

# Myocarditis/pericarditis following mRNA vaccines: Ontario passive vaccine safety surveillance

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Presentation to the Special Advisory Committee (SAC)

July 15, 2021

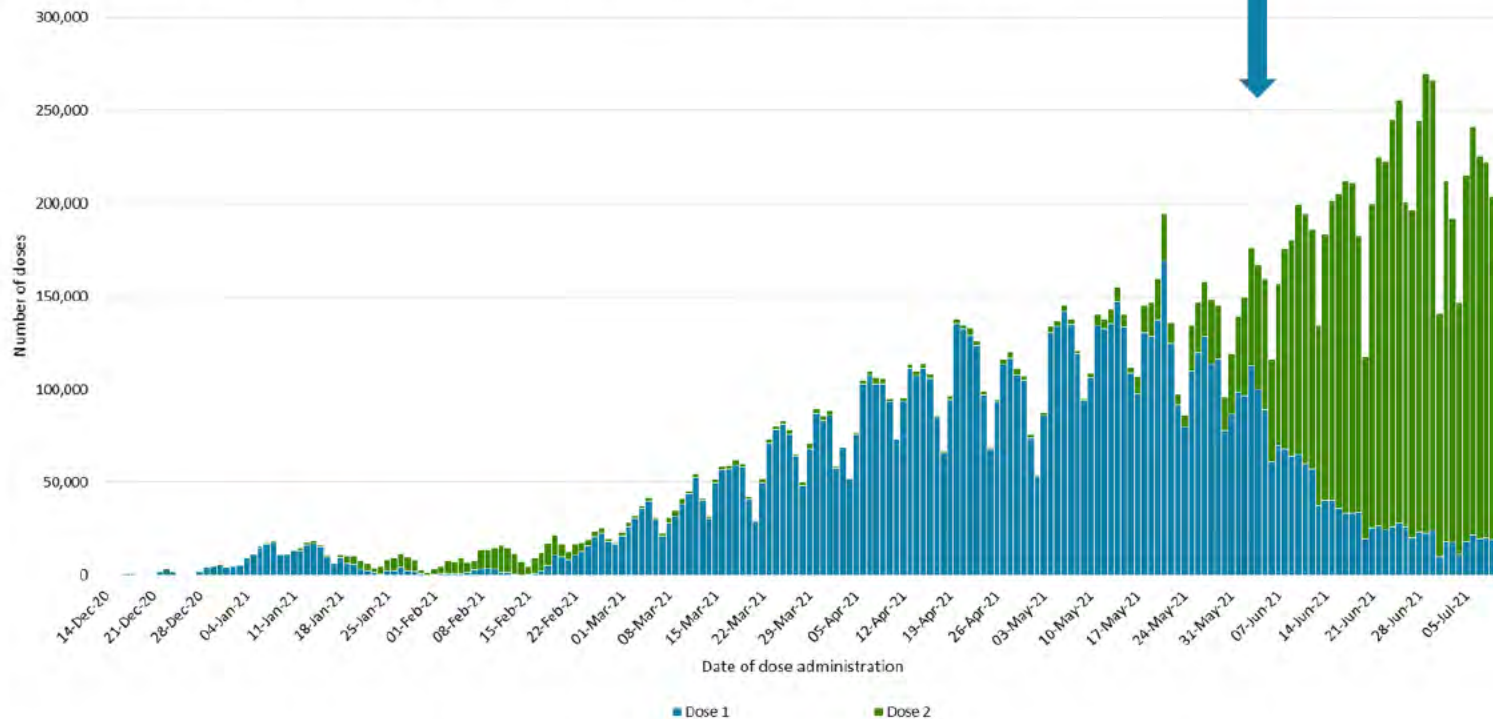
# Outline

- Ontario program and AEFI surveillance context
- Case review process
- Descriptive epidemiology of events
- Reporting rates and observed/expected analyses

