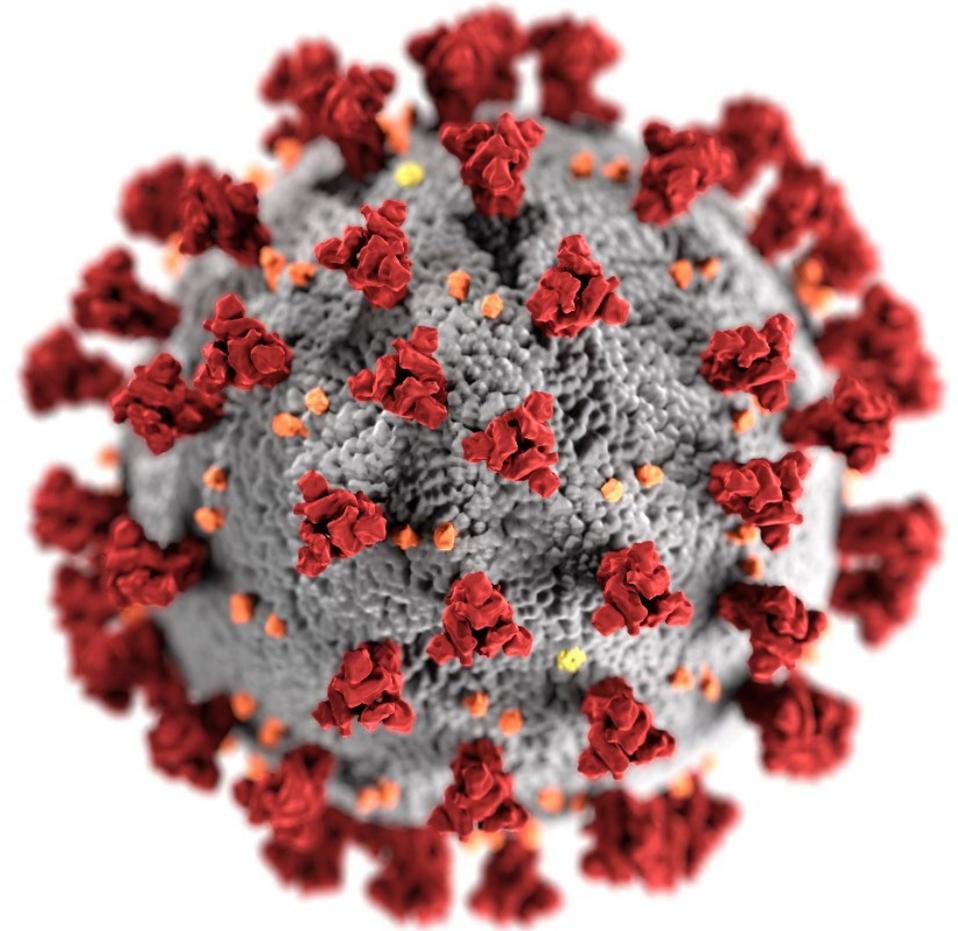


# Myocarditis and COVID-19

## Vaccine Intervals: International Data and Policies

Danielle Moulia, MPH  
ACIP Meeting  
February 4, 2021



[cdc.gov/coronavirus](https://cdc.gov/coronavirus)

# Discussion background and framework

- Goal: Examine international data and policies on preferential recommendations of an mRNA vaccine product or extended primary series intervals as they relate to myocarditis and/or pericarditis\*

## Discussion framework

- International data on risk of myocarditis by mRNA vaccine product, focusing on the highest risk group – young males post dose 2
- International data on extended primary series interval: risk of myocarditis and vaccine effectiveness
- International policies and recommendations

\* Myocarditis and/or pericarditis will be referred to generally as “myocarditis,” unless a specific study is being referenced.

# International Data on Risk of Myocarditis by mRNA Product



# US: Summary of findings

- **VAERS**: National, passive surveillance
- Among **males ages 18–24 years**, the myocarditis\* reporting rate after a **second dose** of Moderna was **40 per million**
- **VSD**: Nine integrated healthcare organizations, active surveillance
- Among **males ages 18–39 years**, the myocarditis/pericarditis\*\* rate after a **second dose** of Moderna was **1.5x** (aRR<sup>‡</sup>: 1.5 [0.86–2.61]) than Pfizer

\*As of January 13<sup>th</sup>, 2022; CDC case definition; 7-day risk period; \*\*As of January 15<sup>th</sup>, 2022; CDC case definition, 7-day risk period

‡Adjusted for VSD site, age, sex, race/ethnicity, and calendar date

**VAERS**: Vaccine Adverse Events Reporting System **VSD**: Vaccine Safety Datalink

**Source**: Su J. Myopericarditis following mRNA COVID-19 vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS). Slides presented to ACIP WG Dec 17, 2020.

