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

February 4, 2022

Presenters: Dr. Matthew Tunis, Dr. Bryna Warshawsky, Susanna Ogunnaike-Cooke

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:

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

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

Age 50 to 64 years

Age 65 to 79 years

Age 80 years
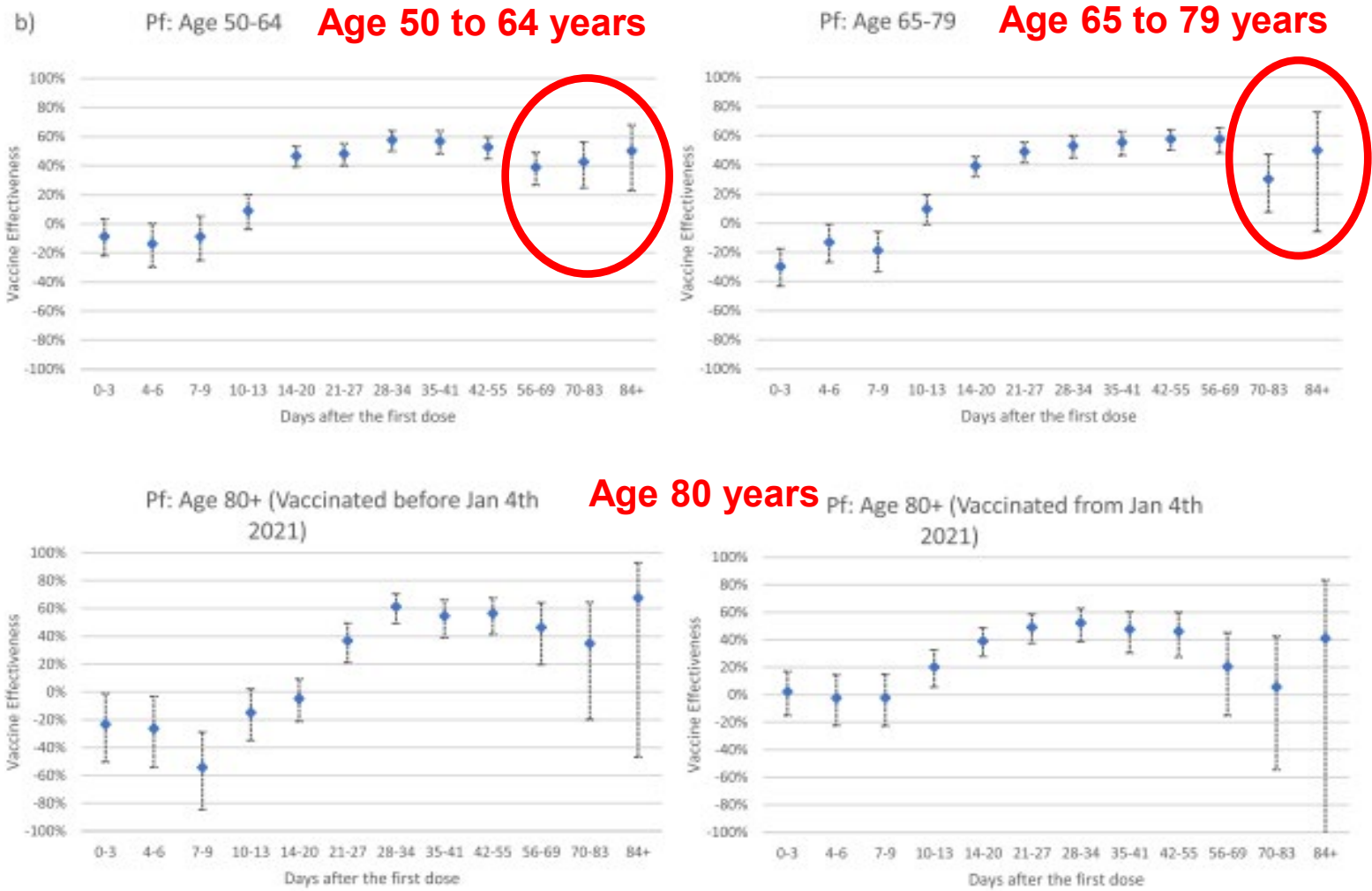
Days after first doses

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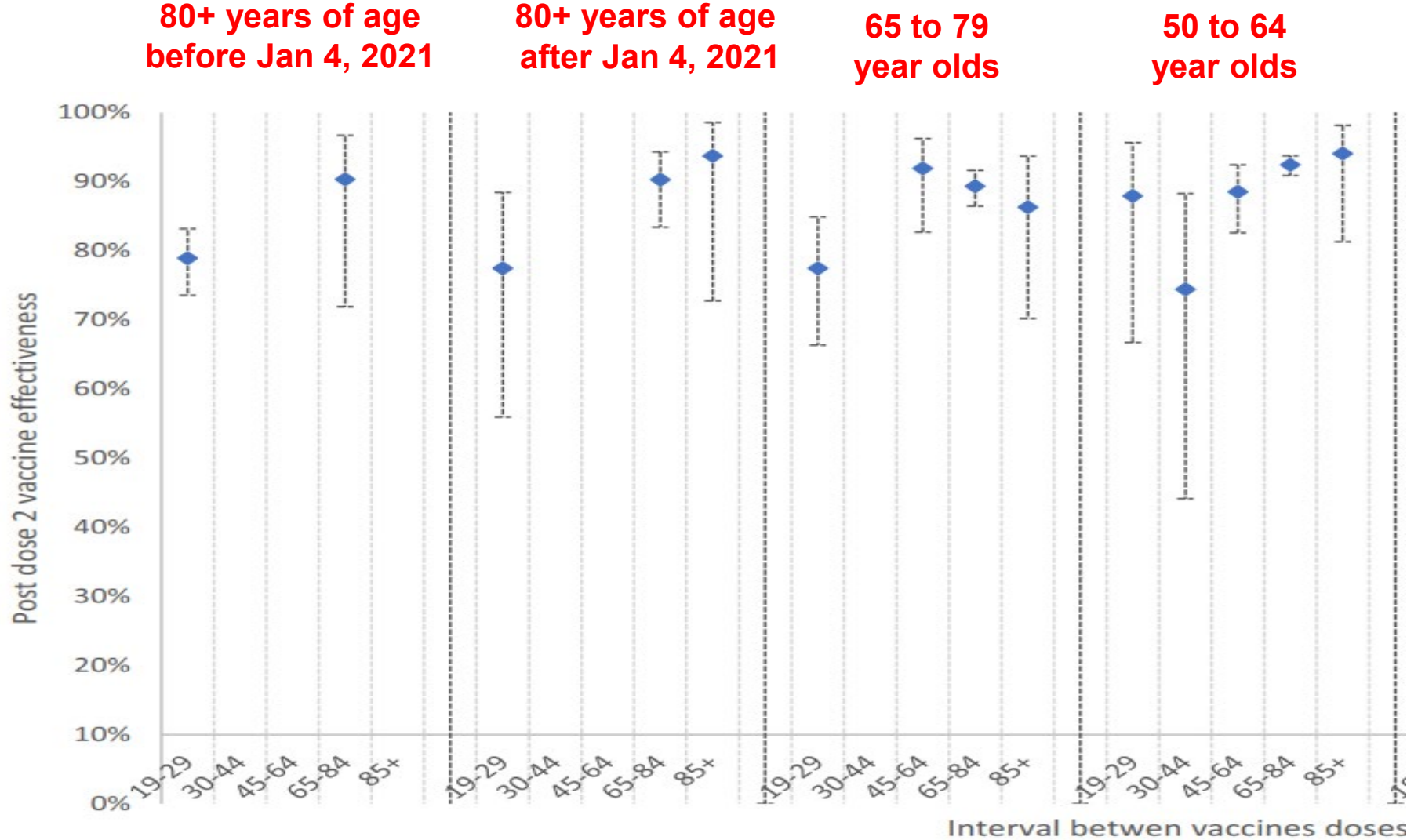
Serologic response in previously uninfected people vaccinated with two doses of Pfizer-BioNTech CONSENSUS cohort in England n=750; 50 years of age and over

Interval between dose 1 and 2	Geometric mean titre (Roche Elecsys anti-S)
19 to 29 days Blood collected 14 to 34 days after dose 2 (n=80)	**694** (95% CI: 540 to 893)
65 to 84 days Blood collected at 7 to 13 days after dose 2 (n=133) Blood collected at 14 to 34 days after dose 2 (n=200)	**7,198** (95% CI: 5,820 to 8,902) **6,703** (95% CI: 5,887 to 7,633)
85 or more days Blood collected at 7 to 13 days after dose 2 (n=9)	**14,437** (95% CI: 4,136 to 50,391)

