Memo

Update on Intervals and Booster Eligibility: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	10 February 2023
To:	Dr Diana Sarfati, Director-General of Health | Te Tumu Whakarae mō te Hauora
Copy to:	Dr Andrew Old, Deputy Director-General, Public Health Agency | Te Pou Hauora Tūmatanui Dr Nick Chamberlain, National Director, National Public Health Service, Te Whatu Ora Dr Nicholas Jones, Director of Public Health, Public Health Agency | Te Pou Hauora Tūmatanui Astrid Koornneef, Director, National Immunisation Programme, Te Whatu Ora Alison Cossar, Manager, Public Health Policy & Regulation, Public Health Agency | Te Pou Hauora Tūmatanui Andrew Oliver, Senior Therapeutics Group Manager, Pharmac Louise Karageorge, Group Manager, Intelligence Knowledge and Surveillance, Public Health Agency | Te Pou Hauora Tūmatanui
From:	Dr Ian Town, Chief Science Advisor
For your:	Information

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) recommendations regarding:
    a. the duration of intervals between COVID-19 vaccine doses
    b. expansion of eligibility for second/additional booster doses

Background and context

2. Following a peak of COVID-19 cases at the end of 2022, case rates and hospitalisations in Aotearoa New Zealand have been decreasing. (1)
3. Due to the emergence of more immune-evasive COVID-19 variants, such as BQ.1.1, and concerns about the antibody levels elicited by vaccines reducing over time, there is interest

in extending eligibility for second or additional booster doses. This is to ensure that people continue to have adequate protection against COVID-19, especially heading into the winter months, when a heightened demand for healthcare services is expected.

4. As part of the COVID-19 response, the government has made it a priority for Pharmac to secure access to the BA.4/5 vaccines, which target the Wild Type (WT) and BA.4/5 variants (the Pfizer BA.4/5 bivalent vaccine). 357,000 doses of the Pfizer BA.4/5 bivalent vaccine were delivered on 30 January 2023 with the remaining Quarter 1 supply (348,600 doses) to be delivered by 31 March 2023 and another 1,042,000 million doses to be delivered by 30 June 2023 (a total of 1.7 million doses of BA.4/5 bivalent vaccine doses available)
5. On 21 December 2022, Medsafe granted provisional approval of the Pfizer BA.4/5 bivalent vaccine on the following approved indication: "A booster dose for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 12 years of age and older who have previously received at least a primary vaccination course against COVID-19".
6. On 2 February 2023, CV TAG reiterated previous advice that the Pfizer monovalent (original WT formulation) vaccine be superseded by the Pfizer BA.4/5 bivalent vaccine for all booster doses.
7. Pfizer's BA.4/5 bivalent vaccine is manufactured as a multi-dose vial that does not require dilution and contains six doses of vaccine.
8. The Director-General has requested a review of the existing data and research on the amount of time that people should wait before getting their next dose of the COVID-19 vaccine. This review is to also consider increasing the eligibility criteria for second/additional boosters.

Previous advice on intervals and booster eligibility

9. On 1 February 2022, CV TAG recommended that the **first booster dose** of the COVID-19 vaccine should be given **from 3 months** after the primary course to all eligible people aged 18 years and over, including immunocompromised individuals and pregnant people.
10. On 22 June 2022, CV TAG recommended a **second booster** for people aged 65 years and over, Māori and Pacific peoples aged 50 years and over, residents of aged care facilities or disability care facilities aged 16 years and over as well as severely immunocompromised people aged 12 years and over who were eligible for and received a three-dose primary course. Additionally:
    a. CV TAG noted that COVID-19 vaccines have consistently been found to be effective in pregnancy and reduce the chance of severe illness, ICU admission and death from COVID-19 illness. (2) However, a second booster was only recommended for pregnant people who fall within the eligibility criteria detailed above.
    b. CVTAG recommended that the second booster dose should be offered from six months after a first booster dose; however, **consideration** should be given to **aligning** the rollout of second boosters with the **influenza immunisation**

programme. CV TAG recommended an interval of greater than or equal to four months for this purpose. They also recommended consideration be given to bringing the age eligibility for the funded influenza vaccine down to align with the age ranges recommended for the COVID-19 second booster vaccines.

c. A second booster dose, if due, should be postponed for three months after SARS-CoV-2 infection. Clinical discretion could be applied when considering vaccination prior to 3 months after infection. This may be appropriate for individuals considered to be at high risk of severe disease from COVID-19 re-infection.

11. On 23 June 2022, the Director-General further authorised (under section 34A of the Medicines Act 1981), the expansion of eligibility for a second booster dose to people aged 50 years and older, and to healthcare workers over the age of 30 years.
    a. The expansion to those over 50 years of age was advised since people without pre-existing conditions between the ages of 50 to 64 years may also be at similar risk to those in the priority groups.
    b. Expansion to health care, aged care and disability workers aged over 30 years was advised because health care workers experience higher infection rates than other monitored occupational groups and the additional dose could provide further protection to individuals, as well as help to preserve health service delivery during a high demand period.
12. On 10 August 2022, CV TAG recommended lowering the age eligibility criteria for second boosters among Māori and Pacific peoples to 40 years because of a higher risk of severe disease from COVID-19. CV TAG did not support making a second booster dose available to otherwise healthy adults aged less than 50 years as at that stage it was unclear whether the benefits outweighed the risks in this population.
13. On 1 November 2022, CV TAG confirmed previous advice to lower the age eligibility criteria for second boosters among Māori and Pacific peoples to 40 years. Updated data showed clear heightened risk of severe outcomes from COVID-19 for this cohort. Expanded eligibility for second boosters in this cohort took effect on 18 November 2022. For people with multiple co-morbidities who were already eligible to receive a second booster, accessibility would be improved by removing the need for prescription.
14. Current booster vaccination guidelines cover first and second booster doses only and do not encompass the minimum time that individuals should wait before receiving further booster doses in the future.

Evidence informing the updated advice in this document

The following is a summary of the collated evidence on the duration of intervals between COVID-19 vaccinations; a more detailed version is available in Appendix 1.

New Zealand context

Vaccine uptake and SARS-CoV-2 infections

15. Aotearoa New Zealand's epidemiological landscape is characterised by relatively high levels of hybrid immunity among the population along with increasing numbers of SARS-CoV-2 subvariants with greater immune escape.

16. Hybrid immunity refers to protection provided to a person as a result of both COVID-19 vaccination and COVID-19 infection. As at 23 January 2023, 2.2 million infections have been reported in Aotearoa New Zealand. Furthermore, over 90% of people aged 12 years and over have completed a primary course of vaccination, with 73% of eligible people aged 18 years and older having received at least one booster, resulting in high levels of hybrid immunity due to high rates of vaccination and high rates of infection from Omicron waves. (3, 4)

17. The number of SARS-CoV-2 subvariants that have a growth advantage over BA.5 continues to evolve with CH.1.1. (52.2%) slightly accounting for more than half of genomically sequenced wastewater samples in Aotearoa New Zealand. This is followed by BA.2.75 (31.9%) and BQ.1.1. (9.1%) as at 29 January 2023. (5) While transmission advantage can lead to an increase in COVID-19 cases, there is currently no evidence of an increase in severity of disease caused by these variants. (6, 7)

18. As of 26 January 2023, approximately 94% of 35- to 49-year-olds and 79% of 50- to 64-year-olds received their first or second booster dose over 6 months ago, compared to 67% of those aged over 65. The proportion of individuals aged 35-49 years who have not received a booster shot beyond 6 months was 94% for Māori, 94% for Pacific peoples, and 97% for European and Others. In the age group of 50-64 years, the corresponding rate was 82% for Māori, 82% for Pacific peoples, and 83% for European and Others.

19. Approximately, 20% of 35- to 49-year-olds and 21% of 50- to 64-year-olds have received their last booster dose more than a year ago. (8)

Hospitalisation and deaths

20. Prevention of severe outcomes/death from COVID-19 remains a key priority. Previous analysis of hospitalisation and mortality data found a low risk of adverse outcomes for those under the age of 50 (with the exception of Māori and Pacific peoples aged 40-49, and individuals with co-morbidities) - *detailed in CV TAG memo: Extending Second Booster Eligibility to Māori and Pacific Peoples aged 40 to 49 years*.

21. Hospitalisation admissions in the third and fourth Quarter of 2022 were consistently higher among Māori and Pacific peoples aged 20 years and over in all age groups compared to Asian, European and Other ethnicities (see Table 1). Mortality risk for people aged 59 years and younger was 2.0 (95% CI 1.2–3.3) times higher for Māori and 1.8 (95% CI 1.0–3.5) times higher for Pacific people compared to European and Other groups after adjusting for sex, ages, ethnicity, comorbidity and vaccination status. (9)

Table 1: Hospitalisation admission rates per 100, 000 of population in Q3 & Q4 2022* (Source: Intel & Analytics, MoH, 2023)*

		Māori		**Pacific**		**Asian**		**European / Other**		**Total**

Age	[redacted]	Rate; 95% CI	[redacted]	Rate; 95% CI	[redacted]	Rate; 95% CI	[redacted]	Rate; 95% CI	N	Rate; 95% CI
0–9		41.3; 32.4–52.8		58.7; 42.3–81.3		63.7; 50.7–80		48.7; 41.2–57.6	310	50.7; 45.3–56.6
10–19		16.6; 11.3–24.4		25.7; 16.2–40.7		12.7; 7.2–22.4		22.6; 18.2–28.2	136	20.2; 17.1–23.9
20–29		44; 34.1–56.8		50.1; 36.5–68.9		33.4; 25–44.8		40.1; 34.3–47	296	40.6; 36.3–45.5
30–39		60.5; 47.5–77.2		80; 60.4–105.8		31.4; 24.5–40.2		48.9; 42.6–56.1	379	48.4; 43.8–53.6
40–49		109; 89.1–133.4		129.3; 101–165.5		45.5; 35.1–58.8		55.8; 48.9–63.6	436	66.2; 60.3–72.7
50–59		188.1; 160.9–219.8		235.7; 193.6–287		82.2; 64.8–104.3		100.7; 92–110.3	789	117.9; 109.9–126.4
60–69		422.9; 374.2–478		401.7; 333.6–483.6		155.8; 128.2–189.4		213.5; 200.1–227.8	1377	237.8; 225.6–250.7
70–79		773.3; 674.4–886.5		971.5; 822.8–1146.8		418.4; 353.3–495.4		496; 472.2–521	2060	525.5; 503.4–548.7
80–89		1476.5; 1230.3–1771.1		1649.3; 1319.2–2060.3		1080.1; 906.5–1286.6		1262; 1207.5–1318.9	2262	1269.6; 1218.6–1322.6
90+		1430; 848.7–2399.9		1863.4; 1061.2–3252		1393.9; 928–2088.9		1936.1; 1803.2–2078.5	795	1901.7; 1775.1–2037.1

* Excluding hospital admissions lasting less than 6 hours

22. Implementation of additional boosters is likely to prevent a certain number of severe outcomes and deaths, however, it needs to be balanced against the risk of rare but serious adverse events such as myocarditis/pericarditis, as well as the probability of vaccine fatigue with uptake being poorer after each subsequent dose recommended. Thus, CV TAG's previous guidance on booster rollouts (June 2022) included consideration for alignment with the winter influenza campaigns.

