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SCIENCE & TECHNICAL ADVISORY | RŌPŪ TOHUTOHU I TE PŪTAIAO ME TE HANGARAU

Request for Advice (RfA)

MINISTRY OF HEALTH
MANATŪ HAUORA

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	Rapid review of current data on extended dosing intervals for the Pfizer/BioNTech COVID-19 vaccine.		
Subject	Vaccines		
Reference No.	274	Date Received	29/07/2021
Requestor	Ashley Bloomfield (DG), CV TAG	Date Due	3/08/2021
Advisor	s 9(2)(a)	Date Completed	5/08/2021
Peer reviewed by	s 9(2)(a)		
Advice issued to	CV TAG		
Approved by	Ian Town		
Deliverables	RfA, Memo on recommendations for dosing interval for Pfizer/BioNTech COVID-19 vaccine		
Request Outline	**Background/Context** • The DG requested a brief update on the emerging concept that we should have a longer interval between doses for everyone, as part of our recommendation on myocarditis for a longer interval for the under 30 year-olds. • A recommendation of a longer interval for the whole population might have several advantages if evidence suggests that a longer interval (than the current 3 week interval) has no deleterious impact on safety or efficacy. If a change to a longer interval is recommended for a subgroup of the population, then recommending this to the whole population may be easier to communicate. • Many countries have a longer interval than 3 weeks for the Pfizer/BioNTech COVID-19 vaccine as standard, including the UK, Canada, and several European countries, with intervals ranging from, approximately, 8 to 16 weeks. • The initial reasons for extending the dosing interval were practical (e.g., covering more of population with at least one dose quickly in an active pandemic situation) and scientific (e.g., prior scientific consensus and basic principles of vaccinology and immunology suggested that, in general, intervals longer than 3 weeks are usually required between the prime and booster doses in order to maximise the immune response). However, it remains true that only		

	the 3 week interval has been evaluated in a Phase 3 clinical trial for safety and efficacy. • This short briefing reviews the recent data from the UK; covers the potential benefits and rollout experiences; and includes a summary of immunogenicity and reactogenicity data. **Questions** 1. What is the evidence for efficacy/effectiveness and safety of mRNA COVID-19 vaccines when using a shorter versus a longer interval between first and second doses? This can included immunological, epidemiological, and other evidence. **Intended application of advice** • RfA to CV TAG for their consideration of the appropriate dosing interval for the Pfizer/BioNTech COVID-19 vaccine Timeline • Draft report to send to CV TAG 02 August 2021 for their review, ahead of the CV TAG meeting 03 August 2021
What are the implications and considerations of this advice on Te Tiriti o Waitangi and equity?	• Data on vaccine efficacy/effectiveness, immunological response, and other data with regard to ethnic differences will be reviewed. • Data on the impact of extending the dosing interval on the immunisation program and vaccine coverage in Māori and Pacific Peoples will be reviewed.

Response to Request for Advice

Key Points

- Data is very limited on extended dosing intervals for the Pfizer/BioNTech COVID-19 vaccine and the impact efficacy and safety. However, emerging data suggests that the immune response is likely improved somewhat by extending the dosing interval. One study that found improved immunogenicity for the longer interval compared a median interval of 3.4 weeks to a median of 10 weeks.[1]
- This is consistent with basic principles of vaccinology and immunology, that suggests that immune responses are generally better with longer intervals.
- Several countries have been using extended intervals, ranging from approximately 6-16 weeks for the Pfizer vaccine for their general populations, including England, Canada, and several countries in Europe. Population data from those countries suggest that the vaccine effectiveness for

Pfizer/BioNTech is high (e.g., 85%-88% for symptomatic disease against the Delta variant). The reported safety profiles appear similar to countries with shorter intervals, such as the US (the US recommends 3 weeks, but allows for up to 6 weeks if 3 weeks is not possible).

- Although the data outside of clinical trials is promising for longer intervals, the efficacy and safety for longer dosing intervals have not been evaluated in large phase 3 clinical trials, and STA is unaware of any clinical trial data that is expected to become available.

