CDC Advisory Committee on Immunization Practices (ACIP) Meeting Report

Date: February 4, 2022

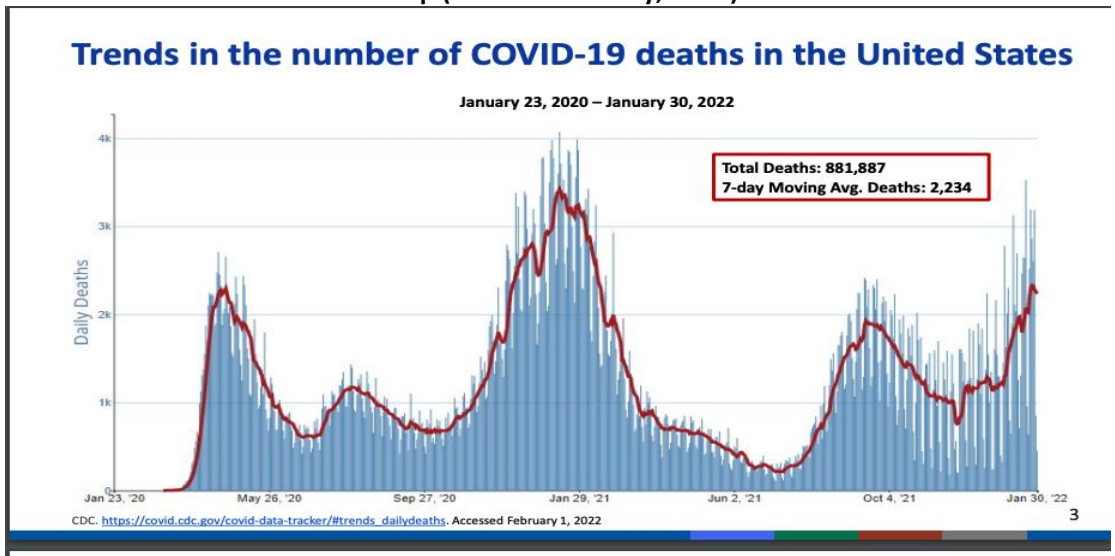
Following the FDA approval of Moderna COVID-19 vaccine (Spikevax) for individuals 18 years and older on 31JAN2022, ACIP met today to review the complete package of data submitted with the BLA on this vaccine. At the end of the first portion of the meeting, the ACIP took a vote on the following policy question: Should vaccination with the Moderna COVID-19 vaccine (Spikevax, 2-dose primary series) be recommended for persons 18 years of age and older?, There was a unanimous vote in favor.

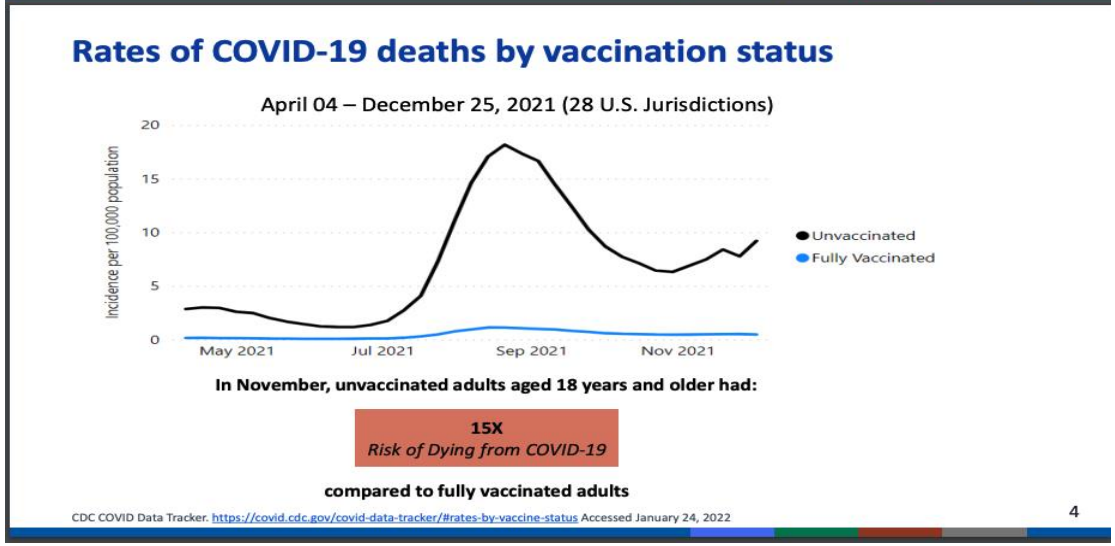
A review of **Clinical Considerations** provided updates for people who are immunocompromised with revised guidance indicating a booster dose should be given at least 3 (no longer 5) months after the 3rd mRNA primary dose series; an additional dose should be given to Janssen vaccine recipients for primary series at least 28 days after dose 1 followed by booster dose at least 2 months later; revised guidance for certain subgroups is being expanded to include patients with other B-cell depleting therapies who received vaccine prior to or during treatment; and case-by-case clinical decision making based on clinical judgement should be allowed re: dosing intervals in immunocompromised patients. They also revised guidance on use of passive antibody products to recommend no deferral period for vaccination, although tixagevimab/cilgavimab should be deferred for at least 2 wks after vaccination.

The committee then went on to hear and discuss a series of presentations updating the status of myocarditis and pericarditis following mRNA vaccines. The **Canadian experience** was reviewed, including data on one dose effectiveness and duration (60-70% lasting 8-10 wks with one dose protection higher against severe disease than infection), immunogenicity with longer intervals (associated with higher antibody response), effectiveness with longer intervals (somewhat higher effectiveness) and myocarditis/pericarditis (risk higher in Moderna recipients vs. Pfizer, several fold higher risk in young males 18-29 yrs of age after dose 2, shorter interval and mRNA heterologous schedule with Moderna as dose 2 associated with higher reporting rates). **VSD update on myocarditis** through 15JAN then was presented with chart review summary of 297 cases (5-39yo, verified adjudication in 213 cases, both vaccines associated with increased risk with suggestion that Moderna may be associated with higher risk than Pfizer) and then head-to head comparison in 18-39yo (0-7d risk interval, matched comparators, no clinical differences, Moderna associated with additional 10.7 cases myocarditis and pericarditis per million second doses -- but both were associated with increased risk). **International summary of myocarditis and COVID vaccine intervals** was presented finding that there was enhanced immunogenicity and vaccine effectiveness with extended primary series interval (findings from US, Canada, UK; myocarditis by vaccine results from Nordic countries, France and Germany; myocarditis by primary interval from Ontario; vaccine effectiveness by primary interval from Canada, England) ending with policies and recommendations implemented in various countries (Canada, UK, Nordic countries, Singapore and Taiwan, Australia, France and Germany). To close, there was a **Summary and Work Group Interpretation for extended intervals** with the work group supporting an interval of 8 wks between first and second dose of mRNA vaccine primary series. No actual vote was taken but an informal poll of members indicated strong support for this to improve immunogenicity, effectiveness and risk of myocarditis.

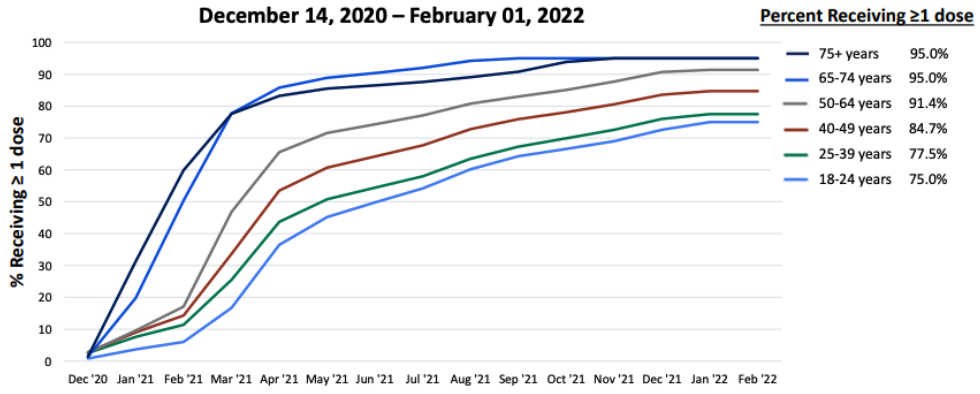
A selection of slides from the various presentations can be found in the attached pdf. The full set of slide presentations can be found HERE.

1. **ACIP COVID-19 Vaccines Work Group (Matthew F. Daley, Chair)**





Percent of COVID-19 vaccination coverage by age and date administered, United States



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed February 01, 2022

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COVID-19-associated hospitalizations and deaths prevented by COVID-19 vaccination in the United States

- COVID-19 associated hospitalizations prevented[1-2]:
  - Estimated up to 10.3 million hospitalizations averted through November 2021
- COVID-19 associated deaths prevented[1-3]:
  - Estimated up to 1.1 million deaths averted through November 2021

1. Moghadas SM, Sah P, Fitzpatrick MC, et al. COVID-19 deaths and hospitalizations averted by rapid vaccination rollout in the United States. medRxiv. Published online July 8, 2021:2021.07.07.21260156. doi:10.1101/2021.07.07.21260156
2. Eric C. Schneider, Arnav Shah, Pratha Sah, Seyed M. Moghadas, Thomas Vilches, Alison Galvani. The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted.
3. Gupta S, Cantor J, Simon KI, Bento AI, Wing C, Whaley CM. Vaccinations Against COVID-19 May Have Averted Up To 140,000 Deaths In The United States. Health Aff (Millwood). 2021;40(9):1465-1472.

FDA updates

Moderna COVID-19 vaccine (Spikevax) received FDA approval

- On January 31, 2022: FDA approved the Moderna COVID-19 vaccine (Spikevax) for individuals 18 years of age and older
  - Spikevax biologics license application (BLA) builds upon the data and information that supported the EUA, such as preclinical and clinical data, as well as details of the manufacturing process and sites where the vaccine is made
  - Spikevax has the same formulation as the EUA Moderna COVID-19 vaccine and can be used interchangeably with the EUA Moderna COVID-19 vaccine to provide the COVID-19 vaccination primary series
  - Moderna COVID-19 vaccine remains under EUA for the following indications:
    - Third primary series doses for individuals 18 years of age and older who have been determined to have certain kinds of immunocompromise
    - Single booster dose for individuals 18 year of age and older at least five months after completing a primary series

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https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-key-action-approving-second-covid-19-vaccine

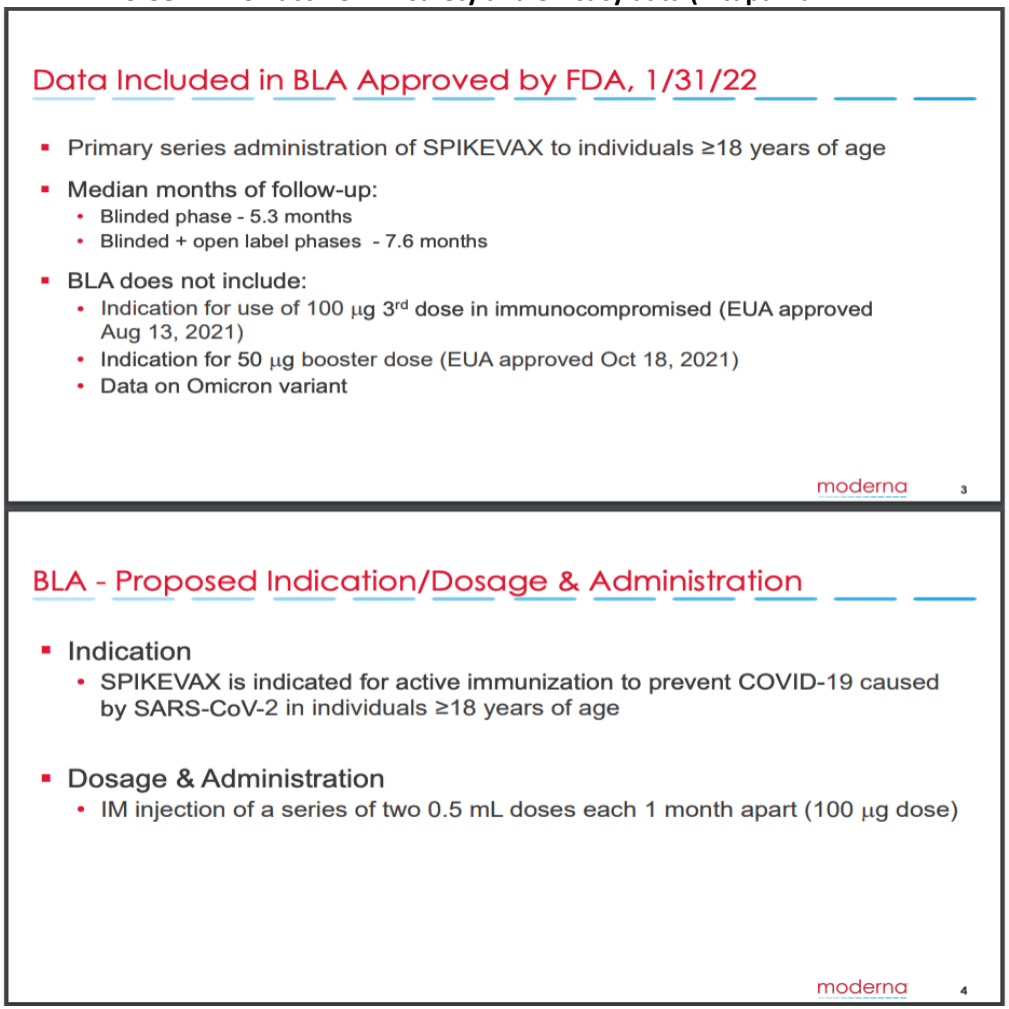
Agenda: Friday February 4, 2022

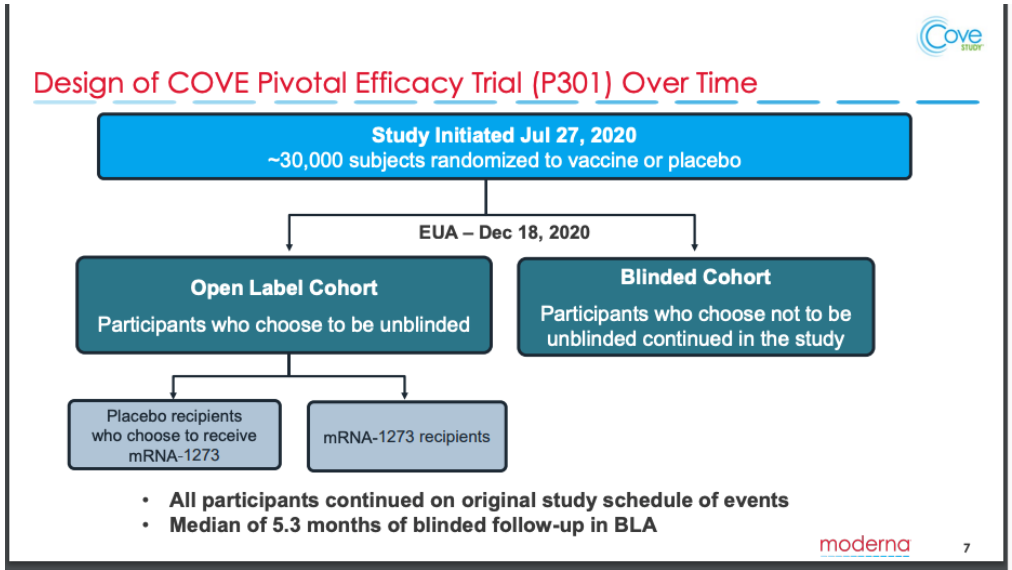
▪ **mRNA 1273 COVID-19 vaccine BLA safety and efficacy data**	Dr. Rituparna Das (Moderna)
Break	
▪ **PUBLIC COMMENT**	
▪ **Updates on myocarditis and pericarditis following Moderna COVID-19 vaccination**	Dr. Shimabukuro (CDC)
▪ **Updates on myocarditis outcomes: MOVING**	Dr. Kracalic (CDC)
▪ **VaST assessment**	Dr. Talbot (VaST Chair)
Break	
▪ **GRADE: Moderna COVID-19 vaccine**	Dr. Wallace (CDC)
▪ **EtR Framework: Moderna COVID-19 vaccine primary series in adults ≥18 years of age**	Dr. Oliver (CDC)
Discussion	
VOTE	
Moderna COVID-19 vaccine for individuals ≥18 years of age	

Agenda (continued): Friday February 4, 2022

▪ **Updates to Clinical Considerations**	Dr. Hall (CDC)
▪ **Canadian experience and evidence with COVID-19 vaccine primary series extended intervals**	Dr. Tunis (PHAC) Dr. Warshawsky (PHAC) Ms. Ogunnaike-Cooke (PHAC)
▪ **VSD: Myocarditis after Moderna and Pfizer/BioNTech COVID-19 vaccines**	Dr. Klein (KPNC)
▪ **Myocarditis and COVID-19 vaccine intervals: International data and policies**	Ms. Moulia (CDC)
▪ **Summary and Work Group Interpretation: Extended intervals for mRNA COVID-19 vaccines**	Dr. Oliver (CDC)
Discussion	

