MANATŪ HAUORA
MINISTRY OF HEALTH

Memo

Decision to use Pfizer's bivalent BA.4/5 vaccine: COVID-19 Vaccine Technical Advisory Group (CV TAG) recommendations

Date:	15 November 2022
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From:	Dr Ian Town, Chief Science Advisor, Ministry of Health
For your:	Information

Purpose of report

1. To summarise the COVID-19 Vaccine Technical Advisory Group's (CV TAG) recommendations on the decision to use Pfizer-BioNTech's Comirnaty Original / Omicron BA.4/5 COVID-19 vaccine (referred hereafter as the BA.4/5 bivalent vaccine).

Background and Context

2. As Omicron variants have emerged, COVID-19 vaccines which were originally designed to target the wild type (WT) variant were found to be less effective, especially against Omicron infections and transmission (as opposed to Delta). After two doses of Pfizer, vaccine effectiveness (VE) against Omicron infection is as low as 40-55%. (1, 2)

3. With vaccines being less effective against emerging variants, as well as immunity waning over time, first booster doses began to be recommended worldwide. Although booster doses will restore VE against infection for a short period of time, the increase in antibody titres is short-lived, with some studies suggesting moderate effectiveness for around 2-3 months. (2, 3)

4. Since early October 2022, COVID-19 cases and hospitalisation, have begun to increase, with hospitalisation and deaths attributed to COVID-19 predicted to increase in the coming weeks.

5. Since mid-July 2022, the Omicron BA.4/5 subvariant has been the predominant variant in New Zealand, making up 78% of whole genome sequencing (WGS) and wastewater samples (as at 2 November 2022). More immune-evasive variants such as BQ1.1 and XBB have also emerged, with BA1.1 now making up 8% of WGS and wastewater samples.

6. With an increasing number of immune-evasive variants and waning of immunity from booster roll outs, increasing attention has been directed to the next booster options, as well as consideration of bivalent vaccines as part of Aotearoa New Zealand's 2023/24 COVID-19 vaccination programme.

7. On 28 July 2022, a memo was issued to the Director-General of Health on the decision not to take up a time-limited offer from Pfizer to purchase doses of its updated BA.1 variant-containing COVID-19 vaccine. The advice included a rapid review conducted by the Science and Technical Advisory team in the Public Health Agency, in consultation with few members of CV TAG. **The decision made by the Director-General at the time was to not proceed with the offer.**

8. On 16 August 2022, CV TAG reviewed the Request for Advice (RfA) on "COVID-19 vaccine formulation options for short- to mid-term future (2023) in Aotearoa". The CV TAG advice was as follows:

    a. Heterologous and homologous boosting (whether with the new Pfizer or Novavax formulation) should remain a future consideration.

    b. A preference for BA.4/5-containing vaccines over BA.1-containing vaccines

    c. For Pfizer vaccines, a BA.4/5-containing bivalent vaccine should be acquired as early as possible. Stocks of the original vaccine formulation of Pfizer, should be maintained until such time as BA.4/5-containing vaccines become available.

    d. For Omicron-containing Novavax formulations, there is currently insufficient data to make recommendations. Stocks of original formulation Novavax vaccine should be maintained until such time as more information is available.

9. On 20 October 2022, Medsafe received an application from Pfizer for provisional approval of its BA.4/5 bivalent vaccine. However, currently only early data evaluating the safety, tolerability, and immunogenicity from a Phase II/III clinical trial has been provided by Pfizer. Medsafe is evaluating this application under priority and is expecting additional clinical data in the near future.

10. CV TAG met on 8 November 2022 to discuss the use of the Pfizer BA.4/5 bivalent vaccine (pending Medsafe approval). This included feedback on the RfA on "Evidence informing decision to use BA.4/5 bivalent vaccine" (see Appendix 1)

11. Pfizer's BA.4/5 bivalent vaccine contains equal parts (15 µg each) of mRNA encoding for the original SARS-CoV-2 virus and the Omicron subvariants BA.4/5.

12. Data from other mRNA COVID-19 vaccines might help inform advice on the use of Pfizer's BA.4/5 bivalent vaccine indirectly:

    a. Pfizer's bivalent BA.1/WT is already available in some countries (e.g., Canada). Since BA.1 bivalent clinical data have been used to assess immunogenicity and safety for BA.4/5 bivalent vaccines, real world evidence from other countries could be used to assess effectiveness.

    b. Moderna's bivalent BA.5/WT vaccine contains the same combination of WT and Omicron BA.4/5 mRNA encoding. Available data includes pre-clinical data on mice primed with a primary course of original Moderna vaccine and boosted with a bivalent BA.4/5 vaccine.

    c. Monovalent vaccines: Although likely to be less useful, monovalent vaccines may provide insights into the role of "immune imprinting" or "original antigenic sin".

