Canadian experience and evidence with COVID-19 vaccine primary series extended intervals

February 4, 2022
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Public Health Agency of Canada
Outline

• Canadian program context

• Highlights of evidence informing Canadian recommendations
  – One dose effectiveness and duration
  – Immunogenicity with longer intervals
  – Effectiveness with longer intervals
  – Safety with longer intervals
Canada’s National Advisory Committee on Immunization (NACI) has been providing advice on COVID-19 vaccine intervals since 2020

- Within the Terms of Reference, even under a regulatory Interim Order throughout much of the pandemic, NACI was permitted to issue off-label advice on COVID-19 vaccines as per usual.
- NACI has provided several updates on extended intervals for the primary series as the evidence evolved:

<table>
<thead>
<tr>
<th>Advice</th>
<th>Date</th>
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<tbody>
<tr>
<td>Alternate interval of 28 days for Pfizer-BioNTech - NACI</td>
<td>December 12, 2020</td>
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<td>Quebec’s provincial immunization committee (CIQ) recommends first doses to all priority groups before second doses</td>
<td>December 18, 2020</td>
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<td>JCVI in the UK recommends 3-12 week interval for Pfizer-BioNTech, 4-12 weeks for AZ, to maximize first doses to priority groups</td>
<td>December 30, 2020</td>
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<td>Alternate interval preferably within 42 days for mRNA vaccines to maximize first doses to priority groups – NACI</td>
<td>January 12, 2021</td>
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<td>Up to 4 month interval for all COVID-19 vaccines - NACI</td>
<td>March 03, 2021</td>
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<td>(full statement April 07, 2021)</td>
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<td>Optimal interval of 8 weeks for adolescents and adults - NACI</td>
<td>October 22, 2021</td>
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<td>At least 8 weeks (5-11 years) - NACI</td>
<td>November 19, 2021</td>
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<td>4-8 weeks, preferentially 8 weeks – WHO/SAGE</td>
<td>January 21, 2022</td>
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Core principles informing NACI interval recommendations

- Extended interval recommendations for up to 16 weeks were informed by the following key principles:
  - Triggered by initial limited supply
  - Early vaccine effectiveness assessments of strong 1-dose protection from mRNA clinical trials and Israel, and later from Canada and UK research/surveillance
  - AstraZeneca 2-dose clinical trial showing longer intervals yield better vaccine efficacy
  - Modelling to optimize program impact (in context of limited supply)
  - Immunology/vaccinology principles
  - Equity, ethics, feasibility, acceptability

- The subsequent move to an 8-week interval was additionally informed by:
  - Canadian and UK vaccine effectiveness data demonstrating increased protection with longer intervals, plateau around 8 weeks
  - Immunological data on breadth and duration of immune response with longer interval
  - Canadian safety surveillance showing lower rates of myocarditis with longer interval
  - Equity, ethics, feasibility, acceptability
Immunologic principles regarding longer intervals

1) **Affinity maturation:** The longer interval between primary and secondary antigen exposures allows immune memory cells more cycles of affinity maturation to develop higher affinity. This may increase the breadth and/or the neutralization activity of immune responses.

2) **Less potential for immune interference:** Circulating antibodies may interfere with the immune responses of subsequent antigen exposures for two reasons:

   a) **Epitope Masking:** Circulating antibodies may occupy antigen binding sites on the surface of the vaccine antigen.

   b) **Reducing antigen availability:** Antibodies bound to their targets (immune complexes) are cleared via liver and spleen and reduce the pool of available antigen.
Vaccine effectiveness between dose 1 and 2

- Review of one dose vaccine effectiveness published in National Advisory Committee on Immunization (NACI) statement on April 7, 2021

- For the mRNA vaccines, the one-dose vaccine effectiveness data is generally between 60 and 80%, with some lower and some higher estimates

- Lower than the one-dose efficacy from the clinical trials (92%) and lower than the two-dose effectiveness data (88% to 95%) and two-dose efficacy data (94% to 95%)

- Protection higher against more serious outcomes (~80% or more)
Duration of protection from symptomatic infection with one dose of Pfizer-BioNTech in England

Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications
Serologic response in previously uninfected people vaccinated with two doses of Pfizer-BioNTech CONSENSUS cohort in England n=750; 50 years of age and over

<table>
<thead>
<tr>
<th>Interval between dose 1 and 2</th>
<th>Geometric mean titre (Roche Elecsys anti-S)</th>
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<tbody>
<tr>
<td>19 to 29 days</td>
<td>Blood collected 14 to 34 days after dose 2 (n=80)</td>
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<tr>
<td>65 to 84 days</td>
<td>Blood collected at 7 to 13 days after dose 2 (n=133)</td>
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<tr>
<td></td>
<td>Blood collected at 14 to 34 days after dose 2 (n=200)</td>
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<tr>
<td>85 or more days</td>
<td>Blood collected at 7 to 13 days after dose 2 (n=9)</td>
</tr>
</tbody>
</table>

Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications
Post dose 2 vaccine effectiveness of Pfizer-BioNTech based on interval between dose 1 and 2