2. **mRNA 1273 COVID-19 vaccine BLA safety and efficacy data (Rituparna**




Design of COVE Pivotal Efficacy Trial (P301) Over Time
Study Initiated Jul 27, 2020
~30,000 subjects randomized to vaccine or placebo
EUA – Dec 18, 2020
Open Label Cohort
Participants who choose to be unblinded
Blinded Cohort
Participants who choose not to be unblinded continued in the study
Placebo recipients who choose to receive mRNA-1273
mRNA-1273 recipients
All participants continued on original study schedule of events
Median of 5.3 months of blinded follow-up in BLA
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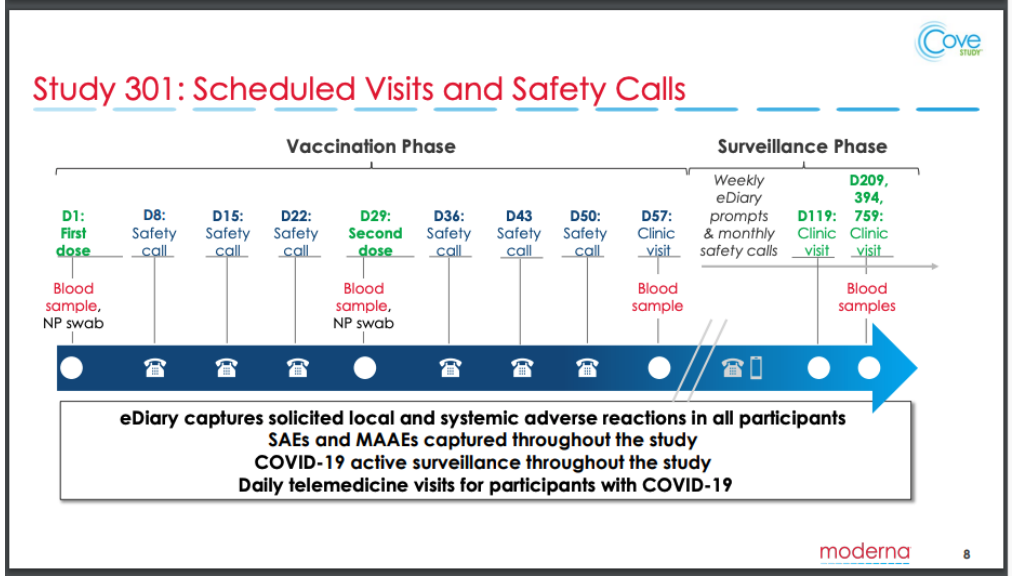
Study 301: Scheduled Visits and Safety Calls
Vaccination Phase
Surveillance Phase
D1: First dose
D8: Safety call
D15: Safety call
D22: Safety call
D29: Second dose
D36: Safety call
D43 Safety call
D50: Safety call
D57: Clinic visit
Weekly eDiary prompts & monthly safety calls
D119: Clinic visit
D209, 394, 759: Clinic visit
Blood sample, NP swab
Blood sample, NP swab
Blood sample
Blood samples
eDiary captures solicited local and systemic adverse reactions in all participants
SAEs and MAAEs captured throughout the study
COVID-19 active surveillance throughout the study
Daily telemedicine visits for participants with COVID-19
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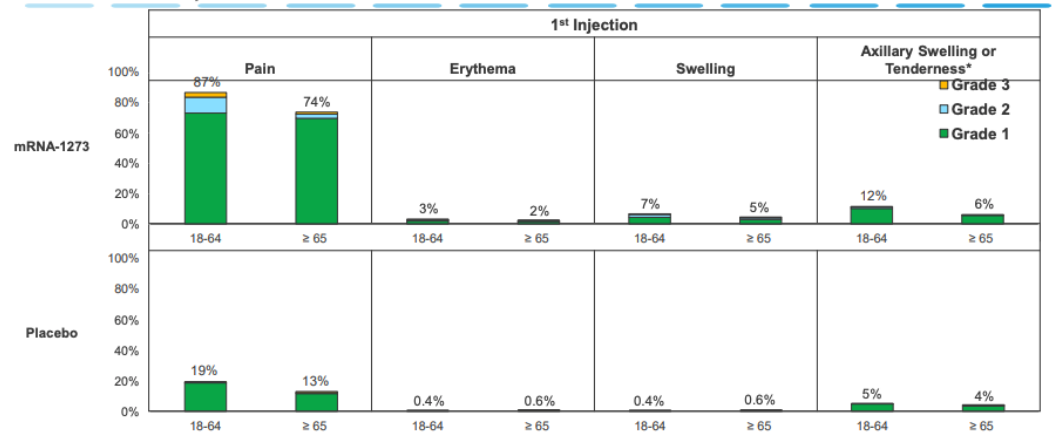
Study 301: Most Solicited Local Adverse Reactions Were Mild-to-Moderate (1st Injection)

Solicited Safety Set



Includes reports within 7 days of injection.
*Localized axillary swelling or tenderness ipsilateral to the vaccination arm.

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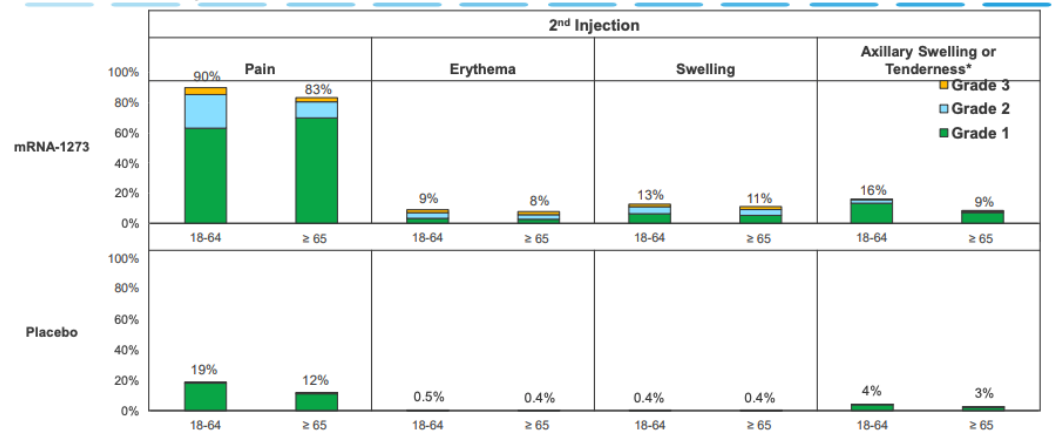
Study 301: Most Solicited Local Adverse Reactions Were Mild-to-Moderate (2nd Injection)

Solicited Safety Set



Includes reports within 7 days of injection.
*Localized axillary swelling or tenderness ipsilateral to the vaccination arm.

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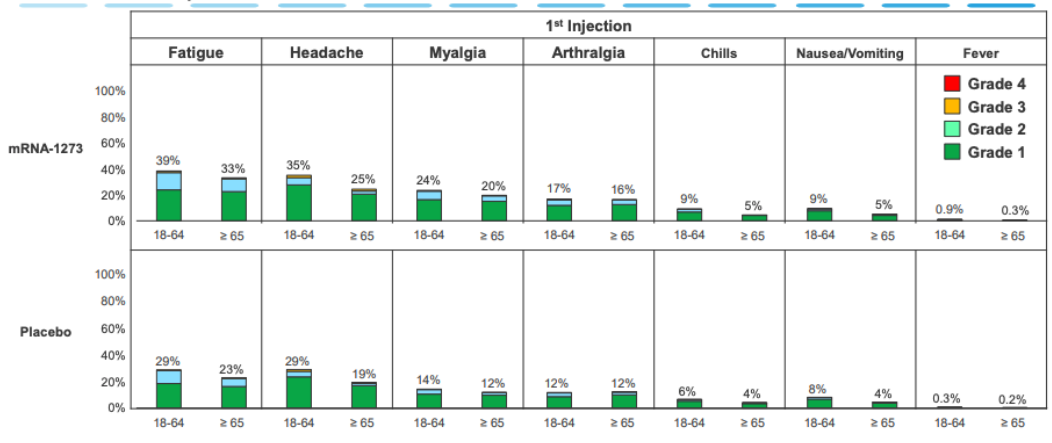
Study 301: Most Solicited Systemic Adverse Reactions Were Mild-to-Moderate (1st Injection)

Solicited Safety Set



Solicited Systemic ARs include reports within 7 days of injection

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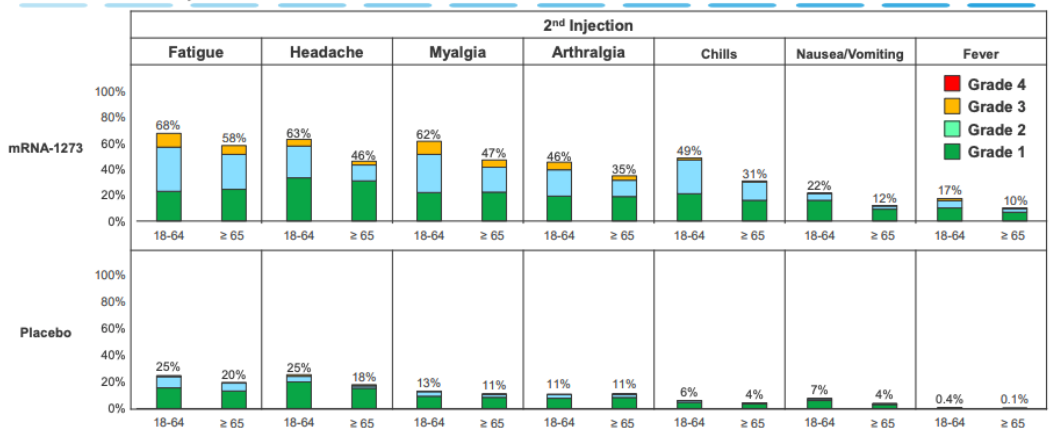
Study 301: Most Solicited Systemic Adverse Reactions Were Mild-to-Moderate (2nd Injection)

Solicited Safety Set



Solicited Systemic ARs include reports within 7 days of injection

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Study 301: Summary of Unsolicited AEs

Safety Set

Unsolicited Adverse Events	mRNA-1273 N = 15,184 n	%	Placebo N= 15,162 n	%
Any Adverse Event (within 28 days)	4752	31.3%	4338	28.6%
Any Medically-Attended Adverse Event (MAAE)	3468	22.8%	4131	27.2%
Any Serious Adverse Event (SAE)	268	1.8%	292	1.9%
Any Death (reported through May 4, 2021)	16	0.1%	16	0.1%

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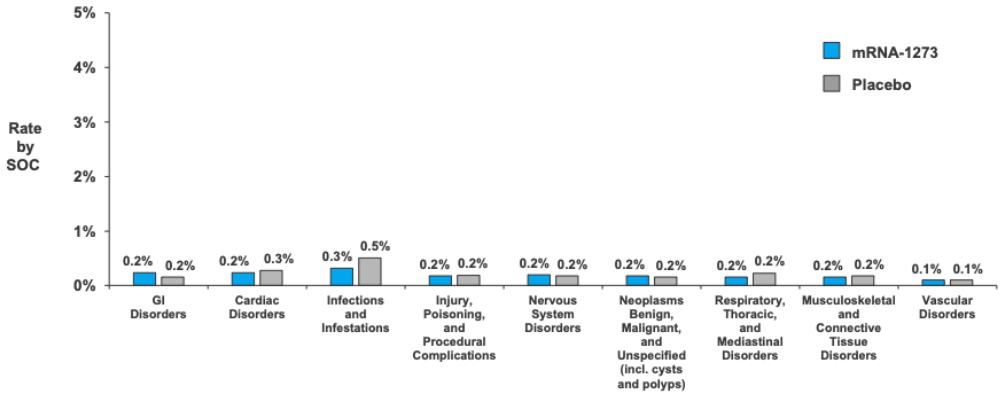
Study 301: Rates of SAEs Were Comparable Between Groups

Safety Set



System Organ Class (SOC) occurring at rate >0.05%
% shown is rounded to nearest 0.1%

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Study 301, Part A (Blinded Phase): Myocarditis/Pericarditis *Safety Set*

Adverse Event	mRNA-1273 n=15,184	Placebo n=15,162
Myocarditis	0	0
Pericarditis	2	2

Pericarditis in 2 mRNA-1273 vaccine recipients:

- 59-year old female:
  - Nonserious chest pain, dyspnea & fatigue Day 4 post dose 2 that resolved within 2 days
  - Presented with chest pain & syncope 68 days post dose 2 leading to hospitalization & diagnosis of pericarditis & pericardial effusion, both of which resolved
  - Classified as vaccine-related by the investigator
- 65-year-old male:
  - Hospitalized with a diagnosis of pericarditis 73 days post dose 2, resolved the following day
  - Occurred 19 days after an SAE of myocardial infarction
  - Classified as not vaccine-related by the investigator

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Study 301, Part B (Open Label Phase): Myocarditis/Pericarditis *Safety Set*

Adverse Event	mRNA-1273 n=27,266
Myocarditis	0
Pericarditis	1

Pericarditis in 1 mRNA-1273 vaccine recipient:

- 23-year-old male
- Diagnosed with COVID-19 during Part A (Placebo participant) 2 months before receiving 1st dose of mRNA-1273
- Bradycardia asymptomatic for a month – no other symptoms
- 43 days after dose 2 diagnosed with bradycardia and pericardial effusion
- Classified as vaccine-related by the investigator

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Background

- ~30,000 participants randomized to vaccine or placebo
- Efficacy of mRNA-1273 initially shown to be 94.1% starting 14 days after receipt of a 2-dose regimen in COVE trial[1] (data as of 11/25/20)
  - Results based on median follow-up of 9 weeks post-dose 2
- Efficacy results in BLA updated to a median of 5.3 months follow-up post-dose 2 through end of the blinded phase of the study (data as of 3/26/21)
- After EUA, subjects were offered unblinding and placebo recipients were offered vaccine
- Booster vaccination commenced in Sept, 2021 and is ongoing

[1] Baden et al *NEJM*, 2020

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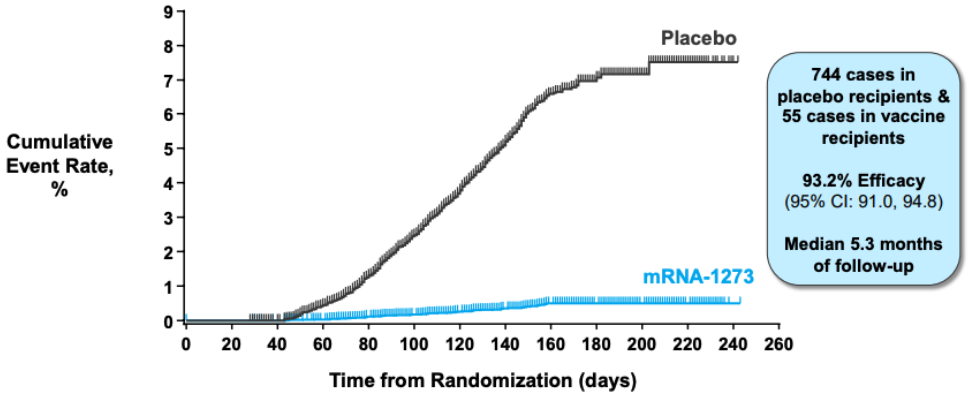
Vaccine Efficacy to Prevent COVID-19 in Individuals ≥18 Years of Age

Cumulative incidence of COVID-19 events starting 14 days after the 2nd dose

Per Protocol Set



Slide 24 El Sahly, NEJM, 2021

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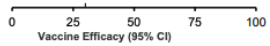
Vaccine Efficacy by Primary and Secondary Endpoints – COVE Efficacy Trial (P301)

Per Protocol Set

Subgroup	Number of Events: Placebo N = 14,164	Number of Events: mRNA-1273 N = 14,287	Vaccine Efficacy (95% CI)
Covid-19	744	55	93.2% (91.0-94.8)
Severe Covid-19	106	2	98.2% (92.8-99.6)
SARS-CoV-2 Infection	1339	280	82.0% (79.5-84.2)
Covid-19 (Secondary definition - CDC)	807	58	93.4% (91.4-94.9)
Death (Covid-19)	3	0	100% (NE-100.0)
Covid-19 (14 days after first injection)	769	56	93.3% (91.1-94.9)
Asymptomatic	498	214	63.0% (56.6-68.5)
Covid-19 (Regardless of prior SARS-CoV-2)*	754	58	92.8% (90.6-94.5)



Dotted line represents lower bound of 95% CI for efficacy required for primary endpoint
* Based on Full Analysis Set (N = 15,166 for placebo & 15,180 for mRNA-1273)

