Rapid Generation of Vaccine Safety Evidence During COVID-19: A summary of work

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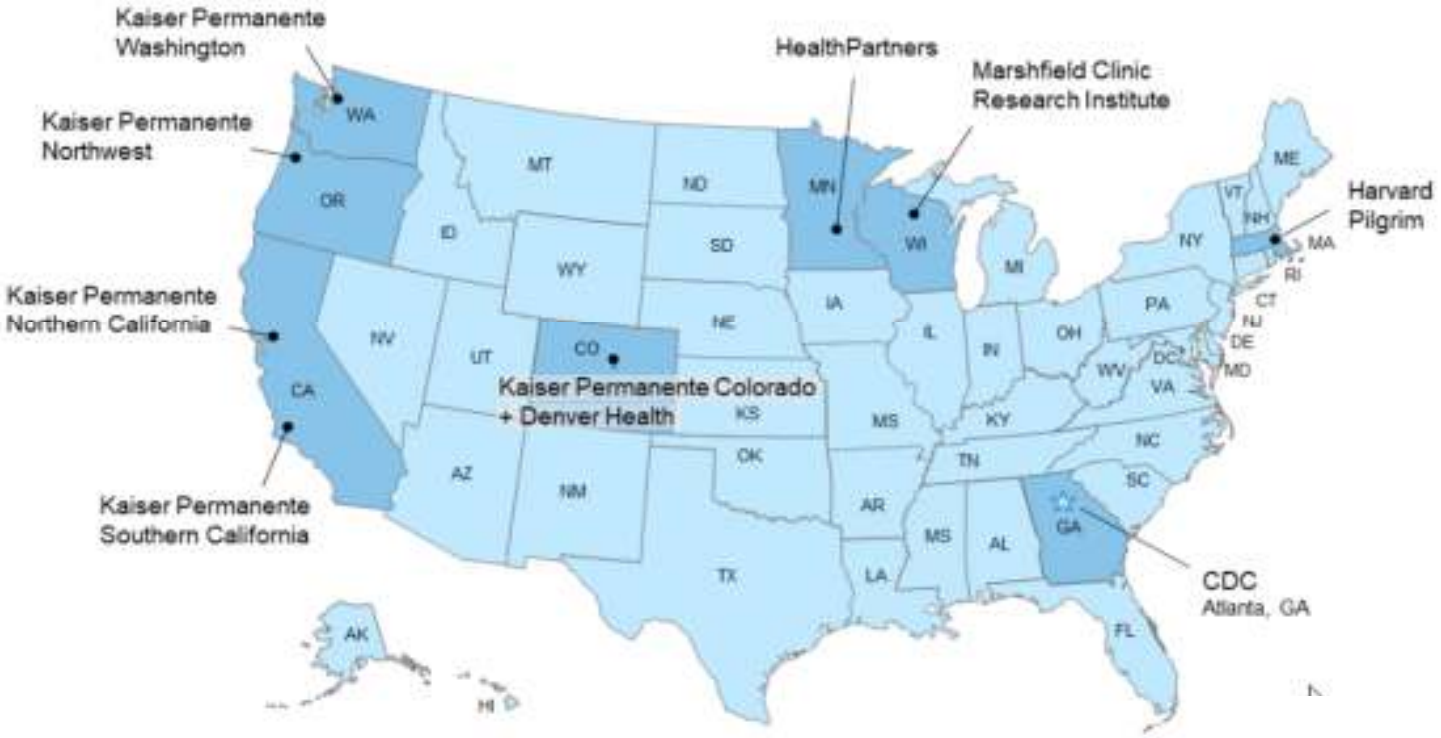
VACCINE STUDY CENTER

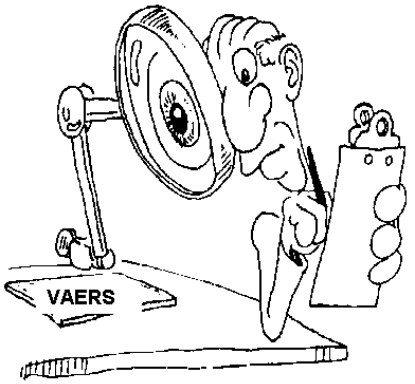
The Vaccine Safety Datalink (VSD)



- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations

Vaccine Safety Datalink

- Active surveillance: newly licensed vaccines
  - Rapid Cycle Analysis (RCA)
- Evaluate vaccine safety:
  - of new recommendations for existing vaccines
  - for vaccines in high-risk populations, particularly pregnant women (+ other groups)
- Develop new methodologies for vaccine safety assessment
- Test hypotheses noted by signals elsewhere (e.g., VAERS, clinical trials, other platforms).