13. BA.4/5 bivalent vaccine has been authorised in the European Union, the US, Canada, the UK and Australia. Numerous countries have also started to roll out BA.4/5 bivalent vaccine programmes (see Use of Pfizer's bivalent vaccine by other jurisdictions).

Evidence informing the advice

14. The RfA "Evidence informing decision to use BA.4/5 bivalent vaccine" presents the available evidence about efficacy, immunogenicity and safety of Pfizer's BA.4/5 bivalent vaccine, as well as other relevant data from other variant vaccines, to inform a decision to use Pfizer's bivalent BA.4/5 vaccine in New Zealand. (see Appendix 1)

NZ epidemiological context

15. With New Zealand having had high rates of Omicron infection, as well as high rates of vaccination (compared to countries internationally), expert immunologists consider that New Zealand has uniquely high levels of hybrid immunity and consequent protection against severe disease, particularly from Omicron variants. However, with emerging immune-evasive variants and waning immunity, there is an increasing call for additional boosters, and more booster options.

16. As at 6 November, the 7-day rolling average of reported COVID-19 case rates increased to 57.6 per 100,000 population, with rates highest in the 65+ age group (66.9 per 100,000).

17. The COVID-19 hospital admissions rate has been increasing since early October, with a 7-day rolling average of 0.9 per 100,000 for the week ending 16 October. The rate was highest in the 65+ age group (3.2 per 100,000).

18. As of 16 October, there were 2,041 deaths attributed to COVID-19 in 2022. The weekly number of deaths attributed to COVID-19 has continued to decrease since peaking in July. However, in the past few weeks the decline has slowed, and is predicted to slightly increase in the coming months.

19. As at 2 November 2022, WGS shows that BA.5 accounts for 84% of community cases in NZ. The proportion of BA.5 cases has declined slowly over the previous weeks, as proportions of several other subvariants increase (with BQ1.1 now accounting for 8% of WGS and wastewater samples). BA.2.75 (8%) and BA.4.6 (3%) continue to be detected. From the 359 sequenced cases in the fortnight to 28 October 2022, 17 BQ.1 cases, 26 BQ.1.1 cases and 15 cases caused by the recombinant lineage XBB. BQ.1.1 and XBB were also detected in wastewater.

20. Emerging variants such as BQ.1.1, which have been suggested as having more immune-evasive properties than previous Omicron variants, are more closely related to BA.5 than to BA.1. Therefore theoretically, this may suggest that BA.5-containing vaccines could confer greater protection against emerging variants for Aotearoa New Zealand.

Waning immunity from boosters

21. 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 (see Figure 1 and Appendix 20

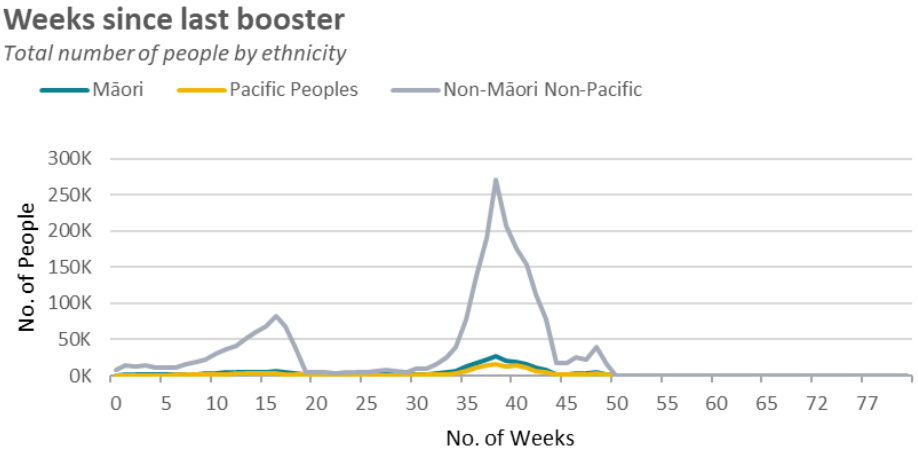

Figure 1: Total number of people by ethnicity in weeks since last booster.