Vaccine effectiveness and duration of protection

23. Neutralising antibody titres elicited by COVID-19 vaccines appear to decrease over time, although this is only one aspect of long-term immunity. Evidence indicates a decrease in antibody titres occurs more rapidly for those who are elderly, and for some people with health conditions that impair their immune response to the vaccine. (10-13) This may highlight a need for more frequent vaccination in these groups.

24. Data on the duration of vaccine effectiveness against severe disease/death suggests protection substantially decreases after 5-6 months from an individual's last dose of vaccine. (14, 15)

Hybrid immunity

25. Evidence suggests that a combination of COVID-19 vaccination and SARS-CoV-2 infection, also known as hybrid immunity, increases mucosal antibody levels and broadens the immune response. Hybrid immunity confers a greater level of protection against both infection and severe disease than either vaccination or prior infection alone and may potentially prevent infection and reduce transmission. (16, 17)

26. While confered protection against infection decreases rapidly, protection against hospitalisation and severe disease remains high. There is limited data on the duration of protection from hybrid immunity. **However, a systematic review suggests that hybrid immunity had high effectiveness against severe COVID-19 related outcomes beyond six months.** (18) It should be noted that this review only includes data published before mid-2022. It is also worth considering the implications of hybrid immunity for New Zealand, where the number of individuals who may have had asymptomatic infections is unknown. A seroprevalence survey could provide some insights in this regard.

Safety

27. The impact of interval length between mRNA booster doses on safety is largely unknown. However, some evidence suggests that longer intervals (> 8 weeks) between a first and second booster dose are associated with a decreased risk of myocarditis in those aged 12 or older. Myocarditis risk from mRNA vaccination is highest in young adults, particularly males(19, 20)

28. There are no data on the safety of further booster doses beyond second boosters. Safety data is inferred from first and second boosters and generally show a favourable and similar safety/side effect profile with more adverse events being reported in younger participants. Adolescent males and young adult males have the highest risk of myocarditis and pericarditis. (21)

29. The National Immunisation Programme (Vaccine Safety, Surveillance and Research) has provided information on myocarditis and pericarditis (reported separately) after COVID-19 vaccination and infection in Aotearoa. The data show risk of **pericarditis** following the second dose of Pfizer's monovalent vaccine was most increased for people aged 5 to 19 years (compared to baseline risk in the same age group). (22) The incidence rate ratio for **myocarditis** in this age group could not be calculated due to low numbers of cases. The data did not show a distinctly greater increase in risk after a second dose compared to baseline among males than it did for females. This was a self-controlled case-study on people aged 5 years and over from February 2021 and February 2022. (22) These results suggest **a longer minimum vaccination interval** (e.g., 12 months, as compared to 6 months) for younger individuals may be warranted.

30. In general, data continue to support the safety profile of BA.4/5 mRNA bivalent vaccines being similar to that of the original formulation monovalent mRNA vaccines. (23, 24)

31. A signal for ischemic stroke following Pfizer bivalent booster vaccination was detected in the US Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink (VSD) database among individuals aged 65 years and over. This signal is being investigated but

has not yet been observed in any other US study/database (including VAERS) or in other countries. (25) The CDC states that no change is recommended in COVID-19 vaccination practice. (25)

32. The CDC presented an update to the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting on 26 January 2023, suggesting that the safety signal for ischemic stroke has weakened since its initial identification. However, it remains statistically significant, and it is unclear what the cause is. The CDC and Food and Drug Administration (FDA) are investigating the possible role of concomitant high-dose or adjuvanted flu vaccination with COVID-19 vaccination. (26)

Peak body recommendations

33. International recommendations on intervals between boosters vary, from as little as two to three months from last dose in US and UK, to six months since last dose or infection in Canada.

34. On 8 February 2023, the Australian Technical Advisory Group on Immunisation (ATAGI) **recommended** people at risk of severe outcomes receive a vaccine booster dose if their last COVID-19 vaccine dose or confirmed infection (whichever is the most recent) was 6 months ago or longer, regardless of the number of prior doses received. This applies for people aged 65 years and over and people aged 18-64 years who have medical comorbidities that increase their risk of severe COVID-19, or disability with significant or complex health needs. (27)

35. ATAGI advises that all people aged 18 – 64 years without risk factors for severe COVID-19 and people aged 5-17 year with medical comorbidities that increase their risk of severe COVID-19, or disability with significant or complex health needs should **consider** a 2023 booster dose, if their last COVID-19 vaccine dose or confirmed infection (whichever is the most recent) was six months ago or longer. This applies regardless of the number of prior doses received, based on an individual risk benefit assessment with their immunisation provider. (27)

36. Administration of a 2023 COVID-19 booster dose should aim to occur prior to June 2023. (27)

37. The UK's National Health Service (NHS) has announced that with the end of its autumn booster campaign on 12 February 2022 it will change booster eligibility criteria for people aged 16 to 49 years. (28) The Joint Committee on Vaccination and Immunisation's (JCVI) recommended a more targeted approach where only people considered to be at risk of serious illness in this age group should be offered a booster dose. (28) Additionally, JCVI advised that there should be another autumn vaccination campaign in 2023, as well as a potential spring campaign for the most vulnerable. (28)

Eligibility and timing of second booster doses

Recommendations

38. CV TAG met on 6 December 2022 and 2 February 2023 to discuss intervals between COVID-19 vaccines and expanding second booster eligibility for people aged 30 years and over.

39. CV TAG noted that:

    a. Emerging evidence suggests that hybrid immunity, offers protection against severe disease from COVID-19 that lasts at least 6 months after their last infection or vaccination. Although the waves of COVID-19 infection in 2020-2022 lack the seasonality seen with other respiratory diseases such as influenza and respiratory syncytial virus (RSV), aligning the campaign with the winter/flu season, as well as whānau based approaches should be considered, including encouraging uptake of both the influenza vaccine and COVID-19 vaccine. This could help simplify communication to encourage uptake, as well as reduce the burden on healthcare systems. Consequently, more efficient use of resources could be achieved, along with a more effective vaccination campaign.

    b. General guidelines could be customised for broad risk categories of the population to account for variations in immune responses to vaccines and infection among population groups. However, multiple schedules can be confusing and challenging to communicate clearly. Simple vaccination eligibility criteria and recommendations will enhance communication with the public.

    c. In Aotearoa New Zealand, a large proportion of individuals are yet to receive their first booster dose, despite also being eligible for a second booster. Coverage of first booster doses is still low among Māori and Pacific peoples (e.g., 40% of Māori aged 30-34 and 47% of Māori aged 35-40 have had a first booster, and 50% and 58% of Pacific peoples in the respective age groups as of 1 February 2023).

    d. Uptake has decreased with every expansion of booster dose eligibility. While primary course uptake in Aotearoa New Zealand is very high at above 90% across all New Zealanders, the first booster rate is lower at 73%. Uptake of second boosters is even lower, with only 47% uptake among those aged 50 years and over. (29)

    e. There is an increased risk of severe morbidity and mortality associated with COVID-19 during pregnancy, especially among symptomatic and unvaccinated pregnant people. (30)

    f. Firm recommendations for additional doses (including a "third booster") beyond the first half of 2023 cannot be made currently due to uncertainty on the future epidemiology of COVID-19 (e.g., seasonality), future variants, and duration of protection against severe disease from hybrid immunity. See Appendix 2 for

Future considerations, including guiding principles for future decisions around additional doses of COVID-19 vaccine.

g. Combination vaccines for COVID-19 and influenza are only in the early stages of clinical trials and are only expected in 2025.

h. Novavax (Nuvaxovid) remains available in the National Immunisation Programme as it has been previously for those who wish to have an alternative vaccine.

40. CV TAG recommends:

a. Improving first booster coverage should be the top priority of the National Immunisation Programme. In particular, the programme should prioritise those who are most at risk of severe disease and severe outcomes (including Māori and Pacific peoples with low first booster uptake).

b. In a pre-winter vaccination programme, the groups **recommended** (i.e., actively encouraged) to receive a second booster dose should be expanded to include those eligible for free influenza vaccine in Aotearoa New Zealand. This is with the exception of the childhood age groups and pregnant people under the age of 30 that are part of free influenza vaccine eligibility. See Appendix 3 for more information.

c. All people aged 30 years and over **should be eligible to receive** a second booster dose (i.e., can consider based on an individual risk benefit discussion with their immunisation provider). This expansion could be aligned with a pre-winter campaign.

d. These second booster doses should be administered **from 6 months** after the previous dose of COVID-19 vaccine, and **from 6 months** after a **SARS-CoV-2 infection,** with flexibility for the dose to be given from 3 months after a SARS-CoV-2 infection. Clinical discretion can be applied when considering vaccination prior to three months after infection for high-risk individuals

e. The benefits of a second booster dose for people under the age of 30 years, who are otherwise healthy, is less certain. People in this group are encouraged to discuss their health needs and risks (e.g., risk of myocarditis or pericarditis) and benefits of a second booster dose with their health care provider.

f. The intervals between doses for Pfizer and Novavax COVID-19 vaccines (including BA.4/5 bivalent vaccines) should be interchangeable and consistent across vaccine schedules to simplify vaccination regimes.

41. Please see Appendix 2 for **Future considerations,** including guiding principles for future decisions around additional doses (including "third boosters") of COVID-19 vaccine.

42. In late February 2023, the Chair and members of CV TAG will meet their Australian counterparts from ATAGI to discuss updates in vaccination programmes and vaccine technologies.