# Ontario program and AEFI surveillance context

ESD issued  
June 4, 2021

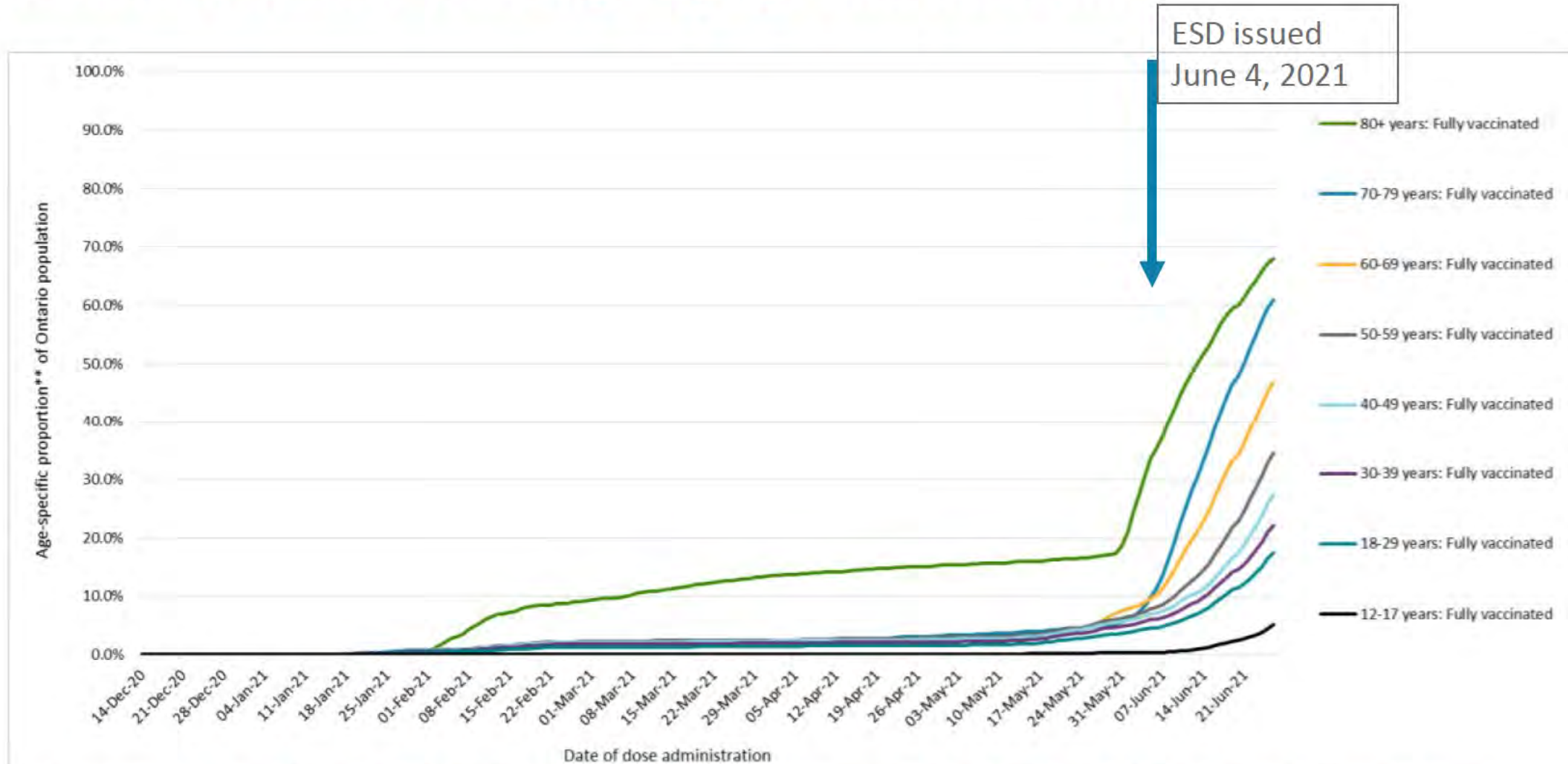
Figure 1a. Number of COVID-19 vaccine doses administered in Ontario by dose number and date



- Acceleration of second dose administration (facilitated by additional Moderna vaccine supply) began in June
- PHO released an enhanced surveillance directive for myocarditis/pericarditis on June 4, 2021
- Numerous events in June increased public and clinician awareness of myocarditis following mRNA vaccines

Available at: [https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?sc\\_lang=en](https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-vaccine-uptake-ontario-epi-summary.pdf?sc_lang=en)

# Ontario two dose coverage by age and over time



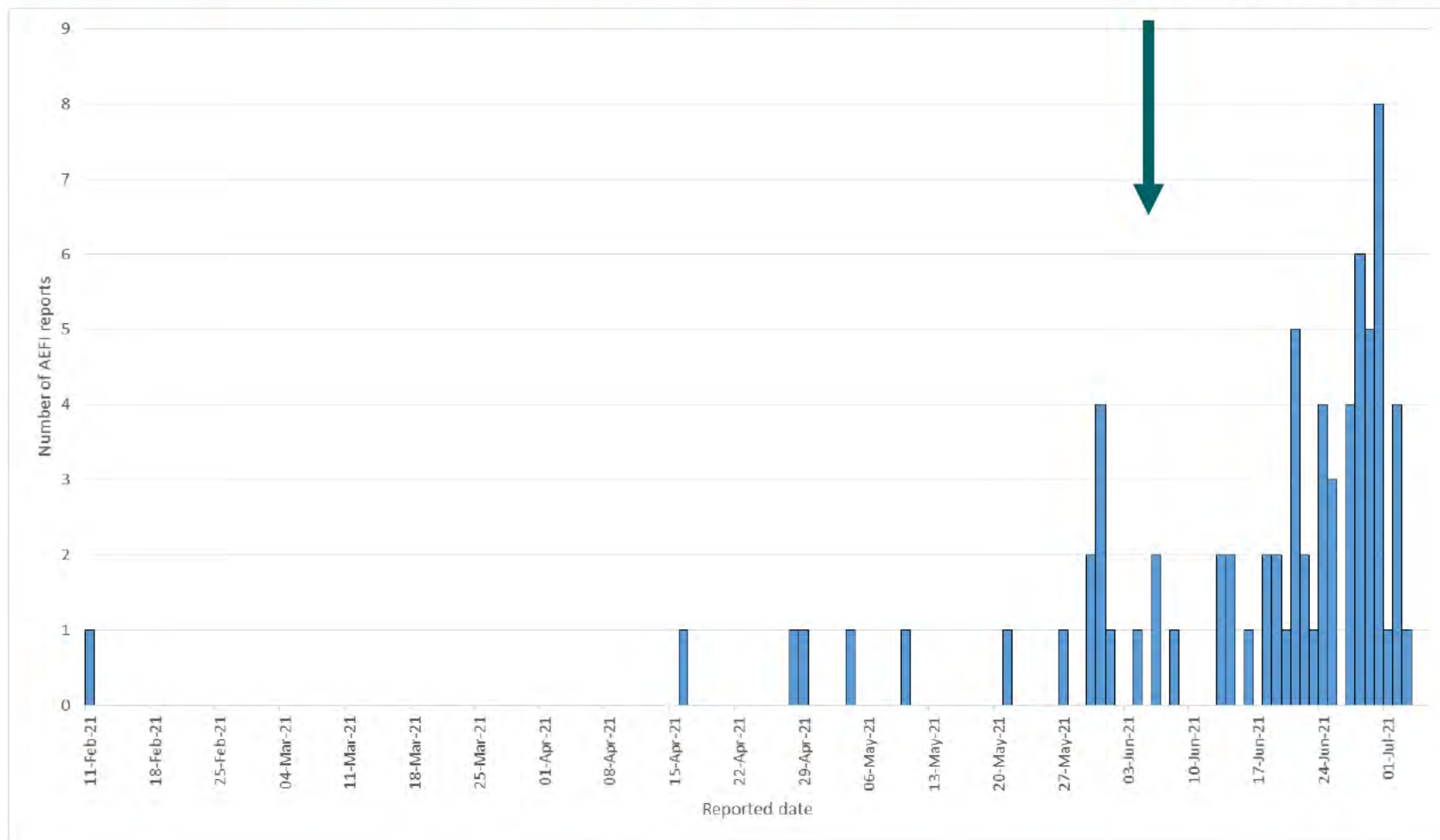
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# Methods: Case review for inclusion in analysis

