Australian Government
Department of Health

ATAGI
Australian Technical Advisory Group on Immunisation

Recommendations on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised

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What has changed:

- *People aged 18 years or older who received a 3-dose primary course due to severe immunocompromise are now recommended to receive a booster (4th) dose ≥ 4 months after their 3rd dose.*
- *Recommendations for children aged 5 to 11 years will be made in due course.*

These recommendations have been prepared in consultation with the Australasian Society of Clinical Immunology and Allergy (ASCIA).

Recommendations

- ATAGI recommends a 3rd primary dose of COVID-19 vaccine in severely immunocompromised populations to address the risk of suboptimal or non-response to the standard 2 dose schedule.
  - The 3rd dose is intended to maximise the level of immune response to as close as possible to the general population.
  - For people who have had a single dose for their primary course (e.g. COVID-19 Vaccine Janssen), this advice would apply to a 2nd primary dose.
- People aged 18 years and over with severe immunocompromise who have received 3 doses of a COVID-19 vaccine are recommended to receive a booster (i.e. 4th dose) at 4 months, in line with the timing for the general population. This is expected to improve protection against symptomatic infection, serious illness or death from COVID-19 caused by the Omicron variant.
- ATAGI recommends that all individuals aged 12 years and over with certain conditions or on therapies leading to severe immunocompromise, as defined in **Box 1**, receive a 3rd primary dose of a COVID-19 vaccine.
- An mRNA vaccine (Pfizer or Moderna) is preferred to Vaxzevria (AstraZeneca) for this 3rd dose. AstraZeneca can be used for the 3rd dose for individuals who have received AstraZeneca for their first 2 doses if there are no contraindications or precautions for use, or if a significant adverse reaction has occurred after a previous mRNA vaccine dose which contraindicates further doses of mRNA vaccine (e.g. anaphylaxis, myocarditis).
- The recommended interval for the 3rd dose is 2 to 6 months after the 2nd dose of vaccine.
  - A minimum interval of 4 weeks may be considered in exceptional circumstances (e.g. anticipated intensification of immunosuppression; outbreaks).
  - People who have received a 2nd dose more than 6 months ago should receive a 3rd dose as soon as feasible.
- An individual with an unlisted condition should only be considered for a 3rd dose where the treating physician has assessed the patient as having a similar level of severe immunocompromise to the listed conditions in **Box 1,** and where the benefits of a 3rd dose of COVID-19 vaccine outweigh the risks.
- Individuals who currently are not severely immunocompromised but who will commence significant immunosuppressive therapy ≥2 weeks after their 2nd dose do not require a 3rd dose, as it can be expected that an adequate response to 2 primary doses will be achieved.

- People with functional or anatomical asplenia do not require a 3rd primary dose.
- Antibody testing is not recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination, including in immunocompromised individuals after a 2nd or 3rd dose. There are no serological assays that provide a definitive correlate of immunity to SARS-CoV-2.
- Protection from 3 primary doses with or without a booster dose in severely immunocompromised individuals may still be lower than the general population. Risk mitigation strategies such as mask wearing and social distancing should continue to be used even after receipt of a 3rd dose or 4th dose.
- ATAGI will continue to monitor the evidence around duration of protection in immunocompromised populations to address waning of protection or risk from variants of concern.
- ATAGI will continue to monitor the evidence on COVID-19 vaccination in children aged 5 to 11 years and will advise on the need for 3rd doses in immunocompromised children.
- For more information on boosters see: ATAGI recommendations on the use of a booster dose of COVID-19 vaccine.

Box 1: People with the following immunocompromising conditions and therapies for which a 3rd primary dose is recommended

N.B. This list is not exhaustive. Clinicians may use their judgement for conditions or medications that are not listed and which are associated with severe immunocompromise.