80+ years of age before Jan 4, 2021
80+ years of age after Jan 4, 2021
65 to 79 year olds
50 to 64 year olds

Intervals between doses

Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications
mRNA vaccine effectiveness against infection and hospitalization by interval
Quebec and British Columbia; May 30 to October 2, 2021; ≥ 18 years of age

A. Any two mRNA vaccines

Skowronski et al, 2021 (Preprint) Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada

https://www.medrxiv.org/content/10.1101/2021.10.26.21265397v1
Figure 6. Adjusted two-dose vaccine effectiveness against infection by interval between doses and time since second dose, BNT162b2, ≥18-year-olds, British Columbia and Quebec, Canada

Skowronski et al, 2021 (Preprint) Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada https://www.medrxiv.org/content/10.1101/2021.10.26.21265397v1
mRNA vaccine effectiveness against infection by time since second dose and interval – Ontario; January to November 2021; ≥16 years of age

Kwong et al. Effectiveness of COVID-19 vaccines over time in Ontario. Presentation January 24, 2022

Time since second doses

Delta longer interval ≥8 weeks
Delta intermediate interval 5 to <8 weeks
Delta shortest interval 2 to <5 weeks
Vaccine effectiveness and immunogenicity summary

- One dose provides approximately 60 to 70% vaccine effectiveness that lasts out to about 8 to 10 weeks.
- One dose protection is higher against severe disease than infection.
- The longer interval between primary series doses results in a higher antibody response.
- The longer interval between primary series doses results in somewhat higher vaccine effectiveness.
Canadian dosing interval by jurisdiction (all vaccines, all ages)

- Majority (52%) had an interval of 50-77 days
- Very few (4%) received their 2nd dose within 28 days of the 1st
- 3 groups:
  - Territories had shorter dosing intervals
  - AB, SK, MB, ON, NB, and NS had more evenly distributed dosing intervals
  - BC, QC, NL, and PE had larger dosing intervals

Figure 2. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses, August 14, 2021.

Figure 3. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses and province or territory of residence, August 14, 2021.
Myocarditis/pericarditis cases following mRNA COVID-19 vaccines in Ontario, Canada, by vaccine product, schedule, and interval, 7-day risk period

- The reporting rate of myocarditis or pericarditis was higher following the second dose of mRNA vaccine than after the first dose, particularly for those individuals receiving Moderna as the second dose of the series.

- The highest reporting rate of myocarditis/pericarditis was observed in males aged 18-24 years following Moderna as the second dose; the rate in this age group after Moderna was 5.1 (95% CI: 1.9 to 15.5) times higher than the rate following Pfizer-BioNTech as the second dose.

- For both vaccine products, overall reporting rates were higher when the interval between doses was shorter (i.e., ≤30 days).

- Among individuals who received Moderna for the second dose, rates were higher for those who had a heterologous as opposed to homologous vaccine schedule.

- Conclusions and relevance: results suggest that vaccine product, inter-dose interval and vaccine schedule combinations may play a role in the risk of myocarditis/pericarditis, in addition to age and sex.

- Ongoing analyses of national passive surveillance from the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) (which includes the Ontario dataset) supports the same interval trend.

Buchan et al, Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval | medRxiv
For both vaccine products, overall myocarditis/pericarditis reporting rates were higher when the interval between doses was shorter (i.e., ≤30 days).

Overall, unadjusted rate ratios comparing ≤30 days vs. ≥56 days were similar:

- Moderna (RR= 5.2, 95% CI: 2.6 to 10.0)
- Pfizer-BioNTech (RR=5.5, 95% CI: 3.1 to 9.6).
Myocarditis/pericarditis Canadian summary

- Myocarditis/pericarditis risk after vaccination appears to be higher in Moderna recipients versus Pfizer-BioNTech recipients.
- Risk is several fold higher in young males aged 18-29 years after dose 2.
- Shorter dose interval and mRNA schedule with Moderna as second dose appears to be associated with higher reporting rates.

References:
- Sarah A Buchan et al. (2021) Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval. [https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1](https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1)
- Myocarditis and pericarditis risk after mRNA vaccination: A population-based analysis of the effect of inter-dose interval and vaccine combination in Canada (In development)
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• Joshua Montroy
• Kelsey Young
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Project Management Support: N St-Pierre, K Ramotar
Current NACI interval recommendations

• 5 to 11 years olds (general population): At least 8 weeks between the first and second doses in the primary series

• 12 years of age and over (general population): 8 weeks between the first and second doses in the primary series

• Moderately to severely immunocompromised (5 years of age and over): 4- to 8-week interval between each dose in the primary series

• Booster dose (18 years of age and over): At least 6 months between the primary series and the booster
Canadian dosing interval by age group

- Majority of most age groups had an 50-77 day interval
- 12 to 17 year olds (8%) and ≥80 year olds (10%) had the highest proportion of recipients who completed their series within 28 days
- While the percent of recipients with a 29-49-day interval decreased with increasing age, the opposite was true for the ≥78 day interval

Figure 4. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses and age group, August 14, 2021.