Summary of data from extended dosing intervals

- In December 2020, the UK chose to extend the recommended Pfizer dosing regimen of 3 weeks to about 12 weeks to avert deaths and prevent hospitalisation due to severe COVID-19, in the context of an active pandemic in the UK. This facilitated the rapid roll-out of one dose of SARS-CoV-2 vaccine providing a degree of cover as quickly as possible to reduce severe disease in a large proportion of higher-risk groups.
- In a summary of the evidence behind this decision in the British Medical Journal in January 2021, authors acknowledged that there were no clinical trial data evaluating the extended dosing interval for the Pfizer vaccine.[2] However, there are data on AstraZeneca for extended dose, and this is sometimes cited to show that extended intervals may maintain or improve effectiveness for COVID-19 vaccines in general, based on general immunological principles. A post-hoc analysis of the clinical trials for the AstraZeneca COVID-19 vaccine, found that vaccine efficacy 14 days after a second dose appeared to be higher in the group that had more than six weeks between the two doses (65.4%, 95%CI: 41.1-79.6%) than in the group that had less than six weeks between doses (53.4%, 95%CI: -2.5-78.8%).[3] The authors noted that there was limited data on mRNA COVID-19 vaccines specifically, but, quoting Andrew Pollard (head of the Oxford Vaccine Group and chief investigator in the AstraZeneca trial), commented that "*Generally, a longer gap between vaccine doses leads to a better immune response*…" and that, broadly speaking, the underlying biology is similar across vaccines: *"…the immune system remembers the first dose and will respond whether the later dose is at three weeks or three months*.".
- A UK study published as a pre-print in May 2021 showed that elderly (over 80 years) participants vaccinated with a 12 week interval of Pfizer had a 3.5-fold higher peak spike-specific antibody response, but a 3.6-fold lower peak T-cell response compared to those vaccinated with the recommended 3 week interval.[4] Neutralising antibodies (NAbs) were not measured but spike-specific antibody and neutralising antibody responses have been highly correlated in previous studies of the Pfizer vaccine.
- Another non-peer reviewed UK study published as a pre-print on 23 July 2021 assessed immunogenicity after short (2-5 weeks) and long (6-14 weeks) dosing intervals of Pfizer in healthcare workers (21-71 years).[1] The median interval in the long interval group was 10 weeks. Following the first dose, there was limited detection of neutralizing antibodies (Nabs) against the Beta (B.1.351) and Delta (B.1.167.2) variants, but NAbs were observed against Gamma (P.1) and the original Victoria strain. Antibody levels (binding and neutralising) decreased markedly during the

extended dosing interval but were boosted following the second dose. In addition, higher binding and NAb titers were observed in infection-naïve individuals vaccinated using the long interval regimen, with a 2-4 fold increase in titer, depending on the variant tested. In contrast to antibody responses, spike-specific T cell responses were maintained during the 10 weeks following the first dose, with responses further boosted by the second dose in those who were infection-naïve. However, the longer dosing interval led to a modestly lower T cell response compared to the shorter interval. Overall, T cell data indicated that a shorter dosing interval in infection-naïve individuals led to a modestly higher effector T cell response and the longer interval a deeper T cell memory response, but the overall clinical impact of this result is currently unclear.

- In general, it is not known how these antibody and cellular responses impact the effectiveness and duration of protection provided by the vaccine. However, these preliminary immunogenicity data following are encouraging and are in line with results from several UK studies that report high effectiveness of the Pfizer vaccine following the extension of dosing interval in December 2020.
- Extending the dosing interval means that more people will have only received one dose for an extended period of time. Vaccine effectiveness against symptomatic disease for Pfizer, particularly against the prevalent Delta variant, is low after one dose: Delta 35.6% (95% CI: 22.7-46.4%), Alpha 47.5% (95% CI: 41.6–52.8).[5] After two doses, the vaccine effectiveness was 88.0% (95%CI: 85.3-90.1%) for the Delta variant, and 93.7% (95% CI: 91.6–95.3%) for the Alpha variant. With regard to severe disease, vaccine effectiveness remained ve y high: vaccine effectiveness against hospitalisation was estimated in the same data to be 96% (95%CI: 86-99) with Delta. However, the risk from COVID-19 is lower in low-prevalence country, but remains an issue for an outbreak situation. Note that these estimates are based on data from the UK, where a 12-week interval for the Pfizer-BioNTech COVID-19 vaccine was used (with peaks in these data occurring and 10, 11 and 12 weeks).
- Estimates for effectiveness of a single dose of Pfizer vaccine covering time points beyond the 3-week dosing interval are between 48.6%-70% for all PCR confirmed infection/symptomatic COVID-19,[6-10] and 81-93% for severe disease/hospitalisation.[8, 11, 12] The effectiveness was calculated over a period that varied between studies but extended to a maximum of 90 days after a single dose. One study indicated that effectiveness might peak at 28-34 days after a first dose of vaccine and then plateau.[11]

International recommendations for dosing interval for Pfizer/BioNTech COVID-19 vaccine

- On 14 May 2021, the the Joint Committee on Vaccination and Immunisation (JCVI) in the UK recommended that the second dose interval be reduced from 12 to 8 weeks for people in priority cohorts 1-9 who have yet to receive their second dose.[13]
- Priority groups in England as of 23 April 2021 are given in Figure 1 (see https://www.gov.uk/government/publications/covid-19-vaccination-care-home-and-healthcare-settings-posters/covid-19-vaccination-first-phase-priority-groups). The clinical conditions that are

part of group 6, include conditions such as blood cancer, diabetes, dementia, and cardiovascular conditions.