Klein, N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and “Head-to-Head” Product Comparisons. Slides.

# Canada: Summary of findings

- Abraham et al. CAEFISS, passive and enhanced surveillance data
- Among males ages 18–29 years the myocarditis/pericarditis\* reporting rate after a second dose of Moderna (**140 per million doses**) was **~5x** (aRR<sup>‡</sup>: 4.73 [3.19–7.20]) higher than Pfizer (**25 per million doses**)
  
- Buchan et al. Ontario, period of enhanced passive surveillance
- Among males ages 18–24 years, the myocarditis/pericarditis\*\* reporting rate after a second dose Moderna (**300 per million doses**) was **~5x** higher than Pfizer (**59 per million doses**)

\*From December 1, 2020 to October 8, 2021; Myocarditis/pericarditis meeting level 1-4 of the Brighton Collaboration case definition, 7 day risk period \*\* From December 14, 2020 to September 4, 2021, myocarditis/pericarditis meeting level 1-4 of the Brighton Collaboration case definition, study length risk period; <sup>‡</sup>Poisson model conditioned by week

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System

Source: [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3988612](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3988612). Accessed 1/23/2022

<https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1.article-metrics>. Accessed 1/23/2022

# United Kingdom: Summary of findings

- **Yellow Card reporting**: Passive and active surveillance of adverse events
- Among **persons ages 18–29 years**, the myocarditis and pericarditis\* reporting rate after a **second dose** of Moderna (**71 per million doses**) was **~2.5x** higher than Pfizer (**24 per million doses**)
- **Patone et al**: Self-controlled case series of myocarditis\*\* hospitalizations in the UK
- Among **males ages <40 years**, additional events of myocarditis after a **second dose** of Moderna (**101 per million doses**) was **>8x** than Pfizer (**12 per million doses**)

\*As of January 19, 2022, reports of suspected myocarditis and pericarditis associated with COVID-19 vaccines ; \*\* As of November 15, 2021, inpatient admission or death due to primary and secondary ICD-10 of myocarditis, 28 day risk period

**Source:** <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#yellow-card-reports>. Accessed 1/22/2022.

Patone M. 2021 MedRxiv preprint. <https://www.medrxiv.org/content/10.1101/2021.12.23.21268276v1.full.pdf>. Accessed 1/22/2022.

# Nordic Countries: Nordic cohort, myocarditis results

- Presented to VaST on 1/10/2022
- All residents ages 12 years and older in Denmark, Finland, Norway, and Sweden (23.1M) from December 2020 – October 2022
- Inpatient care for myocarditis and pericarditis
- Within a 7-day risk period after either dose, the rate ratio of myocarditis for Moderna vaccine vs. an unvaccinated comparator was higher than Pfizer vaccine vs. an unvaccinated comparator
  - The highest rate ratios observed were among those receiving a second dose of Moderna in a heterologous mRNA primary series

# Denmark: SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study

- **Design:** Retrospective cohort
- **Period:** October 2020 – October 2021
- **Population:** 5M persons living in Denmark ages  $\geq 12$  years
- **Outcome:** Hospital diagnosis of myocarditis or pericarditis, increased troponin levels, and a hospital stay lasting  $>24$  hours, 28-day risk period
- **Adjusted using:** Cox proportional hazard model with covariates for age, sex, vaccine priority group, season, and clinical comorbidities

# Denmark: SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study

Population	Product	Absolute Rate per 100,000 doses	aHR, Unvaccinated Comparator
12–39 years	<b>Pfizer, after any dose</b>	1.6 (1.0 to 2.6)	1.48 (0.74 to 2.98)
	<b>Moderna, after any dose</b>	5.7 (3.3 to 9.3)	<b>5.24 (2.47 to 11.12)</b>
Males, ≥12 years	<b>Pfizer, after any dose</b>	1.5 (1.0 to 2.2)	0.82 (0.50 to 1.34)
	<b>Moderna, after any dose</b>	6.3 (3.6 to 10.2)	<b>3.22 (1.75 to 5.93)</b>
Females, ≥12 years	<b>Pfizer, after any dose</b>	1.3 (0.8 to 1.9)	<b>3.73 (1.82 to 7.65)</b>
	<b>Moderna, after any dose</b>	2.0 (0.7 to 4.8)	<b>6.33 (2.11 to 18.96)</b>
Males, 12–39 years	<b>Pfizer, post dose 2</b>	1.8 (0.8 to 3.4)*	1.54 (0.62 to 3.81)*
	<b>Moderna, post dose 2</b>	9.4 (5.0 to 16.0)*	<b>9.80 (4.20 to 22.84)*</b>

\*conducted as part of a post hoc analysis

aHR: Adjusted hazards ratio. Adjusted for age, sex, vaccine priority group, season, and clinical comorbidities.