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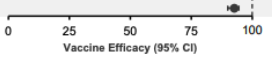
Vaccine Efficacy of mRNA-1273 to Prevent COVID-19 by Age, Sex & Race/Ethnicity

COVID-19 events starting 14 days after the 2nd dose

Per-protocol set

Subgroup	# Events/N: Placebo N = 14,164	# Events/N: mRNA-1273 N = 14,287	Vaccine Efficacy (95% CI)
Overall	744	55	93.2% (91.0-94.8)
Age (Years)			
18 to <65	644/10569	46/10661	93.4% (91.1-95.1)
≥65	100/3595	9/3626	91.5% (83.2-95.7)
65 to <75	81/2898	9/2990	89.7% (79.6-94.9)
≥75	19/697	0/636	100% (NE-100.0)
Sex			
Male	378/7494	30/7439	92.5% (89.1-94.8)
Female	366/6670	25/6848	93.8% (90.7-95.9)
Race*			
White	631/11273	48/11391	93.0% (90.6-94.7)
Black or African American	41/1352	4/1391	91.1% (75.2-96.8)
Asian	29/700	1/628	96.5% (74.2-99.5)
American Indian or Alaska Native	5/113	0/109	100% (NE-100.0)
Native Hawaiian or Other Pacific Islander	0/31	0/36	NE (NE-NE)
Ethnicity†			
Hispanic or Latino	177/2787	10/2831	94.8% (90.2-97.3)
Not Hispanic or Latino	563/11249	45/11322	92.6% (90.0-94.5)



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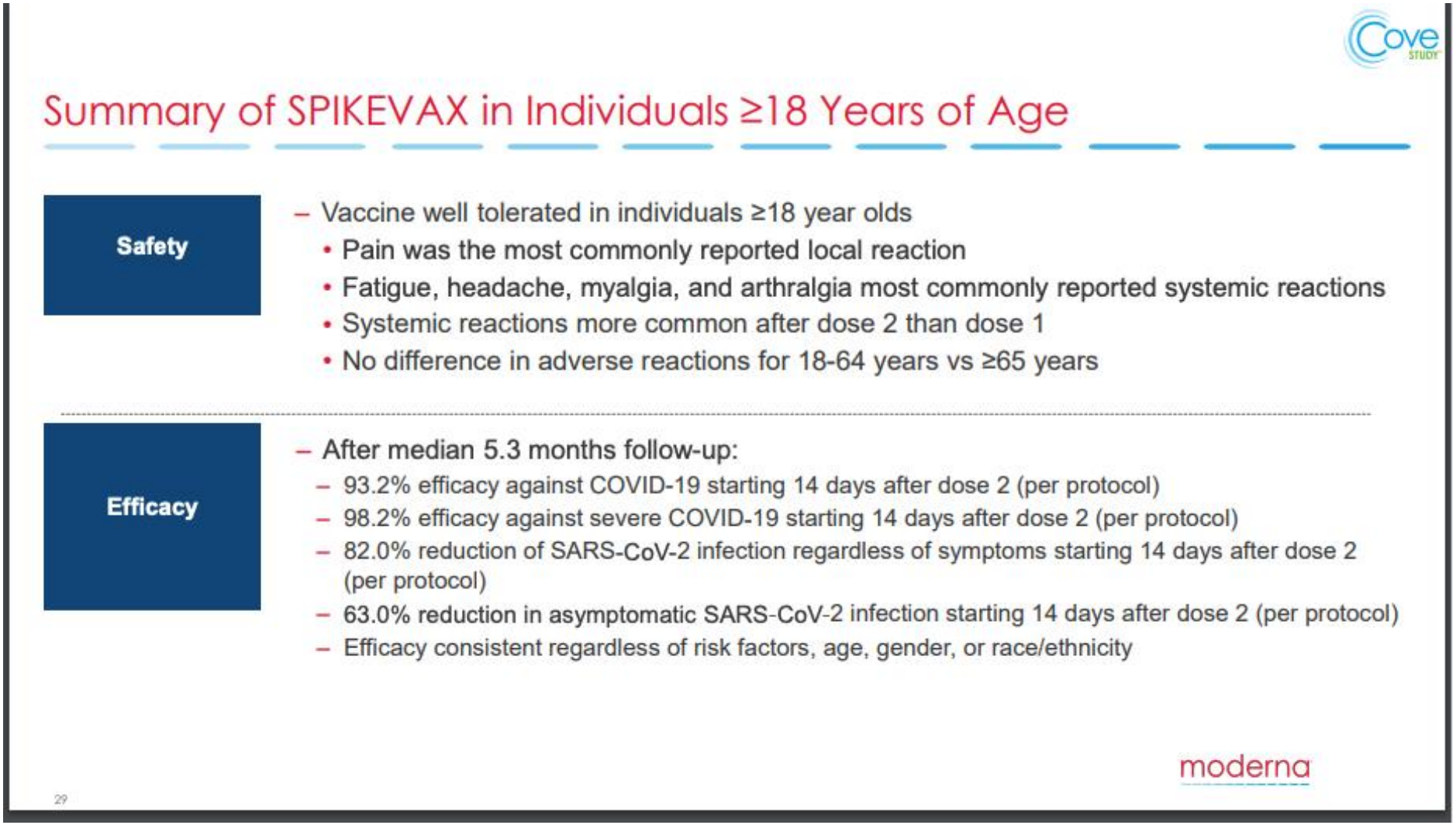
Cove STUDY
Summary of SPIKEVAX in Individuals ≥18 Years of Age
Safety
– Vaccine well tolerated in individuals ≥18 year olds
• Pain was the most commonly reported local reaction
• Fatigue, headache, myalgia, and arthralgia most commonly reported systemic reactions
• Systemic reactions more common after dose 2 than dose 1
• No difference in adverse reactions for 18-64 years vs ≥65 years
Efficacy
– After median 5.3 months follow-up:
– 93.2% efficacy against COVID-19 starting 14 days after dose 2 (per protocol)
– 98.2% efficacy against severe COVID-19 starting 14 days after dose 2 (per protocol)
– 82.0% reduction of SARS-CoV-2 infection regardless of symptoms starting 14 days after dose 2 (per protocol)
– 63.0% reduction in asymptomatic SARS-CoV-2 infection starting 14 days after dose 2 (per protocol)
– Efficacy consistent regardless of risk factors, age, gender, or race/ethnicity
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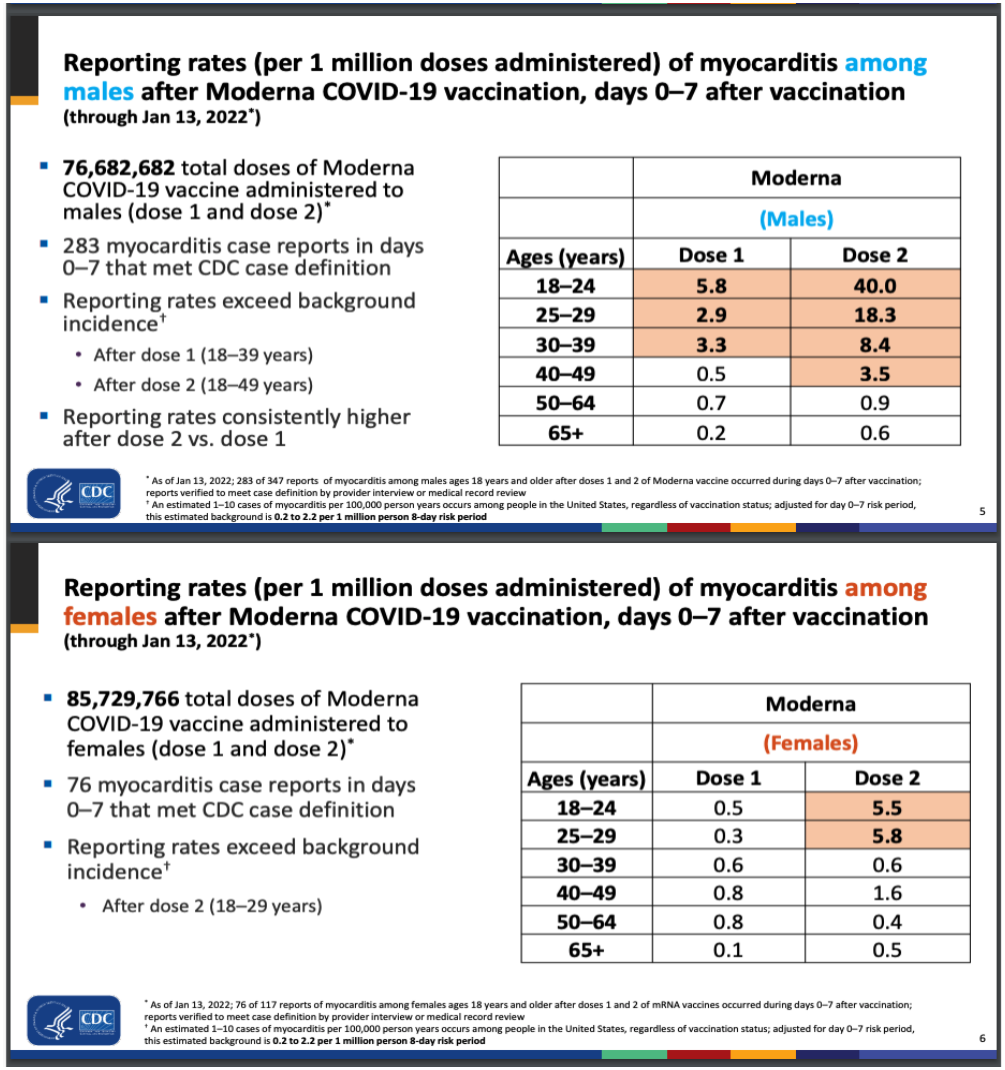
3. Updates on myocarditis and pericarditis following Moderna COVID-19 vaccine (Tom Shimabukuro, CDC)



Reporting rates (per 1 million doses administered) of myocarditis among males after Moderna COVID-19 vaccination, days 0–7 after vaccination
(through Jan 13, 2022*)

- **76,682,682** total doses of Moderna COVID-19 vaccine administered to males (dose 1 and dose 2)*
- 283 myocarditis case reports in days 0–7 that met CDC case definition
- Reporting rates exceed background incidence†
  - After dose 1 (18–39 years)
  - After dose 2 (18–49 years)
- Reporting rates consistently higher after dose 2 vs. dose 1

	Moderna (Males)	
Ages (years)	Dose 1	Dose 2
18–24	5.8	40.0
25–29	2.9	18.3
30–39	3.3	8.4
40–49	0.5	3.5
50–64	0.7	0.9
65+	0.2	0.6

* As of Jan 13, 2022; 283 of 347 reports of myocarditis among males ages 18 years and older after doses 1 and 2 of Moderna vaccine occurred during days 0–7 after vaccination; reports verified to meet case definition by provider interview or medical record review
† An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for day 0–7 risk period, this estimated background is **0.2 to 2.2 per 1 million person 8-day risk period**

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Reporting rates (per 1 million doses administered) of myocarditis among females after Moderna COVID-19 vaccination, days 0–7 after vaccination
(through Jan 13, 2022*)

- **85,729,766** total doses of Moderna COVID-19 vaccine administered to females (dose 1 and dose 2)*
- 76 myocarditis case reports in days 0–7 that met CDC case definition
- Reporting rates exceed background incidence†
  - After dose 2 (18–29 years)

	Moderna (Females)	
Ages (years)	Dose 1	Dose 2
18–24	0.5	5.5
25–29	0.3	5.8
30–39	0.6	0.6
40–49	0.8	1.6
50–64	0.8	0.4
65+	0.1	0.5

* As of Jan 13, 2022; 76 of 117 reports of myocarditis among females ages 18 years and older after doses 1 and 2 of mRNA vaccines occurred during days 0–7 after vaccination; reports verified to meet case definition by provider interview or medical record review
† An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for day 0–7 risk period, this estimated background is **0.2 to 2.2 per 1 million person 8-day risk period**

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Care and outcomes of myocarditis cases reported to VAERS after Moderna COVID-19 primary series vaccination among persons ages 18 years and older, days 0–7 after vaccination (N=359), through Jan 13, 2022*

Of 359 meeting case definition:

- 337 were hospitalized
  - 335 discharged
    - 230 (69%) known to have recovered from symptoms at time of report
  - 2 with disposition under review
- 22 were not hospitalized (seen in emergency department, urgent care, outpatient clinic, not specified)

* As of Jan 13, 2022; 359 reports of myocarditis among persons ages 18 years and older after doses 1 and 2 of Moderna vaccine; reports verified to meet case definition by provider interview or medical record review

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Summary of VAERS findings

- 164 million total doses of Moderna COVID-19 vaccine (doses 1 and 2) administered to persons ages 18 years and older (as of Jan 13, 2022)*
  - 359 total reports of myocarditis to VAERS in the 0–7 days following vaccination that met CDC case definition
  - Reporting rates of myocarditis exceed background rates for males (18–49 years, depending upon dose) and females (18–29 years, after dose 2)
  - Reporting rates of myocarditis were generally higher following dose 2 vs. dose 1, especially in males
  - Most myocarditis patients were hospitalized, and most were discharged home
    - Most discharged patients (69%) had recovered from symptoms at time of discharge

* 76,682,682 in males, 85,729,766 in females, 1,588,270 sex unknown or not reported

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Confirmed myocarditis and pericarditis in the 0–7-day risk interval among persons ages 18–39 years compared with outcome events in vaccinated comparators on the same calendar days for Moderna COVID-19 vaccination

(thru Jan 15, 2022)

Moderna COVID-19 vaccine	Events in risk interval, 0–7d* (per million doses)	Events in comparison interval, 22–42d*	Adjusted rate ratio† (95% CI)	2-sided P-value	Excess cases in risk interval (per million doses)
Both doses	38 (21.1)	7	9.18 (4.12 – 22.89)	<0.001	18.8
Dose 1	9 (9.7)	7	3.46 (1.12 – 11.07)	0.031	6.9
Dose 2	29 (33.0)	4	18.75 (6.73 – 64.94)	<0.001	31.2
Dose 2 males	26 (65.7)	4	16.96 (6.02 – 59.17)	<0.001	61.8
Dose 2 females	3 (6.2)	0	NE‡ (0.93 – ∞)	0.056	6.2

* Risk interval is 0–7 days after either dose, comparison interval is 22–42 days after either dose
† Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date
‡ NE = not estimable

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Summary of VSD findings*

- 923,711 dose 1 and 901,393 dose 2 Moderna COVID-19 vaccinations have been administered in VSD
- VSD analyses with vaccinated concurrent comparators indicate that Moderna COVID-19 vaccination is associated with increased risk of myocarditis and pericarditis in persons ages 18–39 years
  - Increased risk observed after both dose 1 and dose 2 in the 0–7-day risk interval, with risk greater following dose 2
    - Dose 2 adjusted rate ratio=18.75 vs. Dose 1 adjusted rate ratio=3.46
    - Highest excess cases per million doses administered observed after dose 2
      - 31.2 excess cases in 0–7-day risk interval per million doses administered in both males and females
      - 61.8 excess cases in 0–7-day risk interval per million doses administered to males

* Through Jan 15, 2022

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4. Update on myocarditis outcomes: MOVING (Ian Kracalik, CDC)

Outreach focusing on myocarditis patients 12–29 years of age

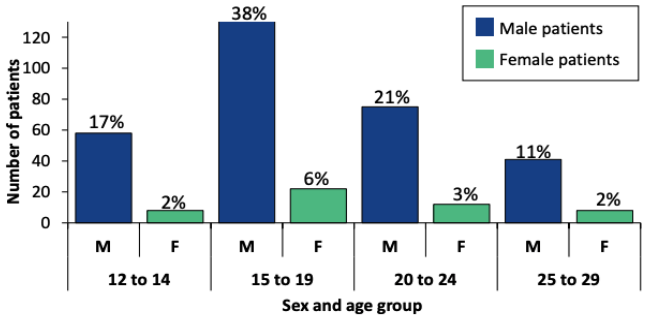
- As of November 2021, VAERS had received ~989 reports of myocarditis or myopericarditis after COVID-19 vaccination that met CDC case definition*
- Of these, ~850 patient ages 12–29 years had reached 90 days post-myocarditis diagnosis
  - Of ~850 patients 90 days post diagnosis, 648 (81%) had a phone number listed
    - Of the ~648 patients who were called, ~360 (56%) completed the survey; ~270 (42%) were unreachable and 18 (3%) declined to participate
    - For the 360 patients interviewed, time from myocarditis onset to interview was 143 days (IQR: 131, 162)