(Source: National Immunisation Programme, 4 November 2022)

22. 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 (see 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)

23. It is important to note that these data are limited to those that have received a booster dose, consequently under-representing populations that have had lower vaccine uptake, including Māori and Pacific Peoples. The data therefore does not accurately reflect the barriers in access for these population groups. This data also does not exclude people with COVID-19 infection in the last 3 months.

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

25. Adjusted VE from a second mRNA vaccine booster against BA.4/5 related hospitalisation is estimated to be 60% (95%CI, 42-73%) up to three months after receiving the second booster and 56% (95% CI, 41-46%) after >3 months. (8)

Data on Pfizer's bivalent vaccines

26. On 31 August 2022, the U.S. Food and Drug Administration (FDA) authorised the emergency use of Pfizer's and Moderna's bivalent BA.4/5 formulation in the U.S. This was authorised without clinical data, unlike BA.1 bivalent mRNA vaccines. (9) Immunogenicity and safety of a booster dose of Pfizer's BA.4/5 bivalent vaccine is inferred from clinical data from the studies of a booster dose of Pfizer's BA.1 bivalent vaccine.

Pfizer's BA.1 bivalent vaccine

Immunogenicity

27. Data from the BA.1 bivalent clinical trial demonstrated that in people aged 55 years and over, without evidence of prior SARS-CoV-2 infection receiving a fourth dose, the BA.1 bivalent vaccine elicited higher neutralising antibody responses against Omicron BA.1 and BA.4/BA.5. It also demonstrated an equivalent neutralising antibody response against the original SARS-CoV-2 variant when compared to Pfizer's original monovalent vaccine.

Safety

28. Clinical and post-market safety data from Pfizer's BA.1 Bivalent and WT original vaccine respectively suggest that BA.4/5 bivalent vaccine will likely be well tolerated with a similar safety profile, when used as a booster dose.

Pfizer's BA.4/5 bivalent vaccine

Immunogenicity

29. Data from two observational pre-prints studies found comparable BA.5 neutralising antibody (NAb) titres elicited by the WT monovalent vaccine and bivalent BA.5 vaccine with 3-5 weeks post-vaccination. (10, 11) These data may be a result immunological imprinting (either from previous exposure or vaccination against WT), leading to a poor immunological response to BA.4/5 from the bivalent. (10, 12)

30. A letter of correspondence in the Lancet suggests that the benefits of Omicron-adapted vaccines may be revealed in longer term studies. Due to B cell affinity maturation processes in response to the BA.4/5 bivalent mRNA vaccines potentially occurring over a longer period of time (>5 weeks), benefits from Omicron-adapted vaccines may not be apparent until a later time (i.e. >6 months post-vaccination). (13, 14) The authors also suggest that Omicron-adapted booster vaccination might extend the duration of immune protection by compensating immune decay (i.e. the decrease in BA.4/5 antibodies over time). (13)

31. One pre-print study has found BA.4/5 bivalent booster vaccines improve the neutralising activity against Omicron subvariants BA.1, BA.5, BA.2.75.2, and BQ.1.1 compared to monovalent (almost certainly licensed WT monovalent, but not explicitly stated) boosters. The study suggests that BA.4/5 bivalent mRNA booster vaccine broadens humoral immunity against the Omicron subvariants. (15)

32. These studies are limited to immunogenicity data, and do not provide data on vaccine effectiveness (e.g. against infection, severe disease, death etc), rate of decay of antibody responses, long-term immunogenicity data, or how T-cell data translates to longer term protection against severe disease/death.

COVID-19 Moderna Spikevax Bivalent WT/ BA.1 vaccine:

Immunogenicity

33. The Moderna bivalent vaccine uses a 50 µg dose (compared to Pfizer's bivalent 30 µg dose), has been found to generate a modestly higher level of antibody response against multiple SARS-CoV-2 Omicron subvariants (approximately 1.6-1.9 times) including BA.1 and BA.4/5,

and a similar antibody response against the original virus, compared with the Moderna original booster vaccine. (16)

34. Immunogenicity data from Moderna's Beta bivalent vaccine suggests that there are long-term benefits to Omicron-adapted vaccines. Although Beta neutralisation titres elicited by the Beta bivalent vaccine were similar to those that received the WT monovalent vaccine, Beta neutralisation titres remained substantially higher (~3-fold higher) six months later than that elicited by the WT monovalent vaccine. (17)

Safety

35. The safety profile of the bivalent vaccine as a booster in adults appears similar to the original vaccine. (16) There are no data on the immunogenicity or safety of the Moderna bivalent vaccine in people under 18 years of age.