Ian G Town

Dr Ian Town

Chief Science Advisor and

Chair of the COVID-19 Vaccine Technical Advisory Group

In addition to the recommendations provided above, it is recommended that you:

1.	Agree	That this memo (version sent to you on 10 February 2023 by the Chief Science Advisor) will be assessed for proactive release 3 weeks after you sign, below. Release will not occur prior to government decision (and public announcement thereof) on the recommendations that CV TAG have provided in this memo. Prior to release, the memo will undergo processes undertaken for an Official Information Act release, Ministers' Offices will be informed, and the Director General's Office will be required to sign off on the final release.	Yes/No

Director-General Comments:

Signature _____ Date:

Dr Diana Sarfati
Te Tumu Whakarae mō te Hauora
Director-General of Health

References

1. Ministry of Health NZ. COVID-19 Trends and Insights Interactive Dashboard 2023 [Available from: https://minhealthnz2.shinyapps.io/covid19/.
2. World Health Organisation (WHO). Questions and Answers: COVID-19 vaccines and pregnancy 15 Feb 2022 [Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-FAQ-Pregnancy-Vaccines-2022.1.
3. Ministry of Health. EpiSurv Data as at 20 November 2022. 2022.
4. Ministry of Health. National Immunisation Programme COVID-19 Vaccination Data as at 30 November 2022. 2022.
5. ESR. Wastewater Surveillance - Week ending 22 Jan 2023 2023 [Available from: https://poops.nz/.
6. Ministry of Health. COVID-19 variants 2023 [updated 08 July 2022. Available from: https://www.health.govt.nz/covid-19-novel-coronavirus/covid-19-response-planning/covid-19-variants.
7. Ministry of Health. SARS-CoV-2 Variants of Concern Update - 24 January 2023 2023 [Available from: https://www.health.govt.nz/system/files/documents/pages/sars-cov-2-variant-of-concern-update-53-24jan23.pdf.
8. Ministry of Health. National Immunisation Programme. Booster Uptake and Eligbility Data. 2023.
9. Ministry of Health. COVID-19 Mortality in Aotearoa New Zealand: Inequities in Risk 2022 [Available from: https://www.health.govt.nz/publication/covid-19-mortality-aotearoa-new-zealand-inequities-risk.
10. Meyer M, Constancias F, Worth C, Meyer A, Muller M, Boussuge A, et al. Humoral immune response after COVID-19 infection or BNT162b2 vaccine among older adults: evolution over time and protective thresholds 2022 [updated Apr 8PMC8990277]. 2022/04/09:[1-12].
11. Collier DA, Ferreira I, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2 2021 [updated Aug; cited The authors declare no competing interests. PMC8373615]. 20210630:[417-22]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34192737.
12. Kontopoulou K, Ainatzoglou A, Ifantidou A, Nakas CT, Gkounti G, Adamopoulos V, et al. Immunogenicity after the first dose of the BNT162b2 mRNA Covid-19 vaccine: real-world evidence from Greek healthcare workers 2021 [updated Aug; cited The authors declare that there are no conflicts of interest. PMC8513631]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34397348.
13. Tober-Lau P, Schwarz T, Vanshylla K, Hillus D, Gruell H, Group ECS, et al. Long-term immunogenicity of BNT162b2 vaccination in older people and younger health-care workers 2021 [updated Nov; cited VMC is named together with Euroimmun on a patent application filed recently regarding the diagnosis of SARS-CoV-2 by antibody testing (application number EP20158626.0). HG and FKI are named on a patent application regarding neutralising antibodies against SARS-related coronaviruses (application number EP20177354). All other authors declare no competing interests. We thank all study participants at Charite - Universitatsmedizin Berlin for their participation. We also thank the entire staff of the Department for Occupational Medicine, the Charite Clinical Study Center at Charite - Universitatsmedizin Berlin, and the Berlin Institute of Health

(BIH) for their support during the study. SARS-CoV-2 RBD variant antigens were kindly provided by InVivo BioTech Services (Hennigsdorf, Germany) to the Seramun Diagnostica (Heidesee, Germany). Parts of this work were supported by grants from the BIH and Berlin University Alliance. This study was further supported by the German Ministry of Education and Research through Forschungsnetzwerk der Universitatsmedizin zu COVID-19, (COVIM, FKZ: 01KX2021) to LES, FKu, FKI, CD, and VMC; through VARIPath projects (01KI2021) to VMC; and through Deutsche Forschungsgemeinschaft (SFB-TR84) to NS and LES. The study was supported by a donation from Zalando to Charite - Universitatsmedizin Berlin. PMC8528470]. 20211020:[e104-e5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34687656.

14. Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 against infection and COVID-19 hospitalization with SARS-CoV-2 Omicron subvariants: BA.1, BA.2, BA.2.12.1, BA.4, and BA.5 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/10/01/2022.09.30.22280573.full.pdf.

15. Link-Gelles R, Levy ME, Natarajan K, Reese SE, Naleway AL, Grannis SJ, et al. Association between COVID-19 mRNA vaccination and COVID-19 illness and severity during Omicron BA.4 and BA.5 sublineage periods 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/10/05/2022.10.04.22280459.full.pdf.

16. Hansen CH, Friis NU, Bager P, Stegger M, Fonager J, Fomsgaard A, et al. Risk of Reinfection, Vaccine Protection, and Severity of Infection with the BA.5 Omicron Subvariant: A Danish Nation-Wide Population-Based Study 18 July 2022 [Available from: https://ssrn.com/abstract=4165630.

17. Malato J, Ribeiro RM, Fernandes E, Leite PP, Casaca P, Antunes C, et al. Stability of hybrid versus vaccine immunity against BA.5 infection over 8 months: Elsevier; 2023 [Available from: https://doi.org/10.1016/S1473-3099(22)00833-7.

18. Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of prior SARS-CoV-2 infection and hybrid immunity against Omicron infection and severe disease: a systematic review and meta-regression 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/10/24/2022.10.02.22280610.full.pdf.

19. Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S, et al. Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada 2022 [e2218505-e]. Available from: https://doi.org/10.1001/jamanetworkopen.2022.18505.

20. Le Vu S, Bertrand M, Jabagi M-J, Botton J, Weill A, Dray-Spira R, et al. Risk of Myocarditis after Covid-19 mRNA Vaccination: Impact of Booster Dose and Dosing Interval 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/08/01/2022.07.31.22278064.full.pdf.

21. Hviid A, Nieminen TA, Pihlström N, Gunnes N, Dahl J, Karlstad Ø, et al. Booster Vaccination with SARS-CoV-2 mRNA Vaccines and Myocarditis Risk in Adolescents and Young Adults: A Nordic Cohort Study of 8.9 Million Residents 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/12/18/2022.12.16.22283603.full.pdf.

22. Te Whatu Ora. Myocarditis and Pericarditis following Comirnaty (Pfizer-BioNTech) or SARS-CoV-2 infection in Aotearoa New Zealand: A Self-Controlled Case Series Study. 2022.

23. Hause AM, Marquez P, Zhang B, Myers TR, Gee J, Su JR, et al. Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged≥ 12 Years—United States, August 31–October 23, 2022 2022 [1401-6]. Available from: https://pubmed.ncbi.nlm.nih.gov/36634021/.
24. Chalkias S, Whatley J, Eder F, Essink B, Khetan S, Bradley P, et al. Safety and Immunogenicity of Omicron BA.4/BA.5 Bivalent Vaccine Against Covid-19 2022 [Available from: https://www.medrxiv.org/content/medrxiv/early/2022/12/13/2022.12.11.22283166.full.pdf.
25. Centers for Disease Control and Prevention (CDC). CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older 13 Jan 2023 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/bivalent-boosters.html.
26. Shimabukuro TT, Klein, N. COVID-19 mRNA bivalent booster vaccine safety - Vaccines and Related Biological Products Advisory Committee meeting - 26 January 2023 2023 [Available from: https://www.fda.gov/media/164811/download.
27. Department of Health and Aged Care A. ATAGI 2023 booster advice 2023 [Available from: https://www.health.gov.au/news/atagi-2023-booster-advice.
28. National Health Service (NHS). NHS offers more than 400,000 final chances to get boosted 2023 [Available from: https://www.england.nhs.uk/2023/02/nhs-offers-more-than-400000-final-chances-to-get-boosted/.
30. Villar J, Soto Conti CP, Gunier RB, Ariff S, Craik R, Cavoretto PI, et al. Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational, observational study 2023 [updated 2023/01/17/. Available from: https://www.sciencedirect.com/science/article/pii/S0140673622024679.
31. Xie X, Zou J, Fontes-Garfias C, Xia H. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera 2021 [Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7805448/.
32. Health Act 1956. Schedule of notifiable diseases - Updated June 2022 2022 [Available from: https://www.health.govt.nz/system/files/documents/pages/schedule-of-notifiable-diseases-updated-jun22.pdf.

Appendix 1

Request for Advice (RfA)

This form contains the details relevant to the questions posed to the Science and Technical Advisory (STA). STA will respond to the request using this form which will also be stored in STA content management system for future reference.

This form, or parts of it, may also be forwarded to other relevant parties as appropriate.

Title	Time interval between COVID-19 vaccines: 2022/3 update		
Subject	Future Vaccination Strategy		
Reference No.	0596	Date Received	8/11/2022
Requestor	Dr Ian Town	Date Due	6/12/2022
Advisor	Section 9 (2)(g)(ii) [redacted]	Date Completed	Click or tap to enter a date.
Peer reviewed by	Section 9 (2)(g)(ii) [redacted]		
Advice issued to	Director-General		
Approved by	COVID-19 Vaccine Technical Advisory Group (CV TAG)		
Deliverables	Request for Advice (RfA by 6/12/2022) CV TAG Memo issued to the Director-General with an update on recommendations		
Request Outline	**Background/Context:** With New Zealand having had high vaccination rates, as well as a large proportion of the population having been recently infected with SARS-CoV-2, hybrid immunity across the country is relatively high, particularly protection against severe disease. However, the length of protection conferred from hybrid immunity is less known and is likely to wane over time. Concerns of protection waning has been heightened, with increasing subvariants, loosening of public health measures and NZ experiencing another COVID-19 wave. The original Pfizer vaccines were tailored to target the Wild Type strain, and not current, more immune evasive strains. The number of subvariants in NZ that have a growth advantage over BA.5 (e.g., BQ.1.1) have increased. Nationally and internationally, there has been loosening of public health measures, such as removal of mask mandates and vaccination requirements. This has been followed by a recent increase in COVID-19 cases, hospitalisations, and deaths.		

	In response to similar concerns, many countries, particularly those approaching winter in the Northern hemisphere, are considering roll out of third boosters, expansion of second booster eligibility, as well as increasing availability of BA.4/5. In New Zealand, Medsafe is currently processing Pfizer's BA.4/5 COVID-19 vaccine, which will likely be approved and available by early 2023. Medsafe has also recently approved Pfizer's booster for children aged 5-11. This brings into question, how long should New Zealanders wait before getting their next booster, and should recommendations differ for specific groups based on age, health status, last infection, and other risk factors? **Questions:** • What is the recommended minimum interval between a booster dose and the previous dose of COVID-19 vaccine in New Zealand (outside of exceptional circumstances)? • What is the recommended minimum interval after a SARS-CoV-2 infection when a person can receive a dose of COVID-19 vaccine in New Zealand (outside of exceptional circumstances)? • Will these vary by population group (e.g., age, health status)? **Intended application of advice** Currently, there is a need to consider expansion of second boosters, and when at-risk groups might be considered for third boosters. The COVID-19 vaccine Technical Advisory Group (CV TAG) needs to consider the decision to use boosters for children aged 5-11 i.e., should it be rolled out as part of the National Immunisation Programme, and if so, what would be the eligibility criteria? **Timeline** • RfA to go to CV TAG by 6/12/2022 • Followed by CV TAG Memo issued to the Director-General with an update on recommendations (~Week ending 11/12/2022)
What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity?	There are some groups that have been found to be more prone to COVID-19 infection and are at greater risk of having poor health outcomes from COVID-19 infection. For example, Māori and Pacific Peoples aged 40-49 were found to have higher COVID-19 related hospitalisation and mortality, compared to other ethnicities in the same age group. Based on such data, eligibility for second boosters has now expanded to include Māori and Pacific Peoples aged 40+. This review of evidence needs to consider interval recommendations and whether these differ for various sub-groups, based on age, ethnicity (e.g., for Māori/ Pacific

Peoples) and disability/co-morbidity (e.g., those meeting the "severely immunocompromised criteria).