Source: Husby et al., SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study. BMJ 2021; 375:e068665 doi:10.1136/bmj-2021-068665.

# France and Germany: Summary of findings

- Germany: National, passive surveillance
- Among **males ages 18–29 years**, the myocarditis/pericarditis\* reporting rate after **any dose** of Moderna (**117 per million doses**) was **>2x** higher than Pfizer (**47 per million doses**)
- France: Regional, enhanced passive surveillance
- Among **males ages 18–24 years**, the myocarditis\*\* reporting rate after a **second dose** of Moderna (**139 per million doses**) was **~3x** higher than Pfizer (**43 per million doses**)

\*As of September 30, 2021; all reports post mRNA vaccination; \*\*As of September 20, 2021; all reports post mRNA vaccine

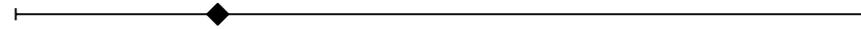
Source: [https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/46\\_21.pdf](https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/46_21.pdf). Accessed 1/23/2022.

[https://www.omedit-auvergne-rhone-alpes.ars.sante.fr/index.php/system/files/2021-10/ANSM\\_Rapport\\_CRPV\\_Moderna\\_22102021.pdf](https://www.omedit-auvergne-rhone-alpes.ars.sante.fr/index.php/system/files/2021-10/ANSM_Rapport_CRPV_Moderna_22102021.pdf). Accessed 1/23/2022.

<https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf>. Accessed 1/23/2022.

# Myocarditis rate ratios (Moderna vs. Pfizer) country, subgroup, and dose

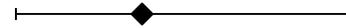
Buchan, Canada-Ontario, M 18–24y, post dose 2\*



Abraham, Canada, M 18–29y, post dose 2<sup>‡</sup>



Husby, Denmark, M 12–39y, post dose 2\*



France, M 18–24y, post dose 2\*



Klein, USA, M 18–39y, post dose 2<sup>¶</sup>



\*Unadjusted rate ratio; <sup>‡</sup>Adjusted with a Poisson model conditioned by calendar week of vaccine administration; <sup>¶</sup> Adjusted for VSD site, age, sex, race/ethnicity, and calendar date

**Source.** Husby et al., SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study. *BMJ* 2021; 375:e068665 doi:10.1136/bmj-2021-068665

<https://ansm.sante.fr/uploads/2021/10/22/20211021-covid-19-vaccins-pfizer-focus-1-2.pdf>. Accessed 1/23/2022.

Klein, N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and “Head-to-Head” Product Comparisons. Slides.

[https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3988612](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3988612). Accessed 1/23/2022

<https://www.medrxiv.org/content/10.1101/2021.12.02.21267156v1.article-metrics>. Accessed 1/23/2022

# Summary of findings: Myocarditis risk by mRNA product

- Risk of myocarditis may be higher for Moderna than Pfizer vaccine
- Limitations: observational data; rates not readily comparable due to differences in:
  - Case definition and risk interval length
  - Subpopulations
  - Case ascertainment
  - Calendar time and vaccine implementation factors, including extended primary series intervals
- A limited number of geographic locations are administering both Moderna and Pfizer and had data available.