VSD has Monitored the Safety of Many New Vaccines: Prior Rapid Cycle Analyses

- RCA: every week VSD updates the data and the analyses.
  - Meningococcal Conjugate (Menactra®)
  - H1N1 Influenza Vaccines
  - Influenza Vaccines
  - DTaP-IPV (Kinrix®)
  - DTaP-IPV/Hib (Pentacel®)
  - COVID-19 Vaccines
  - HPV 4 & 9 (Gardasil®)
  - PCV13
  - Shingrix
  - Rotavirus (Rotateq® and Rotarix®)
  - Measles, Mumps, Rubella, and Varicella (MMRV) (Proquad®)
  - Tdap (Adacel® and Boostrix®)
- VSD's rapid cycle analyses are best suited for outcomes that are:
  - Clinically well-defined and coded in the electronic medical records
  - Acute-onset (i.e., within a few days or weeks) of vaccination
  - Serious

People early in line for a jab may differ in AE risk from those later in line, or not in line, but this source of bias is less with vaccinated controls than with unvaccinated controls

Hesitant

Strengths of VSD Rapid Cycle Analysis (RCA)

- **Population**
  - ~12.5 million people (equal to ~4% of the U.S. population) across VSD data sites are geographically and racially/ethnically diverse
- **Data**
  - Near real-time data, with analyses updated weekly
  - Access to comprehensive medical records, including exposures (vaccination) and outcomes, allowing rapid chart reviews to obtain additional clinical information as needed
- **Innovative Methods**
  - *Vaccinated concurrent comparators:* Recent vaccinees as comparators are expected to be more similar to current vaccinees than unvaccinated individuals with the following advantages
    - Careful adjustment for potential biases associated with calendar time, site, and demographic factors
    - Analyses can begin sooner than alternative methods
  - *Supplemental analyses conducted weekly:* Unvaccinated/un-boosted comparators would also be available to provide context in real time
  - Using vaccinated concurrent comparators with supplemental analyses offers substantial benefits compared with either unvaccinated or historical comparators

VSD COVID-19 Vaccine RCA

Aims:

1. To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

2. To describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity.

Surveillance began in December 2020 and was ready when the first doses of COVID-19 vaccines were given.