Response to Request for Advice

Key points

- Aotearoa has high levels of hybrid immunity conferred by both high rates of vaccination and high rates of infection from Omicron waves this year. Approximately 2 million infections have been reported in New Zealand (~40% of all population), and over 84% have completed a primary course, with 71% having received at least one booster.
- However, number of SARS-CoV-2 subvariants that have a growth advantage over BA.5 have begun to increase, followed by an increase in COVID-19 cases, hospitalisations, and deaths.
- Eligibility criteria for COVID-19 vaccinations currently vary based on age, ethnicity, health status, risk of exposure, last infection, and type of vaccine (with slight variations between Novavax and Pfizer recommendations). Current booster vaccination guidelines cover first and second booster doses only and do not encompass the minimum time that individuals should wait before receiving further booster doses in the future.
- As of 4 November, approximately 92% of 30- to 49-year-olds and 74% of 50- to 64-year-olds received their first or second booster dose over 6 months ago, compared to 40% of those aged over 65. The median time since last vaccination in the population aged 16 and over ranges between 325 days and 337 days, highlighting that many of the population are approaching one year since their last vaccination against COVID-19.
- Data on waning effectiveness of vaccination against severe disease/death, suggests protection substantially decreases after 5-6 months from an individual's last dose of vaccine. Less is known about the duration of protection from hybrid immunity.
- Neutralising antibody titres appear to decrease over time, although this is only one aspect of long-term immunity. Evidence indicates decreases in antibody titres occur more rapidly for those who are elderly, and for some people with other health conditions that make their immune response to the vaccine lower. This may highlight a need for more regular vaccination schedules in these groups.
- There are no data on the safety of further booster doses beyond second boosters. Safety is inferred from first and second boosters and generally show a favourable and similar safety/side effect profile with more adverse events being reported in younger participants. Male adolescent and young adult males have the highest risk of myocarditis and pericarditis, and therefore a longer minimum vaccination interval for this group may therefore be warranted.

- International recommendations on intervals between boosters vary, from as little as 2-3 months from last dose in US and UK, to 6 months since last dose or infection in Canada.

Background

Context

Aotearoa New Zealand has high levels of hybrid immunity (protection provided to a person by vaccination and infection combined). This is due to a combination of high vaccination rates, and high rates of infection from later variants (i.e., BA.2 and BA.5), as compared to many other countries. Approximately 2 million infections have been reported in New Zealand (~40% of all population), (1) and 84% of the total population have received a primary course, with 71% having received at least one booster dose. (2) The consequent hybrid immunity has meant that New Zealand has high levels of protection against severe disease.

However, concerns have begun to increase with rising number of COVID-19 variants emerging and neutralising antibody titres, a key aspect of long-term immunity, appearing to decrease over time. More variants have begun to emerge in Aotearoa that have a growth advantage over BA.5. For example, BA.2.75 consists of 23% of community cases sequenced, followed by 15% being BQ.1.1 (as at 25 November). COVID-19 vaccines, such as Pfizer's original formulation, were initially designed to target the Wild Type (WT) COVID-19 variant. Although these vaccines are effective against severe disease and death, they have been found to be less effective at preventing infection from Omicron subvariants (as opposed to Delta). Furthermore, there is evidence to suggest vaccine effectiveness (VE) against severe disease/death wanes substantially after 5-6 months, with faster waning observed among older age groups. Less is known about hybrid immunity and the duration of protection it confers.

Since early October 2022, there has been an increase in COVID-19 cases, hospitalisations and now deaths (since November) observed in Aotearoa. The 7-day rolling average of reported case rates was 73.8 per 100,000 population for the week ending 27 November. (3) This was an increase from the previous week, which was 65.6 per 100,000. The proportion of cases that were reinfections has increased, making up 24% of cases. The COVID-19 hospital admissions rate decreased substantially from mid-July but then increased from early October to early November. However, in the week ending 20 November, the 7-day rolling average of hospital admissions was 1.4 per 100,000 population which was similar to the previous week. The rate was highest in the 65+ age group (4.6 per 100,000). As of 27 November, there were 2,158 deaths attributed to COVID-19 in 2022. The weekly number of deaths attributed to COVID-19 declined substantially after peaking early August.

This recent change, along with loosening of public health measures in Aotearoa and internationally (e.g., removal of mask mandates) has raised questions about the availability of additional boosters, particularly for at-risk groups. Several countries, including US and Australia, have expanded eligibility of second boosters, started roll out bivalent boosters, and are also beginning to consider roll out of "third boosters" for at-risk groups. Medsafe is now processing an application for Pfizer's BA.4/5 bivalent booster, which if approved, could be rolled out in early 2023. Medsafe has also recently approved Pfizer's booster for children aged 5-11 in New Zealand.

The Ministry of Health is now reviewing the evidence and recommendations on the minimum time that individuals should wait before getting the next (likely updated) COVID-19 booster.

Current recommendations in NZ

The COVID-19 Vaccine Technical Advisory Group (CV TAG) has issued a series of recommendations on the minimum duration of time between COVID-19 doses:

- In December 2021 CV TAG advised that based on emerging evidence of waning immunity provided by COVID-19 vaccines, and the threat posed by the Omicron variant, the booster dose interval should be reduced from 6 months after the second primary vaccination to 5 months. After further consideration and advice from the Director-General of Health, Cabinet decided to reduce the dose interval to a 4 month (minimum) from second primary dose. In February 2022, CV TAG recommended that a booster dose of Pfizer's COVID-19 vaccine should be given from **three months after the primary course.** This resulted in increased uptake of vaccines by the population, thus enabling Aotearoa to be well protected against the emerging wave.
- In March 2022, CV TAG advised that an interval of **three months after infection** is recommended as it allows for a better immunological response to develop. **Clinical discretion can be applied** when considering **vaccination prior to three months** after infection. This may be appropriate for those individuals considered to be at high risk of severe disease from COVID-19 re-infection.
- In April 2022, CV TAG issued recommendations on second boosters, stating that **for those who were eligible,** the second booster dose should be offered **from six months after a first booster dose.** This recommendation applied to all COVID-19 vaccines currently approved in New Zealand and in use within the National Immunisation Programme (i.e. Comirnaty (Pfizer) and Nuvaxovid (Novavax))**.** All recommendations were subject to the conditions in which they have been approved by Medsafe, and therefore younger age groups could only receive a second booster from a vaccine for which the primary course had already been approved
- In May 2022, CV TAG recommended that Nuvaxovid (Novavax) can be used on prescription as a booster dose if other available COVID-19 vaccines are not considered suitable for that individual. Nuvaxovid can be used as a homologous or heterologous booster dose in those aged 18 years and over and can be given from **six months after the primary vaccine course.** A shorter interval (from **a minimum of three months** after the primary course) could be considered in circumstances **where the risk from SARS-CoV-2 infection is considered to be high** and to outweigh any risk of a shorter interval, or **where a booster is required to meet vaccination requirements** (e.g. for work).
- The following table summarises current eligibility and recommendations on COVID-19 vaccines and intervals:

Table 1: COVID-19 vaccination recommendations from Covid-19 Vaccine Technical Advisory Group:

Ages	Pfizer			Novavax		
	Primary Course (PC)	**Booster**	**2nd booster**	**Primary Course**	**Booster**	**2nd booster**
0-5	Not required[1]	-	-	-		
5-11	Recommended, 8 weeks apart, 2 doses for general population and 3 doses for severely immunocompromised[2]	Medsafe has approved on 29 November 2022.				
12-15		Not required[2]	Not required[2]	Available as alternative to Pfizer, at (2 doses, 3 weeks apart)[3]	Not required	Not required
16-17		Available and recommended for at-risk groups[4], 6 months after primary course	Not required[2,5]			

[1] Available for those whom are severely immunocompromised, or who have complex and/or multiple health conditions which increase the risk of severe disease from COVID-19 (following the Starship Child Health table of underlying comorbidities) . This is to be administered at a schedule in line with the Medsafe datasheet (a three-dose course, with intervals of 3 or more weeks between first and second dose and 8 or more weeks between the second and third dose).

[2] Recommended for those meeting severely immunocompromised criteria outlined here

[3] No prescription if homologous primary course, and prescription needed for a mixed (heterologous) primary course when a different COVID-19 vaccine dose was given previously

[4] Adolescents with underlying Health condition or severe immunocompromise, including those meeting criteria outlined here, Māori and Pacific adolescents and those who are household contacts of persons who are severely immunocompromised

[5] Recommended for residents of age or disability care facility, and those with medical condition or living with disability with significant or complex health needs.

18-29		Recommended, **3 months** after primary Course			Available as alternative to Pfizer**, 6 months** after primary course	
30-39			Available for frontline health care, age care or disability workers, 6 months after 1st booster[2,5]			Available (as alternative to Pfizer) for frontline health care, age care or disability workers, 6 months after 1st booster
40-49			Available for Māori and Pacific Peoples, frontline health care, age care or disability workers, 6 months after 1st booster [2,5]			Available (as alternative to Pfizer) for Māori and Pacific Peoples, frontline health care, age care or disability workers, 6 months after 1st booster
50-64			Available for all, Recommended for Māori and Pacific Peoples, 6 months after 1st booster [2,5]			Available (as alternative to Pfizer) for all, Recommended for Māori and Pacific Peoples, 6 months after 1st booster
65+			Recommended, 6 months after 1st booster [2,5]			Recommended (as alternative to Pfizer), 6 months after 1st booster

Consistent with international recommendations, CV TAG advice on intervals between doses have been specific to "minimum", and not "maximum" intervals. Implementation of third boosters have been discussed informally through the Chair of CV TAG (some details included in Peak body Advice below). Below are key considerations for additional doses, along with intervals between doses, including New Zealand's immunological landscape, duration of vaccine effectiveness, vaccine safety and uptake of vaccines.

Evidence and information

Reduction in Vaccine Effectiveness (VE)

Severe disease (Hospitalisation/Death)

Multiple studies have shown an initial high VE protection from one booster dose (after previously receiving a primary course) of Pfizer's monovalent Wild Type (WT) vaccine against COVID-19 associated hospitalisation. However, this has been found to reduce over time to less than 50% after three to six months across all age groups. (4-7)

Adjusted VE from a second monovalent WT mRNA vaccine booster against BA.4/5 related hospitalisation is estimated to be 60% (95%CI, 42-73%) up to two months after receiving the second booster and 56% (95% CI, 41-46%) after more than two months (median 84 days). (8)

During BA.4/5-dominant period, one booster dose of monovalent WT mRNA vaccines showed VE against hospitalisation or urgent care visit was 68% (95% CI: 50 – 80) at 7-119 days (1 week to 4 months) post-vaccination and 36% (95% CI: 29 – 42 at >120 days i.e. more than 4 months) post-vaccination. A second booster dose restored VE against hospitalisation to 66% (95% CI: 53-75%) at 7-59 days post-vaccination, comparable to the first booster VE. (9) This suggests that reduced VE against severe disease due waning can be restored to prior levels by additional booster doses.