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

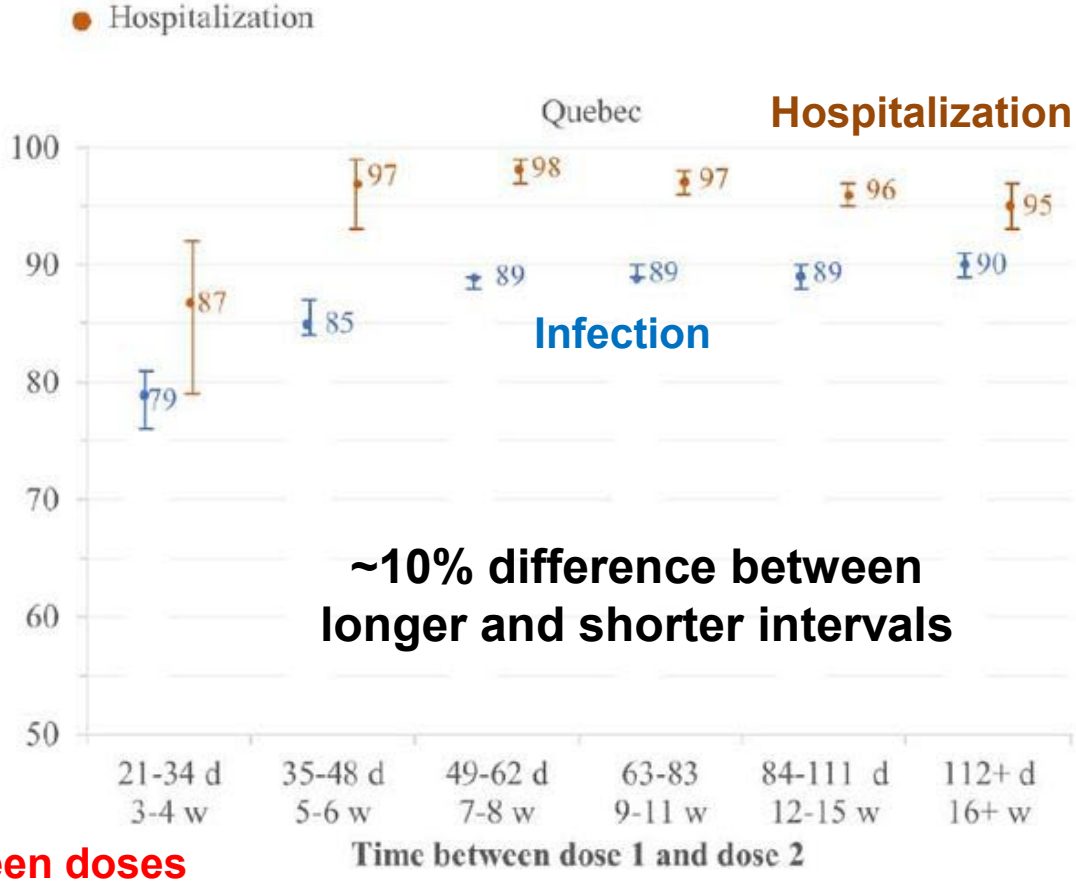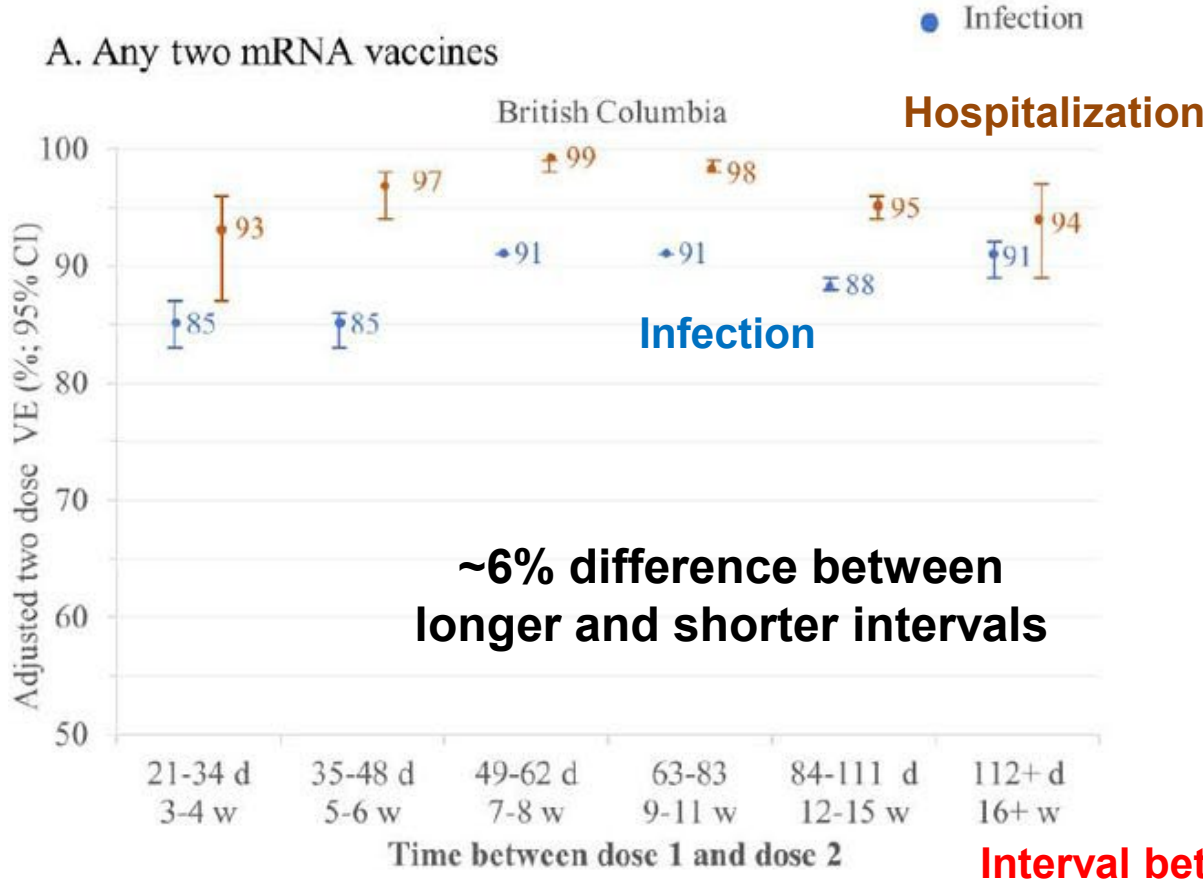80+ years of age after Jan 4, 2021

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

British Columbia

Quebec

● Infection   ● Hospitalization

A. Any two mRNA vaccines

Hospitalization (British Columbia)

Infection

~6% difference between longer and shorter intervals

Hospitalization (Quebec)