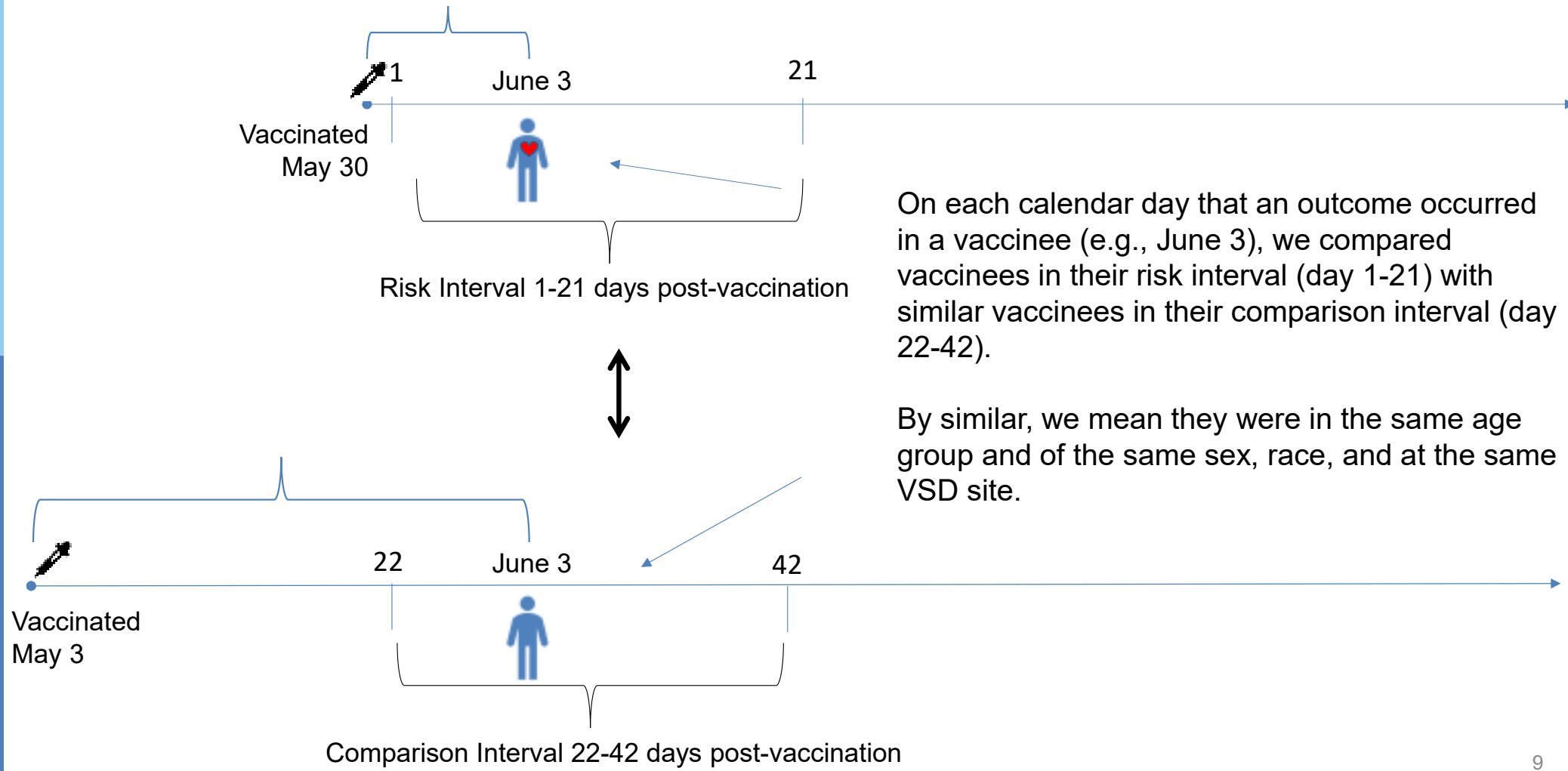
COVID Vaccine Safety RCA Surveillance: Analytic Strategy

- For the primary analysis, the number of outcomes observed in the risk interval (1-21 days) after COVID-19 vaccination were compared to the number expected.

- The expected was derived from “vaccinated concurrent comparators” who were in a comparison interval (days 22-42) after COVID-19 vaccination.

- On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval.
  - Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, as well as calendar date.

Vaccinee with Myocarditis in Risk Interval and a Concurrent Comparator



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.

COVID Vaccine Safety RCA Surveillance: Monitoring 23 Serious Outcomes

Inclusion in prior vaccine safety studies

- Acute disseminated encephalomyelitis
- Anaphylaxis*
- Encephalitis / myelitis
- Guillain-Barré syndrome
- Immune thrombocytopenia
- Kawasaki disease
- Narcolepsy and cataplexy*
- Seizures
- Transverse myelitis

Outcomes added due to emerging concerns

- Cerebral venous sinus thrombosis
- Myocarditis / pericarditis
- Thrombosis with thrombocytopenia syndrome

Hypothetical concerns regarding an association with COVID-19 disease

- Acute myocardial infarction
- Acute respiratory distress syndrome*
- Disseminated intravascular coagulation
- Multisystem Inflammatory Syndrome*
- Pulmonary embolism
- Stroke, hemorrhagic
- Stroke, ischemic
- Thrombotic thrombocytopenic purpura
- Venous thromboembolism