VE against infection

Prevention of infection is not a primary goal of New Zealand's COVID-19 vaccination programme currently. However, this may be a modest, short term side effect of implementing booster doses in the face of an impending wave, to decrease the number of infections (and subsequently interrupt some chains of transmission). This is not a guaranteed effect however, and the effectiveness of this effect will largely depend on the type of vaccine used and circulating variants at the time.

A study showed bivalent Omicron BA.4/5 mRNA vaccines were moderately effective in preventing symptomatic infection. Over the period of September to November 2022 found for those that had received more than 2 doses of the monovalent WT mRNA vaccine, absolute VE against symptomatic SARS-CoV-2 infection ranged from 43% (95% CI: 39-46) in those aged 18-49 years and 28% (95 %CI: 22-23) in 50-64 years to 22% (95% CI: 15-29) in those aged 65 and older. (10) However, it is unclear how durable this protection is, with indication that protection against infection conferred from boosters could last approximately 3 months.

Any evidence on Long COVID outcomes

Currently, there are no studies that have investigated the impact of booster doses on long-covid outcomes. Most studies compare the effect of one or two doses of the primary course of a COVID-19 vaccine to those unvaccinated, on long-covid outcomes.

The effectiveness of vaccination against long COVID is a critical area of research, but significant uncertainties remain. Much of the evidence to date points to a protective effect of vaccination. However,

the lack of randomised controlled trials and predominance of observational studies mean that causality cannot be easily determined (11) and it is difficult to truly know the effect of vaccination.

The effect of vaccination on pre-existing long COVID remains uncertain and contentious, as published studies have generally been small and with self-selected participants. (12) Anecdotal reports and some studies (13, 14) suggest a range of experiences following COVID-19 vaccination ranging from improvement, deterioration, and no change in long COVID symptoms.

Decreasing antibody levels

General population:

A study of antibody responses following the second dose of Pfizer has been conducted using data from the UK's national COVID-19 Infection Survey. This study found that antibody responses can last for over a year. (15)

Groups at higher risk of severe disease:

Several studies evaluating antibody titres have shown that antibody titres do not decrease at the same pace for everyone, and appears to decrease faster for the elderly, and for some people with other health conditions their immune response to the vaccine is lower. (16-19) It is unclear whether the decrease in antibody titres is correlated to the decrease in VE against hospitalisation and/or death but does appear to correlate with a decrease in VE against infection.

Immunogenicity data suggests that cancer, transplant, and dialysis patients, and those on immunosuppressant therapy, have a reduced response to a first dose of vaccine which can improve with a second dose, (20-27) although the response may still not be optimal, with both reduced antibody and T cell responses. (28-36) Furthermore, lower immunogenicity responses to the vaccine have been noted in those with diabetes. (37)

The UK's national COVID-19 Infection Survey found antibody responses declined more rapidly in older people, males, and those with underlying health conditions. The greatest antibody half-life was observed among those previously infected by SARS-CoV-2. (15)

Safety data

Safety data on further booster doses

General population:

The safety of further booster doses needs to be considered when implementing additional doses. There are no data available on the safety of booster doses beyond second booster doses, therefore any safety data is implied from first and second booster studies.

Data from studies comparing first and second mRNA booster dose safety and reactogenicity, generally show a favourable and similar safety/side effect profile with more adverse events being reported in younger participants. (38-40)

A study in Israel evaluated the safety profile of a second BNT162b2 mRNA COVID-19 booster vaccine using data from a retrospective cohort and a prospective cohort. Within the retrospective cohort, comparison of the 42 days before and after vaccination, found a second booster dose was not associated with 25 of the adverse events investigated (including myocarditis and pericarditis). Data obtained from the prospective cohort, showed 67% of participants (436/648) did not report any new signs or symptoms after receiving the second booster dose. The most frequently reported reactions were fatigue, headache, muscle pain,

cold, and a sore throat. These reactions faded in nearly all participants within 3 days of receiving the second vaccine. The study also found that participants who reported more severe reactions to the first booster tended to likewise report more severe reactions to the second booster. (31)

Groups at higher risk associated with vaccination:

Data suggests that the risks associated with vaccination whilst rare, are highest in those under the age of 30. Data from the US CDC suggests that although myocarditis is a rare event following mRNA COVID-19 booster vaccination, there is an increased risk of myocarditis following a first booster dose (as compared to background incidence). This risk was observed primarily in adolescent and young adult males. However, it was noted that reported rates of myocarditis are lower following first booster doses versus the second dose of the primary series. (41)

Effect of interval length on safety

The effect of interval length between mRNA booster doses on safety, is largely unknown. However, studies on primary course vaccination have shown that a longer interval (8 weeks) between the first and second dose, is associated with a lower incidence of myocarditis/pericarditis compared to a shorter interval (4 weeks),with the incidence of myocarditis/pericarditis highest amongst males aged 18 to 24 years. (31)

Findings from a pre-print case-control study from France suggest that longer intervals between each consecutive dose (including booster doses) are likely to decrease occurrence of vaccine-associated myocarditis. (43)

It is likely that the safety of booster dose intervals may be comparable to that of intervals between the first two doses. Safety signals on the effect of booster dose intervals will need to be closely monitored.

As other countries such as the USA and UK are already beginning to implement autumn booster campaigns based on either a 2-month (USA) or 3-month (UK) interval between vaccination doses, it is likely any safety signals seen with further booster doses will be identified overseas before New Zealand implements the equivalent booster dose.

Immune landscape of New Zealand

The need for further booster doses should consider the immunity landscape at the time.

Vaccine uptake and duration since last booster

New Zealand's population is highly vaccinated against COVID-19, with 84% of the total population having received a primary course and 71% having received at least one booster dose as of 30 November 2022. (2)

Vaccination data from 4 November 2022 showed that out of 2,716,374 people in Aotearoa New Zealand who have received a booster dose, 73% (1,977,253) have received their first or second booster dose more than 26 weeks or 6 months ago. Overall, this rate is higher for Māori and Pacific peoples (76% and 77%, respectively) compared to 72% of non-Māori-non-Pacific peoples. (Figure 1)

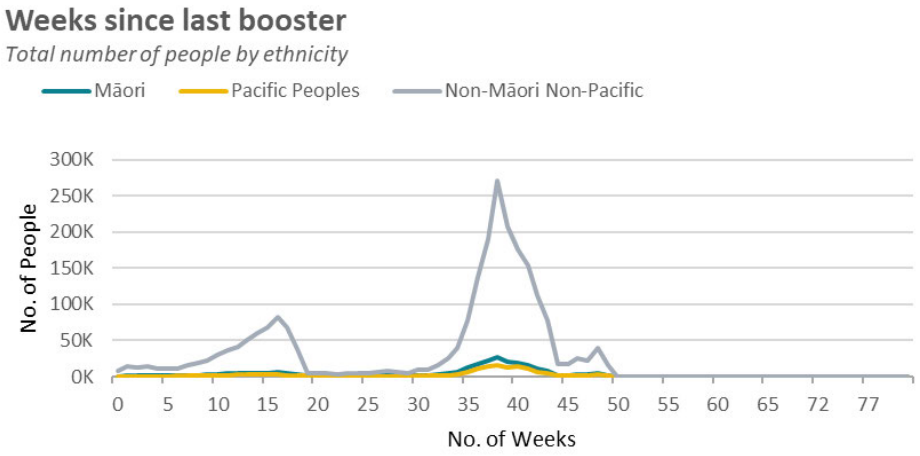

Figure 1: Total number of people by ethnicity in weeks since last booster.

(Source: National Immunisation Programme, 4 November 2022)

Approximately 92% of those aged 30 to 49 years and 74% of people aged 50 to 64 years have received their first or second booster dose more than 6 months ago compared to 40% of those aged 65 years and older. The proportion of people who had their booster more than 6 months ago increases the younger the age groups is across all ethnicities. (Figure 2)

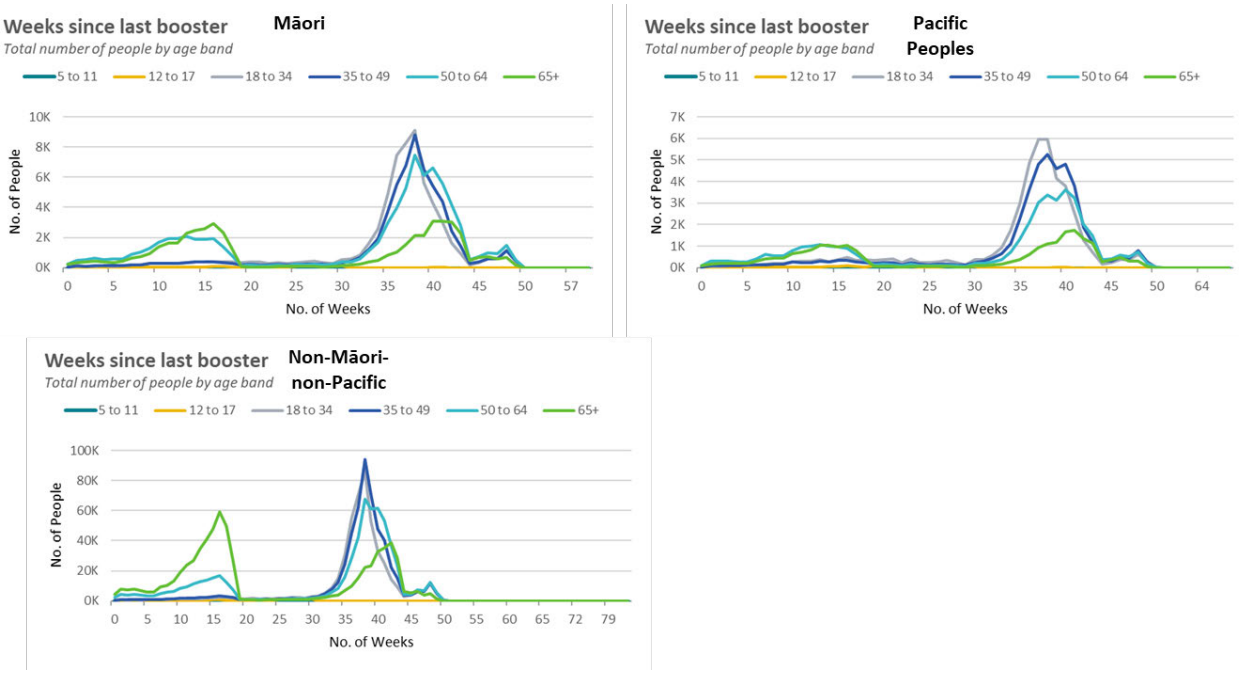

Figure 2: Total number of people by ethnicity and age band in weeks since last booster.