- Events identified through keyword search on all Ontario AEFI reports (both confirmed and PUIs) for 'myocarditis' or 'pericarditis' and review of all AEFI reports with event reported as 'COVID-19 AESI: cardiovascular injury'
- Reports classified as myocarditis or pericarditis are those that have:
  - Diagnosis of myocarditis and meeting Brighton Collaboration level of diagnostic certainty 1 to 3 for myocarditis (please see Appendix)
  - Diagnosis of pericarditis and meeting the CDC working case definition of pericarditis (please see Appendix)
  - Diagnosis of myopericarditis or perimyocarditis and meeting either the Brighton Collaboration levels 1 to 3 for myocarditis or the CDC case definition of pericarditis

# Myocarditis/pericarditis events following mRNA vaccines by reported date in Ontario as of July 5, 2021



75 confirmed reports  
29 PUIs

Following case review described earlier:  
73 reports of myocarditis/pericarditis included in analysis

- 27 myocarditis (37.0%)
- 25 pericarditis (34.2%)
- 21 myopericarditis or perimyocarditis (28.8%)

# Characteristics of myocarditis/pericarditis reports for all ages in Ontario as of July 5, 2021

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	Myocarditis or pericarditis reports after dose 1 (n=35)	Myocarditis or pericarditis reports after dose 2 (n=38)	Total myocarditis or pericarditis reports (n=73)
<b>Pfizer-BioNTech</b>	31	15	46
<b>Moderna</b>	4	23	27
<b>Median age, years (range)</b>	25 (12 – 78)	25 (14 – 79)	25 (12 – 79)
<b>Median time to onset, days (range)*</b>	7 (0 – 37)*	2 (1 – 12)*	3 (0 – 37)*
<b>Gender: male (%)</b>	29 (82.9%)	30 (78.9%)	59 (80.8%)

\*Six reports with unknown time to onset (four after dose 1 and two after dose 2) are excluded from the calculation of median time to onset (range)

# Schedule and second dose intervals among myocarditis/pericarditis events

## Events in those < 40 years of age (n=56)

- Events after dose 1 (n=28)
- Events after dose 2 (n=28)

Product Schedule	n	Median interval in days (range)
Pfizer-Pfizer	10 (35.7%)	31 (21 – 76)
Moderna-Moderna	12 (42.9%)	38 (28 – 63)
Pfizer-Moderna	6 (21.4%)	42 (30 – 54)
Moderna-Pfizer	0	