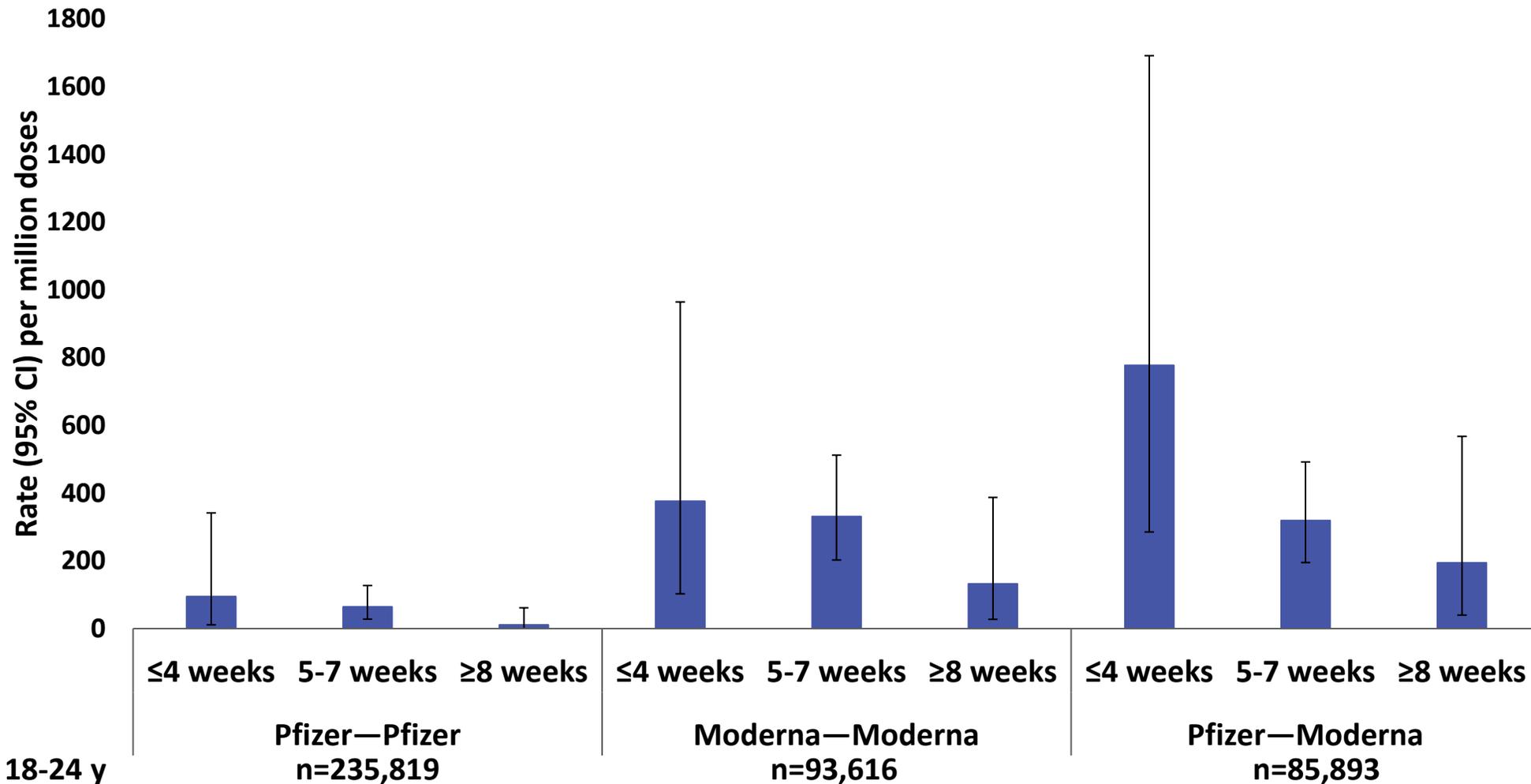
# International Data on Risk of Myocarditis with an Extended Primary Series Interval



# Ontario, Canada: Myocarditis/pericarditis by interval

- **Design:** Retrospective, population-based cohort, using provincial vaccine registry and passive vaccine safety surveillance
- **Period:** December 14, 2020 to September 4, 2021
- **Population:** Adults ages  $\geq 18$  years receiving dose 2 on or after June 1, 2021 in Ontario; 19,740,741 doses of mRNA vaccines
- **Outcome:** Myocarditis/pericarditis meeting level 1–3 of the Brighton Collaboration case definition
- **Analysis:** Crude reporting rates; overall rate following dose 2 by product estimated using Poisson regression, adjusted for dose 1 product and interval
  - Dosing intervals:  $\leq 30$  days ( $\leq 4$  weeks), 31–55 days (5–7 weeks),  $\geq 56$  days ( $\geq 8$  weeks)

# Ontario, Canada: Reporting rate of myocarditis/pericarditis per million doses among males ages 18–24 years by vaccine product\* and interval



Males ages 18-24 y

Source: Buchan S et al. Dec 2021, MedRxiv preprint.

\*Moderna-Pfizer not shown here because there were no reported events in males ages 18–24 years; a smaller number of males in this age group received this schedule (n=8,853).

# Summary of data: Myocarditis risk with extended primary series interval

- Rates of myocarditis may be lower with extended primary series interval
- Reduced rates of myocarditis with extended interval were observed with Moderna and Pfizer vaccines

