunology, an additional dose in the immunocompromised is unlikely to be associated with any significant risks, and may offer benefits to some individuals.

8. The Pfizer vaccine has been provisionally approved in Aotearoa New Zealand on the basis that two doses, not three, would be administered to a consumer. However, an unapproved indication, such as an additional dose for immunocompromised individuals, can be prescribed with informed consent.

9. On 12 August 2021, the US Food and Drug Administration (FDA) approved the use of an additional dose of the Pfizer COVID-19 vaccine at least 28 days following the original two-dose regimen in those who are immunocompromised.[10] The US Centers for Disease Control (CDC) have recommended that *"…moderately to severely immunocompromised people receive an additional dose. This includes people who have:*

- *Been receiving active cancer treatment for tumours or cancers of the blood*
- *Received an organ transplant and are taking medicine to suppress the immune system*
- *Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system*
- *Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)*
- *Advanced or untreated HIV infection*
- *Active treatment with high-dose corticosteroids or other drugs that may suppress their immune response*

People should talk to their healthcare provider about their medical condition, and whether getting an additional dose is appropriate for them."[7]

10. On 01 September 2021, the UK's Joint Committee on Vaccination and Immunisation (JCVI) issued guidance for COVID-19 vaccinations for individuals aged 12 years and over with severe immunosuppression.[11-13] JCVI recommended that a third dose should be offered to people aged 12 and over who were severely immunosuppressed at the time of their first or second dose, including those with leukaemia, advanced HIV, and recent organ transplants.

11. JCVI noted that the guidance for third doses for severely immunocompromised groups was separate to any potential booster programme for the general population: "*A third primary dose is an extra 'top-up' dose for those who may not have generated a full immune*

response to the first 2 doses. In contrast, a booster dose is a later dose to extend the duration of protection from the primary course of vaccinations."[11]

Recommendations

12. CV TAG met on 31 August and 07 September 2021 to discuss recommendations for the use of an additional dose in the immunocompromised.

13. CV TAG noted that:

    a. An additional dose of the Pfizer COVID-19 vaccine is likely to be beneficial and well-tolerated in the severely immunocompromised.

    b. An additional dose would offer extra protection to severely immunocompromised people and may help to reduce transmission from immunocompromised individuals who become infected.

    c. People with functional or anatomical asplenia and those with chronic liver or kidney disease not taking immunosuppressants (including those receiving hemodialysis) may also have immunocompromise. In addition, those with diabetes are at higher risk of severe infection. Thus, emerging information for these groups will be monitored and considered for any potential recommendations as data become available.

    d. 'Ring-fencing' of immunocompromised people through vaccination of household contacts can provide indirect protection to people with immunocompromise.

    e. People with immunocompromise may have a suboptimal immune response to vaccination and should be counselled to continue other protective measures against COVID-19 even after vaccination, such as physical distancing, wearing a face mask, practicing hand hygiene, and isolation or quarantine as advised by public health authorities.

14. CV TAG recommend that:

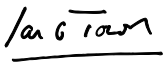
    a. Those with severe immunocompromise be offered an additional dose of the Pfizer vaccine. The list of eligible individuals is taken from the one developed by JCVI and is provided in Appendix 1.

    b. The additional dose should be administered more than 8 weeks after the second dose, with special attention paid to current or planned immunosuppressive therapies. Where possible, the third primary dose should be delayed until 2 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 at a nadir of immunosuppression between doses of treatment.

    c. The administration of an additional dose is covered by s25 of The Medicines Act 1981, and as such, should only be offered by an authorised prescriber with informed consent from the consumer.

    d. The standard two-dose course of vaccine should be offered to any eligible unvaccinated household contacts aged 12 and over, of immunocompromised individuals.

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

JCVI list of eligible individuals[12]

1. Individuals with primary or acquired immunodeficiency states at the time of vaccination due to conditions including:
    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 (note: this list is not exhaustive).
    c. immunosuppression due to HIV/AIDS with a current CD4 count of <200 cells/µl for adults or children 12 years of age and over.
    d. primary or acquired cellular and combined immune deficiencies – those with lymphopaenia (<1,000 lymphocytes/ul) 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 immunosuppressive or immunomodulating therapy at the time of vaccination including:
    a. those who were receiving or had received immunosuppressive therapy for a solid organ transplant in the previous 6 months.
    b. those who were receiving or had received in the previous 3 months targeted therapy for autoimmune disease, such as JAK inhibitors or biologic immune modulators including B-cell targeted therapies (including rituximab but in this case the recipient would be considered immunosuppressed for a 6-month period), T-cell co-stimulation modulators, monoclonal tumour necrosis factor inhibitors (TNFi), soluble TNF receptors, interleukin (IL)-6 receptor inhibitors, IL-17 inhibitors, IL 12/23 inhibitors, IL 23 inhibitors (note: this list is not exhaustive).
    c. those who were receiving or had received in the previous 6 months immunosuppressive 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:
    a. high-dose corticosteroids (equivalent to ≥ 20mg prednisolone per day) for more than 10 days in the previous month.
    b. long-term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day for more than 4 weeks) in the previous 3 months.
    c. non-biological oral immune modulating drugs, such as methotrexate >20mg per week (oral and subcutaneous), azathioprine >3.0mg/kg/day, 6-mercaptopurine >1.5mg/kg/day, mycophenolate >1g/day in the previous 3 months.

   d. certain combination therapies at individual doses lower than above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months.

4. Individuals who had received high-dose steroids (equivalent to >40mg prednisolone per day for more than a week) for any reason in the month before vaccination. Individuals who had received brief immunosuppression (≤40mg prednisolone per day) for an acute episode (for example, asthma / chronic obstructive pulmonary disease / COVID-19) and individuals on replacement corticosteroids for adrenal insufficiency are not considered severely immunosuppressed sufficient to have prevented response to the primary vaccination.

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