- Active haematological malignancy
- Non-haematological malignancy with current active treatment (e.g., chemotherapy, whole body irradiation)
- Solid organ transplant with immunosuppressive therapy
- Haematopoietic stem cell transplant (HSCT) recipients or chimeric antigen receptor T-cell (CAR-T) therapy within 2 years of transplantation.
    - These patients require *revaccination with 3 additional doses* of COVID-19 vaccine, irrespective of doses given prior to transplantation, commencing generally ≥3-6 months after their transplant after discussion with their treating specialist.
    - Those beyond 2 years from transplant should discuss with their treating specialist about the need for a 3rd dose.
- Immunosuppressive therapies including:
    - High dose corticosteroid treatment equivalent to >20mg/day of prednisone for ≥14 days in a month, or pulse corticosteroid therapy.
    - Multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.
    - Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDS):
        - including mycophenolate, methotrexate (≥10 mg/week), leflunomide, azathioprine (≥ 1mg/kg day), 6-mercaptopurine (≥ 0.5mg/kg/day), alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors (e.g. cyclosporin, tacrolimus).
        - excluding hydroxychloroquine or sulfasalazine when used as monotherapy.
    - Biologic and targeted therapies anticipated to reduce the immune response to COVID-19 vaccine. Refer to Table 1 below for examples. However, clinicians may use their judgement for medications which are not listed.
- Primary immunodeficiency including combined immunodeficiency and syndromes, major antibody deficiency (e.g. common variable immune deficiency (CVID) or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies.
- Advanced or untreated HIV with CD4 counts <250/μL or those with a higher CD4 count unable to be established on effective anti-retroviral therapy.
    - a 3rd primary dose is not required for people living with HIV, receiving ART with CD4 counts ≥250/μL.
- Long term haemodialysis or peritoneal dialysis.

Table 1(a): A 3rd dose is recommended for people taking the following biologics

Class	Examples
Anti-CD20 antibodies	rituximab, obinutuzumab, ocrelizumab, ofatumumab
BTK inhibitors	ibrutinib, acalabrutinib, zanubrutinib
JAK inhibitors	tofacitinib, baricitinib, ruxolitinib
Sphingosine 1-phosphate receptor modulators	fingolimod, siponimod
Anti-CD52 antibodies	Alemtuzumab
Anti-complement antibodies	eculizumab
Anti-thymocyte globulin	anti-thymocyte globulin

Table 1(b): A 3rd primary dose is not recommended for people taking the following biologics*

Class	Examples
Anti-integrins	natalizumab, vedolizumab
Anti-TNF-α antibodies	infliximab, adalimumab, etanercept, golimumab, certolizumab
Anti-IL1 antibodies	anakinra
Anti-IL6 antibodies	Tocilizumab
Anti-IL17 antibodies	secukinumab, ixekizumab
Anti-IL4 antibodies	dupilumab
Anti-IL23 antibodies	ustekinumab
Immune checkpoint inhibitors	nivolumab, pembrolizumab, ipilimumab, atezolizumab

*A 3rd primary dose is recommended for people taking multiple immunosuppressants where the cumulative effect is considered to be severely immunosuppressive.

Rationale for recommendations:

Increased morbidity from SARS-CoV-2 infection in the immunocompromised

People with immunocompromising conditions or therapies have been recognised as being at increased risk of severe outcomes due to COVID-19. As a whole, studies have shown that the immunocompromised population with COVID-19 have a 1.5-2.0 times higher risk of death than the general population.[1-3]

In addition, immunocompromised individuals can have prolonged SARS-CoV-2 infection and viral shedding, which can increase the risk of viral evolution during infection, and the subsequent risk of development of viral variants.[4-10]

Decreased immune response to COVID-19 vaccination

COVID-19 vaccination is highly effective at preventing infection, hospitalisation and death in immunocompetent adults and adolescents. Most studies report seroconversion (development of titres above the antibody assay threshold for a positive response, in a person who was previously seronegative) in close to 100% of healthy vaccinated individuals after the first dose of mRNA vaccine.[11,12] Seroconversion also occurred in >99% of the general population after 2 doses of Vaxzevria (AstraZeneca).[13] However, in immunocompromised individuals, immunogenicity studies have revealed that some groups can have a suboptimal immune response with evidence of reduced antibody levels or SARS-CoV-2-specific T cell responses after a standard 2 dose schedule of COVID-19 vaccines Comirnaty (Pfizer), Spikevax (Moderna) or AstraZeneca.[14-16] In some circumstances, such individuals may have no detectable antibody or T cell response to vaccination (non-responders). While the absence of an established correlate of protection means there is

uncertainty as to what degree this reduces protection against infection, the presence of a neutralising antibody response is thought to be important for prevention of SARS-CoV-2 infection.[17]

Increased breakthrough infections despite vaccination with 2 doses

Severe COVID-19 in fully vaccinated individuals is very uncommon. There have been reports of breakthrough infections with SARS-CoV-2 in some populations of severely immunocompromised individuals such as solid organ transplant recipients who have received a full course of mRNA COVID-19 vaccines, and these individuals have been found to have absent or low antibody titres despite completing their vaccination.[18-20] 44% of vaccinated patients hospitalised due to breakthrough infections in a US study were immunocompromised.[21]

