Myocarditis and COVID-19
Vaccine Intervals: International Data and Policies

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ACIP Meeting
February 4, 2021
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‡: 1.5 [0.86–2.61]) than Pfizer

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*As of January 13th, 2022; CDC case definition; 7-day risk period; **As of January 15th, 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

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‡: 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; ‡Poisson model conditioned by week

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System

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


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

VaST: Vaccine Technical Advisory Workgroup
Source: Hovi et al., Slides not publicly available.
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 ≥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

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

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

\*conducted as part of a post hoc analysis

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

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

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†
- Husby, Denmark, M 12–39y, post dose 2*
- France, M 18–24y, post dose 2*
- Klein, USA, M 18–39y, post dose 2§

*Unadjusted rate ratio; †Adjusted with a Poisson model conditioned by calendar week of vaccine administration; §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

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 ≥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: ≤30 days (≤4 weeks), 31–55 days (5–7 weeks), ≥56 days (≥8 weeks)

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


*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 ≥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, ≥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 ≥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

**Source:** Amirthalingam G. 2021, Nat Commun.
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.

Source: Amirthalingam G. 2021, Nat Commun.
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). 1-4
  - mRNA vaccine effectiveness against infection and hospitalization was 5–10% higher with an extended interval (7–8 weeks vs. 3–4 weeks). 5

- Limitation: Data collected prior to Omicron surge

1 Payne R. 2021, Cell.
2 Grunau B. 2022, Clin Infect Dis.
3 Amirthalingam G. 2021, Nat Commun
4 Parry H. 2022, Npj Vaccines
International Policies and Recommendations
Canada

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

<table>
<thead>
<tr>
<th>mRNA vaccine product</th>
<th>Immunization schedule</th>
<th>Minimum interval</th>
<th>Authorized interval</th>
<th>Optimal interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech Comirnaty</td>
<td>2-dose schedule</td>
<td>19 days</td>
<td>21 days</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Moderna Spikevax</td>
<td>2-dose schedule</td>
<td>21 days</td>
<td>28 days</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

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

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 ≥ 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

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 ≥5 years

- **Denmark**: Both Pfizer and Moderna vaccines are approved for persons ages ≥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 ≥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
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
Acknowledgements

- Katie Curran
- Sara Oliver
- Megan Wallace
- Monica Godfrey
- Amy Blain
- Amimah Asif
- Sarah Mbaeyi
- Evelyn Twentyman
- Tara Jatloui
- Susan Goldstein
- Jack Gersten
- Jefferson Jones
- Eddie Shanley
- Anthony Fiore

- Stephen Hadler
- Valerie Morelli
- JoEllen Wolicki
- Elisha Hall
- Erin Ricketts
- Faisal Minhaj
- Heather Scobie
- 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
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.