36. With Moderna's BA.5/WT vaccine containing the same combination of Pfizer's WT and Omicron BA.4/5 mRNA encoding, we could infer these data as also being applicable to Pfizer's BA.4/5 vaccine.

Use of Pfizer's bivalent vaccine by other jurisdictions

37. Table 1 provides on overview of approval and availability of mRNA bivalent vaccines in other Five Eyes countries.

38. More information on peak body advice is available in Appendix 1.

	Bivalent Pfizer-BioNTech Booster		**Bivalent Moderna Booster**		
Country	Approved	Available	Approved	Available	**Reference**
United States of America	Yes***, +	BA.4/5	Yes *** (6 years), +	BA.4/5	FDA, Moderna, Pfizer
United Kingdom	Yes**	BA.1	Yes*	BA.1	JCVI, Pfizer, Moderna
Canada	Yes	BA.1	Yes	BA.4/5	Moderna, Pfizer
Australia	Yes	BA.1	Yes	BA.1	Moderna, Pfizer

* = Available from 18 years old
** = Available from 12 years old
*** = Available from 5 years old
+ = Monovalent mRNA vaccines are no longer authorized as booster doses in the U.S.

Table 1: Approval and availability of mRNA bivalent vaccines

Other considerations

39. As vaccine hesitancy towards receiving further boosters has been increasing with less uptake of each dose, health officials internationally have raised concerns about vaccine wastage and the need to make more carefully informed vaccine purchases. With some countries such as Canada, rolling out BA.5 vaccines only eight weeks after BA.1, concerns have been raised about vaccine redundancy and the impact this may have on vaccine uptake.

Recommendations

40. CV TAG met on 8 November 2022 to discuss the use of Pfizer's bivalent BA.4/5 vaccine.

41. **CV TAG noted that**:

    a. The New Zealand population has high levels of hybrid immunity, particularly against Omicron variants. However, in line with international evidence, vaccine effectiveness against severe disease from booster doses is likely to be decreasing over time, with much of the population having received a booster dose more than 6 months prior.

    b. With COVID-19 related hospitalisations on the rise and increasing number of sub-variants emerging with immune-evasive properties (such as BQ1.1 and XBB), there is a need to ensure the population is well protected and has access to the most effective vaccines.

    c. Data on Pfizer's B.4/5 bivalent vaccine are still emerging, and longer-term studies are required to assess vaccine effectiveness including breadth and duration of protection.

    d. Available data indicate that Pfizer's BA.4/5 vaccine is suitable for use as a booster dose for all people eligible for an adult formulation of a booster dose.

    e. Emerging data suggest that BA.5-containing bivalent booster vaccines provide a broader level of humoral immunity against Omicron subvariants (BA.1, BA.5, BA.2.75.2, and BQ.1.1) when compared to monovalent boosters.

    f. Data from Moderna's bivalent vaccine indicate positive long-term benefits from Omicron-adapted vaccines.

    g. The BA.5 sub-variant remains the predominant COVID-19 variant in New Zealand (over 84% of COVID-19 cases), and emerging variants such as BQ1.1 are also more closely related to BA.5 than to BA.1 or WT. Therefore, rolling out the updated Pfizer vaccine which target the BA.4/5 variants is likely to be more effective in the New Zealand context, than the use of original formulations.

    h. "Variant chasing" is not a long-term solution, and vaccine strategy for 2023/4 need to consider vaccines which strengthen breadth and duration of protection.

    i. A National Immunisation Technical Advisory Group (NI TAG) will be established in 2023, which will continue to monitor all relevant information (including vaccine effectiveness data against variants of concern and emerging evidence on the duration of immunity) and to update their recommendations as further evidence becomes available.

42. **CV TAG recommends that:**

    a. Closing the gaps in vaccine uptake and coverage in Aotearoa New Zealand takes priority over the type or composition of the COVID-19 vaccine offered. As previously noted, the immediate emphasis should be on extending the uptake of first boosters for all eligible people.

b. People who are due for a booster should not delay receiving one in anticipation of the bivalent vaccine becoming available.

c. Based on currently available data, once available, it would be preferable to use Pfizer's updated BA.4/5 bivalent COVID-19 vaccine, in place of Pfizer original monovalent wild-type vaccine for both primary courses and all booster doses for people aged 16 years and over.

d. In line with previous recommendations, booster doses should not normally be offered less than 6 months after the most recent dose of COVID-19 vaccine and not less than 3 months after SARS-CoV-2 infection.

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