Reduced vaccine effectiveness against confirmed SARS-CoV-2 infection in vaccinated immunocompromised individuals

ATAGI does not currently recommend 3rd doses for people with mild-to-moderate immunocompromising conditions or therapies, or for immunocompetent people, based on data showing high vaccine effectiveness. Two doses remain highly protective against severe disease/hospitalisation in the general population (≥93% vaccine effectiveness). Protection has remained high even during the period of delta variant predominance, with little waning against hospitalisation up to 6 months after vaccination.[22-25]

It should also be noted that in spite of concerns about immunogenicity in the immunocompromised population, early vaccine effectiveness studies largely show reassuring vaccine effectiveness against SARS-CoV-2 infection (52%-90%), albeit slightly lower as compared with the general population.[26-30] These analyses have mostly involved broad immunocompromised populations defined using administrative data, meaning that the specific types of immunocompromising conditions in individuals are not clear or clinically validated. As such, they have limited capacity to identify more severely immunocompromised groups who may have poorer protection from the standard two dose schedule of vaccination. Results from limited vaccine effectiveness studies are becoming available as preprint articles (yet to be peer-reviewed) or brief communications, which examined specific conditions such as inflammatory bowel disease,[31] kidney transplant[32] and solid organ transplants.[33] These have also suggested good protection overall, with estimates of effectiveness of 2 doses up to 74% in kidney transplant recipients[32] and 81% incidence rate reduction for infection compared with unvaccinated patients in solid organ transplant recipients.[33] Both these populations had been shown to have some of the largest reductions in vaccine response in immunogenicity studies compared with the general population.

Maximising protection against COVID-19 from vaccination for the immunocompromised

ATAGI recognises that a substantial proportion of vaccinated individuals among some groups with severe immunocompromise show no immune response or a suboptimal response to COVID-19 vaccine, and that this is likely to place them at ongoing increased risk of SARS-CoV-2 infection despite vaccination. ATAGI considers it important to offer a third primary dose to provide a higher level of protection for these individuals, aiming to attain a level as close as possible to that seen in healthy individuals. Provision of a 3rd dose to severely immunocompromised individuals does not guarantee equivalent protection to immunocompetent individuals, therefore ongoing risk mitigation measures are warranted.

Immunocompromised populations recommended for a 3rd primary dose of COVID-19 vaccine

ATAGI has identified the following immunocompromised groups who would potentially benefit from a 3rd primary dose of COVID-19 vaccine.

1. *Active haematological malignancy*

Patients with haematological malignancy have lower seroconversion rates (approximately 39-85%) after mRNA vaccines compared with patients with solid tumours and healthy controls.[34-39] The lowest rates of seropositivity were in those with the most common B cell malignancies (44-79%). Seronegativity was reported in almost all patients with non-Hodgkin lymphoma, and in a significant proportion of those with mantle cell lymphoma (56%), marginal zone lymphoma (38%), chronic lymphocytic leukaemia (36%), Waldenstrom's macroglobulinaemia (26%), follicular lymphoma (22%) and diffuse large B cell lymphoma (21%).[35]

The impaired vaccine response may be related to treatments for these malignancies which include anti-B cell therapies and cytotoxic chemotherapy, both therapies associated with lower rates of seroconversion and lower antibody titres.[40] However, impaired vaccine response was also seen in some patients who had received no treatment for 2 years, suggesting reduced responses are also due to underlying disease.[35]

2. *Non-haematological malignancy with current active treatment (e.g. chemotherapy, whole body irradiation), but excluding immunotherapy with immune checkpoint inhibitors*

Patients with solid cancer who are on cytotoxic chemotherapy have been shown to have lower response to vaccines and antibody titres. Estimates of seroconversion range from 81-98%.[15,34,40-46] Radiotherapy was associated with failure of vaccine response.[15] Chemotherapy was a predictor of poorer response to vaccination with 14% of patients being non-responders.[45] Antibody titres in chemotherapy patients are significantly lower than in the healthy population.[46]

Immunotherapy with immune checkpoint inhibitors (ICI) are not expected to cause significant immunosuppression. Patients on ICIs have shown variable vaccine responses, some studies showing impairment[47] while others showing preserved responses.[48] ATAGI does not currently recommend a 3rd dose for individuals treated only with ICIs but will continue to monitor future evidence.