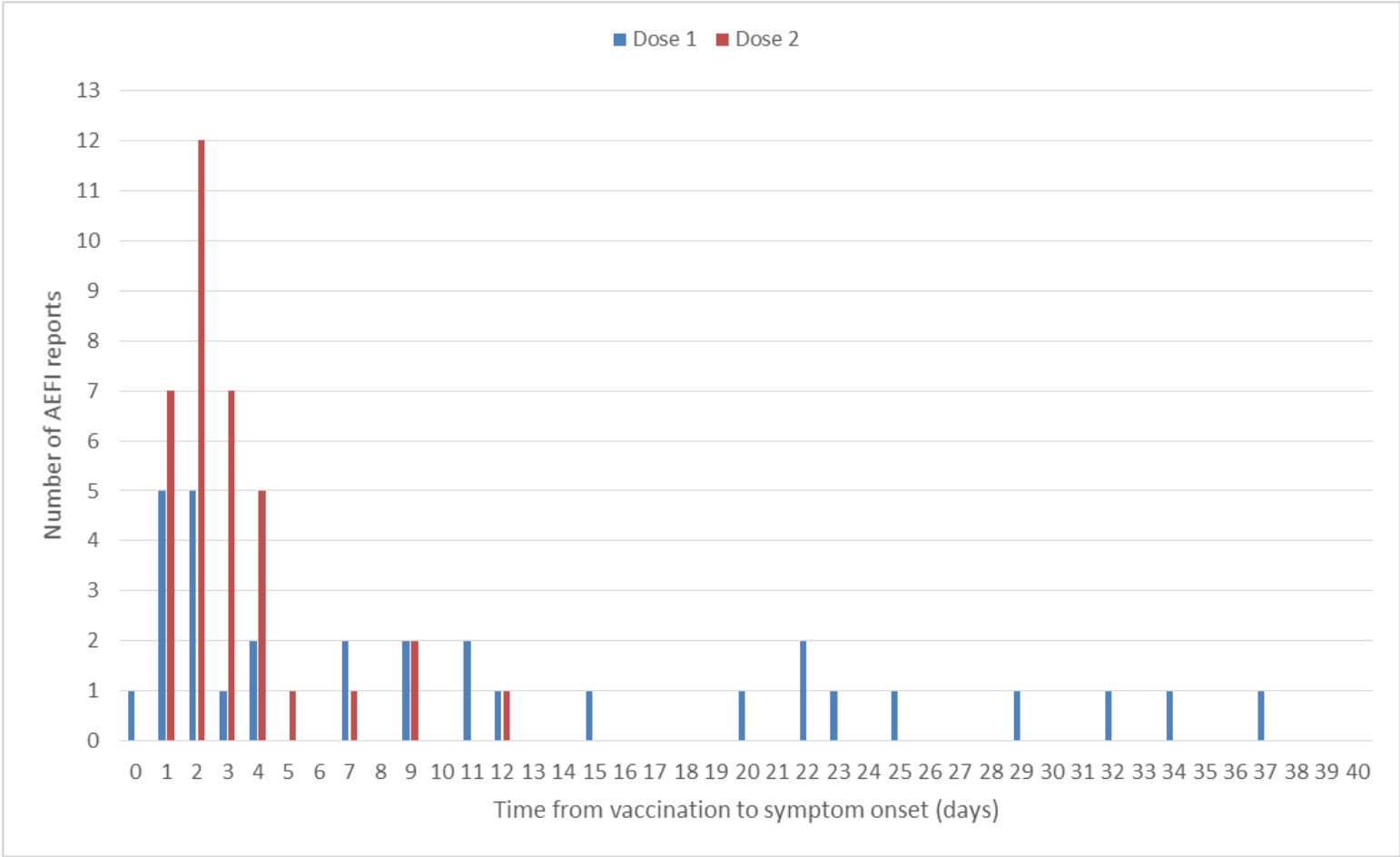
## Events in those ≥ 40 years of age (n=17)

- Events after dose 1 (n=7)
- Events after dose 2 (n=10)

Product Schedule	n	Median interval in days (range)
Pfizer-Pfizer	5 (50%)	80 (65 – 105)
Moderna-Moderna	4 (40%)	55 (41 – 76)
Pfizer-Moderna	0	
Moderna-Pfizer	0	
AZ-Moderna	1 (10%)	53



# Myocarditis/pericarditis events following mRNA vaccines by dose number and time to symptom onset in Ontario as of July 5, 2021



\* Excludes 6 reports with unknown time to onset

# Severity of myocarditis/pericarditis reports in Ontario as of July 5, 2021

- 70/73 reported an ED visit; 3/73 unknown at the time of analysis
- 52/73 reports required hospitalization (71.2%)
  - Median length of stay was 2 days<sup>1</sup>
  - 25/27 (92.6%) hospitalized for myocarditis
  - 18/21 (85.7%) hospitalized for myopericarditis/perimyocarditis
  - 9/25 (36.0%) hospitalized for pericarditis
  - % hospitalized varies by age group (available in Appendix)
- 2/73 reported ICU admission<sup>2</sup>, no fatal reports

1. Among 41 reports where both the date of admission and discharge was available for review

2. Events requiring ICU: 30 year old male with myocarditis (level 1) after dose 1 of Pfizer vaccine, differential diagnosis in AEFI report included MIS-A (lab confirmed COVID five weeks prior to vaccination); 59 year old female with multiple medical comorbidities, myocarditis (level 1) after dose 1 of Moderna vaccine, medically complex picture with other diagnoses in addition to myocarditis

# Age distribution of myocarditis/pericarditis reports in Ontario as of July 5, 2021

Age group	Number of events after dose 1	Number of events after dose 2	Total number of events
12-17 years	7	4	11
18-24 years	10	15	25
25-29 years	5	4	9
30-39 years	6	5	11
40-49 years	0	2	2
50-59 years	3	3	6
60-69 years	2	3	5
70-79 years	2	2	4
80+ years	0	0	0
<b>All ages</b>	<b>35</b>	<b>38</b>	<b>73</b>