Imbalances in phase 3 COVID-19 vaccine clinical trials

- Appendicitis
- Bell's palsy

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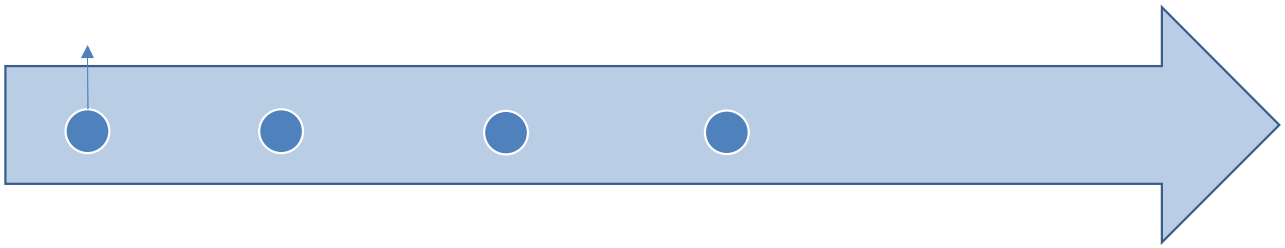
Only chart confirmed cases

*monitored without comparators

Chart Review and Adjudication Process

Case identified within appropriate interval following a COVID-19 vaccination.



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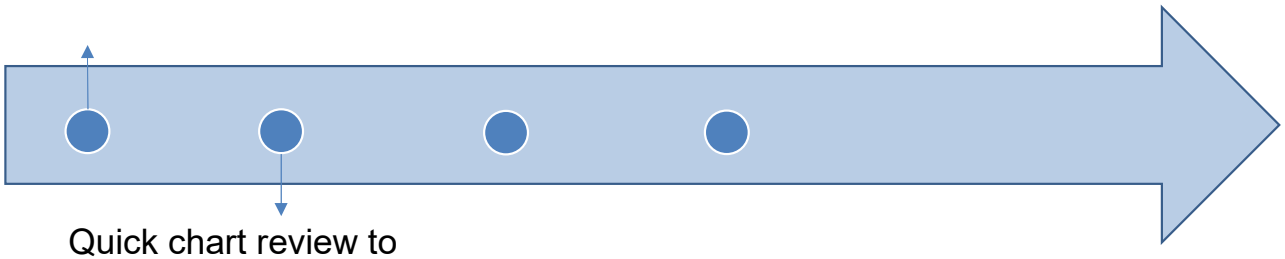

Quick chart review to determine if the case appears to be incident with symptom onset after COVID-19 vaccination. “Quick reviews” generally occur within one week.

Chart Review and Adjudication Process

Case identified within appropriate interval following a COVID-19 vaccination.

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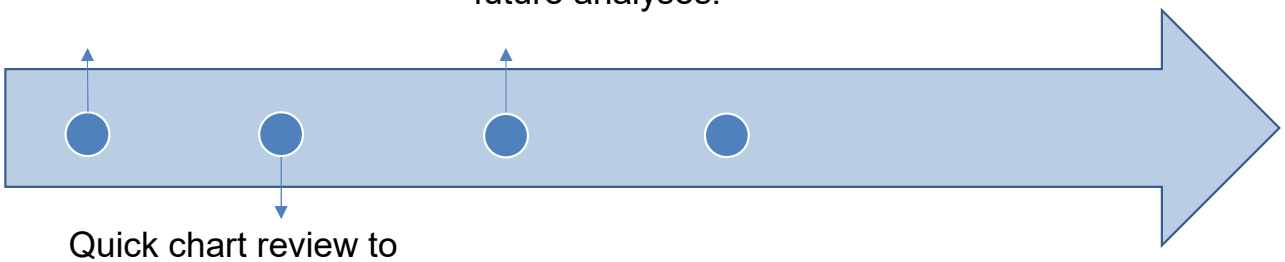
If the case does not meet the VSD incident definition, then it is excluded from all future analyses.