3. *Solid organ transplant with immunosuppressive therapy*

Solid organ transplant recipients require long term immunosuppression and show reduced vaccine responses.[14,15,38,49-51] Estimates of seroconversion for mRNA vaccines in these studies have ranged from 18% to 66%. In one study, the seroconversion rate after AstraZeneca was 44% in kidney transplant patients.[51] Immunosuppression regimens including corticosteroids, mycophenolate or triple agents (calcineurin inhibitor, mycophenolate and corticosteroids) were associated with increased rates of non-response to vaccination.[52] Reports of documented breakthrough infections with SARS-CoV-2 in this population have been associated with low or undetectable antibody titres after two doses in individuals after vaccination.[18-20]

4. *Haematopoietic stem cell transplant (HSCT) recipients or chimeric antigen receptor T-cell (CAR-T) therapy*

HSCT recipients had seroconversion rates after Pfizer ranging from 75 to 88% after 2 doses.[16,38,53,54] Shorter time since transplantation, lower levels of CD19 B cells, and use of immunosuppressants were associated with lower vaccine response.[53-55] CAR T cell therapy was also associated with a low seroconversion rate (0-36%).[35,38,40,53]

As protective immunity to vaccine-preventable diseases is partially or completely lost after an allogeneic or autologous HSCT[56] or CAR-T cell therapy these patients require **re-vaccination with 3 additional doses of COVID-19 vaccine** after their transplant, even if they were vaccinated prior to transplantation. Response to vaccines can be poor during the first 6 months after HSCT;[56] therefore, vaccination is usually advised to commence from 3-6 months after transplantation. The optimal time to commence vaccination should be guided by the treating specialist who is best placed to assess the degree of immune reconstitution. The schedule for vaccination should follow recommended dosing intervals for the chosen vaccine for 1st and 2nd doses (i.e. 3-6 weeks for Pfizer, 4-6 weeks for Moderna and 4-12 weeks for AstraZeneca, with the 3rd dose given 2-6 months after the 2nd dose.

5. *Immunosuppressive therapies including:*

    a. **High dose corticosteroid treatment equivalent to >20mg/day of prednisone for ≥14 days in a month or treatment with pulse corticosteroid therapy**

A meta-analysis of 8 studies of corticosteroid treatment in immune mediated inflammatory diseases showed a pooled seroconversion rate of 78%.[57] Corticosteroid treatment has been shown to also be an independent predictor of negative serology in other populations including kidney transplant recipients[52] and haematological cancers.[39]

    b. **Selected conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) excluding hydroxychloroquine or sulfasalazine when used as monotherapy**

Conventional synthetic DMARDs that have been shown to reduce vaccine response to 2 doses of mRNA vaccine include mycophenolate mofetil,[38,50,57] leflunomide,[57] and methotrexate.[57] Based on expert advice and vaccine responses with other vaccines, antimetabolite agents[15,49] such as azathioprine/6-mercaptopurine, alkylating agents (e.g. cyclophosphamide, chlorambucil), and systemic calcineurin inhibitors[58] also warrant a 3rd dose of vaccine.

Vaccine responses are expected to be minimally affected with hydroxychloroquine and sulfasalazine and therefore these patients are not recommended for an additional 3rd dose of vaccine.[57,59]

    c. **Biologic and targeted therapies including B-cell depleting agents (e.g. anti-CD20 monoclonal antibodies, BTK inhibitors), JAK inhibitors, S1P antagonists, anti-CD52 monoclonal antibodies (alemtuzumab), anti-complement antibodies (e.g., eculizumab), anti-thymocyte globulin (ATG) and abatacept, but excluding those with minimal effect on vaccine response such as immune checkpoint inhibitors, anti-integrins, anti-tumour necrosis factor, anti-IL1, anti-IL6, anti-IL17, anti-IL-4, and anti-IL23 antibodies.**

Numerous biologic therapies have the potential to impair the immune response to COVID-19 vaccination. Studies have demonstrated that patients treated with B cell depleting therapies (e.g. anti-CD20 therapy and BTK inhibitors) often have an absent or reduced response to the vaccine and low levels of antibodies.[14,35,38,40,60-62] In a pooled analysis of 8 studies, only 39% of patients on anti-CD20 treatment developed antibodies.[57] Fingolimod also has a poor vaccine response due to decreased peripheral lymphocytes.[62] Low levels of circulating naïve B cells which result from therapy have been associated with a poor vaccine response.[63]

A meta-analysis[57] found that seroconversion can also substantially impaired with the use of JAK inhibitors and abatacept (CTLA4 analog). The evidence about immune checkpoint inhibitors has been detailed above.