# Myocarditis/pericarditis reporting rates following mRNA vaccines in Ontario (n=73)

Age groups (yrs)	Overall reporting rate per million doses			Reporting rate in females per million doses			Reporting rate in males per million doses		
	All doses	Dose 1	Dose 2	All doses	Dose 1	Dose 2	All doses	Dose 1	Dose 2
<b>12-17</b>	15.2	11.3	38.3	2.8	0.0	18.4	27.8	22.5	60.4
<b>18-24</b>	19.9	10.9	43.4	4.6	2.2	10.2	36.8	20.0	87.5
<b>25-39</b>	6.4	5.1	9.1	3.7	2.7	5.6	9.3	7.6	13.5
<b>40+</b>	1.8	1.3	2.6	0.8	0.7	0.9	3.1	2.0	4.6

ACIP rates for  
Dose 1 (males):  
**9.8** per million  
for 12-17 yrs  
**8.7** per million  
for 18-24 yrs

Analysis includes all AEFIs reported (no restriction on post-vaccination observation time).

ACIP rates for  
Dose 2 (females):  
**9.1** per million for  
12-17 yrs  
**5.5** per million for  
18-24 yrs

ACIP rates for  
Dose 2 (males):  
**66.7** per million  
for 12-17 yrs  
**56.3** per million  
for 18-24 yrs  
**20.4** per million  
for 25-29 yrs



# Myocarditis/pericarditis crude reporting rates (passive vaccine safety surveillance) following mRNA vaccines in the United States

## Preliminary myocarditis/pericarditis crude reporting rates to VAERS following mRNA COVID-19 vaccination (data thru Jun 11, 2021)

Age groups	Overall reporting rate per million doses			Reporting rate in females per million doses			Reporting rate in males per million doses		
	All doses	Dose 1	Dose 2	All doses	Dose 1	Dose 2	All doses	Dose 1	Dose 2
12-17 yrs	18.1	5.3	37.0	4.2	1.1	9.1	32.4	9.8	66.7
18-24 yrs	15.9	4.8	28.4	3.6	1.5	5.5	30.7	8.7	56.3
25-29 yrs	6.7	2.5	10.8	2.0	0.8	2.6	12.2	4.5	20.4
30-39 yrs	4.2	1.7	5.6	1.8	1.4	1.8	6.9	2.0	10.0
40-49 yrs	2.7	0.9	3.8	2.0	0.9	2.8	3.5	1.0	5.1
50-64 yrs	1.7	1.0	2.0	1.6	1.0	1.8	1.9	1.0	2.3
65+ yrs	1.1	0.7	1.3	1.1	0.6	1.2	1.2	0.7	1.4



- Myocarditis/pericarditis reports per million mRNA vaccine doses administered by sex and dose number with no restrictions on post-vaccination observation time

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Presented at June 23, 2021 ACIP meeting. Available at: <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/03-COVID-Shimabukuro-508.pdf>



# Myocarditis/pericarditis reporting rates, 12-17 year olds

<b>Males</b>				
<b>Vaccine(s) dose #)</b>	<b>Cases</b>	<b>Doses admin</b>	<b>Rate per million doses</b>	<b>95% CI</b>
<b>mRNA (both doses)</b>	10	360140	27.8	13.3 - 51.1
<b>mRNA (dose 1)</b>	7	310430	22.5	9.1 - 46.5
<b>mRNA (dose 2)</b>	3	49710	60.4	12.4 - 176.4
<b>Pfizer-BioNTech (dose 1)</b>	7	310430	22.5	9.1 - 46.5
<b>Pfizer-BioNTech (dose 2)</b>	3	49231	60.9	12.6 - 178.1
<b>Moderna (dose 1)</b>	0	0	0.0	
<b>Moderna (dose 2)</b>	0	479	0.0	
<b>Females</b>				
<b>Vaccine(s) dose #)</b>	<b>Cases</b>	<b>Doses admin</b>	<b>Rate per million doses</b>	<b>95% CI</b>
<b>mRNA (both doses)</b>	1	360578	2.8	0.1 - 15.5
<b>mRNA (dose 1)</b>	0	306191	0.0	
<b>mRNA (dose 2)</b>	1	54387	18.4	0.5 - 102.4
<b>Pfizer-BioNTech (dose 1)</b>	0	306191	0.0	
<b>Pfizer-BioNTech (dose 2)</b>	1	53853	18.6	0.5 - 103.5
<b>Moderna (dose 1)</b>	0	0	0.0	
<b>Moderna (dose 2)</b>	0	534	0.0	

# Myocarditis/pericarditis reporting rates, 18-24 year olds

Males				
Vaccine(s) dose #)	Cases	Doses admin	Rate per million doses	95% CI
mRNA (both doses)	22	598395	36.8	23 - 55.7
mRNA (dose 1)	9	449776	20.0	9.1 - 38
mRNA (dose 2)	13	148619	87.5	46.6 - 149.6
Pfizer-BioNTech (dose 1)	9	343915	26.2	12.0 - 49.7
Pfizer-BioNTech (dose 2)	2	81280	24.6	3.0 - 88.9
Moderna (dose 1)	0	105861	0.0	
Moderna (dose 2)	11	67339	163.4	81.5 - 292.3
Females				
Vaccine(s) dose #)	Cases	Doses admin	Rate per million doses	95% CI
mRNA (both doses)	3	655979	4.6	0.9 - 13.4
mRNA (dose 1)	1	460841	2.2	0.1 - 12.1
mRNA (dose 2)	2	195138	10.2	1.2 - 37
Pfizer-BioNTech (dose 1)	1	364115	2.7	0.1 - 15.3
Pfizer-BioNTech (dose 2)	0	121967	0.0	
Moderna (dose 1)	0	96726	0.0	
Moderna (dose 2)	2	73171	27.3	3.3 - 98.7