Priority	Risk group
1	Residents in a care home for older adults and staff working in care homes for older adults
2	All those 80 years of age and over and frontline health and social care workers
3	All those 75 years of age and over
4	All those 70 years of age and over and clinically extremely vulnerable individuals (not including pregnant women and those under 16 years of age)
5	All those 65 years of age and over
6	Adults aged 16 to 65 years in an at-risk group (see clinical conditions below) [footnote 1]
7	All those 60 years of age and over
8	All those 55 years of age and over
9	All those 50 years of age and over
10	Rest of the population (to be determined)

Figure 1 Priority groups for COVID-19 vaccination from Public Health England as of 23 April 2021

- The main exception to the 8 week lower interval are those about to commence immunosuppressive treatment. In these individuals, the NHS recommends that *"…minimal intervals (21 days for Pfizer BioNTech vaccine or 28 days for Moderna and AstraZeneca vaccines) may be followed to ensure that the vaccine is given whilst their immune system is better able to respond*".[14].
- The vaccine effectiveness observed in England using the 12-week dosing interval for Pfizer/BioNTech COVID-19 vaccine has been high, even against variants of concern: vaccine effectiveness against symptomatic disease was 93.7% (95% CI: 91.6 - 95.3%) among persons with the alpha variant and 88.0% (95% CI: 85.3 - 90.1%) among those with the delta variant.[5] With regard to safety, broadly speaking, the safety profile for the Pfizer/BioNTech COVID-19 vaccine that has been observed in England is consistent with that observed globally.[15]
- In Europe, the EMA recommends an interval of 3 weeks for the Pfizer/BioNTech COVID-19 vaccine, but allows up to 42 days: the product information states that the participants in the phase 3 trial received their second dose within 19 to 42 days after their first dose, with the majority (93.1%) of the participants receiving the second dose 19 to 23 days after the first dose.[16] Several countries in Europe have employed extended dosing intervals for Pfizer, such as Denmark and Norway, with the recommended intervals ranging between 6 and 12 weeks, although recommendations in different countries have changed over time in response to the changing pandemic situation.
- Th United States has consistently recommended an interval of 3 weeks, allowing up to 6 weeks if the 3 week interval is not possible.[17] However, in general, the safety profiles and efficacy data as described by the Summary of Product Characteristics[16] in Europe (EMA) and in the Fact Sheet for

Healthcare Providers Administering Vaccine (Pfizer-BioNTech COVID-19 vaccine) in the US (FDA)[18] are similar.

- In Canada, in early March 2021, the immunisation schedule for the Pfizer COVID-19 vaccine extended the interval from 3-4 weeks to an interval of up to 16 weeks (4 months).[19] The National Advisory Committee on Immunization (NACI) rationale for extending the dosing interval is consistent with those cited by JCVI and others, namely that extending the dosing interval provides some protection to more of the population quickly, while likely ultimately improving the immune response: "*Extending the interval to the second dose of a COVID-19 vaccine maximizes vaccine supply to immunize the largest number of people as quickly as possible. Principles of immunology indicate that a longer interval between priming and boosting doses of a vaccine series results in a better, more durable response*". Effectiveness in Canada also appears to be high even against the Delta variant, with vaccine effectiveness of 85% (95% CI: 59 - 94%) from 14 days after two doses.[20]
- ATAGI recommends that the second dose of the Pfizer/BioNTech COVID-19 vaccine be administered within 3 to 6 weeks after the first.[21]
- There are no data on dosing interval for the Pfizer/BioNTech vaccine stratified by ethnicity. However, generally speaking, any approach associated with increasing the immune response, may provide greater protection in people with pre-existing conditions, such as obesity or diabetes, that are associated with lower vaccine efficacy; these conditions also tend to have a greater prevalence in Māori and Pacific Peoples in Aotearoa New Zealand.

Other considerations

- Arguably, extending the dosing interval for the general population, instead of only for those in the 16-29 year-old age group, could remove the potential for concerns and vaccine hesitancy in the younger age group, while potentially maintaining, or even improving, the overall effectiveness for the general population. However, ultimately the impact on vaccine hesitancy or acceptance is unknown.
- With regard to practical considerations, an extension of the dosing interval for all groups may also be more efficient to co-ordinate, compared to restricting the extension of the dosing interval to people under 30 years. However, changing the dosing interval for everyone may impact the completion of the rollout, and may mean a delay in delivering full protection to high-risk populations, such as the elderly and those with comorbidities.

Next Steps	Draft memo, including noting considerations for extended dosing interval
In the development of this work, the following parties have been consulted with:	CV TAG for final review

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	

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