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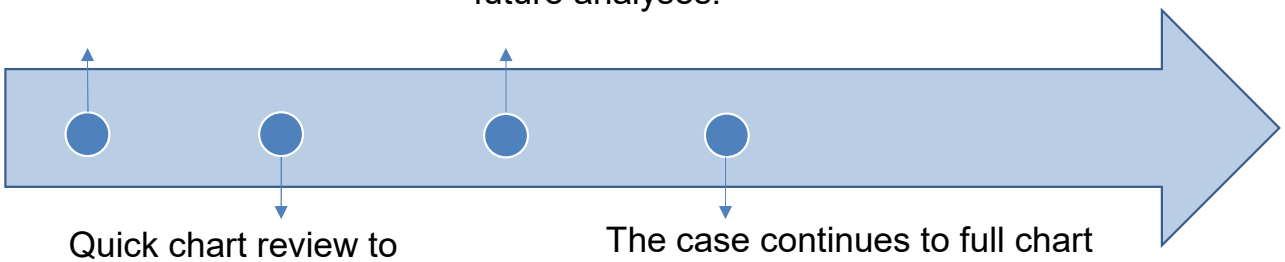

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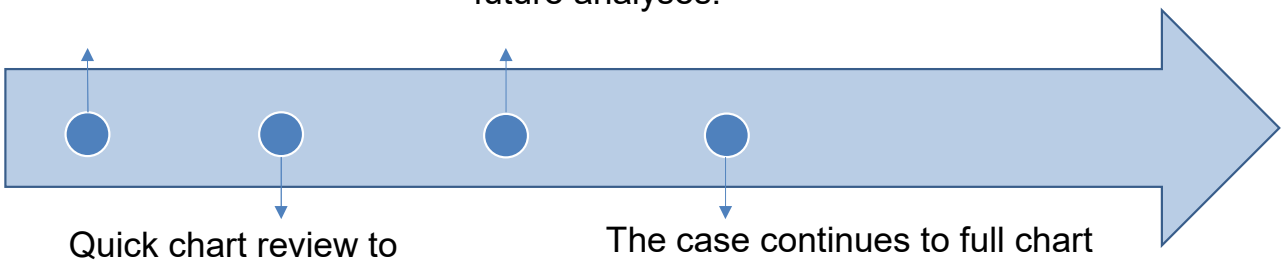

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For each week's analyses, VSD RCA results included a mix of:
1) all cases confirmed after full chart abstraction and adjudication
2) all quick-reviewed cases pending full chart abstraction

This allowed for a balance between analyzing quick chart-confirmed data (i.e., timely but still higher quality) while ultimately only including cases with complete follow-up.

It also meant that case counts could change across analytic weeks.

JAMA | Original Investigation

Surveillance for Adverse Events After COVID-19 mRNA Vaccination

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JAMA. doi:10.1001/jama.2021.15072
Published online September 3, 2021.

Results using vaccinated concurrent comparators

Table 3. Outcome Events in the 21-Day Risk Interval After Either Vaccine Dose Compared, on the Same Calendar Day, With Outcome Events in Individuals 22-42 Days After Their Most Recent Dose, December 14, 2020-June 26, 2021