Infection

~10% difference between longer and shorter intervals

Interval between doses

Pfizer-BioNTech vaccine effectiveness against infection by time since second dose and interval - Quebec and British Columbia

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
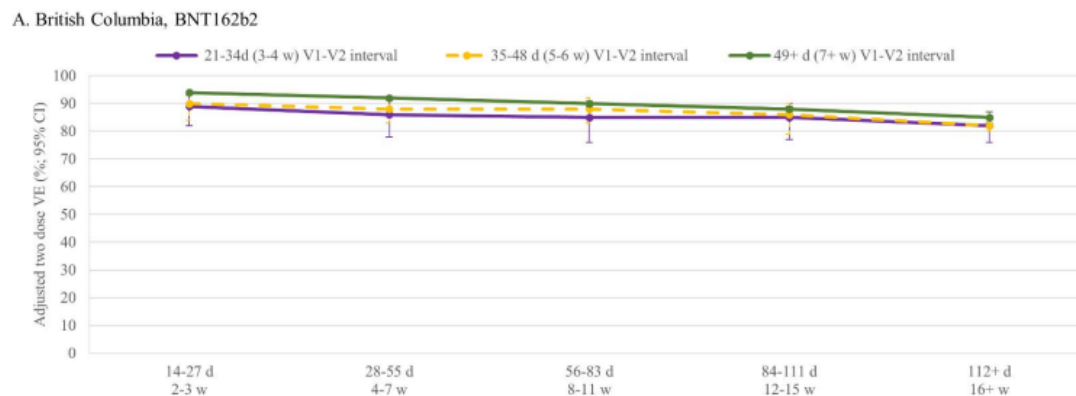
Skowronski et al, 2021 (Preprint) Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada
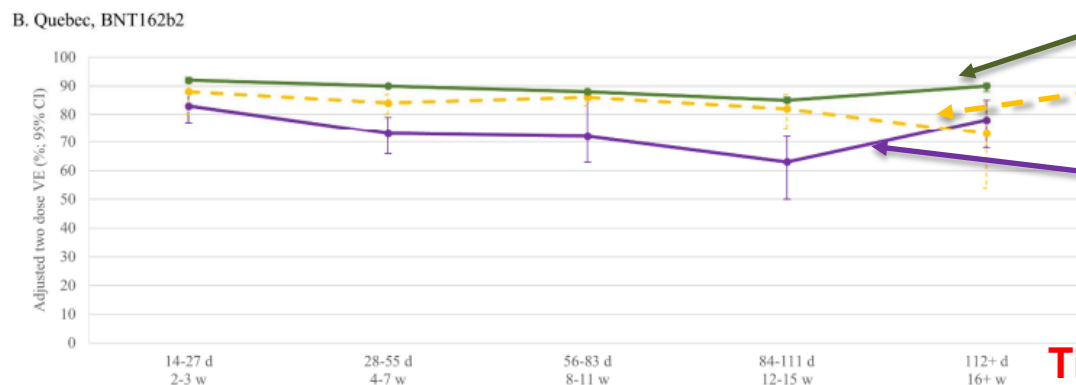https://www.medrxiv.org/content/10.1101/2021.10.26.21265397v1

British Columbia

Quebec

7+ week interval

5 to 6 week interval
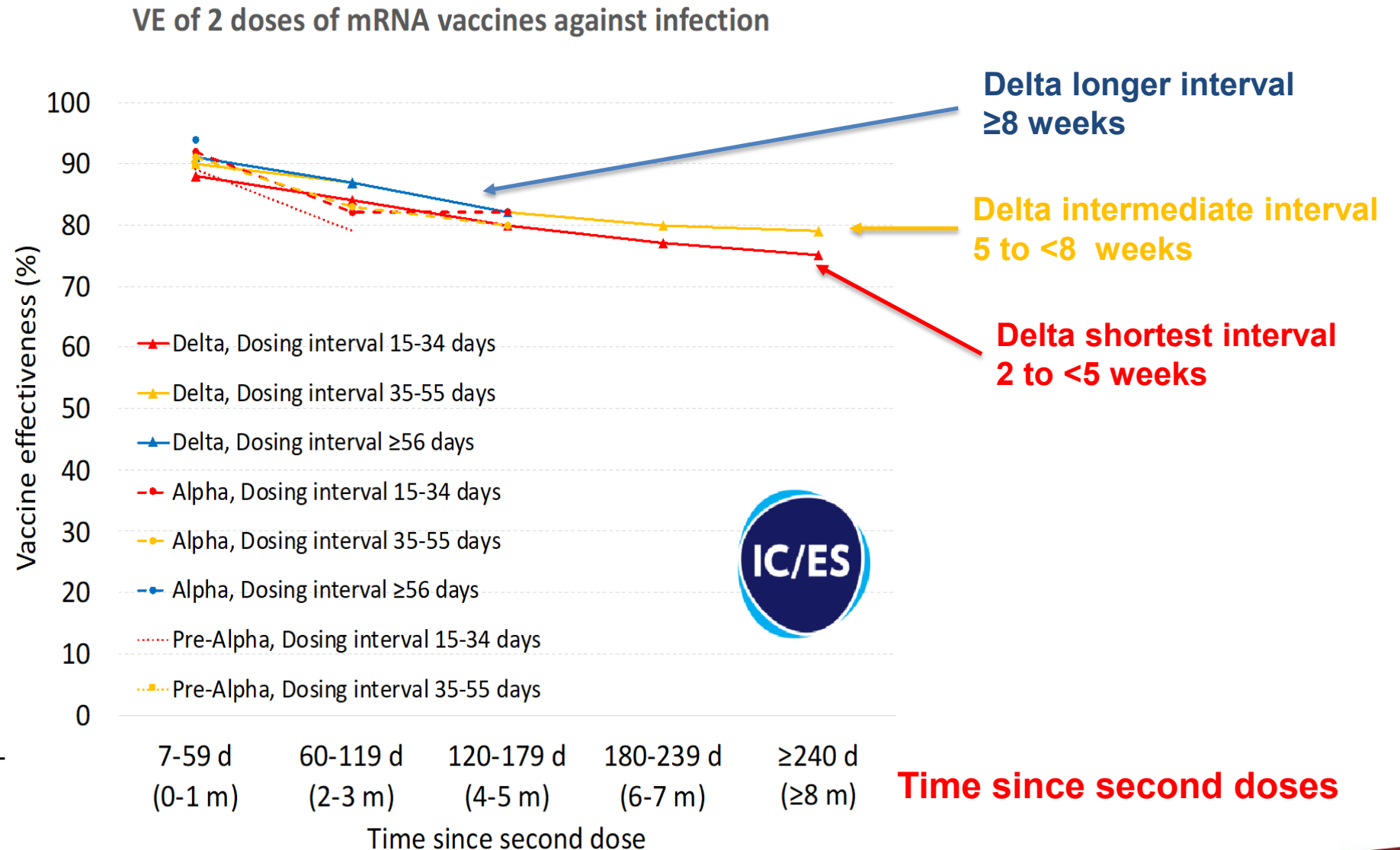
3 to 4 week interval