* https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

6

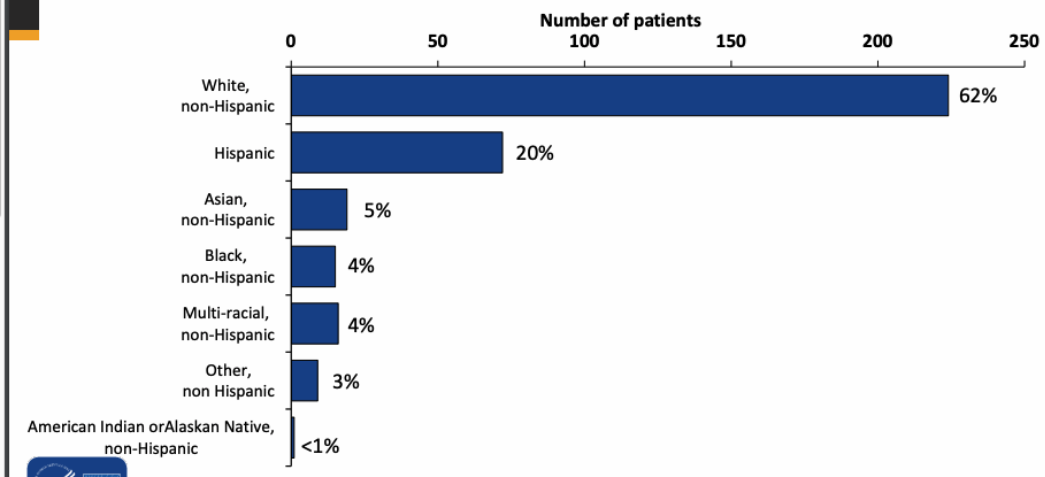
Most patients diagnosed with myocarditis were young males

- Median patient age was 18 years (IQR: 15–22);
- Of the 360 patients 90 days post myocarditis diagnosis, 86% (308) were male



7

Race and ethnicity of myocarditis patients (N=360)



*4 patients did not provide a response

8

Prior to their myocarditis diagnosis, most patients received two doses of a COVID-19 vaccine

- **87% (314/360)** received two doses of a COVID-19 vaccine
  - Of those who received two doses, **98% (307/314)** reported receiving both doses before they were diagnosed with myocarditis
  - **9% (31/360)** had a positive COVID-19 test before their myocarditis diagnosis

9

Self reported previous medical history among patients with myocarditis after mRNA COVID-19 vaccination (N=360)

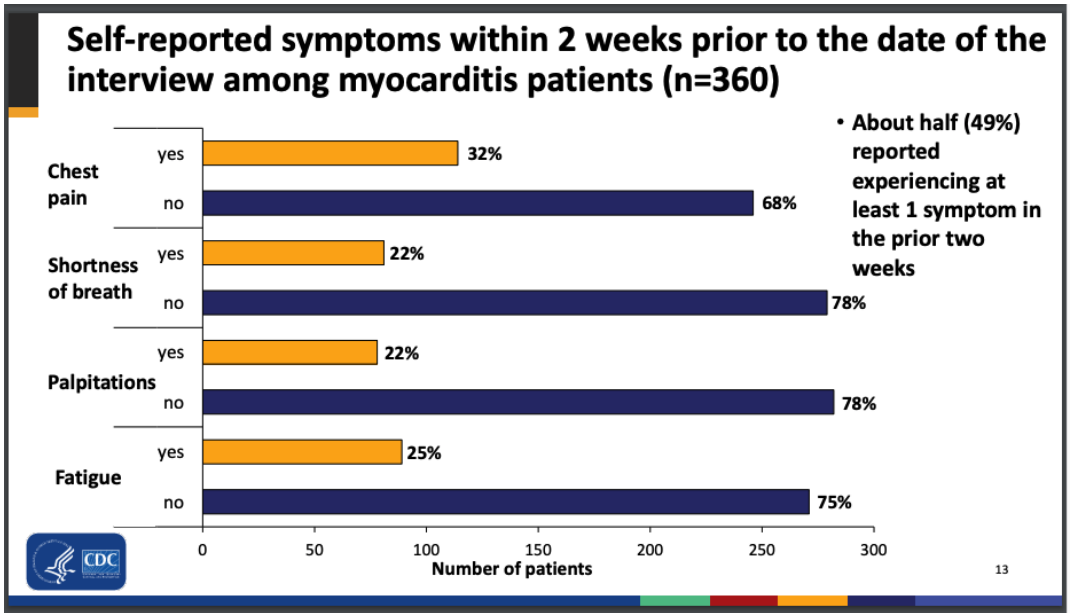
- **60 (17%)** had any condition
  - **11 (3%)** had an arrhythmia
  - **6 (2%)** had congenital heart disease
  - **6 (2%)** had a history of myocarditis
  - **2 (<1%)** had Kawasaki disease
  - **1 (<1%)** had previous heart failure
  - **32 (9%)** had a history of asthma
  - **7 (2%)** had an autoimmune disorder
  - **5 (1%)** genetic or chromosomal condition
  - **4 (1%)** were immunosuppressed
  - **1 (<1%)** had a history of Leukemia
  - **1 (<1%)** had type 1 diabetes

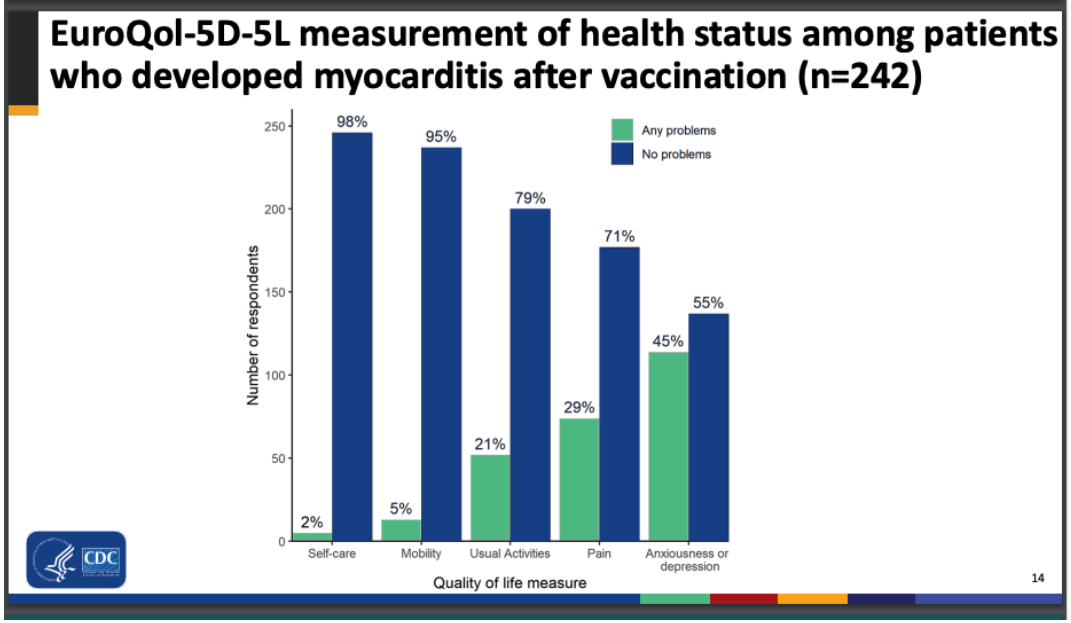
10

Most patients with myocarditis after vaccination reported being hospitalized at the time of myocarditis diagnosis (n=360)

- **92% (324)** were hospitalized
  - **4% (13)** were readmitted following myocarditis; **8 of 13 (62%)** were readmitted because of a concern with the heart
  - **20% (71)** were prescribed medication for their heart as of their last appointment with the provider

11


Self-reported symptoms within 2 weeks prior to the date of the interview among myocarditis patients (n=360)
• About half (49%) reported experiencing at least 1 symptom in the prior two weeks
Chest pain
yes
32%
no
68%
Shortness of breath
yes
22%
no
78%
Palpitations
yes
22%
no
78%
Fatigue
yes
25%
no
75%
0
50
100
150
200
250
300
Number of patients
13


EuroQol-5D-5L measurement of health status among patients who developed myocarditis after vaccination (n=242)
Any problems
No problems
Number of respondents
250
200
150
100
50
0
98%
95%
79%
71%
55%
45%
29%
21%
5%
2%
Self-care
Mobility
Usual Activities
Pain
Anxiousness or depression
Quality of life measure
14

Outreach to cardiologists or other healthcare providers

- Of the 360/648 patients interviewed, ~346 (96%) listed contact information for a cardiologist or other healthcare provider
  - Of the 346 providers with contact information listed, 229 completed a survey
  - An additional 151 providers completed surveys they had submitted for multiple patients in VAERS or provided contact information via the VAERS report
  - We were unable to contact 268 providers
  - In total, 380 providers completed the survey with a median of 191 days (IQR: 170, 216) from patient myocarditis onset to date of provider survey

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The proportion of myocarditis patients cleared for physical activity by their cardiologist or healthcare provider has increased (n=380)

At time of myocarditis diagnosis, 83% of patients had restrictions on their physical activity

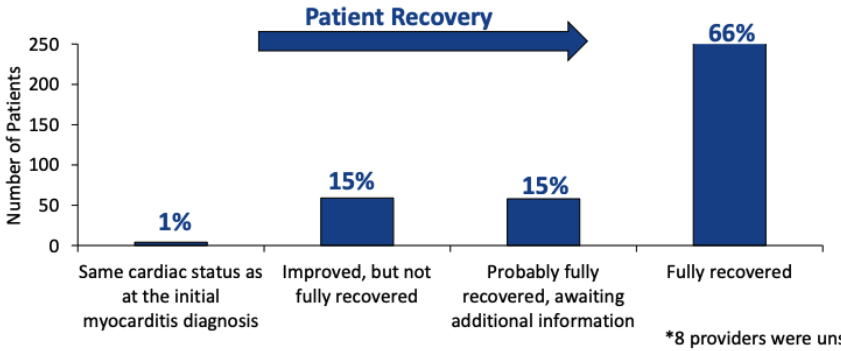
At time of provider survey, at least 90 days post diagnosis, only 39% had restrictions

*25 (7%) were unsure

17

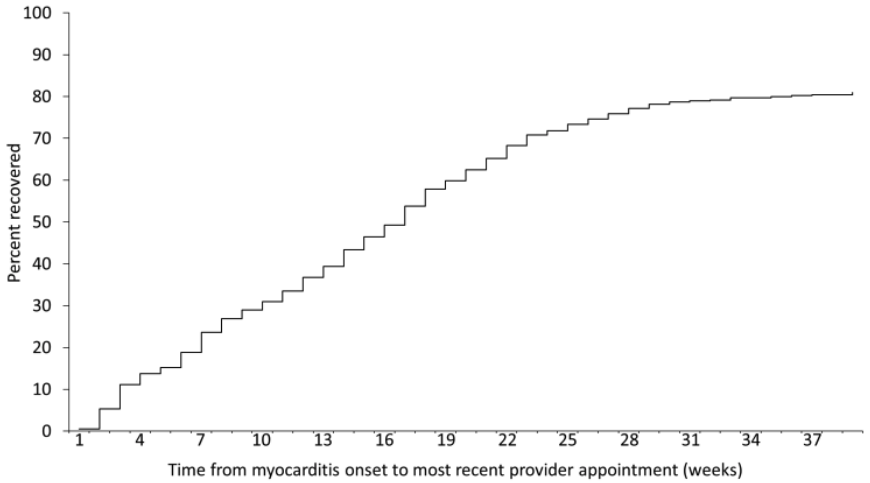
Based on the cardiologists/healthcare provider assessment, most patients appear to have fully or probably recovered from their myocarditis (n=380)

- 81% (309) of cardiologists or healthcare providers indicated the patient was fully or probably recovered

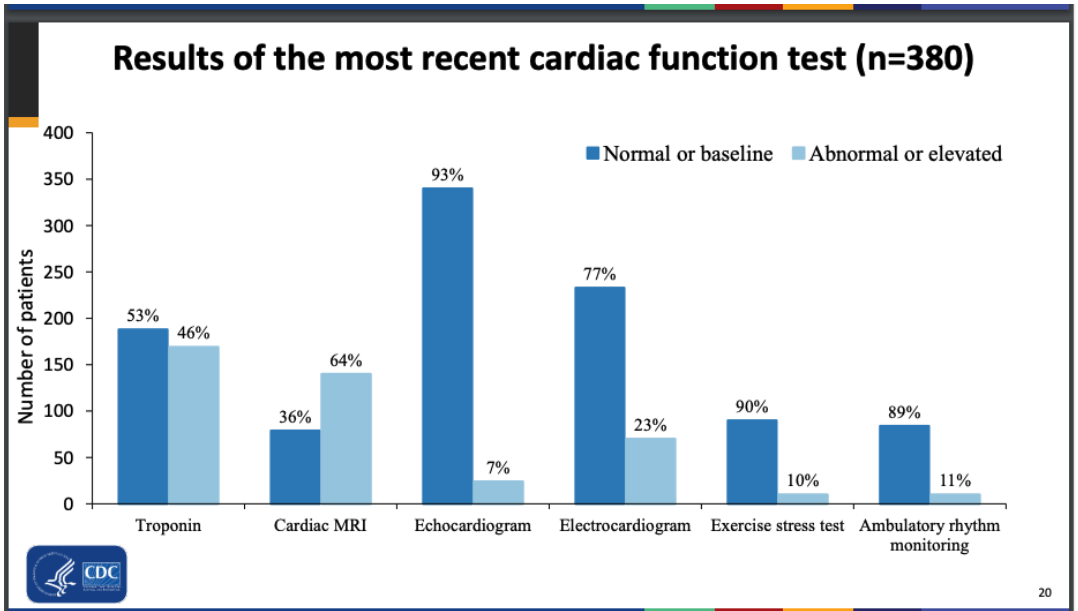


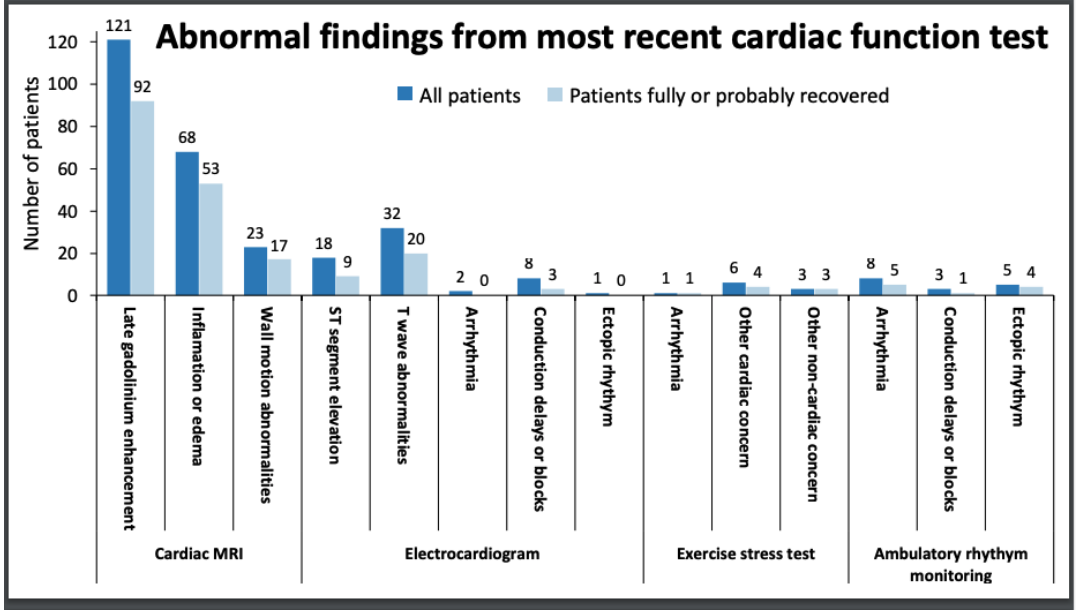
18

Proportion of myocarditis patients deemed to be fully or probably recovered by their healthcare provider (n=309)



19


Results of the most recent cardiac function test (n=380)
Number of patients
400
350
300
250
200
150
100
50
0
Normal or baseline
Abnormal or elevated
53%
46%
36%
64%
93%
7%
77%
23%
90%
10%
89%
11%
Troponin
Cardiac MRI
Echocardiogram
Electrocardiogram
Exercise stress test
Ambulatory rhythm monitoring
CDC
20


Abnormal findings from most recent cardiac function test
Number of patients
120
100
80
60
40
20
0
All patients
Patients fully or probably recovered
121
92
68
53
23
17
18
9
32
20
2
0
8
3
1
0
1
1
6
4
3
3
8
5
3
1
5
4
Late gadolinium enhancement
Inflamation or edema
Wall motion abnormalities
ST segment elevation
T wave abnormalities
Arrhythmia
Conduction delays or blocks
Ectopic rhythym
Arrhythmia
Other cardiac concern
Other non-cardiac concern
Arrhythmia
Conduction delays or blocks
Ectopic rhythym
Cardiac MRI
Electrocardiogram
Exercise stress test
Ambulatory rhythym monitoring