# Myocarditis/pericarditis reporting rates, 25-39 year olds

<b>Males</b>				
Vaccine(s) dose #)	Cases	Doses admin	Rate per million doses	95% CI
mRNA (both doses)	14	1501342	9.3	5.1 - 15.6
mRNA (dose 1)	8	1058490	7.6	3.3 - 14.9
mRNA (dose 2)	6	442852	13.5	5.0 - 29.5
Pfizer-BioNTech (dose 1)	7	806389	8.7	3.5 - 17.9
Pfizer-BioNTech (dose 2)	2	247711	8.1	1.0 - 29.2
Moderna (dose 1)	1	252101	4.0	0.1 - 22.1
Moderna (dose 2)	4	195141	20.5	5.6 - 52.5
<b>Females</b>				
Vaccine(s) dose #)	Cases	Doses admin	Rate per million doses	95% CI
mRNA (both doses)	6	1636274	3.7	1.3 - 8
mRNA (dose 1)	3	1095766	2.7	0.6 - 8
mRNA (dose 2)	3	540508	5.6	1.1 - 16.2
Pfizer-BioNTech (dose 1)	2	866538	2.3	0.3 - 8.3
Pfizer-BioNTech (dose 2)	2	346961	5.8	0.7 - 20.8
Moderna (dose 1)	1	229228	4.4	0.1 - 24.3
Moderna (dose 2)	1	193547	5.2	0.1 - 28.8

# Myocarditis/pericarditis reporting rates, 40+ year olds

<b>Males</b>				
<b>Vaccine(s) dose #)</b>	<b>Cases</b>	<b>Doses admin</b>	<b>Rate per million doses</b>	<b>95% CI</b>
<b>mRNA (both doses)</b>	13	4241896	3.1	1.6 - 5.2
<b>mRNA (dose 1)</b>	5	2492755	2.0	0.7 - 4.7
<b>mRNA (dose 2)</b>	8	1749141	4.6	2.0 - 9.0
<b>Pfizer-BioNTech (dose 1)</b>	5	1979482	2.5	0.8 - 5.9
<b>Pfizer-BioNTech (dose 2)</b>	4	1134752	3.5	1.0 - 9.0
<b>Moderna (dose 1)</b>	0	513273	0.0	
<b>Moderna (dose 2)</b>	4	614389	6.5	1.8 - 16.7
<b>Females</b>				
<b>Vaccine(s) dose #)</b>	<b>Cases</b>	<b>Doses admin</b>	<b>Rate per million doses</b>	<b>95% CI</b>
<b>mRNA (both doses)</b>	4	5077181	0.8	0.2 - 2
<b>mRNA (dose 1)</b>	2	2929711	0.7	0.1 - 2.5
<b>mRNA (dose 2)</b>	2	2147470	0.9	0.1 - 3.4
<b>Pfizer-BioNTech (dose 1)</b>	0	2365916	0.0	
<b>Pfizer-BioNTech (dose 2)</b>	1	1469572	0.7	0.0 - 3.8
<b>Moderna (dose 1)</b>	2	563795	3.5	0.4 - 12.8
<b>Moderna (dose 2)</b>	1	677898	1.5	0.0 - 8.2

# Methods: Observed vs. Expected Analysis

- Compared observed events with expected based on amount of follow up time after dose 1 and 2 by product, gender, and age
- Observed: all events meeting inclusion criteria of myocarditis/pericarditis that occurred within 7 days of vaccination (N=49)
- Expected:
  - Age and sex-specific background rates (from 2015-2020) were estimated at ICES
  - Person-years of follow up using 7 day risk interval were calculated for each strata (i.e., number of individuals receiving 1 dose x 7 days and converted to person-years)
  - Background rates were applied to PY to estimated expected number of events within risk interval
  - Given varying definitions to identify myopericarditis in administrative data, we estimated expected values using both narrow and broad definitions. The range in expected cases was estimated using the lower confidence limit of the rate from the narrow definition and the upper confidence limit of the rate from the broad definition
- Analysis was repeated using 21 day interval

Mahaux, O., Bauchau, V., and Van Holle, L. (2016) Pharmacoepidemiological considerations in observed-to-expected analyses for vaccines. *Pharmacoepidemiol Drug Saf*, 25: 215–222. doi: [10.1002/pds.3918](https://doi.org/10.1002/pds.3918).