Time since second doses

Shown are adjusted vaccine effectiveness (VE) estimates and 95% confidence intervals (CI) against infection (timed on specimen collection date) by interval between the first and second dose (3-4 weeks in purple; 5-6 weeks in dashed yellow; 7+ weeks in green) and time since the second dose among adults ≥18 years old who were vaccinated with two BNT162b2 vaccines in the provinces of British Columbia (BC) and Quebec. All VE estimates are adjusted for age group (18-49, 50-69, 70-79, ≥80 years); sex (men, women); individual epidemiological week of the analysis period (weeks 22-39, categorical); and region of the province (5 in each province). For additional details including corresponding sample sizes and precise unadjusted and adjusted estimates and 95%CI, see Supplementary Table 19 (by vaccine type, including mRNA combined and by mRNA vaccine type, as well as ChAdOx1).

mRNA vaccine effectiveness against infection by time since second dose and interval – Ontario; January to November 2021; ≥16 years of age

VE of 2 doses of mRNA vaccines against infection

Delta longer interval ≥8 weeks

Delta intermediate interval 5 to <8 weeks

Delta shortest interval 2 to <5 weeks

Time since second doses

Legend:
- Delta, Dosing interval 15-34 days
- Delta, Dosing interval 35-55 days
- Delta, Dosing interval ≥56 days
- Alpha, Dosing interval 15-34 days
- Alpha, Dosing interval 35-55 days
- Alpha, Dosing interval ≥56 days
- Pre-Alpha, Dosing interval 15-34 days
- Pre-Alpha, Dosing interval 35-55 days

Y-axis: Vaccine effectiveness (%)

X-axis (Time since second dose):
- 7-59 d (0-1 m)
- 60-119 d (2-3 m)
- 120-179 d (4-5 m)
- 180-239 d (6-7 m)
- ≥240 d (≥8 m)

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

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
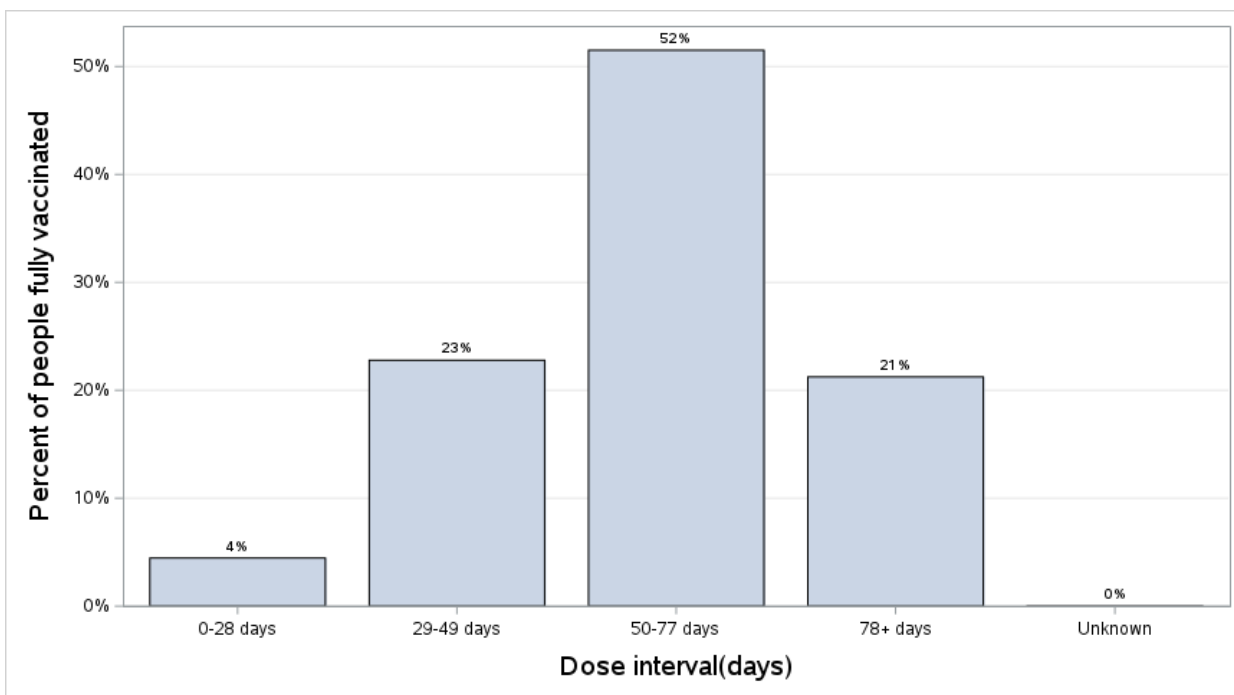 - BC, QC, NL, and PE had larger dosing intervals