(Source: National Immunisation Programme, 4 November 2022)

The median time since last vaccination dose is lowest in both the 5- to 15-year-olds and 12- to 15-year-olds age groups. This is due to these age groups being the most recently added to eligibility criteria for

COVID-19 vaccination. For those aged 16 years and older, the median time since last vaccination dose ranges from 325 days to 337 days. (Table 2).

This means the majority of the vaccinated population aged 16 and older, have approached or are approaching 12 months since their last vaccination dose for COVID-19.

Age group	Median days since last vaccination
5 to 15	183.5
12 to 15	266.5
16 to 29	332
30 to 39	336.5
40 to 49	327
50 to 59	324.5
60 and over	330

Table 2: Median days since last vaccination dose

(Source: National Immunisation Programme, 30 November 2022)

SARS-CoV-2 infections

Based upon whole genome sequencing (WGS) of COVID-19 cases within New Zealand from late January to 28 October 2022, ESR has estimated that of all the 1,810,000 COVID-19 cases reported within this timeframe, 8.7% were BA.1., 65% were BA.2., 0.6% were BA.2.75, 2.8% were BA.4 and 23.5% were BA.5. (44)

The median time since infection for BA.2 infections was 205 days and was 94 days for BA.5. infections. (44) However, this data is based upon WGS estimates of when each subvariant was dominant. The total number of infections reported are approximately 2,000,000, which represents roughly 40% of the population of New Zealand.

The vast majority of (~80%) of currently reported cases, are first-time infections. Reinfections made up 17.9% of reported cases in the week ending 13 November. Cumulatively, reinfections have made up 2.8% of total cases reported to 13 November 2022. (45)

ESR reported that the median time between infections was 198 days (~6 months) and did not appear to differ significantly between variant, however this data is based upon a small number of reinfection samples. The BA.2 subvariant was dominant at the time of the initial infection for most reinfections. (46)

Reinfections made up 24% of reported cases in the week ending 27 November 2022. The proportion of reported cases has increased in the past three weeks after being stable prior. (3)

New Zealand data shows that as of 5 December 2022, the median time since last vaccination dose and a reported SARS-CoV-2 infection is 140 days. However, this analysis is confounded by the timing of the vaccine rollout campaign and the peaks of Omicron outbreaks.

Hybrid immunity

There is evidence to suggest the combination of vaccination and infection (known as hybrid immunity), increases mucosal antibody levels and broadens the immune response that may aid in protection against severe disease and potentially prevent infection and reduce transmission. (47, 48)

Furthermore, evidence is accumulating showing that hybrid immunity confers a greater level of protection against both infection and severe disease than either vaccination or prior infection alone. (49-51)

A systematic review and meta-regression analysis of studies investigating the protective effectiveness of hybrid immunity against Omicron, found that hybrid immunity provided protection against hospitalisation and severe disease greater than that of prior infection or vaccination (booster + primary course) alone. Against hospitalization or severe disease at 6 months, hybrid immunity with first booster vaccination (95% [95% CI: 82-99%]) or with primary series alone (97% [95% CI: 90-97%]) provided significantly greater protection than prior infection alone (80% [95% CI: 70-87%]), first booster vaccination alone (77% [95% CI: 73-80%]), or primary series alone (65% [95% CI: 55-74%]). (50)

Against reinfection, hybrid immunity involving primary series vaccination was 69% [95% CI: 59-78%] at 3 months after the most recent infection or vaccination, and 42% [95% CI: 32-53%] at 12 months, while hybrid immunity involving first booster vaccination was 69% [95% CI: 59-77%] at 3 months, and 47% [95% CI: 36-57%] at 6 months. (50) This suggests that although hybrid immunity provides a high level of protection against reinfection, it also wanes over time. The protection conferred by hybrid immunity against severe disease does not appear to wane as rapidly and remains above 90% at 6 months.

Previous Omicron infection in triple-vaccinated individuals provides a high level of protection against BA.5 and BA.2 infections. The study assessed outcomes across the period of 10 April to 30 June 2022. (51)

- Protection against BA.5 infection was estimated to be 92.7% (95% CI: 91.6 – 93.7).
- Protection against BA.2 infection was estimated to be 97.1% (95% CI: 96.6 – 97.5).
- High levels of protection against hospitalisation were conferred by infection with BA.5 at 96.4% (95% CI: 74. 2 – 99.5) and BA.2 at 91.2% (95% CI: 76.3 – 96.7).

Future immunity landscape of the population

Currently, the majority of the population have either had at least two doses of a COVID-19 vaccine, been infected, or both, generating a high level of immunity across the population. However, despite this there will be groups at higher risk of poor outcomes from COVID-19 infection. For example, those who are most vulnerable, that may have both avoided infection and also are experiencing a longer time frame since their last vaccination dose. Many people within this same group are likely to have a faster rate of waning immunity compared to the general population and will become more at risk as time elapses without further booster doses.

Waves of COVID-19 infection currently lack the seasonality seen with other respiratory diseases such as influenza and RSV. This makes it difficult to anticipate whether an annual vaccination campaign or 'one-size-fits-all' approach to intervals will be suitable for everyone, particularly those with a poorer immunological response to both vaccination and infection.

Other considerations

Risk differences across groups

There are significant differences in risk between groups both for infection and the risks associated with vaccination.

For adults aged between 30 to 59 years of age, there are low risks associated with COVID-19 vaccination and a moderate to low risk of poor outcomes from COVID-19 infection. Immune responses to both vaccination and infection in this population will be sufficient to protect against severe disease and may not require as frequent a minimum interval as those at higher risk of poor outcomes from COVID-19 infection.

For those who are at a substantially higher risk of poor outcomes from COVID-19 infection (i.e. elderly, immunocompromised, cancer patients or individuals with high or complex medical needs), the benefit of a shorter minimum interval between subsequent doses is likely to be higher.

The benefits of further booster doses and a shorter minimum interval between doses, is likely lower for those aged under 30 years. Individuals within this age group also are more likely to have had a recent infection with COVID-19, which would confer a high level of hybrid immunity amongst this population. Furthermore, individuals that fall within this age group are more likely to experience adverse effects from COVID-19 vaccination and are at a higher risk of myocarditis/pericarditis. Studies have shown that an increased length in the interval between vaccine doses, reduces the risk of myocarditis/pericarditis and thus it is likely a longer minimum interval may have a lower risk to benefit ratio in this population. The high rates of hybrid immunity in this population also make the benefit of a shorter interval for further booster doses unclear.

Strategic approach to timing of intervals

Long-term, it may be anticipated that, as with influenza, an annual/seasonal COVID-19 booster vaccination may need to be implemented, approaching winter. Countries like Canada and Australia have begun planning in similar ways, with vaccine recommendations focused on at-risk groups, and instead of second or third boosters, the terminology shifting to "updated" or "seasonal" boosters. (52-56) It is likely that simple and consistent messaging will support vaccination uptake considering the increasing complexity of COVID-19 vaccination requirements.

Peak body Advice

Australia (ATAGI) (52)

The Ministry of Health met with representatives from ATAGI and Australian Health officials, on 1 December 2022 and plans for COVID-19 vaccination strategy were compared and discussed. ATAGI officials mentioned consideration of a fifth dose (third booster) and recently recommended no change for current booster settings. ATAGI had also noted that high levels of infection in Australia had produced high levels of hybrid immunity and that they estimate the protection against severe disease/death will likely last around 12 months, suggesting the need for further boosters is not currently warranted. They acknowledged that immunity is complex and that antibodies are just one aspect to consider when assessing the need for more boosters. Less is known about duration of protection from T cell responses, which appear to be more durable and contribute greatly to severe disease protection from COVID-19 infection.

ATAGI recommendations include:

- All people are recommended to defer COVID-19 vaccination for 3 months after a confirmed SARS-CoV-2 infection. The next scheduled dose should then be given as soon as possible. All recommended doses should still be received, and no doses should be omitted from the schedule.

- The recommended interval between completing the primary COVID-19 vaccine course (the second dose for most people and vaccine brands) and the first booster dose is 3 months.
- The recommended interval between the first booster dose and a second booster dose (for those who are recommended to receive a second booster dose) is 3 months.
- Severely immunocompromised people aged 16 years or older who have received a third primary dose are recommended to receive a first booster dose (a fourth dose) 3 months after the primary course, and a second booster dose (a fifth dose) 3 months after the first booster.
- A person may be vaccinated earlier than the recommended 3-month interval in exceptional circumstances, such as before starting an immunosuppressant, before overseas travel or if someone cannot reschedule vaccination easily (such as in an outreach vaccination program).
- ATAGI advises that the absolute minimum interval between the first and second dose of any COVID-19 vaccine is 14 days.

Canada (53)

COVID-19 booster doses may be offered at an interval of 6 months after a previous COVID-19 vaccine dose or SARS-CoV-2 infection, regardless of the product offered. However, a shorter interval of at least 3 months may be warranted in the context of heightened epidemiologic risk, as well as operational considerations for the efficient deployment of the vaccine program.

Maximizing the benefit of protection of a booster dose may be affected by the interval between doses. A longer time between doses may result in a better response after any subsequent dose, as this allows time for the immune response to mature in breadth and strength. A longer interval may, however, also increase the chance of a period with waning (lower) protection while awaiting a next dose.

United States of America (54)

The US CDC recommends that people ages 5 years and older receive one updated (bivalent) booster if it has been at least 2 months since their last COVID-19 vaccine dose, whether that was:

- Their final primary series dose, or
- An original (monovalent) booster

People who have gotten more than one original (monovalent) booster are also recommended to get an updated (bivalent) booster.

They recommend that if someone has recently had COVID-19, they may consider delaying their next vaccine dose (whether a primary dose or booster) by 3 months from when their symptoms started or, if they had no symptoms, when they first received a positive test.

United Kingdom (55)

The UK is offering a seasonal booster to some groups, and it is recommended to receive a booster (Pfizer or Moderna) at least 3 months after their last dose of vaccine.

People can receive a seasonal booster dose (autumn booster) of the COVID-19 vaccine if they are:

- aged 50 or over
- pregnant

- aged 5 and over and at high risk from COVID-19 due to a health condition or a weakened immune system
- aged 5 and over and live with someone who has a weakened immune system
- aged 16 and over and a carer, either paid or unpaid
- living or working in a care home for older people
- a frontline health and social care worker

Europe (ECDC) (32)

The regulatory approval allows the administration of additional booster doses with an interval as short as 3 months after the previous dose, if deemed needed. However, longer intervals may be considered in vaccination campaigns, based on real-world evidence of high level of protection against severe disease restored after the first booster dose and maintained for at least 4 months. Intervals longer than 4 months could be considered, based on the evidence of stronger immune response obtained with longer intervals between doses, but this needs to be balanced with waning protection and the local epidemiological situation. Priority for booster doses should be given to individuals from vulnerable groups who received their last vaccination more than 6 months ago. Synchronising booster vaccination just before or at the beginning of high viral circulation, as is normally expected with respiratory viruses at the start or during the cold season, would be highly desirable. Consideration should also be given to combining campaigns for vaccination against COVID-19 and influenza. Although it is still unknown how the virus will evolve in the coming months, it may be anticipated that in the longer-term, annual booster vaccination could be necessary at the beginning of the cold season similarly to influenza.