# Expected vs. Observed myocarditis and/or pericarditis reports following dose 1 COVID-19 vaccination using a 7 day risk window

Pfizer – Dose 1							Moderna – Dose 1						
Age group	Females			Males			Age group	Females			Males		
	Individuals with 1 dose	Expected*	Observed	Individuals with 1 dose	Expected*	Observed		Individuals with 1 dose	Expected*	Observed	Individuals with 1 dose	Expected*	Observed
12-15	195,905	0.1-0.2	0	201,597	0.2-0.4	0	12-15	0	0	0	0	0	0
16-19	205,791	0.2-0.5	0	198,411	0.9-1.5	6	16-19	25,172	0.0-0.1	0	26,027	0.1-0.2	0
20-24	269,268	0.5-0.8	1**	254,819	1.3-2.0	2	20-24	71,740	0.1-0.2	0	79,974	0.4-0.6	0
25-29	291,165	0.5-1.0	0	277,658	1.3-2.1	1	25-29	75,978	0.1-0.3	0	87,152	0.4-0.7	1**
30-39	576,145	1.1-2.1	0	529,435	2.5-4.0	3	30-39	153,528	0.3-0.6	1**	165,335	0.8-1.3	0
40-49	518,236	1.0-2.2	0	423,523	1.7-3.1	0	40-49	128,021	0.3-0.6	0	126,997	0.5-0.9	0
50-59	581,169	1.5-3.5	0	497,951	2.0-4.2	0	50-59	138,404	0.4-0.8	1**	138,317	0.6-1.2	0
60-69	545,330	1.6-4.4	0	471,623	2.1-5.1	0	60-69	133,737	0.4-1.1	0	128,820	0.6-1.4	0
70-79	451,743	1.7-5.4	0	392,022	2.0-5.8	0	70-79	84,026	0.3-1.0	0	75,633	0.4-1.1	0

\*The expected range is the lower confidence limit of the narrow myopericarditis definition to the upper confidence limit of the broad myopericarditis definition

\*\* If analysis used 21 day risk window instead of 7, the observed would no longer exceed the expected in these cells

There were no observed cases in 80+

# Expected vs. Observed myocarditis and/or pericarditis reports following dose 2 COVID-19 vaccination using a 7 day risk window

Pfizer – Dose 2							Moderna – Dose 2						
Age group	Females			Males			Age group	Females			Males		
	Individuals with 2 doses	Expected*	Observed	Individuals with 2 doses	Expected*	Observed		Individuals with 2 doses	Expected*	Observed	Individuals with 2 doses	Expected*	Observed
12-15	28,865	0	0	27,792	0.0-0.1	2	12-15	0	0	0	0	0	0
16-19	60,427	0.1-0.1	1	48,995	0.2-0.4	1**	16-19	10,699	0	1	9,856	0	2
20-24	117,158	0.2-0.4	0	81,346	0.4-0.7	1**	20-24	32,436	0.1-0.1	1	30,424	0.2-0.2	8
25-29	138,897	0.3-0.5	0	102,207	0.5-0.8	1**	25-29	36,038	0.1-0.1	0	35,887	0.2-0.3	3
30-39	282,790	0.6-1.0	2**	221,628	1.1-1.7	1	30-39	78,613	0.2-0.3	1	78,231	0.4-0.6	1**
40-49	262,809	0.5-1.1	0	175,834	0.7-1.3	0	40-49	70,357	0.1-0.3	0	62,119	0.3-0.5	2
50-59	333,895	0.9-2.0	0	242,792	1.0-2.0	1	50-59	84,583	0.2-0.5	0	76,215	0.3-0.6	1**
60-69	364,607	1.1-2.9	0	290,983	1.3-3.1	1	60-69	91,885	0.3-0.7	0	83,307	0.4-0.9	0
70-79	361,716	1.3-4.3	0	313,071	1.6-4.7	2	70-79	64,973	0.2-0.8	0	57,786	0.3-0.9	0

\*The expected range is the lower confidence limit of the narrow myopericarditis definition to the upper confidence limit of the broad myopericarditis definition.

\*\* If analysis used 21 day risk window instead of 7, the observed would no longer exceed the expected in these cells

There were no observed cases in 80+

# Summary

- Clinical description of events similar to ACIP analysis
  - Smaller % of events requiring hospitalization than VAERS reports described in ACIP meeting/MMWR
- Reporting rates (after application of Brighton/CDC case definitions) are higher in Ontario than ACIP crude reporting rates for several age/gender strata
  - Possible explanations include difference in time periods (ACIP data to early June), greater spectrum of clinical severity represented in Ontario events, difference in surveillance systems, and others
- Findings for product specific trends need to be interpreted in the context of enhanced surveillance coinciding with increased Moderna vaccine supply
- Additional analyses are ongoing

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  - Michelle Murti
  - Leigh Hobbs
- ICES
  - Jeff Kwong
  - Sharifa Nasreen
  - Andrew Calzavara
- 34 Ontario Public Health Units

# APPENDIX



# Draft Brighton Collaboration case definition for myocarditis

Level of Certainty - 1 (Definitive Case)<sup>1</sup>

Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation

OR

≥1 elevated myocardial biomarker (Troponin T OR Troponin I)

AND

Abnormal imaging study:

- ≥1 cardiac magnetic resonance (CMR) abnormality

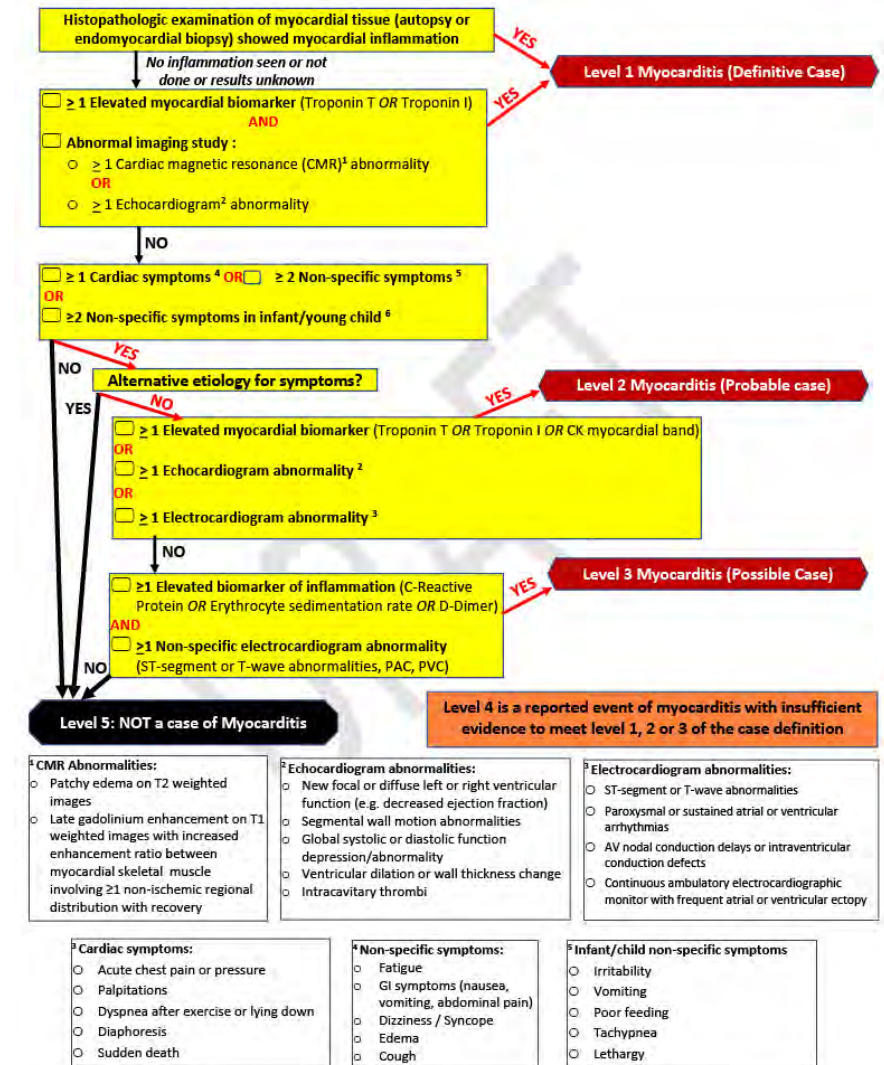
OR

- ≥1 echocardiogram abnormality

Available at: [https://brightoncollaboration.us/wp-content/uploads/2021/05/Myocarditis-CD\\_Version\\_1.4.2\\_30.May\\_.2021\\_LOC\\_ALL\\_FINAL.POSTING.pdf](https://brightoncollaboration.us/wp-content/uploads/2021/05/Myocarditis-CD_Version_1.4.2_30.May_.2021_LOC_ALL_FINAL.POSTING.pdf)

# Draft Brighton Collaboration case definition for myocarditis

- Considerations for probable or possible case definition:
  - Cardiac symptoms: Acute chest pain, palpitations, dyspnea after exercise or lying down, diaphoresis, sudden death
  - Non-specific symptoms: Fatigue, GI symptoms, dizziness/syncope, edema, cough
  - Alternative etiology for symptoms
  - Elevated myocardial biomarker
  - Elevated biomarker of inflammation
  - Non-specific echocardiogram abnormalities
  - Electrocardiogram abnormalities



Available at: [https://brightoncollaboration.us/wp-content/uploads/2021/05/Myocarditis-CD\\_Version\\_1.4.2\\_30.May\\_.2021\\_LOC\\_ALL\\_FINAL.POSTING.pdf](https://brightoncollaboration.us/wp-content/uploads/2021/05/Myocarditis-CD_Version_1.4.2_30.May_.2021_LOC_ALL_FINAL.POSTING.pdf)

## CDC working case definition for acute pericarditis

Presence of at least **two** new or worsening of the following clinical features:

- Acute chest pain\*
- Pericardial rub on exam
- New ST-elevation or PR-depression on EKG or
- New or worsening pericardial effusion on echocardiogram or MRI

\*Typically described as pain made worse by lying down, deep inspiration, or cough and relieved by sitting up or leaning forward, although other types of chest pain may occur.

Note: autopsy case may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

Available at: <https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf>

# Age distribution of hospitalized reports of myocarditis/pericarditis in Ontario as of July 5, 2021

Age group	Total number of events	Number hospitalized	% hospitalized
12-17 years	11	7	63.6%
18-24 years	25	19	76.0%
25-29 years	9	8	88.9%
30-39 years	11	7	63.6%
40-49 years	2	2	100.0%
50-59 years	6	3	50.0%
60-69 years	5	3	60.0%
70-79 years	4	3	75.0%
80+ years	0	0	0.0%
<b>All ages</b>	<b>73</b>	<b>52</b>	<b>71.2%</b>