Figure 2. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses, August 14, 2021.
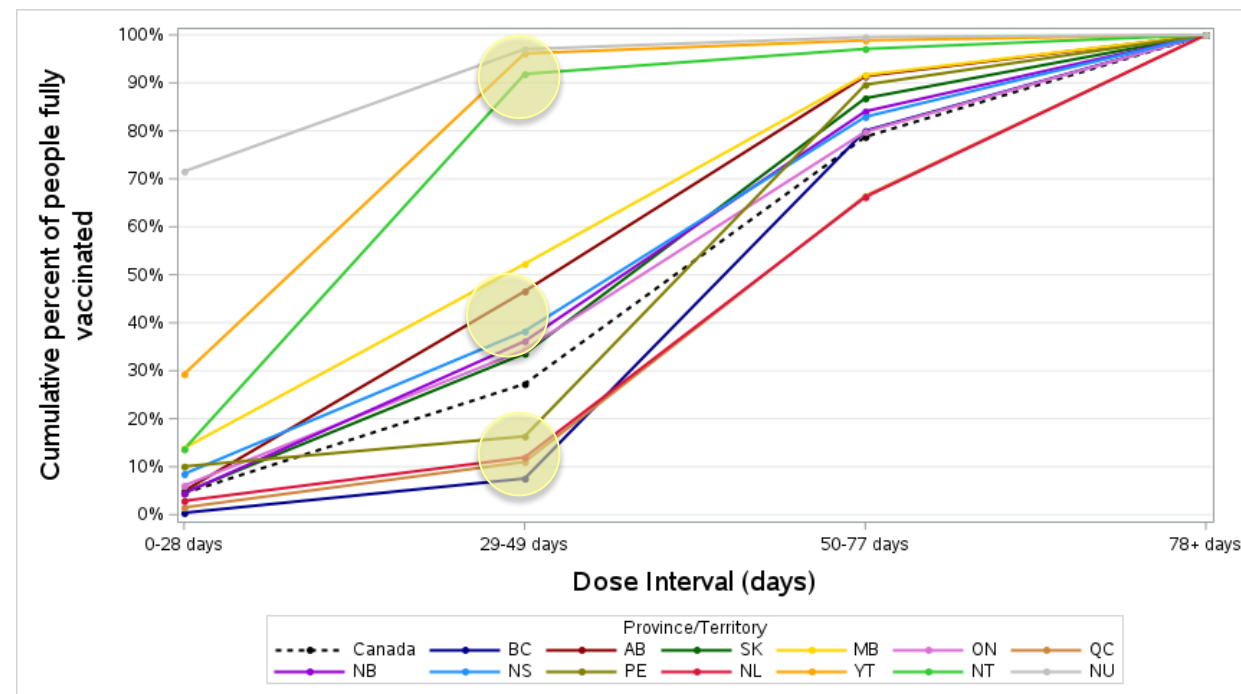
Figure 3. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses and province or territory of residence, August 14, 2021.