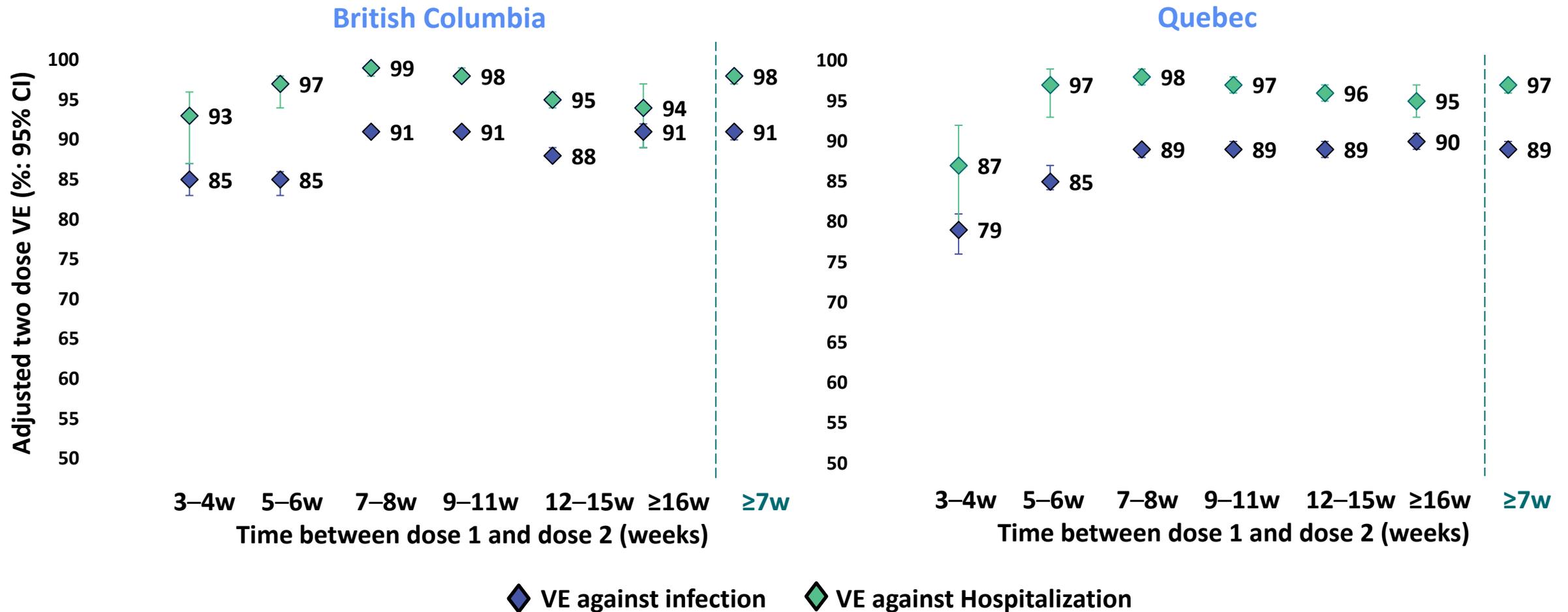
# International Data on Vaccine Effectiveness with an Extended Primary Series Interval



# British Columbia and Quebec, Canada: Vaccine effectiveness by primary series interval

- **Design:** Test-negative case-control design to estimate vaccine effectiveness
- **Period:** May 30 to October 2, 2021
- **Population:** Community-dwelling adults ages  $\geq 18$  years in British Columbia (BC) and Quebec, Canada; 1,235,447 specimens, including 44,673 test-positive cases and 2,460 hospitalizations
- **Outcome:** Infections and hospitalizations due to SARS-CoV-2, confirmed by RT-PCR
- **Analysis:** Multivariable logistic regression to estimate odds ratios:
  - Adjusted for age group (18–49, 50–69, 70–79,  $\geq 80$  years); sex; epi week of the analysis period (weeks 22–39, categorical); and region of the province
  - Dosing intervals: 3–4 weeks, 5–6 weeks, 7–8 weeks, 9–11 weeks, 12–15 weeks, 16+ weeks

# British Columbia and Quebec, Canada: Vaccine effectiveness of any two doses of mRNA vaccines by primary series interval