Summary

- At least 90 days after myocarditis diagnosis, most patients reported no impact on their quality of life, and most did not report missing school or work
- Only 13 (4%) were readmitted to the hospital
- Most (81%) healthcare providers indicated the patient was probably fully or fully recovered
- There did not appear to be a single test that was indicative of recovery
- To our knowledge, there were no vaccine-associated myocarditis deaths in this group
- Ongoing efforts to continue patient follow-up and contact myocarditis patients who were not yet recovered at time of survey
- Surveys are being modified for children aged 5-11 and follow-up to start in February 2022

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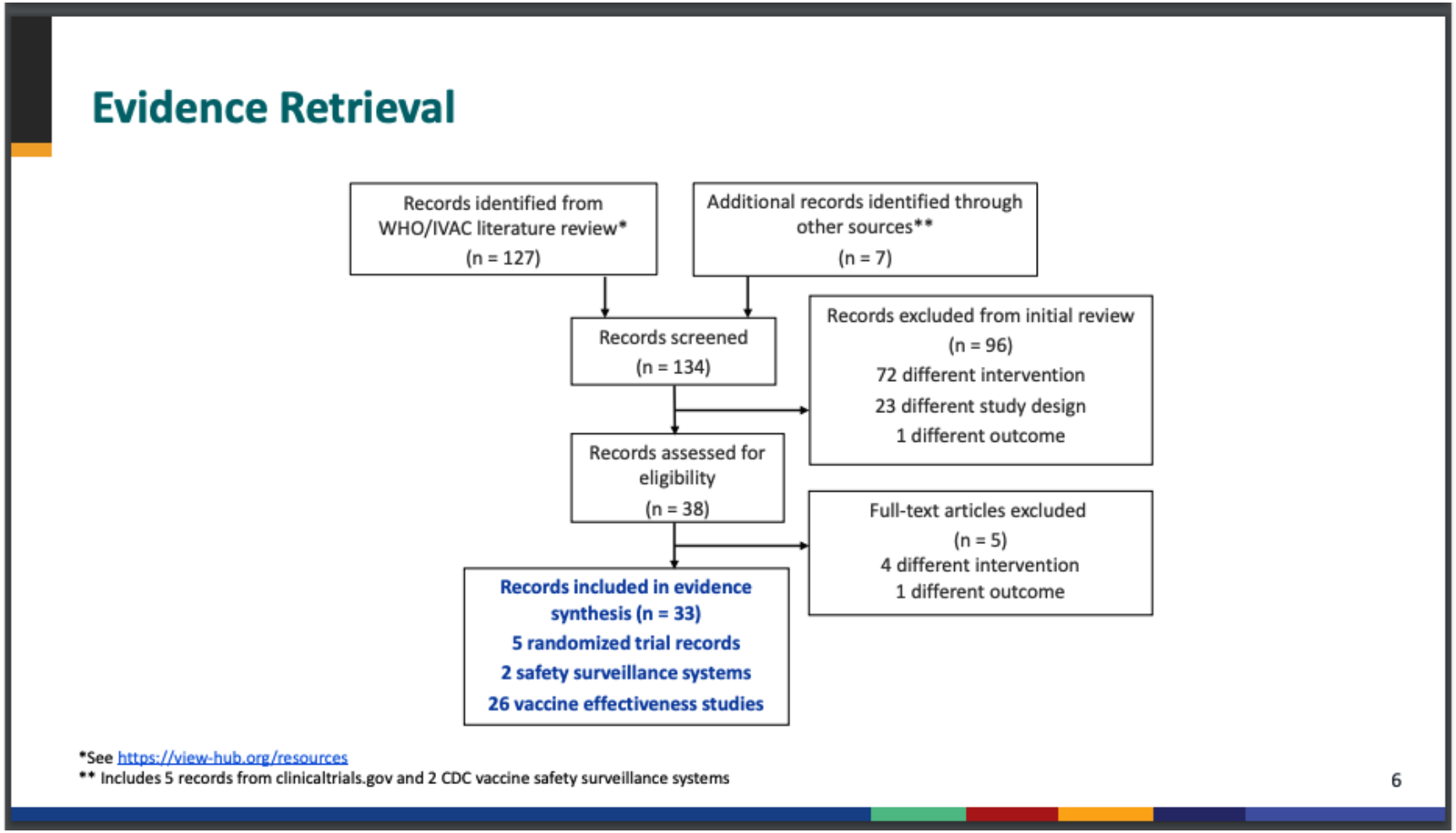
5. VaST assessment (Kipp Talbot, chair)

6. GRADE: Moderna COVID-19 vaccine (Megan Wallace, CDC)



Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (1) OBS (11)	Moderna COVID-19 vaccine is effective in preventing symptomatic COVID-19	**High**
Hospitalization due to COVID-19	Critical	RCT (1) OBS (15)	Moderna COVID-19 vaccine prevents hospitalization due to COVID-19	**Moderate**
Death due to COVID-19	Important	RCT (1) OBS (5)	Moderna COVID-19 vaccine prevents death due to COVID-19	**Moderate**
Asymptomatic SARS-CoV-2 infection	Important	RCT (1) OBS (3)	Moderna COVID-19 vaccine is effective in preventing asymptomatic SARS-CoV-2 infection	**High**
Harms				
Serious adverse events	Critical	RCT (2)	In the RCT, SAEs were balanced between vaccine and placebo arms. In post-authorization safety monitoring, myocarditis and anaphylaxis were rare but more common following vaccination	**Moderate**
Reactogenicity	Important	RCT (2)	Severe reactions within 7 days were more common in vaccinated; any grade ≥3 reaction was reported by 21.3% of vaccinated vs. 4.5% of placebo group	**High**

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Limitations

- In this rapidly evolving pandemic, the available body of evidence often does not represent the most recent epidemiology, including the impact of a new dominant variant on VE.
  - The evidence available for inclusion in this GRADE does not capture the impact of the Omicron variant on vaccine effectiveness
- The VE estimates presented represent the best estimates within the context of the pandemic during the time of the studies but may not be representative of VE in different phases of the pandemic or with different circulating variants.
  - The evidence available for inclusion in this GRADE is predominantly from time periods in which Alpha and Delta were the dominant circulating variants

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Conclusion

- Policy question focuses on recommendation following licensure of Moderna COVID-19 vaccine primary series that has been in use for a year under an emergency use authorization
- **Benefits**: Supported by body of evidence from RCTs and observational studies
  - RCT evidence demonstrated efficacy for all beneficial outcomes, including the 2 critical outcomes: symptomatic disease and hospitalization. Efficacy data were further supported by body of evidence from observational studies.
- **Harms**:
  - Grade 3 reactions were more common in vaccine than placebo recipients
  - Serious adverse events occurred at a similar frequency in vaccine and placebo groups
  - Two specific, rare SAEs have been associated with vaccination through safety surveillance

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7. EtR Framework: Moderna COVID-19 vaccine primary series in adults at least 18 yrs (Sara Oliver, CDC)

Policy question

- Should vaccination with the Moderna COVID-19 vaccine (Spikevax, 2-dose primary series) be recommended for persons 18 years of age and older?

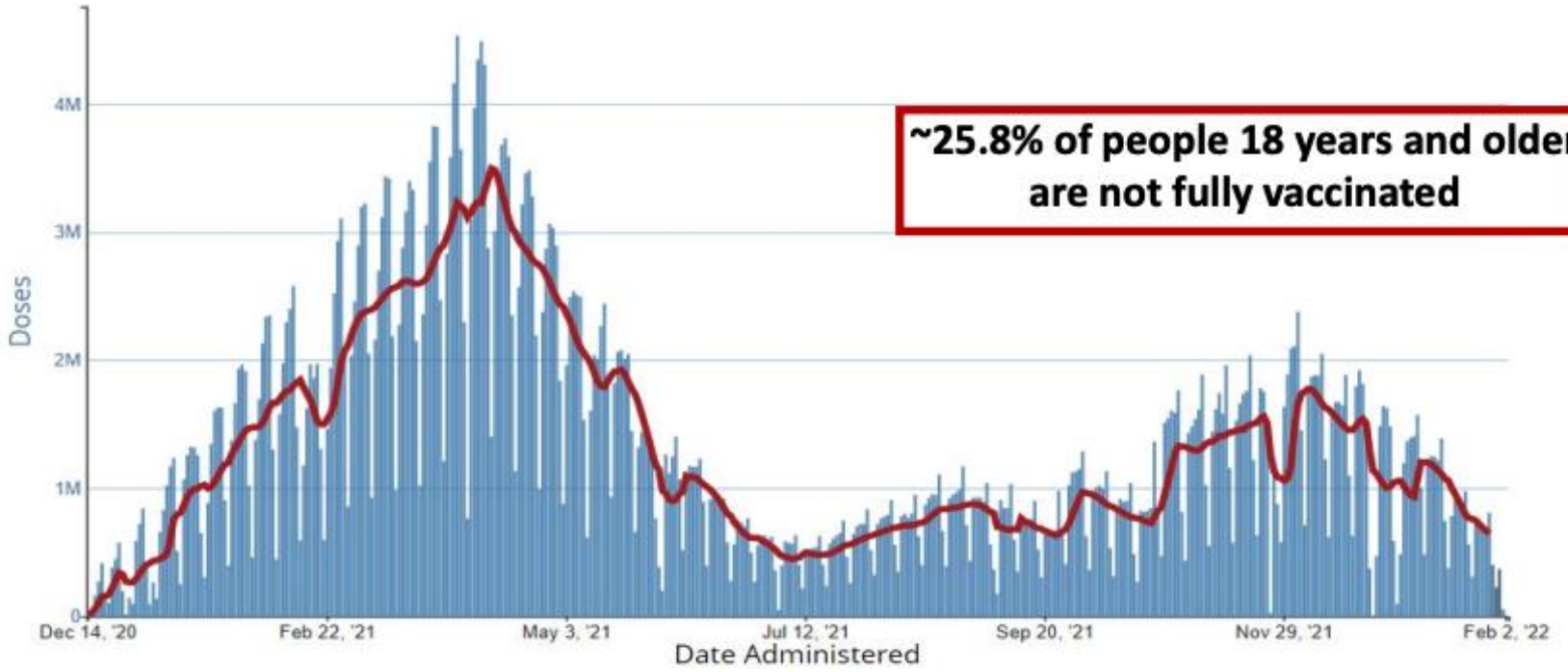
Regulatory action, GRADE, Evidence to Recommendation Framework, Vote

Moderna COVID-19 vaccine	Compared to	**No COVID-19 vaccine**

3

Daily trends in doses of COVID-19 vaccine administered

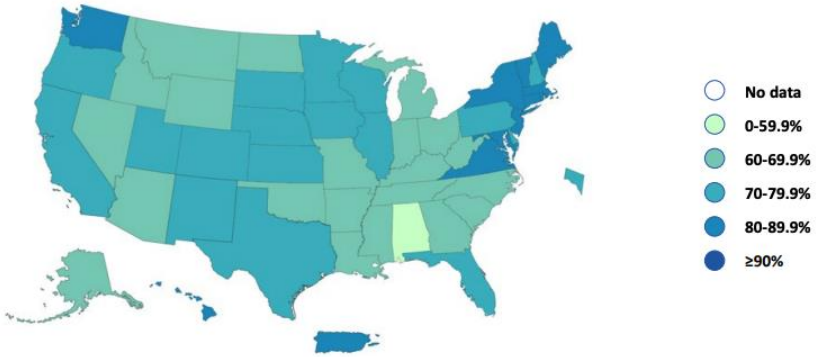
December 14, 2020 – February 1, 2022



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total Accessed February 3, 2022

20

Percent of population fully vaccinated ≥18 years of age

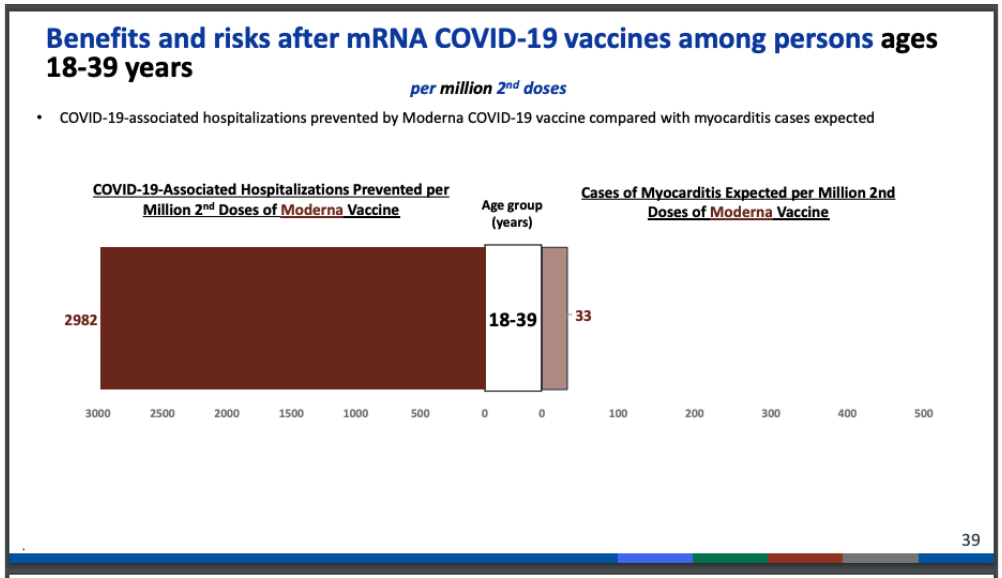


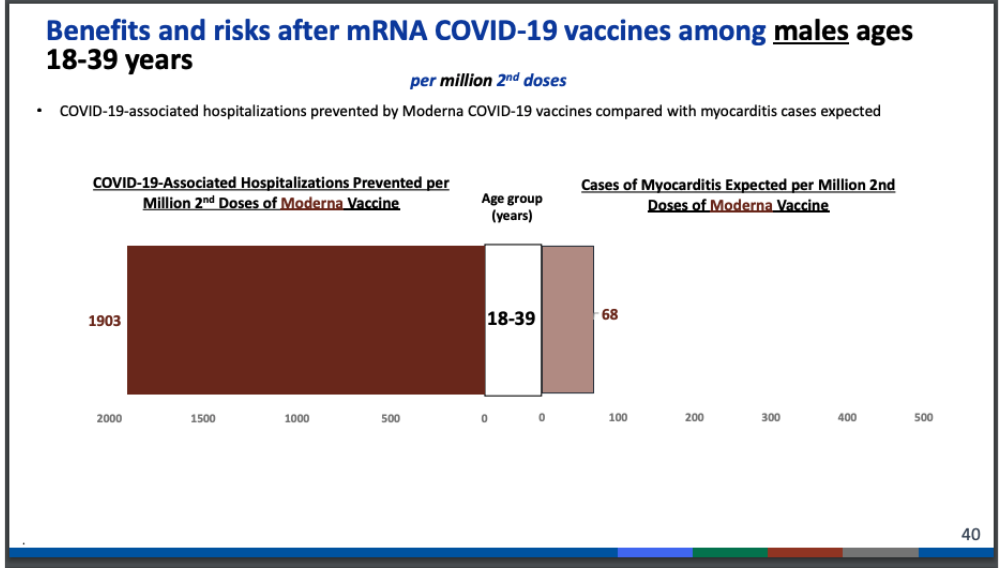
CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-fully-percent-pop18 Accessed February 3, 2022

25

Summary

- The Omicron variant is the dominant circulating variant of SARS-CoV-2 in the United States
- As of January, COVID-19 cases, hospitalizations, and deaths have increased
  - In November 2021, unvaccinated adults ages 18 years and older had **4X** risk of testing positive and **15X** risk of dying from COVID-19 compared to fully vaccinated adults
- Increasing cases are taxing healthcare resources, with many states facing ICU bed shortages again
- Over 212 million people (63.9%) are fully vaccinated in the United States; however, vaccination coverage varies by age and geography





N.B. scales for L and R sides are very different = huge benefit vs. risk

Limitations

- Benefit-risk analysis considers direct benefits and risk over a 180-day period comparing vaccine vs. no vaccine
- VE assumptions used in the model do not yet include Omicron-specific VE estimates
- The model assumes static hospitalization rate over 5 months
  - Benefit/risk profile might change as hospitalization rates change
- Model does not account for booster doses or prior infection

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Benefits and Harms
Summary

- Clinical trial and observational studies demonstrated Moderna COVID-19 vaccine is effective in the prevention of COVID-19 in persons ages 18 years and older
- Risk of myocarditis/pericarditis noted after mRNA COVID-19 vaccines
  - The highest risk was seen after the second dose among younger males
- Benefits for the Moderna COVID-19 vaccine **far outweigh** any possible vaccine-associated risks