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

Myocarditis/pericarditis cases (≥12 years of age) following mRNA COVID-19 vaccines in Ontario, Canada, by vaccine product, schedule, and interval, 7-day risk period (n=297)*
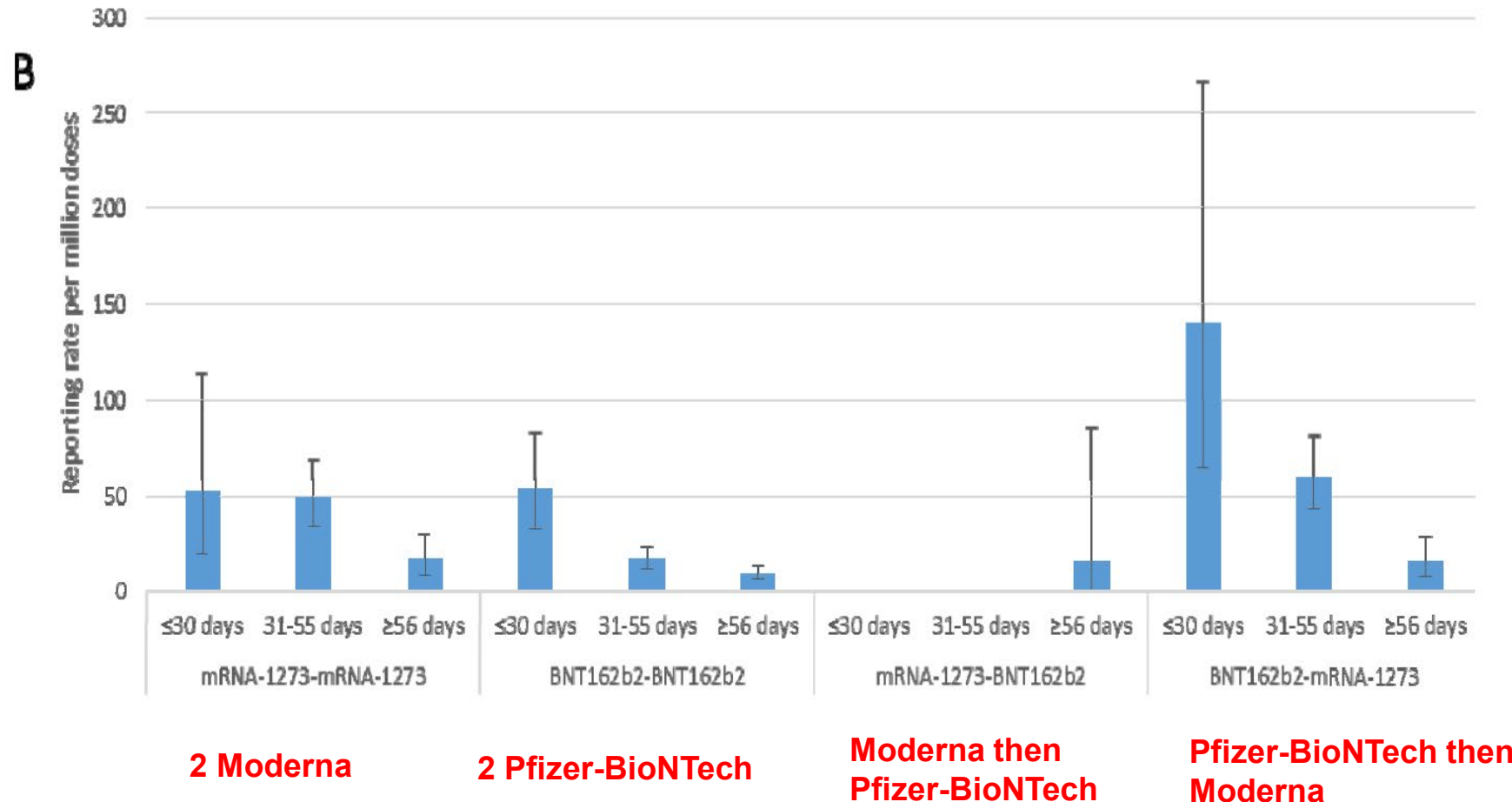
- For both vaccine products, overall myocarditis/pericarditis reporting rates were higher when the interval between doses was shorter (i.e., ≤30 days).

- 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).

2 Moderna **2 Pfizer-BioNTech** **Moderna then Pfizer-BioNTech** **Pfizer-BioNTech then Moderna**

*Overall reporting rate of myocarditis/pericarditis among people who have completed their two-dose series with dose 2 on or after June 1, 2021 by homologous/heterologous schedule by inter-dose interval

Buchan et al, Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval | medRxiv

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:

- Natalia K Abraham et al. (2021) Myocarditis and/or Pericarditis Risk After mRNA COVID-19 Vaccination: A Canadian Head to Head Comparison of BNT162b2 and mRNA-1273 Vaccines https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3988612
- 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
- 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)

Acknowledgements

- Dr. Natalia Abraham
- Dr. Marina Salvadori
- Dr. April Killikelly
- Dr. Joseline Zafack
- Dr. Nicole Forbes
- Eva Wong
- Joshua Montroy
- Kelsey Young

NACI Membership

Members: S Deeks (Chair), R Harrison (Vice-Chair), M Andrew, J Bettinger, N Brousseau, H Decaluwe, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, J Papenburg, A Pham-Huy, B Sander, S Smith, and S Wilson

Liaison representatives: L Bill / M Nowgesic (Canadian Indigenous Nurses Association), LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), D Fell (Canadian Association for Immunization Research and Evaluation), S Funnell (Indigenous Physicians Association of Canada), J Hu / N Ivers (College of Family Physicians of Canada), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), A Ung (Canadian Pharmacists Association)

Ex-officio representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), C Lourenco (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), S Ogunnaike-Cooke (CIRID, PHAC), K Robinson (Marketed Health Products Directorate, HC), G Poliquin (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada)

NACI High Consequence Infectious Disease Working Group

WG Chair: R Harrison

PHAC Leads: SJ Ismail, K Young

Working Group Members: R Harrison (Chair), Y-G Bui, S Deeks, K Dooling, K Hildebrand, M Miller, M Murti, J Papenburg, and S Vaughan