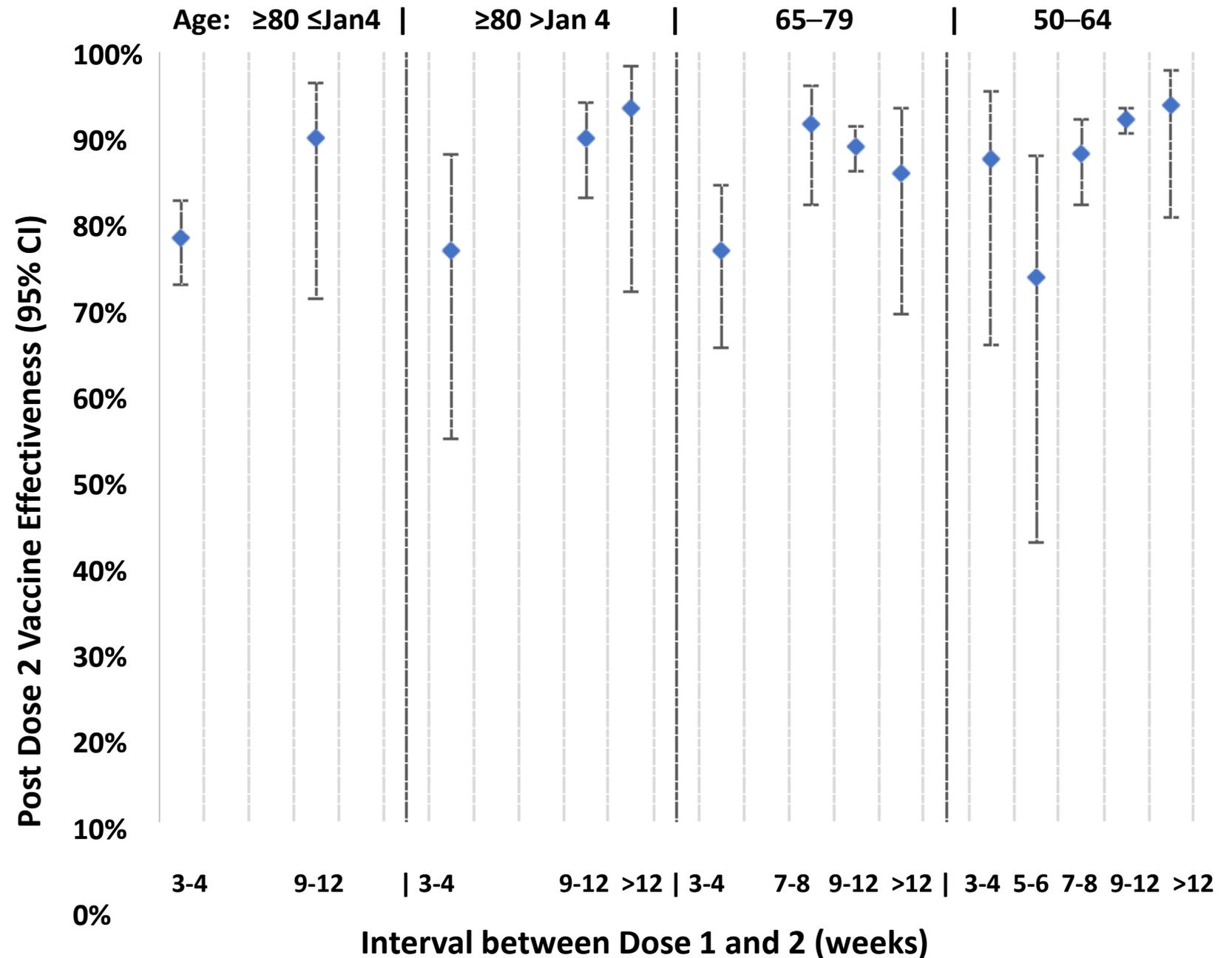


# England: Serological responses and vaccine effectiveness by primary series interval

- **Design:** Test-negative case-control design to estimate vaccine effectiveness
- **Period:** October 2020 to June 2021
- **Population:** Symptomatic adults ages  $\geq 50$  years attending community testing (n=308,764 unvaccinated persons; n=16,237 persons received Pfizer primary series vaccine); serological responses of 421 immunocompetent adults ages 50–89 years given two doses of Pfizer at different intervals
- **Outcome:** Testing SARS-CoV-2 positive by PCR through NHS, following COVID-19 compatible symptoms; serological responses 14–34 days post-dose 2
- **Analysis:** Logistic regression to estimate odds ratios by vaccination status
  - Adjusted for a week of onset, age group, gender, region, index of multiple deprivation, ethnicity, health/social care worker, care home resident, flagged as clinically at extremely increased risk for COVID-19 illness, and flagged as extended risk groups among adults ages  $< 65$  years
  - Dosing intervals: 3–4, 5–6, 7–8, 9–12 and  $> 12$  weeks

# England: Pfizer vaccine effectiveness by primary series interval

- Pfizer vaccine effectiveness against symptomatic SARS-CoV-2 infection was higher with an extended interval (>6 weeks) compared to a standard interval (3–4 weeks) for all age groups.



# Summary: Immunogenicity with extended primary series interval

- **Payne et al.** (UK ): Among SARS-CoV-2 infection naïve persons in an observational cohort, serological responses were higher after an extended dosing interval (6–14 week) compared to a standard interval (3–4 week).
  - Among persons with an extended interval, there were higher antibody and B cell responses, as well as sustained B and T cell responses, compared to a standard interval.
  - An extended interval may promote efficient T cell expansion and long-term memory cell persistence.
- **Amirthalingam et al.** (England), **Parry et al.** (England), & **Grunau et al** (Canada): Neutralizing antibody titers were higher following an extended dosing interval with mRNA vaccine, compared to a standard interval.

# Summary of data: Vaccine effectiveness with extended primary series interval

- Extended primary series interval may improve immunogenicity and vaccine effectiveness.
  - Neutralizing antibody titers were higher following an extended dosing interval (6–14 week) with mRNA vaccine, compared to a standard interval (3–4 week).<sup>1-4</sup>
  - mRNA vaccine effectiveness against infection and hospitalization was 5–10% higher with an extended interval (7–8 weeks vs. 3–4 weeks).<sup>5</sup>
- Limitation: Data collected prior to Omicron surge

<sup>1</sup> Payne R. 2021, Cell.

<sup>2</sup> Grunau B. 2022, Clin Infect Dis.