People taking anti-integrins, anti-tumour necrosis factor, anti-IL1, anti-IL6, anti-IL17 or anti-IL23 antibodies generally have similar vaccine responses to that seen in the general population.[57] However, combination therapy with multiple biologic therapies may have additive effects.[57,64] If the additive effects are considered to produce severe immunosuppression, a 3rd dose is recommended.

6. *Primary immunodeficiency including combined immunodeficiency and syndromes; major antibody deficiency (e.g. common variable immune deficiency (CVID) or agammaglobulinemia), defects of innate immunity (including phagocytic cells), defects of immune regulation, complement deficiencies and phenocopies of primary immunodeficiencies.*

Individuals with these causes of primary immunodeficiency are likely to have significantly impaired immunity which would require a 3rd primary dose of vaccine. Estimates of serological response to 2 doses of vaccine in individuals with primary immunodeficiency range from 0% to 93%.[38,63,65,66] Responses are particularly decreased with X-linked agammaglobulinemia due to absence of mature B cells.[38,65,66]

Individuals unlikely to have a significant level of immune impairment requiring a 3rd dose of vaccine include IgA deficiencies, IgG subclass deficiency, specific antibody deficiency with normal immunoglobulins and mannose-binding lectin deficiency.

7. Advanced or untreated HIV with CD4 counts <250/μL or those with a higher CD4 count unable to be established on effective antiretroviral therapy

People living with HIV who are well controlled (on anti-retroviral therapy with CD4 counts ≥250 and low or undetectable viral load) do not require a 3rd primary dose as they have been shown to have similar immune responses after 2 doses compared with HIV negative individuals, in studies of Pfizer,[67-69] Moderna[70] and AstraZeneca.[71,72] Both the proportion who seroconvert and the titre of antibodies produced appear similar in well controlled HIV positive and HIV negative patients. T cell responses were also similar.[68,71]

One preprint study showed that people with HIV who have CD4 counts <250 had significantly lower immunogenicity than those with HIV and higher CD4 counts and HIV negative controls.[70] People with HIV with CD4 counts >250 had similar responses to controls.

ATAGI therefore recommends a 3rd dose in those with HIV who have CD4 counts <250 or those with higher counts who are not established on ART.

8. Long term haemodialysis or peritoneal dialysis

Patients on dialysis have reduced seroconversion to vaccination; this is more significant for individuals with a previous transplant[73], those on concurrent immunosuppressive medication[16,73] and those on haemodialysis compared with peritoneal dialysis.[58] Estimates of seroconversion range from 80% to 97% for 2 doses of AstraZeneca or mRNA vaccines.[58,73-75] However, antibody titres were substantially reduced compared with healthy controls[58] and lower antibody titres were associated with decreased durability of the antibody response.[76] Despite 2 doses of mRNA vaccine, 11% of fully vaccinated haemodialysis patients in a national registry study died after acquiring COVID.[77]

In addition, dialysis patients often require frequent visits to hospital or other healthcare facilities. Suboptimal protection from vaccination may increase the risk of these patients acquiring the infection and inadvertently introducing the infection into these facilities.

Evidence of immune responses to a 3rd dose of vaccine.

An increasing number of studies[77-90] demonstrate that a 3rd dose of COVID-19 vaccine, administered one or more months after the initial 2 doses, can improve antibody levels and T cell responses in immunocompromised individuals (solid organ transplant / kidney transplant recipients, haemodialysis patients, lymphoid malignancies, autoimmune disorders) with suboptimal responses to 2 doses. Moreover, these studies demonstrate that a 3rd dose can seroconvert some individuals who are seronegative (non-responders) to 2 doses. Almost all studies involved primary schedules and 3rd doses using mRNA vaccines. A few studies[79,81,89,90] provide data on mixed (heterologous) schedules where a different vaccine was used between the 3rd dose and the first 2 primary doses. These studies have used AstraZeneca, Pfizer/Moderna or Ad26.COV2.S vaccine (Johnson & Johnson/Janssen) as 3rd doses after Pfizer/Moderna or Ad26.COV2.S vaccine for 1st and 2nd doses. It is noted that no published studies that used Pfizer/Moderna as a 3rd dose after a primary schedule of AstraZeneca have been identified.