The ECDC recommends individuals with primary vaccination and a recent SARS-CoV-2 infection to wait at least 3 months or preferably even longer than 4 months after the infection before receiving a booster can therefore be considered.

Japan (31)

Japan's Ministry of Health approved a plan to shorten the minimum interval period to receive third and subsequent COVID-19 vaccine shots to three months from the current five months, for people aged 12 and older.

Next Steps	• RfA to be taken to CV TAG for feedback and recommendations, including any variation between (1) general population (2) those at higher risk of myocarditis/pericarditis and (3) those at higher risk of severe disease • CV TAG recommendations on intervals to be sent to Director General
In the development of this work, the following parties have been consulted with:	The COVID-19 Vaccine Technical Advisory Group

Resources used:		
Ministry of Health Policies and Procedures	☐ Yes ☒ No	
External Health Scientific organisations	☒ Yes ☐ No	
Existing database of RFAs	☒ Yes ☐ No	
Internal Ministry of Health Advice	☒ Yes ☐ No	
External Expert Advice	☒ Yes ☐ No	
Literature Review	☒ Yes ☐ No	

References (for appendix 1)

1. Ministry of Health. EpiSurv Data as at 20 November 2022. 2022.
2. Ministry of Health. National Immunisation Programme COVID-19 Vaccination Data as at 30 November 2022. 2022.
3. Ministry of Health. COVID-19 Trends and Insights Report – 02 December 2022, Unpublished Ministry of Health report 2022
4. McMenamin ME, Nealon J, Lin Y, Wong JY, Cheung JK, Lau EHY, et al. Vaccine effectiveness of two and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong 2022 [2022.03.22.22272769]. Available from: http://medrxiv.org/content/early/2022/03/24/2022.03.22.22272769.abstract
5. Tartof SY, Slezak JM, Puzniak L, Hong V, Xie F, Ackerson BK, et al. BNT162b2 (Pfizer–Biontech) mRNA COVID-19 Vaccine Against Omicron-Related Hospital and Emergency Department Admission in a Large US Health System: A Test-Negative Design 2022 [Available from: http://dx.doi.org/10.2139/ssrn.4011905
6. Tartof SY, Slezak JM, Puzniak L, Hong V, Frankland TB, Ackerson BK, et al. BNT162b2 vaccine effectiveness against SARS-CoV-2 omicron BA.4 and BA.5. The Lancet Infectious Diseases. https://doi.org/10.1016/S1473-3099(22)00692-2
7. Surie D BL, Adams K, et al. Effectiveness of Monovalent mRNA Vaccines Against COVID-19–Associated Hospitalization Among Immunocompetent Adults During BA.1/BA.2 and BA.4/BA.5 Predominant Periods of SARS-CoV-2 Omicron Variant in the United States — IVY Network, 18 States, December 26, 2021–August 31, 2022: MMWR Morb Mortal Wkly Rep 2022;71:1327–1334; 2022 [Available from: http://dx.doi.org/10.15585/mmwr.mm7142a3
8. CDC. Updates on COVID-19 Vaccine Effectiveness during Omicron 2022 [Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/04-COVID-Link-Gelles-508.pdf
9. Link-Gelles R, Levy ME, Natarajan K, Reese SE, Naleway AL, Grannis SJ, et al. Association between COVID-19 mRNA vaccination and COVID-19 illness and severity during Omicron BA.4 and BA.5 sublineage periods 2022 [2022.10.04.22280459]. Available from: https://www.medrxiv.org/content/medrxiv/early/2022/10/05/2022.10.04.22280459.full.pdf
10. Ruth Link-Gelles, Allison Avrich Ciesla, Katherine E. Fleming-Dutra, Zachary R. Smith, Amadea Britton, Ryan E. Wiegand, et al. Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022: Morbidity and Mortality Weekly Report (MMWR); 2022 [Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm
11. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. BMJ. 2022;377:e069676. http://www.bmj.com/content/377/bmj-2021-069676.abstract
12. Sivan M, Greenhalgh T, Milne R, Delaney B. Are vaccines a potential treatment for long covid? BMJ. 2022;377:o988. http://www.bmj.com/content/377/bmj.o988.abstract
13. Tsuchida T, Hirose M, Inoue Y, Kunishima H, Otsubo T, Matsuda T. Relationship between changes in symptoms and antibody titers after a single vaccination in patients with Long COVID. Journal of Medical Virology. 2022;94(7):3416-20. https://doi.org/10.1002/jmv.27689

14. UK Health Security Agency. The effectiveness of vaccination against long COVID. A rapid evidence briefing 2022 [Available from: https://ukhsa.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=fe4f10cd3cd509fe045ad4f72ae0dfff
15. Wei J, Stoesser N, Matthews PC, Ayoubkhani D, Studley R, Bell I, et al. Antibody responses to SARS-CoV-2 vaccines in 45,965 adults from the general population of the United Kingdom. Nature Microbiology. 2021.
16. Collier DA, Ferreira IATM, Kotagiri P, Datir R, Lim E, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature. 2021.
17. Kontopoulou K, Ainatzoglou A, Ifantidou A, Nakas CT, Gkounti G, Adamopoulos V, et al. Immunogenicity after the first dose of the BNT162b2 mRNA Covid-19 vaccine: real-world evidence from Greek healthcare workers. Journal of Medical Microbiology. 2021;70(8).
18. Meyer M, Constancias F, Worth C, Meyer A, Muller M, Boussuge A, et al. Humoral immune response after COVID-19 infection or BNT162b2 vaccine among older adults: evolution over time and protective thresholds. 2021.
19. Tober-Lau P, Schwarz T, Vanshylla K, Hillus D, Gruell H, Suttorp N, et al. Long-term immunogenicity of BNT162b2 vaccination in the elderly and in younger health care workers. 2021.
20. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, et al. Weak anti-SARS-CoV-2 antibody response after the first injection of an mRNA COVID-19 vaccine in kidney transplant recipients. Kidney Int. 2021. https://www.ncbi.nlm.nih.gov/pubmed/33775674
21. Monin-Aldama L, Laing AG, Munoz-Ruiz M, McKenzie DR, Barrio IdMd, Alaguthurai T, et al. Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines 17 March 2021 [Available from: https://www.medrxiv.org/content/10.1101/2021.03.17.21253131v1
22. Goupil R, Benlarbi M, Beaubien-Souligny W, Nadeau-Fredette A-C, Debashree C, Goyette G, et al. Short-term antibody response and tolerability of one dose of BNT162b2 vaccine in patients receiving hemodialysis 1 April 2021 [Available from: https://www.medrxiv.org/content/10.1101/2021.03.30.21254652v1
23. Kennedy NA, Goodhand JR, Bewshea C, Nice R, Chee D, Lin S, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. Gut. 2021;70(5):865-75. https://www.ncbi.nlm.nih.gov/pubmed/33753421
24. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, El-Qunni AA, et al. Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. medRxiv. 2021. https://www.ncbi.nlm.nih.gov/pubmed/33851176
25. Palich R, Veyri M, Marot S, Vozy A, Gligorov J, Maingon P, et al. Weak immunogenicity after a single dose of SARS-CoV-2 mRNA vaccine in treated cancer patients. Ann Oncol. 2021. https://www.ncbi.nlm.nih.gov/pubmed/33932501
26. Jerome B, Emmanuel C, Zoubir A, Olivier C, Abakar M, Sabine M, et al. Impaired immunogenicity of BNT162b2 anti SARS-CoV-2 vaccine in patients treated for solid tumors. Ann Oncol. 2021. https://www.ncbi.nlm.nih.gov/pubmed/33932508
27. Weigert A, Bergman M-L, Gonçalves L, Godinho I, Duarte N, Abrantes R, et al. Longitudinal analysis of antibody responses to the Pfizer BNT162b2 vaccine in Patients Undergoing Maintenance Hemodialysis. 2021.
28. Tzarfati KH, Gutwein O, Apel A, Rahimi-Levene N, Sadovnik M, Harel L, et al. BNT162b2 COVID-19 Vaccine is significantly less effective in patients with hematologic malignancies. Am J Hematol doi: 101002/ajh26284. 2021. https://www.ncbi.nlm.nih.gov/pubmed/34185336

29. Prendecki M, Thomson T, Clarke CL, Martin P, Gleeson S, De Aguiar RC, et al. Comparison of humoral and cellular responses in kidney transplant recipients receiving BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines. 14th July 2021.
30. Clarke CL, Martin P, Gleeson S, Thomson T, Edwards H, Mortimer P, et al. Comparison of immunogenicity between BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines in a large haemodialysis population. 14th July 2021.
31. Whitaker H, Tsang R, Byford R, Andrews N, Sherlock J, Pillai PS, et al. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response among individuals in clinical risk groups 9th July 2021 [Available from: https://khub.net/documents/135939561/430986542/RCGP+VE+riskgroups+paper.pdf/a6b54cd9-419d-9b63-e2bf-5dc796f5a91f
32. Espi M, Charmetant X, Barba T, Koppe L, Pelletier C, Kalbacher E, et al. The ROMANOV study found impaired humoral and cellular immune responses to SARSCov-2 mRNA vaccine in virus unexposed patients receiving maintenance hemodialysis. Kidney International. 2021.
33. Hadjadj J, Planas D, Ouedrani A, Buffier S, Delage L, Nguyen Y, et al. Immunogenicity of BNT162b2 vaccine Against the Alpha and Delta Variants in Immunocompromised Patients. 9th August 2021.
34. Del Bello A, Abravanel F, Marion O, Couat C, Esposito L, Lavayssière L, et al. Efficiency of a boost with a third dose of anti–SARS-CoV-2 messenger RNA–based vaccines in solid organ transplant recipients. American Journal of Transplantation. 2021.
35. Labriola L, Scohy A, Van Regemorter E, Robert A, Clerbaux G, Gillerot G, et al. Immunogenicity of BNT162b2 SARS-CoV-2 Vaccine in a Multicenter Cohort of Nursing Home Residents Receiving Maintenance Hemodialysis. American Journal of Kidney Diseases. 2021.
36. Cotugno N, Pighi C, Morrocchi E, Ruggiero A, Amodio D, Medri C, et al. HUMORAL AND CELLULAR IMMUNOGENICITY and SAFETY UP TO 4 MONTHS AFTER VACCINATION WITH BNT162B2 mRNA COVID-19 VACCINE IN HEART AND LUNG TRANSPLANTED YOUNG ADULTS. 2021.
37. Priddy FH, Williams M, Carson S, Lavender B, Mathieson J, Frampton C, et al. Immunogenicity of BNT162b2 COVID-19 vaccine in New Zealand adults. Vaccine. 2022;40(34):5050-9. https://www.sciencedirect.com/science/article/pii/S0264410X22008854
38. Romero-Ibarguengoitia ME, González-Cantú A, Rivera-Salinas D, Hernández-Ruíz YG, Armendariz-Vázquez AG, Barco-Flores IA, et al. Analysis of Immunization, Adverse Events, and Efficacy of a Fourth Dose of BNT162b2 Vaccine in Health Workers in Mexico, a Pilot Study. Vaccines. 2022;10(7):1139. https://www.mdpi.com/2076-393X/10/7/1139
39. Regev-Yochay G, Gonen T, Gilboa M, Mandelboim M, Indenbaum V, Amit S, et al. 4th Dose COVID mRNA Vaccines' Immunogenicity & Efficacy Against Omicron VOC 2022 [2022.02.15.22270948]. Available from: http://medrxiv.org/content/early/2022/02/15/2022.02.15.22270948.abstract
40. Yechezkel M, Mofaz M, Painsky A, Patalon T, Gazit S, Shmueli E, et al. Safety of the fourth COVID-19 BNT162b2 mRNA (second booster) vaccine: a prospective and retrospective cohort study 2022 [updated 2022/11/18/. Available from: https://www.sciencedirect.com/science/article/pii/S2213260022004076
41. Shimabukuro TT. COVID-19 vaccine safety update: Primary series in young children and booster doses in older children and adults. 2022.
42. Buchan SA, Seo CY, Johnson C, Alley S, Kwong JC, Nasreen S, et al. Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval