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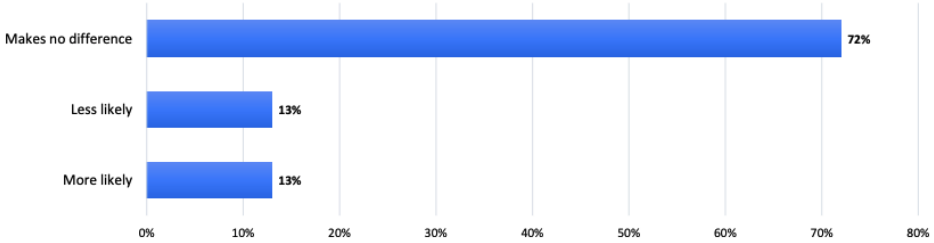
Vaccination intent among unvaccinated adults ages 18 years and older

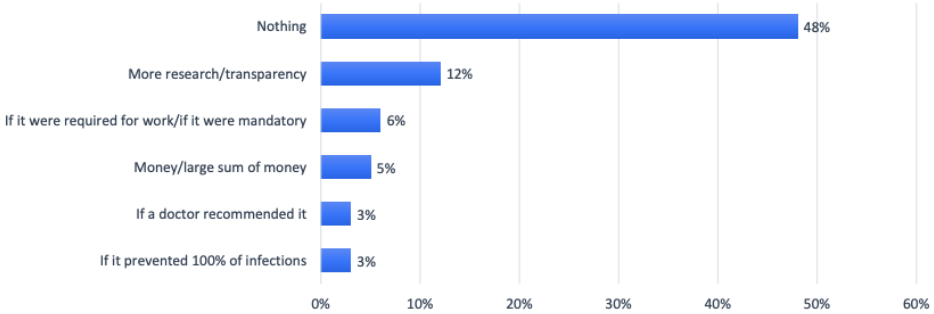
- A survey of the American general population (N = 1,094) was conducted on individuals ≥ 18 years between January 7 – 10, 2022
  - Unvaccinated survey respondents were asked, *"Does the discovery of the Omicron variant make you more likely or less likely to get the COVID-19 vaccine?*



Axios/Ipsos Poll. January 2022. https://www.ipsos.com/en-us/news-polls/axios-ipsos-coronavirus-index Accessed January 19, 2022

About half of unvaccinated adults say nothing will convince them to get a COVID-19 vaccine

- Among unvaccinated adults: *"What, if anything, will convince you to get vaccinated for COVID-19?"*



KFF COVID-19 Vaccine Monitor: Early Omicron Update (Dec 15 – 20, 2021). https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-early-omicron-update/. Accessed January 19, 2022

N.B. Not very hopeful…

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Large
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention (Moderna COVID-19 vaccine)
	What is the overall certainty of the evidence for the critical outcomes?	High to Moderate
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Large
	Is there important variability in how patients value the outcomes?	Probably important uncertainty or variability
Acceptability	Is the Moderna COVID-19 vaccine acceptable to key stakeholders?	Yes
Feasibility	Is the Moderna COVID-19 vaccine feasible to implement?	Yes
Resource Use	Is Moderna COVID-19 vaccine a reasonable and efficient allocation of resources?	Yes
Equity	What would be the impact of the intervention on health equity?	Probably no impact

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Evidence to Recommendations Framework

Summary: Work Group Interpretations

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

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Evidence to Recommendations Framework

Summary: Work Group Interpretations

Type of recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on shared clinical decision-making	We recommend the intervention

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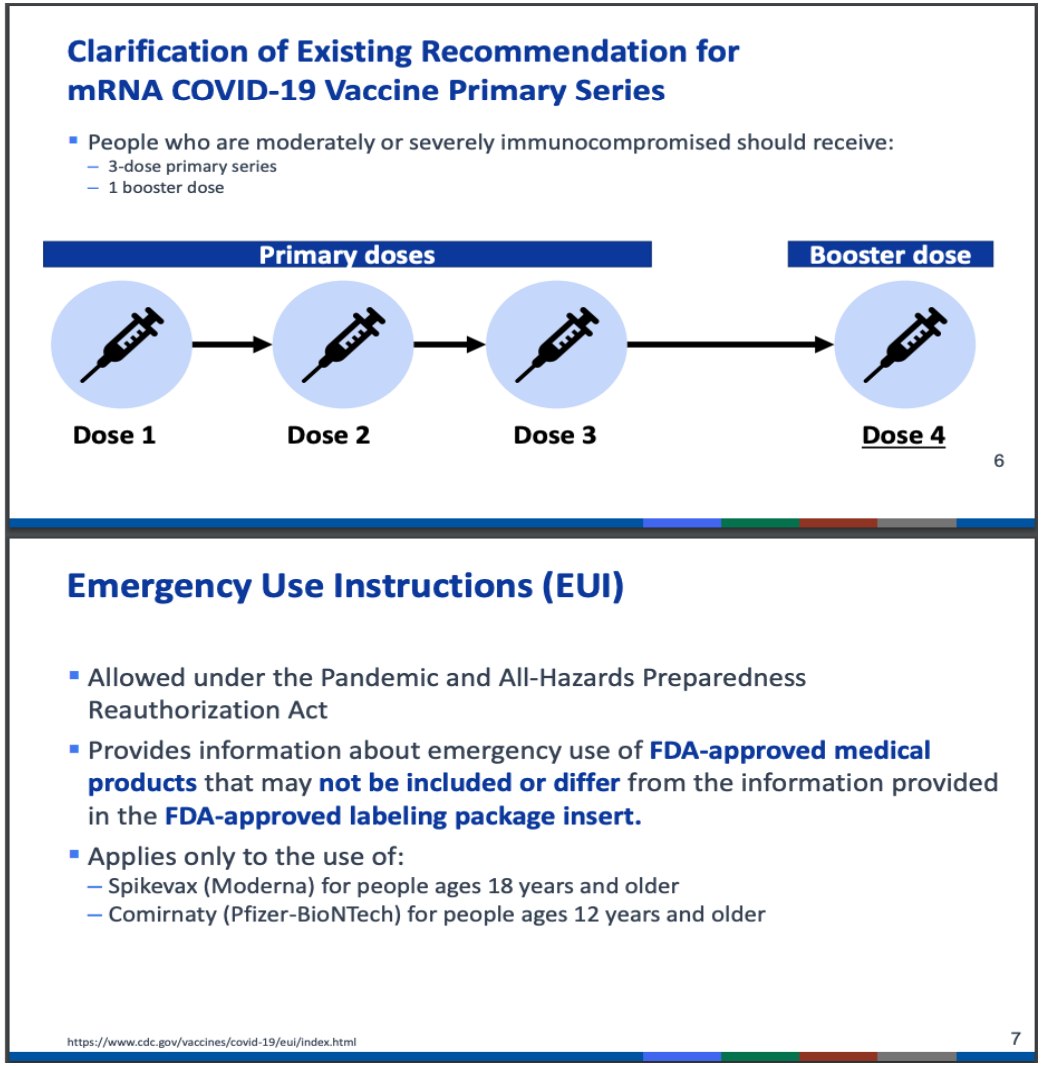
8. Updates to Clinical Considerations (Elisha Hall, CDC)



Revised Guidance for a 3-Month Booster Interval After an mRNA COVID-19 Vaccine Primary Series

Current guidance

People who are moderately or severely immunocompromised should receive a booster dose **at least 5 months** after the last (third) dose of an mRNA COVID-19 vaccine.

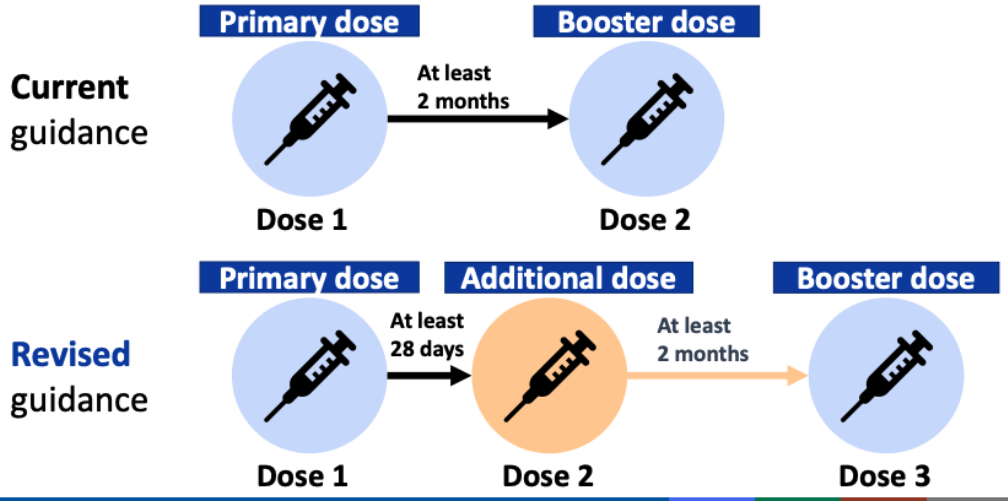
Revised guidance

People who are moderately or severely immunocompromised should receive a booster dose **at least 3 months** after the last (third) dose of an mRNA COVID-19 vaccine.

1. Kamar, N., Abravanel, F., Martion, O. (2021). Assessment of 4 Doses of SARS-CoV-2 Messenger RNA–Based Vaccine in Recipients of a Solid Organ Transplant. *Infectious Diseases, 4*(11), e2136030.
2. Benotmane, I., Bruel, T., Planas, D., et al. (2021). A fourth dose of the mRNA-1273 SARS-CoV-2 vaccine improves serum neutralization against the delta variant in kidney transplant recipients. *medRxiv*. Preprint. doi.org/10.1101/2021.11.25.21266704
3. Alejo, J.L., Mitchell, J., Chiang, T., et al. (2021). Antibody Response to a Fourth Dose of a SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series. *Transplantation, 105*(12), e280-281.
4. Munro, A., Janani, L., Cornelius, V. (2021). Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet, 398*, 2258-76.
5. Atmar, R.L., Lyke, K.E., Deming, M.E. (2021). Heterologous SARS-CoV-2 booster vaccinations-preliminary report. *medRxiv*. Preprint. doi: 10.1101/2021.10.10.21264827

10

Schedule for People Who Received a Janssen COVID-19 Vaccine Primary Series



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Revaccination for Certain Sub-Groups

- **Current** guidance: Limited to recipients of hematopoietic cell transplant (HCT) and chimeric antigen receptor (CAR)-T-cell therapy.
- **Revised** guidance: Recipients of HCT, CAR-T-cell, **or other B-cell depleting therapies** who received doses of COVID-19 vaccine **prior to or during treatment** should be revaccinated for doses received before or during treatment.
- Based on clinical judgement, revaccination may also be considered once immune competence is regained for people who received COVID-19 vaccine doses during **chemotherapy or radiation treatment**.

Case-by-Case Decision Making Based on Clinical Judgement

- On a case-by-case basis, providers who care for moderately or severely immunocompromised patients may administer mRNA COVID-19 vaccines outside of the FDA and CDC dosing intervals **based on clinical judgement** when the benefits of vaccination are deemed to outweigh the potential and unknown risks.

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REVISED COVID-19 Vaccination Schedule for People Who Are Moderately or Severely Immunocompromised

Vaccine	Vaccination Schedule				
Pfizer-BioNTech (ages 5 years and older)	1st dose	2nd dose (21 days after 1st dose)	3rd dose (at least 28 days after 2nd dose)		Booster dose* (at least 3 months after 3rd dose)
Moderna (ages 18 years and older)	1st dose	2nd dose (28 days after 1st dose)	3rd dose (at least 28 days after 2nd dose)		Booster dose* (at least 3 months after 3rd dose)
Janssen (ages 18 years and older)	1st dose	Additional dose† (at least 28 days after 1st dose)		Booster dose* (at least 2 months after additional dose)	

*Any COVID-19 vaccine can be used for the booster dose in people ages 18 years and older, though mRNA vaccines are preferred. For people ages 12–17 years, only Pfizer-BioNTech can be used. People ages 5–11 years should not receive a booster dose.
†Only Pfizer-BioNTech or Moderna COVID-19 Vaccine should be used

Passive Antibody Products

Current guidance

Defer COVID-19 vaccination for:

- 30 days if product used for post exposure prophylaxis
- 90 days if product used for treatment
- No guidance for pre-exposure prophylaxis

Revised guidance

- No recommended deferral period
- However, tixagevimab/cilgavimab (EVUSHELD™) should be deferred for at least two weeks after vaccination

Benschop, et al. (2021). The effect of anti-SARS-CoV-2 monoclonal antibody, bamlanivimab, on endogenous immune response to COVID-19 vaccination. *medRxiv*. Preprint.
doi: https://doi.org/10.1101/2021.12.15.21267605

18

9. Canadian experience and evidence with COVID-19 vaccine primary series extended intervals (Matthew Tunis, Bryna Warshawsky, Susanna Ogunnaike-Cooke)

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

PUBLIC HEALTH AGENCY OF CANADA > 4

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.

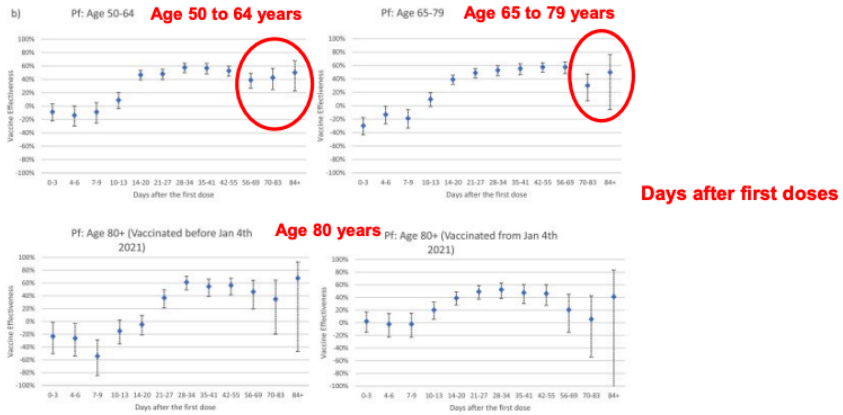
2) **Less potential for immune interference:** Circulating antibodies may interfere with the immune responses of subsequent antigen exposures for two reasons:

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.

PUBLIC HEALTH AGENCY OF CANADA > 5

Duration of protection from symptomatic infection with one dose of Pfizer-BioNTech in England



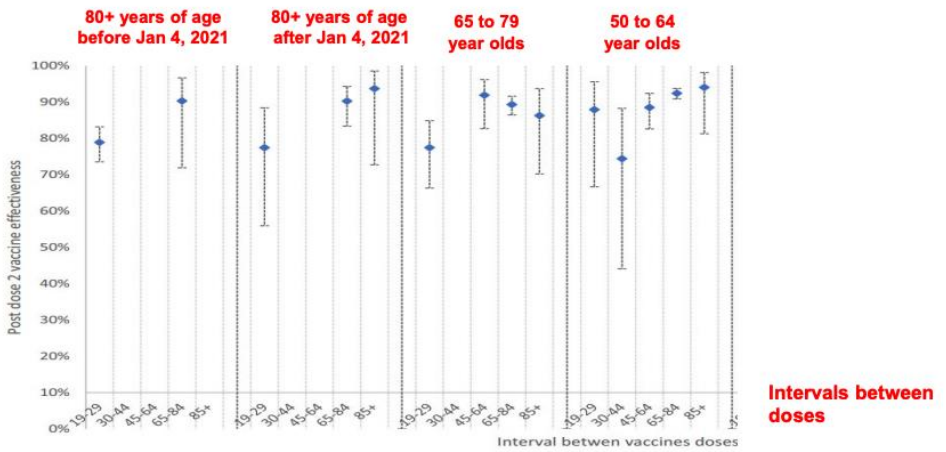
Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications

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

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)	**7,198** (95% CI: 5,820 to 8,902)
Blood collected at 14 to 34 days after dose 2 (n=200)	**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

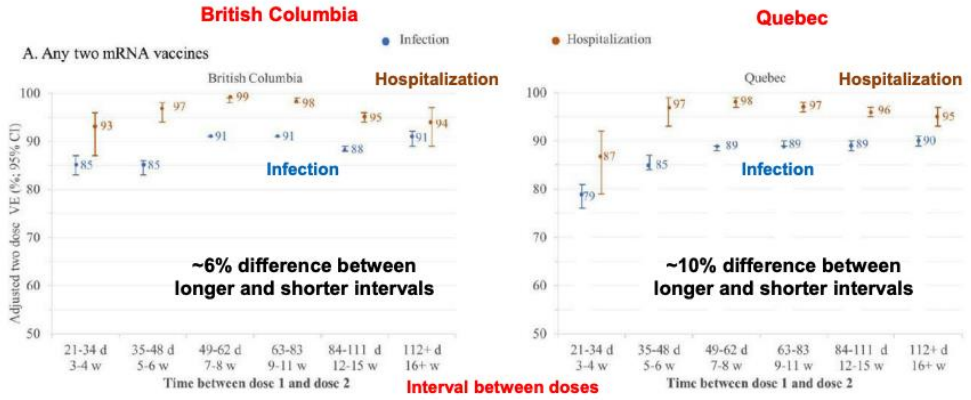
Post dose 2 vaccine effectiveness of Pfizer-BioNTech based on interval between dose 1 and 2



Amirthalingam et al. Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England | Nature Communications

PUBLIC HEALTH AGENCY OF CANADA > 9

mRNA vaccine effectiveness against infection and hospitalization by interval Quebec and British Columbia; May 30 to October 2, 2021; ≥ 18 years of age



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

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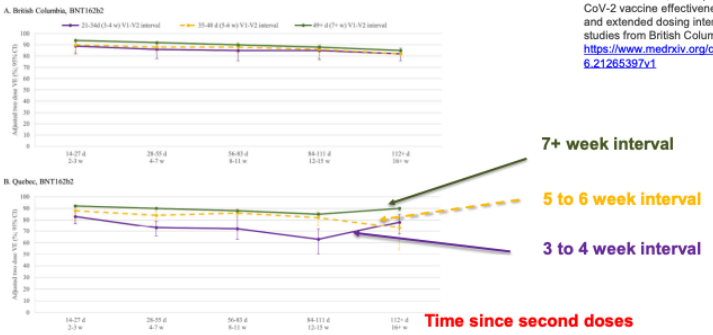
Pfizer-BioNTech vaccine effectiveness against infection by time since second dose and interval - Quebec and British Columbia

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



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).