Almost all studies showed that between 32% and 50% of patients, who were seronegative after 2 primary doses, responded and developed antibodies after the 3rd dose. Vaccinated individuals with a low but positive antibody titre after the 2nd dose of vaccine generally had a substantial boost in antibody levels with the 3rd dose.

Serology is not currently recommended before or after 3rd doses as variation in assays and a lack of an accepted correlate of protection make interpretation difficult.

There are no data to support the use of any additional primary doses of COVID-19 vaccine after a 3rd primary dose. Patients who do not respond to 3rd doses may not respond to subsequent doses. However, due to the current outbreak with the Omicron variant of concern, ATAGI recommends that immunocompromised individuals who have received 3 primary doses of a COVID-19 vaccine have a booster dose at 4 months, in line with the timing for the general population.

As response after a 3rd dose may still be lower than the general population, risk mitigation strategies including mask wearing and social distancing should continue to be employed by immunocompromised individuals.

Safety of 3rd primary doses appears similar to 1st and 2nd doses

The profile of adverse events after the 3rd dose[77-81,83,84,86-88,90] is similar to that of preceding doses, and studies have not reported vaccine-related serious adverse events. However, these studies were conducted in small numbers of patients, and rare side effects may not have been detected. There are currently no data on safety of 3rd doses of vaccine in relation to the risk of myocarditis after mRNA vaccines, or thrombosis and thrombocytopenia syndrome (TTS) after AstraZeneca. ATAGI will continue to monitor the evidence around safety of additional doses of COVID-19 vaccine.

Considerations for recommendations regarding the timing of 3rd doses

ATAGI recommends that a 3rd dose of COVID-19 vaccine be administered to eligible immunocompromised individuals 2 – 6 months after the 2nd dose. In exceptional circumstances where more rapid protection is required (e.g. an outbreak setting or a significant increase in immunosuppression such as a patient on chronic immunosuppressive therapy requiring the urgent addition of an additional immunosuppressive agent), ATAGI considers a minimum interval of 4 weeks between the 2nd and 3rd dose to be acceptable. It is thought to take at least 2 weeks to generate an adequate immune response to the vaccine, therefore ideally vaccination should occur at least 2 weeks prior to the addition of a new immunosuppressive agent, where relevant.

It has been recognised that longer intervals between 1st and 2nd vaccine doses lead to improvement of peak antibody levels and/or efficacy for Pfizer[91,92] and AstraZeneca. [93] A longer interval between 2nd and 3rd doses may have a similar benefit. However, this improved vaccine response needs to be weighed against the possibility that protection against COVID-19 from 2 doses could remain suboptimal until a 3rd dose is administered.

Vaccine choice for 3rd doses

ATAGI recommends that:

- Pfizer or Moderna be preferentially administered for the 3rd primary dose.
- Where individuals have received 1st and 2nd doses of AstraZeneca, it is acceptable for AstraZeneca to be used for the 3rd dose if there are no contraindications or precautions for receiving AstraZeneca since the last dose.
- Where individuals have received 2nd doses of Pfizer or Moderna and further doses are contraindicated (e.g. anaphylaxis, myocarditis secondary to an mRNA vaccine), an alternative brand (e.g. AstraZeneca) should be considered. The benefits of improved protection with AstraZeneca need to be balanced against the very small risk of adverse events such as thrombosis and thrombocytopaenia syndrome and the epidemiological context (e.g. risk of COVID-19 exposure). See also the ATAGI clinical guidance on COVID-19 vaccine for further information on mixed (heterologous) schedules.

ATAGI acknowledges that Pfizer and Moderna product information sheets have been updated to allow for a 3rd dose in certain circumstances including for individuals that are severely immunocompromised. For AstraZeneca ATAGI notes that the recommendation to administer a 3rd dose is a variation from the product information currently available and that the booster dose is currently under evaluation by the TGA.

These recommendations are based on the fact that most studies of 3rd doses of COVID-19 vaccine in immunocompromised individuals have involved the use of mRNA vaccines for all doses. There are currently no studies in immunocompromised populations to directly inform the use of a 3rd dose of vaccine after 1st and 2nd doses of AstraZeneca. Limited studies of a 3rd dose after mRNA 1st and 2nd doses using a homologous mRNA vaccine vs a heterologous dose of AstraZeneca have not been designed to assess differences between types of 3rd dose vaccines but appear to demonstrate similar boost responses with either homologous (same 3rd dose vaccine) or heterologous (different 3rd dose vaccine) dosing.[79,89]

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