Among Adolescents and Adults in Ontario, Canada. JAMA Network Open. 2022;5(32)2022;5(32):e2218505-e. https://doi.org/10.1001/jamanetworkopen.2022.18505
43. Le Vu S, Bertrand M, Jabagi M-J, Botton J, Weill A, Dray-Spira R, et al. Risk of Myocarditis after Covid-19 mRNA Vaccination: Impact of Booster Dose and Dosing Interval. medRxiv. 2022:2022.07.31.22278064. https://www.medrxiv.org/content/medrxiv/early/2022/08/01/2022.07.31.22278064.full.pdf
44. de Ligt J, Douglas JGJ, Hadfield J, Winter D, Jefferies S, Welch D, et al. COVID-19 Genomics Insights (CGI) Report #26 – 02 November 2022, Unpublished ESR report. 2022.
45. Ministry of Health. COVID-19 Trends and Insights Report – 18 November 2022. 2022.
46. de Ligt J, Douglas JGJ, Hadfield J, Winter D, Jefferies S, Welch D, et al. COVID-19 Genomics Insights (CGI) Report #27 – 16 November 2022, Unpublished ESR report. 2022.
47. Sano K, Bhavsar D, Singh G, Floda D, Srivastava K, Gleason C, et al. SARS-CoV-2 vaccination induces mucosal antibody responses in previously infected individuals. Nat Commun. 2022;13(1):5135. https://doi.org/10.1038/s41467-022-32389-8
48. Reynolds CJ, Pade C, Gibbons JM, Otter AD, Lin K-M, Sandoval DM, et al. Immune boosting by B.1.1.529 (Omicron) depends on previous SARS-CoV-2 exposure [Available from: https://www.science.org/doi/abs/10.1126/science.abq1841
49. Altarawneh HN, Chemaitelly H, Ayoub HH, Tang P, Hasan MR, Yassine HM, et al. Effect of prior infection, vaccination, and hybrid immunity against symptomatic BA.1 and BA.2 Omicron infections and severe COVID-19 in Qatar. medRxiv. 2022:2022.03.22.22272745. https://www.medrxiv.org/content/medrxiv/early/2022/03/22/2022.03.22.22272745.full.pdf
50. Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of prior SARS-CoV-2 infection and hybrid immunity against Omicron infection and severe disease: a systematic review and meta-regression. medRxiv. 2022:2022.10.02.22280610. https://www.medrxiv.org/content/medrxiv/early/2022/10/24/2022.10.02.22280610.full.pdf
51. Hansen CH, Friis NU, Bager P, Stegger M, Fonager J, Fomsgaard A, et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark: Elsevier; [Available from: https://doi.org/10.1016/S1473-3099(22)00595-3
52. Australian Technical Advisory Group on Immunisation (ATAGI). Clinical recommendations for COVID-19 vaccines 2022 [updated 01 December 2022. Available from: https://www.health.gov.au/our-work/covid-19-vaccines/advice-for-providers/clinical-guidance/clinical-recommendations#booster-dose-recommendations-
53. Government of Canada. COVID-19 vaccine: Canadian Immunization Guide 2022 [updated 18 November 2022. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html
54. Centers for Disease Control and Prevention (CDC). Stay Up to Date with COVID-19 Vaccines Including Boosters 2022 [updated 01 November 2022. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html
55. UK health Security Agency. A guide to the COVID-19 autumn booster 2022 [updated 28 September 2022. Available from: https://www.gov.uk/government/publications/covid-19-vaccination-autumn-booster-resources/a-guide-to-the-covid-19-autumn-booster
56. European Centre for Disease Prevention and Control (ECDC) and European Medicines Agency (EMA). ECDC-EMA statement on booster vaccination with Omicron adapted bivalent COVID-19

vaccines 2022 [updated 06 September 2022. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/ECDC-EMA-Statement-on-Adapted-Vaccines.pdf
57. The Japan Times. Panel Oks shorter COVID-19 vaccination interval in Japan 2022 [updated 20 October 2022. Available from: https://www.japantimes.co.jp/news/2022/10/20/national/science-health/covid-vaccine-shorter-interval-ok/

Appendix 2

Future Considerations

Following are some guiding principles proposed by CV TAG members for future decisions around additional doses of COVID-19 vaccines (i.e., "third booster" or subsequent doses)

a. Improving first booster coverage should be the top priority of the National Immunisation Programme. In particular, the programme needs to prioritise those who are most at risk of severe disease and severe outcomes (including Māori and Pacific peoples with low first booster uptake).

b. Firm recommendations for additional doses beyond the first half of 2023 cannot be made currently due to uncertainty on the future epidemiology of COVID-19 (e.g., seasonality), future variants, and duration of protection against severe disease from hybrid immunity.

c. A flexible approach should be applied to current and future decisions on intervals between additional doses (boosters). This will provide the ability to adapt to changing variant, immunological, and epidemiological landscapes, as well as clinical decisions by an individual's healthcare provider.

d. Terminology should shift from the number of doses/boosters (i.e., first booster, second booster) towards terms such as 'additional doses' or 'autumn/annual vaccine doses', to minimise confusion and account for variations between populations.

e. Based on the likelihood of hybrid immunity providing protection against severe disease for many months, the potential programmatic advantages of aligning the COVID-19 vaccination programme to the pre-winter influenza vaccination programme, as well as a need to mitigate the risk of over-burdening hospitals with winter respiratory illness, the Programme may be heading towards making an annual pre-winter COVID-19 booster recommended (i.e. actively encouraged) for those at higher risk of severe COVID-19, and available (i.e. can be administered on request) to all those aged 30 and over.

f. Additional doses, such as a "third booster", (including more frequent doses for those at higher risk of severe COVID-19, or in high-risk epidemiological situations) could be considered in line with the following:

    i. For the general population, a schedule which has **six months or more** between additional doses should generally be implemented unless epidemiologically indicated (for example, a wave of severe COVID-19 is anticipated), in which case a schedule with as little as three months before a subsequent dose could be used. This includes the preferred interval between completion of the primary course and the first booster dose being six months or more. The previous three-month interval was based on epidemiological considerations at the time, which are no longer applicable to the current Aotearoa New Zealand situation. As above, schedules with longer intervals between additional doses (for example, twelve months after the previous dose) would be supported by this

recommendation if the risk of severe COVID-19 remains low in the general population.

ii. Current and future decisions on intervals between additional doses should also provide schedules for both those at higher risk of severe COVID-19 (e.g., the elderly, those with co-morbidities, and Māori and Pacific Peoples in high-risk age groups) and those at lower risk (e.g., those under 30 years of age). In general, higher risk groups would have a shorter recommended interval than the general population, and lower risk groups would have a longer interval. Some low-risk groups, such as young healthy children, may have no additional doses recommended until they reach a given age (or otherwise enter a group at higher risk of severe-COVID-19 disease).

g. An additional booster dose, if due, should be postponed for **at least three months, and preferably from six months, after SARS-CoV-2 infection.** Clinical discretion can be applied when considering vaccination prior to three months after infection. This may be appropriate for those individuals considered to be at high risk of severe disease from COVID-19 re-infection.

Appendix 3

CV TAG has recommended that in a pre-winter vaccination programme, the groups **recommended** (i.e., actively encouraged) to receive a second booster dose should be expanded to include those eligible for free influenza vaccine in Aotearoa New Zealand. This is with the exception of the childhood age groups and pregnant people under the age of 30 that are part of free influenza vaccine eligibility.

h. The groups recommended a second booster would therefore include:
    i. People aged 65 years and over
    ii. Māori and Pacific people aged 50 years and over (Influenza vaccine eligibility is currently 55 years and over for this cohort)
    iii. Pregnant people aged 30 years and over (Influenza vaccine eligibility is currently 16 years and over for this cohort)
    iv. Individuals with underlying health conditions
    v. People with serious mental health or addiction needs

Current eligibility conditions for funded influenza vaccinations

1. People aged 65 years and over
2. Māori and Pacific people aged 55 to 64 years
3. People under 65 years of age who:

have any of the following cardiovascular diseases:

- *ischaemic heart disease*
- *congestive heart failure*
- *rheumatic heart disease*
- *congenital heart disease*
- *cerebrovascular disease*

have either of the following chronic respiratory diseases:

- *asthma if on a regular preventative therapy*
- *other chronic respiratory disease with impaired lung function*

have diabetes

have chronic renal disease

have any cancer, excluding basal and squamous skin cancers if not invasive

have any of the following other conditions:

- *autoimmune disease*

- *immune suppression or immune deficiency*
- *HIV*
- *transplant recipient*
- *neuromuscular or CNS disease/disorder*
- *haemoglobinopathy*
- *cochlear implant*
- *error of metabolism at risk of major metabolic decompensation*
- *prior post-splenectomy*
- *Down syndrome*

are pregnant (any trimester)

4. Children aged 4 years or under who have been hospitalised for respiratory illness or have a history of significant respiratory illness.
5. People under 65 years of age who:

   have any of the following serious mental health conditions:

   - *schizophrenia*
   - *major depressive disorder*
   - *bipolar disorder*

   are currently accessing secondary or tertiary mental health and addiction services;

6. Children 3 to 12 years of age (inclusive), from 1 July 2022.