Version: 26 October, 2021

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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

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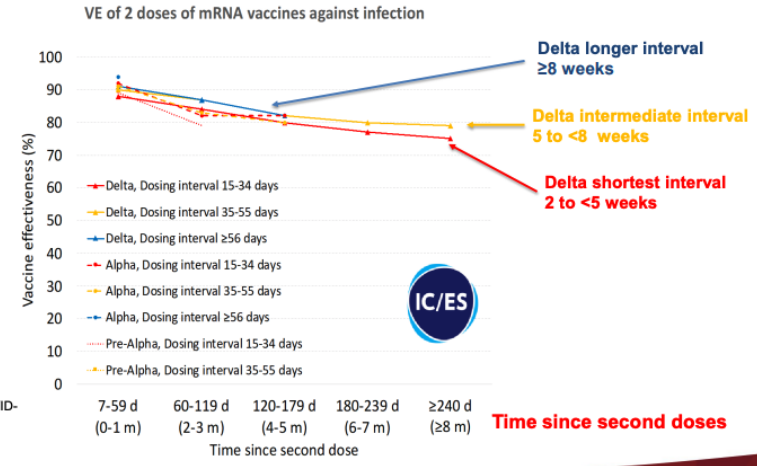
mRNA vaccine effectiveness against infection by time since second dose and interval – Ontario; January to November 2021; ≥16 years of age



Delta longer interval ≥8 weeks

Delta intermediate interval 5 to <8 weeks

Delta shortest interval 2 to <5 weeks

Time since second doses

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

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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

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Data up to and including September 04, 2021

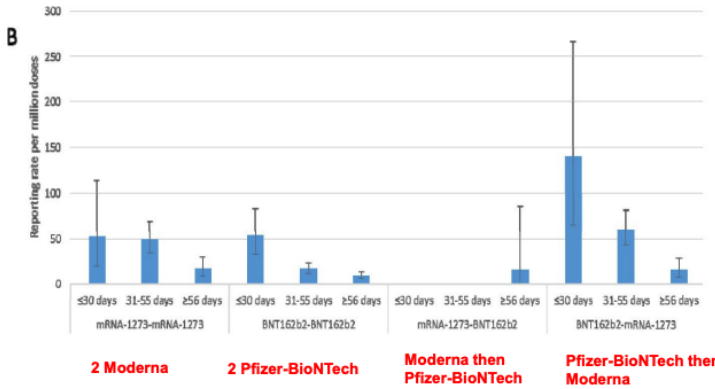
Myocarditis/pericarditis cases following mRNA COVID-19 vaccines in Ontario, Canada, by vaccine product, schedule, and interval, 7-day risk period

- 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

Data up to and including September 04, 2021

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).

*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)

10. VSD: Myocarditis after Moderna and Pfizer COVID-19 vaccine (Nicola Klein, NCKP)

Overview

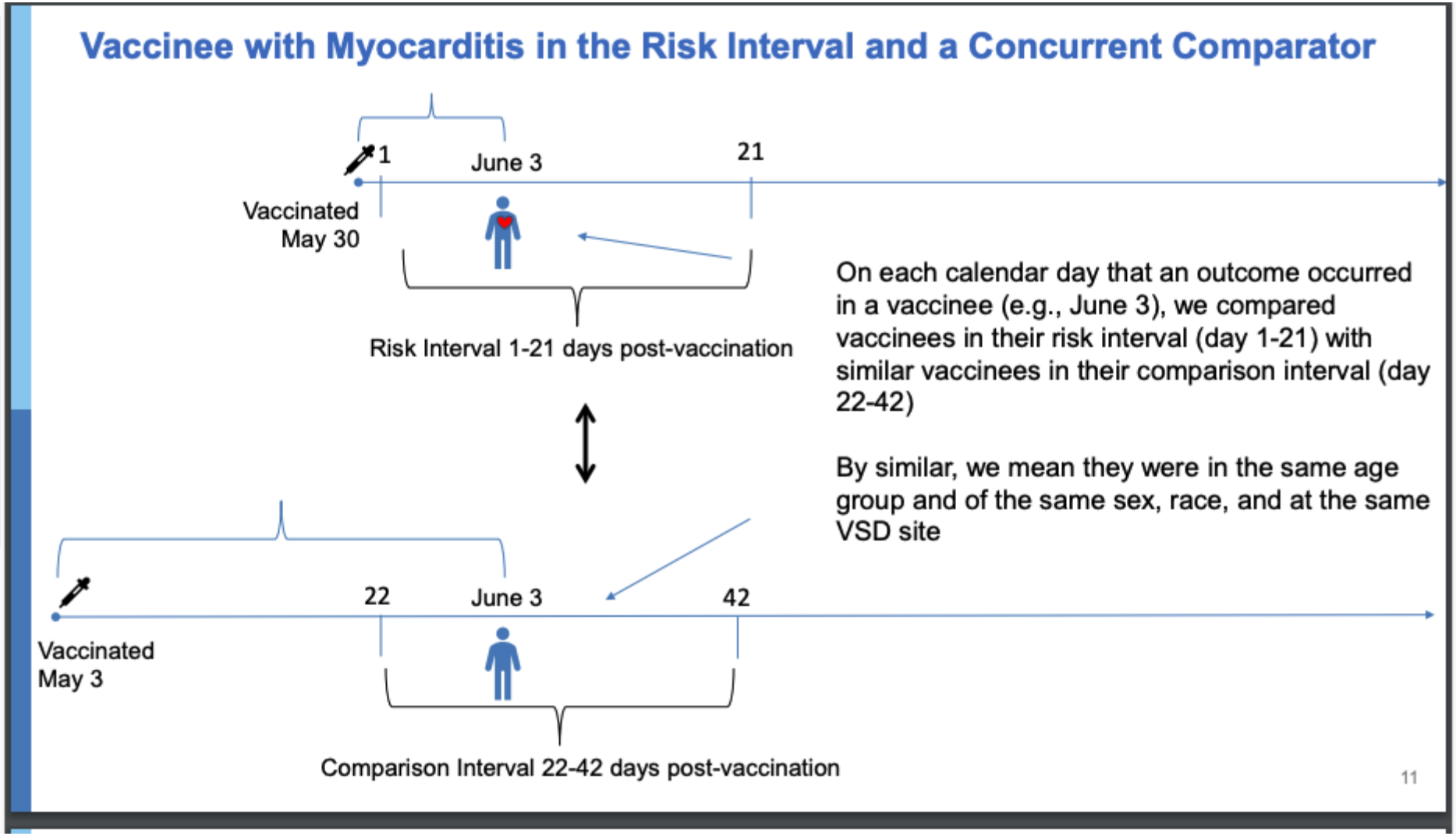
- Brief review of the rapid cycle analyses monitoring COVID-19 vaccine safety conducted by the Vaccine Safety Datalink
- Myocarditis and pericarditis during days 0-7 after mRNA vaccination:
  - Risk after each vaccine compared with risk among comparators who were 22-42 days after vaccination
  - Direct head-to-head comparisons of the Moderna vaccine versus the Pfizer vaccine during days 0-7 after vaccination

2

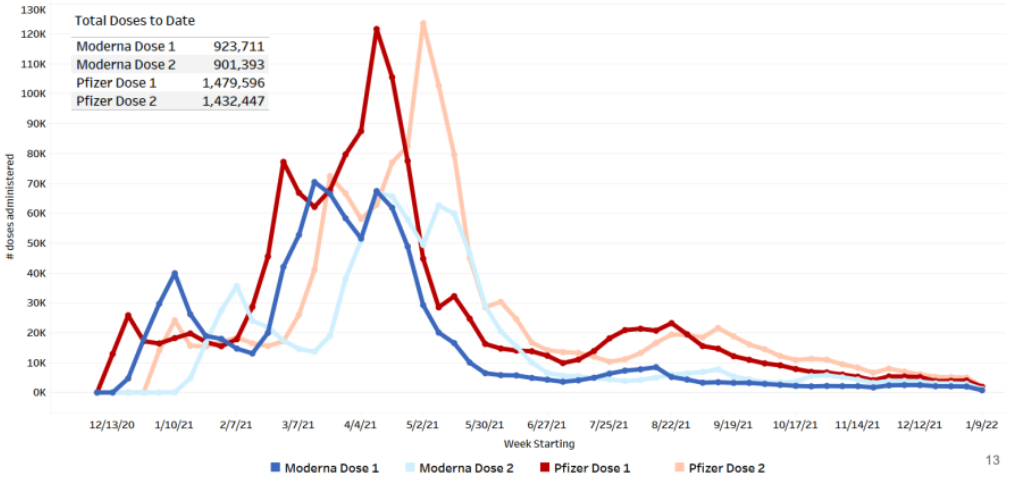
Myocarditis and Pericarditis: Electronic Case Identification using ICD-10 Codes

Initial Code List (based on consultation with cardiologist)	Revised Code List (based on VSD feedback)
• B33.22 Viral myocarditis • B33.23 Viral pericarditis • I30.* Acute pericarditis • I40.* Acute myocarditis	• B33.22 Viral myocarditis • B33.23 Viral pericarditis • I30.* Acute pericarditis • I40.* Acute myocarditis • I51.4 Myocarditis, unspecified • I31.9 Disease of the pericardium, unspecified

6

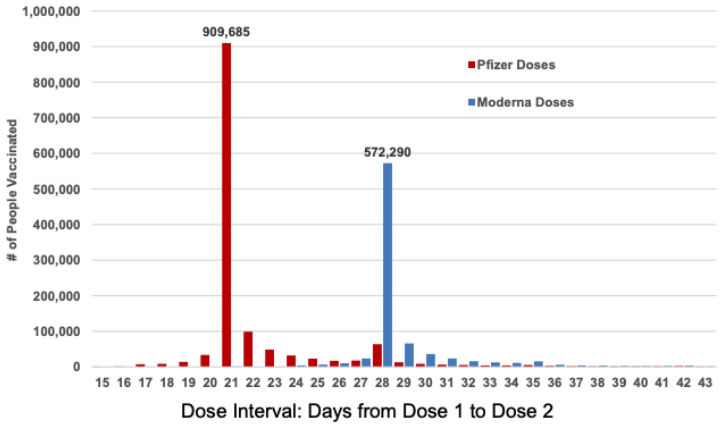

Vaccinee with Myocarditis in the Risk Interval and a Concurrent Comparator
1
June 3
21
Vaccinated
May 30
Risk Interval 1-21 days post-vaccination
On each calendar day that an outcome occurred in a vaccinee (e.g., June 3), we compared vaccinees in their risk interval (day 1-21) with similar vaccinees in their comparison interval (day 22-42)
By similar, we mean they were in the same age group and of the same sex, race, and at the same VSD site
22
June 3
42
Vaccinated
May 3
Comparison Interval 22-42 days post-vaccination
11

Doses Administered for 18–39-Year-Olds by Week



13

Days Between Dose 1 & Dose 2 Among 18–39-Year-Olds



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Myocarditis and Pericarditis after an mRNA Vaccine: Chart Review Summary

- Chart review completed for 297 cases through **January 15, 2022** for cases (19 pending, all under 18 years of age)
  - 5–39-year-olds
  - Cases identified any time post-vaccination
- Initial chart review followed with adjudication by an infectious disease clinician and/or a cardiologist
  - Confirm incident following vaccination
  - Meet CDC case definition (myocarditis, pericarditis, or myopericarditis)
  - Evaluate level of certainty for myocarditis
- **Adjudication verified 213/297 (71%) myocarditis and pericarditis cases**
  - 79 verified cases among 18–39-year-olds with onset in the 0-7 day risk interval: 16 after dose 1 and 63 after dose 2

15

Verified Myocarditis and Pericarditis in the 0-7 Day Risk Interval, among 18–39-Year-Olds by Product and Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Vaccine	Dose	Events in Risk Interval (Events/Million Doses)	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Either mRNA vaccine	Both Doses	79 (16.8)	20	**7.55**	4.52 – 13.04	<.001	14.6
	Dose 1	16 (6.7)	20	**3.29**	1.52 – 7.07	0.003	4.6
	Dose 2	63 (27.5)	13	**13.63**	7.39 – 26.55	<.001	25.5
Pfizer	Both Doses	41 (14.2)	13	**6.94**	3.57 – 14.13	<.001	12.1
	Dose 1	7 (4.7)	13	**3.02**	1.03 – 8.33	0.044	3.2
	Dose 2	34 (24.1)	8	**14.34**	6.45 – 34.85	<.001	**22.4**
Moderna	Both Doses	38 (21.1)	7	**9.18**	4.12 – 22.89	<.001	18.8
	Dose 1	9 (9.7)	7	**3.46**	1.12 – 11.07	0.031	6.9
	Dose 2	29 (33.0)	4	**18.75**	6.73 – 64.94	<.001	**31.2**

[1]Comparison interval is 22–42 days after either dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

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Verified Myocarditis and pericarditis 0-7 Days after Any Dose of mRNA Vaccine: Level of Care and Status by Age Group/Product

Level of Care and Status	18–39-Year-Olds (Pfizer) N=41	18-39–Year-Olds (Moderna) N=38
Highest level of care		
Outpatient	1 (2%)	1 (3%)
Emergency department	5 (12%)	7 (18%)
Admitted to hospital	35 (85%)	30 (79%)
Admitted to ICU	0 (0%)	0 (0%)
Length of hospital stay, median (range)	1 day (0–2 days)	1 day (0–13 days)
0 days (same day discharge)	8 (20%)	7 (18%)
1 day	18 (44%)	19 (50%)
2 days	15 (37%)	9 (25%)
3 days	0 (0%)	2 (5%)
4 days	0 (0%)	0 (0%)
5 days	0 (0%)	0 (0%)
6+ days	0 (0%)	1 (3%)
Discharged to home	41 (100%)	38 (100%)
At least one follow-up visit noted at the time of chart review	37 (90%)	34 (90%)

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Is There a Difference in Risk of Myocarditis and Pericarditis between mRNA Vaccines?