<sup>3</sup> Amirthalingam G. 2021, Nat Commun

<sup>4</sup> Parry H. 2022, Npj Vaccines

<sup>5</sup> Skowronski DM. 2021, MedRxiv preprint.

# International Policies and Recommendations



# Canada

- NACI strongly recommends a complete mRNA COVID-19 vaccine series for persons ages  $\geq 12$  years.
  - Ages 12–29 years: Pfizer is preferred for the primary series.
  - Ages 18–20 years: Pfizer may be preferred for a booster.

mRNA vaccine product	Immunization schedule	Minimum interval	Authorized interval	Optimal interval
<b>Pfizer-BioNTech Comirnaty</b>	2-dose schedule	19 days	21 days	8 weeks
<b>Moderna Spikevax</b>	2-dose schedule	21 days	28 days	8 weeks

Source: National Advisory Committee on Immunization: Updated Guidance on the use of COVID-19 Vaccines. (slides)

<https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/vaccines/safety-side-effects.html#myocarditis-and-pericarditis>. Accessed 1/23/2022

<https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html#a5.4>. Accessed 2/1/2022.

# United Kingdom

- Preferential recommendation for Pfizer in persons ages 12–17 years
- Interval: at least 8 weeks
  - Ages **16–17** years, at higher risk\*: at least 8 weeks
  - Ages **16–17** years, not at high risk: 12 week
  - Ages **12–15** years, higher risk of severe COVID-19: at least 8 weeks
  - Ages **12–15** years, contact of immunosuppressed person: 8 weeks
  - Ages **12–15** years, not high risk, no contacts: 12 weeks

\*In a recognized clinical risk group (see table 3) and those who work in health and social care should receive two doses of vaccine at an interval of at least eight weeks. This includes those aged 16 to 17 years who expect to share living accommodation on most days (and therefore for whom continuing close contact is unavoidable) with individuals of any age who are immunosuppressed

Source: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1045852/Greenbook-chapter-14a-11Jan22.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1045852/Greenbook-chapter-14a-11Jan22.pdf). Accessed 1/22/2022

# Nordic countries

- **Sweden**: Pfizer is recommended for persons ages 12–30 years over Moderna.
- **Interval**: 3–4 weeks
- **Norway**: Pfizer should be offered to persons ages 12–30 years. Children and adolescents ages 5–15 years may receive 1 or 2 doses based on parents' decision; persons ages  $\geq 16$  years should receive 2 doses
- **Interval**: 3–12 weeks
  - Persons ages 16–18 years: 8–12 weeks
  - Children ages 5–15 years with severe underlying conditions: 8–12 weeks, but can be adapted down to 3 weeks based on medical assessment

Source: <https://www.fhi.no/en/id/vaccines/coronavirus-immunisation-programme/coronavirus-vaccine/#vaccination-of-children-and-adolescents>. Accessed 1/22/2022

<https://www.lakemedelsverket.se/en/coronavirus/covid-19-vaccine>. Accessed 1/23/2022

<https://thl.fi/en/web/infectious-diseases-and-vaccinations/what-s-new/coronavirus-covid-19-latest-updates/vaccines-and-coronavirus/getting-vaccinated-against-covid-19-how-why-and-when>

<https://www.sst.dk/en/English/Corona-eng/Vaccination-against-covid-19/COVID-19-vaccines-in-Denmark>

# Nordic Countries

- **Finland**: Boys and men ages 12–30 years only offered Pfizer. Girls and women ages >12 years are offered Pfizer or Moderna.
- **Interval**: 6–12 weeks for persons ages  $\geq 5$  years
  
- **Denmark**: Both Pfizer and Moderna vaccines are approved for persons ages  $\geq 12$  years.
- **Interval**: 3–6 weeks (median interval: 5 weeks)

# Singapore and Taiwan

- **Singapore**: Children under age 18 years should receive Pfizer vaccine.
- **Interval**: At least 21 days; guidance notes myocarditis risk may decrease with a longer interval, but encourages a second dose at 21 days due to Omicron
  
- **Taiwan**: Both Pfizer and Moderna vaccines are approved for persons ages  $\geq 12$  years.
- **Interval**: At least 12 weeks

# Australia

- Both Pfizer and Moderna vaccines are approved for persons ages 12 years and older.
- Interval: At least 3 weeks (Pfizer) or 4 weeks (Moderna)
  - Children ages 5–11 years (Pfizer): 8 weeks
    - Can be shortened in special circumstances to a minimum of 3 weeks, such as in an outbreak response, prior to the initiation of significant immunosuppression, or international travel

# France and Germany

- **France**: HAS recommends persons under the age of 30 years be given Pfizer over Moderna when available.
- **Interval**: 6 weeks
  
- **Germany**: STIKO recommends persons under the age of 30 years be given Pfizer over Moderna.
- **Interval**: 3–6 weeks

**HAS**: Haute Autorité de Santé; **STIKO**: Standing Committee on Vaccination

**Source**: [https://www.nitag-resource.org/sites/default/files/2021-12/48\\_21.pdf](https://www.nitag-resource.org/sites/default/files/2021-12/48_21.pdf). Accessed 1/23/2022.