PHAC Participants: NK Abraham, N Alluqmani, L Coward, N Forbes, C Jensen, CY Jeong, A Jirovec, A Killikelly, R Krishnan, SH Lim, N Mohamed, J Montroy, A Nam, S Pierre, R Pless, M Salvadori, A Sinilaite, A Stevens, R Stirling, E Tice, A Tuite, MC Tunis, B Warshawsky, E Wong, R Ximenes, MW Yeung, J Zafack

Project Management Support: K Ramotar, N St-Pierre, C Mauviel

NACI Vaccine Safety Working Group (VSWG)

WG Chair: J Bettinger

PHAC Leads: J Zafack, R Pless

Working Group Members: J Bettinger (Chair), N Brousseau, E Castillo, V Dubey, D Fell, K Hildebrand, A Pham-Huy, S Wilson, G Lacuesta, B Seifert, K Top

PHAC Participants: R Krishnan, C Jensen, E Abrams, N Dayneka, H Anyoti, J Montroy, M Tunis, K Johnson, A Shaw, K Hutchings, A Stevens, N Forbes, M Salvadori, B Warshawsky, NK Abraham, S Ismail, K Young, L Coward, R Goddard

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
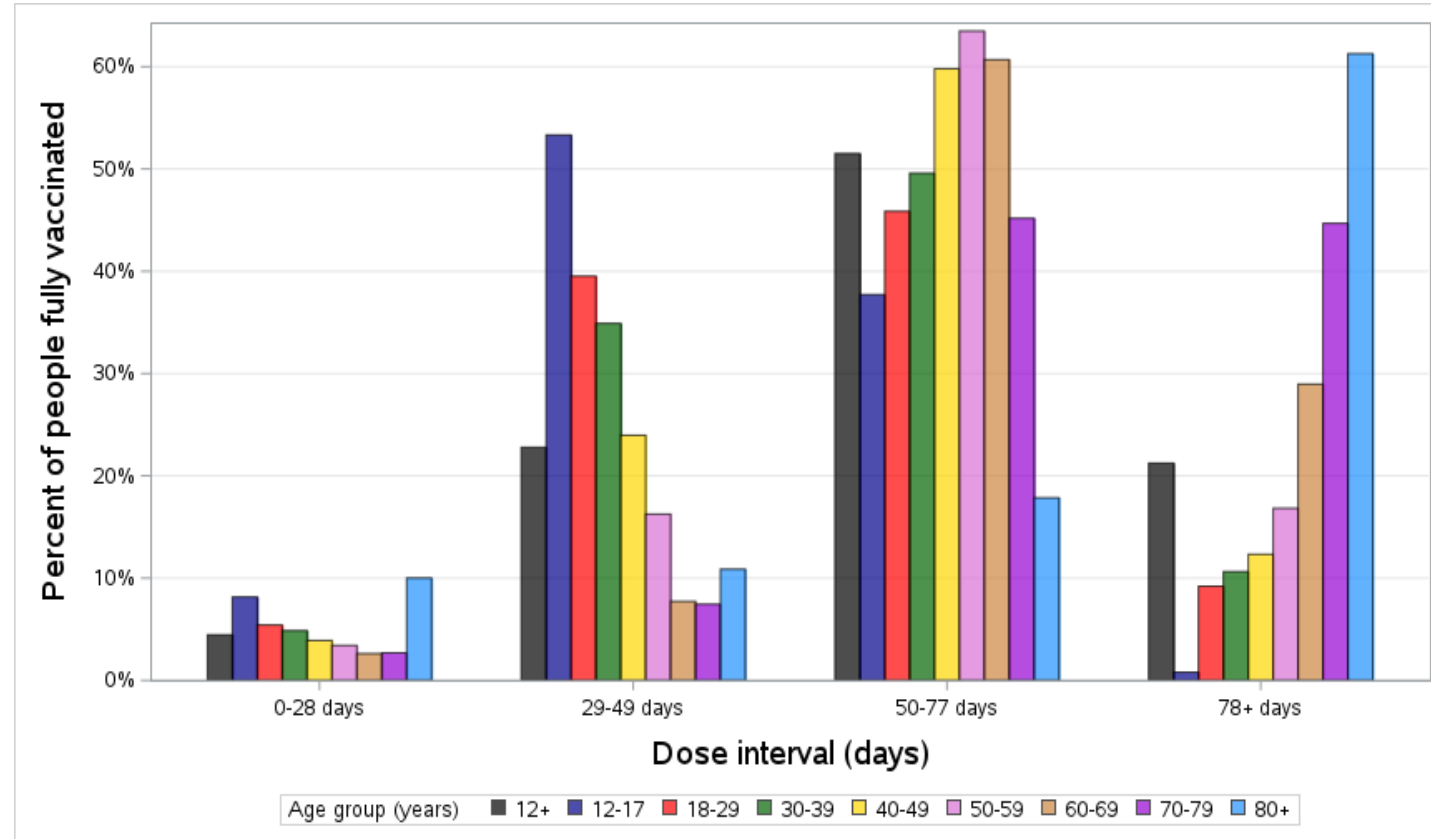

Figure 4. Percent distribution of people fully vaccinated with a COVID-19 vaccine in Canada by interval between doses and age group, August 14, 2021.