- Analyses with vaccinated concurrent comparators indicate that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in 18–39-year-olds
- Analyses with vaccinated concurrent comparators indirectly suggest that Moderna may be associated with more risk of myocarditis/pericarditis than Pfizer
- To directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, we conducted head-to-head comparisons among 18–39-year-olds

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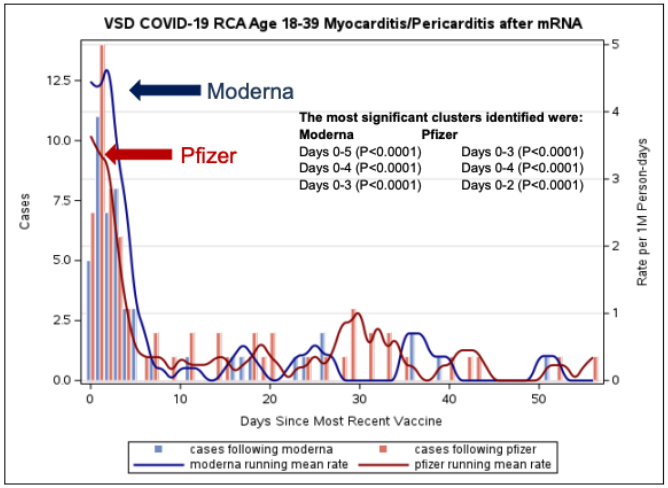
Symptom Onset of Verified Myocarditis and Pericarditis among 18–39-Year-Olds by Vaccine Product



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Moderna vs Pfizer "Head-to-Head" Comparison

- **Moderna** and **Pfizer** vaccinees were directly compared during the risk interval within groups
- The groups are comprised of:
  - Individuals inside the risk interval (days 0-7 post-vaccination)
  - Individuals of the same age group, sex, and race/ethnicity and from the same VSD site
  - On a calendar day when an mRNA vaccinee had myocarditis/pericarditis
- We estimated rate ratios with 95% confidence intervals (rate post-Moderna / rate post-Pfizer)
- We tested the null hypothesis that the rate of myocarditis and pericarditis after vaccination does not differ between Moderna and Pfizer

22

Myocarditis and Pericarditis in 18–39-Year-Olds in the 0-7 Day Risk Interval: Moderna vs Pfizer

	Sex	Moderna (N)	Pfizer (N)	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer[2]
Either Dose	All	38	41	**1.61**	**1.02 – 2.54**	**0.041**	**8.0**
	Male	32	36	1.52	0.93 – 2.48	0.097	13.4
	Female	6	5	2.34	0.65 – 8.71	0.188	3.5
Dose 1	All	9	7	2.27	0.80 – 6.65	0.122	5.5
	Male	6	6	1.65	0.49 – 5.57	0.414	5.6
	Female	3	1	6.79	0.65 – 197.90	0.116	5.1
Dose 2	All	29	34	1.48	0.88 – 2.50	0.141	10.7
	Male	26	30	1.50	0.86 – 2.61	0.152	21.9
	Female	3	4	1.35	0.23 – 7.15	0.714	1.6

[1]Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.
[2]Excess cases is an estimate of the Moderna rate minus the Pfizer rate. Excess cases per million doses were estimated by dividing the Moderna incidence rate by the rate ratio estimate and subtracting the result from the Moderna rate.

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Myocarditis/Myopericarditis, Pericarditis Excluded, in 18–39-Year-Olds in the 0-7 Day Risk Interval: Moderna vs Pfizer

	Sex	Moderna (N)	Pfizer (N)	Adjusted Rate Ratio[1]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer[2]
Either Dose	All	30	39	1.35	0.82 – 2.19	0.237	4.3
	Male	27	35	1.32	0.78 – 2.22	0.288	8.1
	Female	3	4	1.57	0.27- 8.12	0.585	1.1
Dose 1	All	6	6	1.84	0.54 – 6.30	0.320	3.0
	Male	4	5	1.43	0.33 – 5.86	0.612	2.9
	Female	2	1	4.28	0.28 – 151.15	0.311	3.0
Dose 2	All	24	33	1.24	0.70 – 2.14	0.454	5.2
	Male	23	30	1.31	0.73 – 2.31	0.361	13.6
	Female	1	3	0.53	0.02 – 5.81	0.658	-1.8

[1]Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.
[2]Excess cases is an estimate of the Moderna rate minus the Pfizer rate. Excess cases per million doses were estimated by dividing the Moderna incidence rate by the rate ratio estimate and subtracting the result from the Moderna rate.

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Summary

- Among 18–39-year-olds, both mRNA vaccines were associated with increased risk of myocarditis and pericarditis in the 0-7 days post-vaccination, particularly after dose 2
  - We estimated 22.4 excess cases per million second doses after Pfizer and 31.2 excess cases per million second doses after Moderna
- Among 18–39-year-olds, there were no noticeable clinical differences between cases after Moderna and those after Pfizer
  - Most had hospital length of stay of 0-1 days
  - None were admitted to the ICU
- Direct head-to-head comparisons provide evidence that the risk of myocarditis and pericarditis may be higher after Moderna than after Pfizer
  - Comparing Moderna vs Pfizer, we estimated that Moderna was associated with an additional 10.7 cases of myocarditis and pericarditis per million second doses
- Both mRNA vaccines were associated with increased risk of myocarditis and pericarditis for individuals aged 18-39 years

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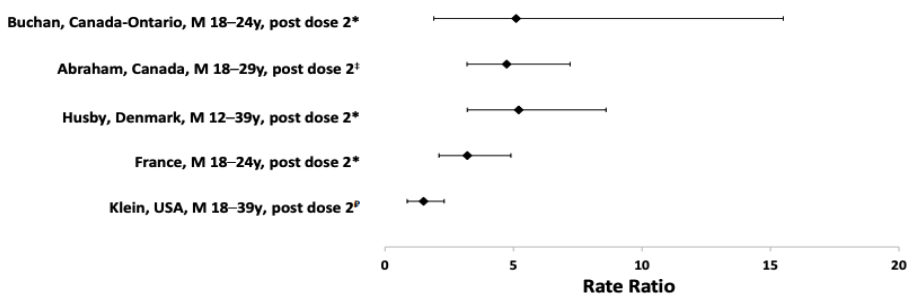
11.Myocarditis and COVID-19 vaccine intervals: international data and policies (Danielle Moulia, CDC)

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

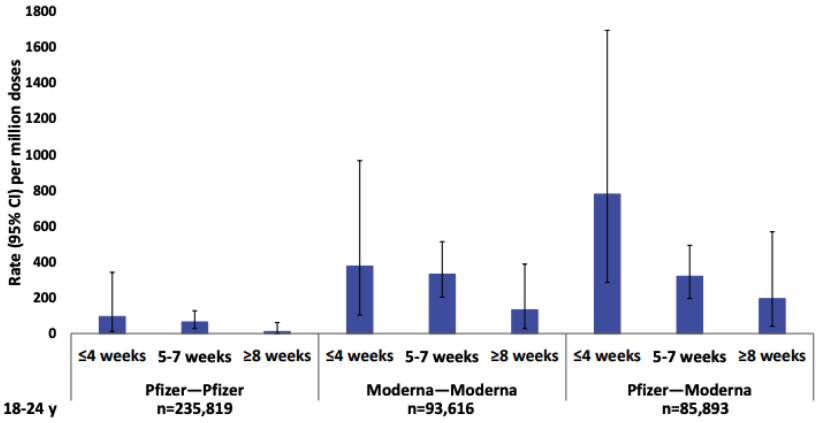


*Unadjusted rate ratio; ‡Adjusted with a Poisson model conditioned by calendar week of vaccine administration; ᵖ Adjusted for VSD site, age, sex, race/ethnicity, and calendar date
Source. Husby et al., SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study. BMJ 2021; 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. 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.

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



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

Source: Buchan S. Dec 2021, MedRxiv preprint.

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.

Source: Payne R. 2021, Cell.; Amirthalingam G. 2021, Nat Commun.; Parry H. 2022, Npj Vaccines.; Grunau B. 2022, Clin Inf Dis.

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
[5] Skowronski DM. 2021, MedRxiv preprint.

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.

mRNA vaccine product	Immunization schedule	Minimum interval	Authorized interval	Optimal interval
Pfizer-BioNTech Comirnaty	2-dose schedule	19 days	21 days	8 weeks
Moderna Spikevax	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. 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 ≥ 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 ≥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

Source: https://www.cdc.gov.tw/En/Bulletin/Detail/YPIDZwC4HjqBMtGi4jynHQ?typeid=158. Accessed 1/31/22
https://www.moh.gov.sg/covid-19/vaccination/faqs---children-related-vaccination-matters. Accessed 1/31/22

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

Source: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/advice-for-providers/clinical-guidance/doses-and-administration. Accessed 1/30/2022.
https://www.health.gov.au/sites/default/files/documents/2021/12/atagi-recommendations-on-pfizer-covid-19-vaccine-use-in-children-aged-5-to-11-years_0.pdf. Accessed 1/30/2022.

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. Accessed 1/23/2022.
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

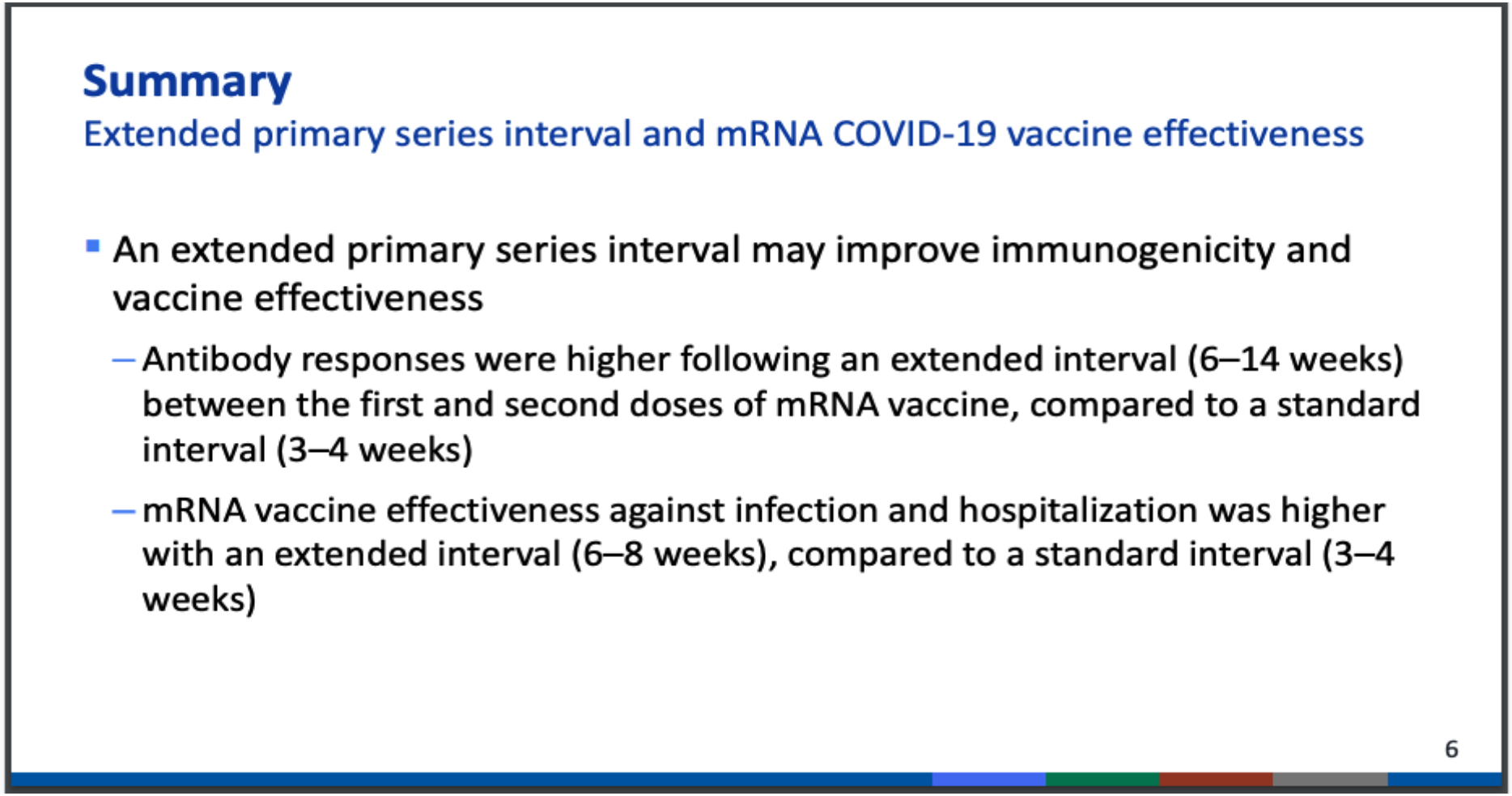
- Not a systematic review; data are biased toward findings that influenced national vaccine policy
- Limited number of countries are administering both Moderna and Pfizer
- Caution should be used when comparing myocarditis/pericarditis rates across studies as surveillance systems, case definitions and 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

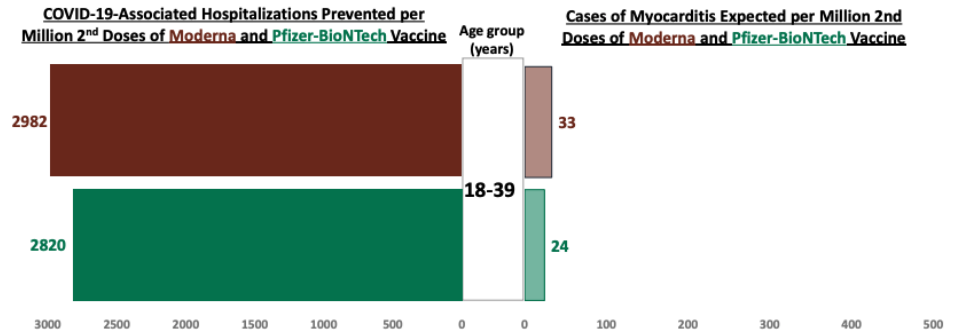
12. Summary and Work Group interpretation: Extended intervals for mRNA COVID-19 vaccines (Sara Oliver, CDC)



Benefits and risks after mRNA COVID-19 vaccines among persons ages 18–39 years

per million 2nd doses

- COVID-19-associated hospitalizations prevented by mRNA COVID-19 vaccines compared with myocarditis cases expected
- Presented by vaccine product



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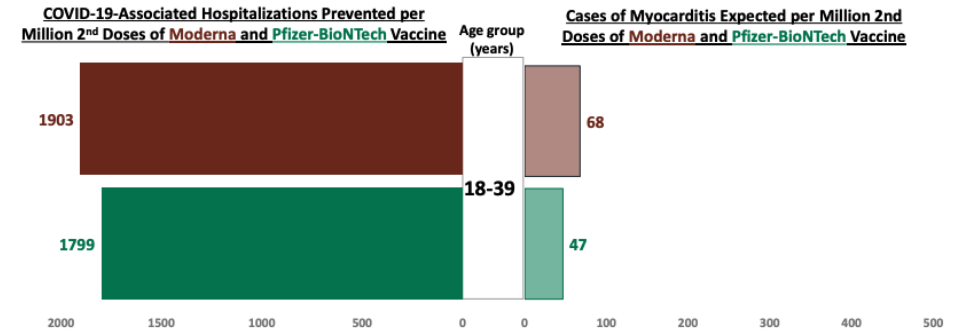
Benefits and risks after mRNA COVID-19 vaccines among males ages 18–39 years

per million 2nd doses

- COVID-19-associated hospitalizations prevented by mRNA COVID-19 vaccines compared with myocarditis cases expected
- Presented by vaccine product



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Summary: Benefit/risk balance

- Benefits for both mRNA COVID-19 vaccines **far outweigh** risk of myocarditis, compared with no vaccine
- When compared to the benefit-risk balance for Pfizer-BioNTech COVID-19 vaccine, the Moderna vaccine prevents more COVID-19 hospitalizations, however more myocarditis cases would also be expected

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Summary: Myocarditis and Intervals

- When comparing the two mRNA COVID-19 vaccines, the risk of myocarditis/pericarditis was higher for Moderna than Pfizer vaccine
  - The highest risk was seen after the second dose among younger males
- Rates of myocarditis/pericarditis were **lower** with **extended interval** between first and second dose of mRNA vaccine primary series
- Extended primary series interval may **improve immunogenicity** and **vaccine effectiveness**

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Considerations regarding extended intervals between first and second doses of mRNA vaccine (primary series)

Possible Benefits

- **Safety**:
  - Extended interval appears to reduce the risk of myocarditis
  - Lowest rates of myocarditis with interval at 8 weeks
- **Effectiveness**:
  - Extended interval appears to increase VE for primary series
  - Benefit may 'level out' at ≥8 weeks
- **Implementation**:
  - Possibility that uptake for COVID-19 vaccine primary series could increase if individuals/parents desire action to lower risk for myocarditis

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Considerations regarding extended intervals between first and second doses of mRNA vaccine (primary series)

Possible Risks

- **Effectiveness**:
  - Longer duration of time where individual only have the benefit of a single dose of mRNA vaccine
- **Implementation**:
  - For aspects that require being 'fully vaccinated' (shorter quarantine, travel or restaurants, etc), extending interval would extend the time before being 'fully vaccinated'

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Work Group Interpretation

- An individual's **risk** of getting COVID-19 likely increases the longer they are only partially vaccinated with a single dose
- The risk would need to be balanced with the **benefits** of **lowering rates** of myocarditis and optimizing the **long-term vaccine effectiveness**
- This balance is influenced by trajectory of pandemic and recent epidemiology of COVID-19, and can change over time
- Early in the pandemic, the priority was for individuals to have **optimum protection** from the primary series as **quickly** as possible
  - Guidance around COVID-19 vaccines can be updated as **new data** become available and the focus expands to the **future** of the COVID-19 vaccine program

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Work Group Interpretation

- **Clear communication** for COVID-19 vaccines and preferred intervals is important
- May be populations where the benefits of earlier interval (3 or 4 weeks) would outweigh possible risks of myocarditis
  - Licensed intervals of 3 weeks (Pfizer-BioNTech) or 4 weeks (Moderna) continue to be recommended, especially in circumstances where early protection is desired
- The Work Group supported a preferred interval of **8 weeks** between the first and second dose of an mRNA COVID-19 vaccine primary series

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Safety Platforms for Emergency vACcines (SPEAC)
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