[https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/46/Art\\_03.html](https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/46/Art_03.html). Accessed 1/23/2022.

<https://www.reuters.com/business/healthcare-pharmaceuticals/french-health-authority-advises-against-moderna-covid-19-vaccine-under-30s-2021-11-09/>. Accessed 1/23/2022.

# Limitations

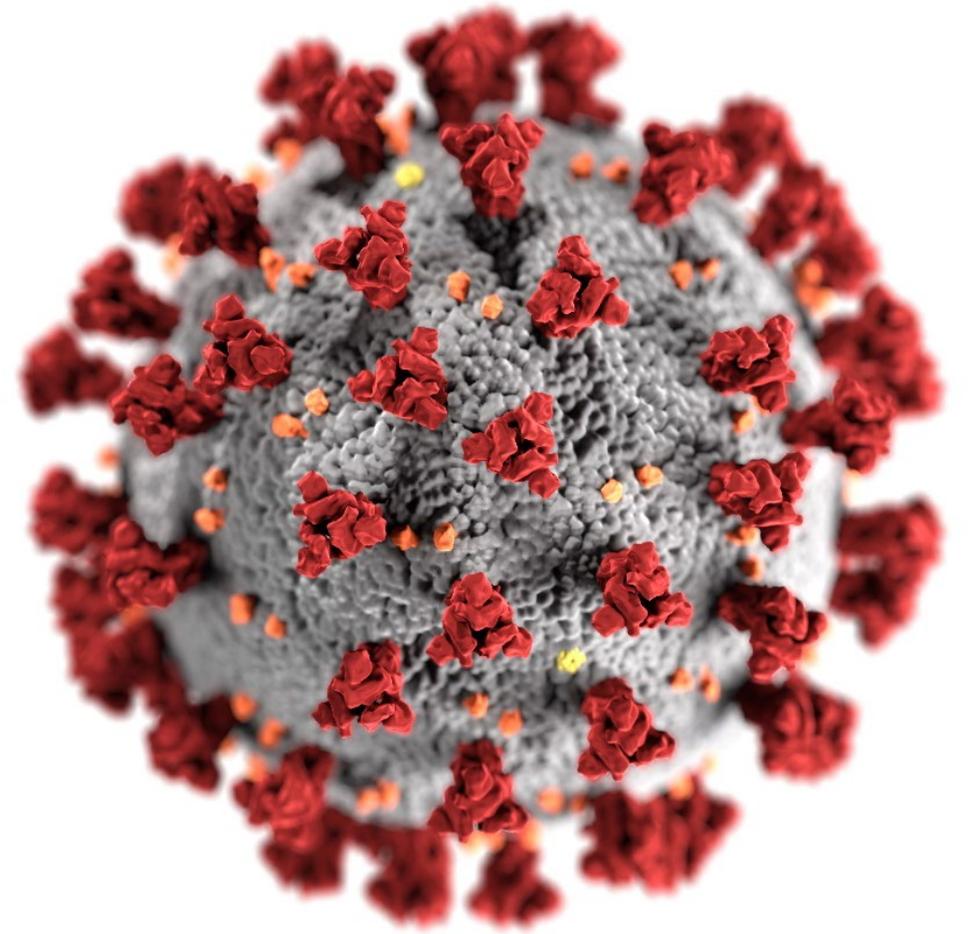
- Not a systematic review; data are biased toward findings that influenced national vaccine policy
- Limited number of countries are administering both Moderna and Pfizer
- Caution should be used when comparing myocarditis/pericarditis rates across studies as surveillance systems, case definitions and risk intervals, subpopulation age ranges, and vaccine implementation differ substantially
- National vaccine policies have evolved; some policies extending the primary series interval evolved from implementation strategies to reach the most people with a first dose

# Conclusion

- Observational data suggest myocarditis/pericarditis may be associated with
  - Moderna vs. Pfizer in persons ages 18–29 years, especially males
  - Shorter primary series interval
- Several countries have implemented policies or recommendations to lengthen the interval between doses (range: 6-12 weeks) in the primary series and/or preferentially recommend use of Pfizer among males and/or persons aged <30 years, which may mitigate the risk of myocarditis/pericarditis and improve vaccine effectiveness

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- Faisal Minhaj
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- VTF ACIP WG Team
- ACIP COVID-19 Vaccines Work Group
- Vaccine Task Force
- Epi Task Force
- Data Analytics and Visualization Task Force
- Respiratory Viruses Branch



For more information, contact CDC  
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TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

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