Outcome	Events in risk interval (events/million person-years)[a]	Events in comparison interval (events/million person-years)[a,b]	Adjusted rate ratio[c] (95% CI)[d]	P value		Signal, 1-sided P < .0048[e]	Excess cases in risk interval per million doses (95% CI)[f]
				2-Sided[d]	1-Sided		
Thrombotic thrombocytopenic purpura	6 (9.1)	2 (5.5)	2.60 (0.47-20.66)	.29	.23	No	0.3 (-0.6 to 0.5)
Cerebral venous sinus thrombosis[g]	7 (10.6)	3 (8.2)	1.55 (0.37-8.17)	.59	.41	No	0.2 (-1.1 to 0.5)
Transverse myelitis[g]	2 (3.0)	1 (2.7)	1.45 (0.10-47.73)	.82	.64	No	0.1 (-1.6 to 0.2)
Encephalitis/myelitis/ encephalomyelitis	16 (25.7)	5 (13.7)	1.27 (0.45-4.10)	.69	.44	No	0.3 (-1.8 to 1.1)
Myocarditis/pericarditis	87 (131.7)	39 (106.9)	1.18 (0.79-1.79)	.44	.25	No	1.2 (-2.1 to 3.3)
Venous thromboembolism	626 (951.9)	327 (895.9)	1.16 (1.00-1.34)	.05	.03	No	7.5 (-0.1 to 14.0)
Immune thrombocytopenia	48 (72.6)	23 (63.0)	1.12 (0.65-1.97)	.70	.40	No	0.4 (-2.2 to 2.1)
Convulsions/seizures	285 (431.3)	150 (411.0)	1.04 (0.84-1.29)	.74	.39	No	0.9 (-4.8 to 5.6)
Acute myocardial infarction	613 (935.3)	375 (1030.2)	1.02 (0.89-1.18)	.75	.39	No	1.2 (-6.9 to 8.3)
Pulmonary embolism	503 (762.8)	290 (794.6)	1.01 (0.86-1.19)	.92	.48	No	0.4 (-7.2 to 6.9)
Bell palsy	535 (821.8)	301 (824.7)	1.00 (0.86-1.17)	.99	.52	No	0.0 (-7.9 to 6.7)
Stroke, ischemic	1059 (1611.8)	650 (1780.9)	0.97 (0.87-1.08)	.61	.70	No	-2.7 (-13.8 to 7.2)
Stroke, hemorrhagic	240 (364.7)	149 (408.2)	0.90 (0.72-1.13)	.37	.83	No	-2.3 (-8.3 to 2.5)
Thrombosis with thrombocytopenia syndrome	73 (112.0)	53 (145)	0.86 (0.58-1.27)	.45	.81	No	-1.0 (-4.6 to 1.4)
Appendicitis	762 (1178.9)	491 (1345.2)	0.82 (0.73-0.93)	.002	>.99	No	-14.8 (-25.5 to -5.3)
Guillain-Barré syndrome[g]	10 (15.1)	6 (16.4)	0.70 (0.22-2.31)	.53	.83	No	-0.4 (-3.0 to 0.5)
Disseminated intravascular coagulation	30 (45.4)	25 (68.5)	0.70 (0.39-1.28)	.25	.91	No	-1.1 (-4.1 to 0.6)
Kawasaki disease	0	2 (5.5)	0.00 (0.00-2.52)	.16	.16	No	-0.3 (-0.3 to 0.0)
Acute disseminated encephalomyelitis[g]	2 (3.0)	0	NE (0.07-NE)	.66	.66	No	0.2 (-2.5 to NE)

Abbreviation: NE, not estimable.

[a] There were 660 766 person-years of follow-up in the risk interval and 364 988 person-years in the comparison interval.

[b] Comparison interval was 22 to 42 days after either dose 1 or 2. The smaller case counts were due to the reduced available person-time of follow-up in the comparison interval. Most comparator follow-up was 22 to 42 days after dose 2 but some was 22 to 42 days after dose 1 in individuals who had not received dose 2.

[c] Overall estimate from Poisson regression stratified by site, 5-year age group, sex, race and ethnicity, and calendar date.

[d] CIs and P values do not account for the multiple chances for a false-positive signal during surveillance.

[e] One-sided P < .0048 required for a signal. This keeps the probability of a false-positive signal (owing to chance alone) below .05 in 2 years of surveillance.

[f] CIs for the excess risk estimates were based on the CIs of the corresponding adjusted rate ratios.

[g] Only medical record–confirmed cases are included in the analysis.

N=11,845,128 doses

Klein NP, Lewis N, et. al. *JAMA*. Published online September 03, 2021. doi:10.1001/jama.2021.15072

VSD COVID-19 RCA Surveillance: Outcomes monitored due to emerging concerns

Myocarditis and Pericarditis following mRNA vaccines

World Health Organization

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26 May 2021 | Statement | Reading time: 2 min (429 words)

The COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) is reviewing reports of a small number of cases of myocarditis reported in individuals vaccinated with the COVID-19 mRNA vaccines. The subcommittee noted that in most of the reported cases, the individuals have recovered. The subcommittee is soliciting and monitoring for additional information to assess for any relationship to COVID-19

Related

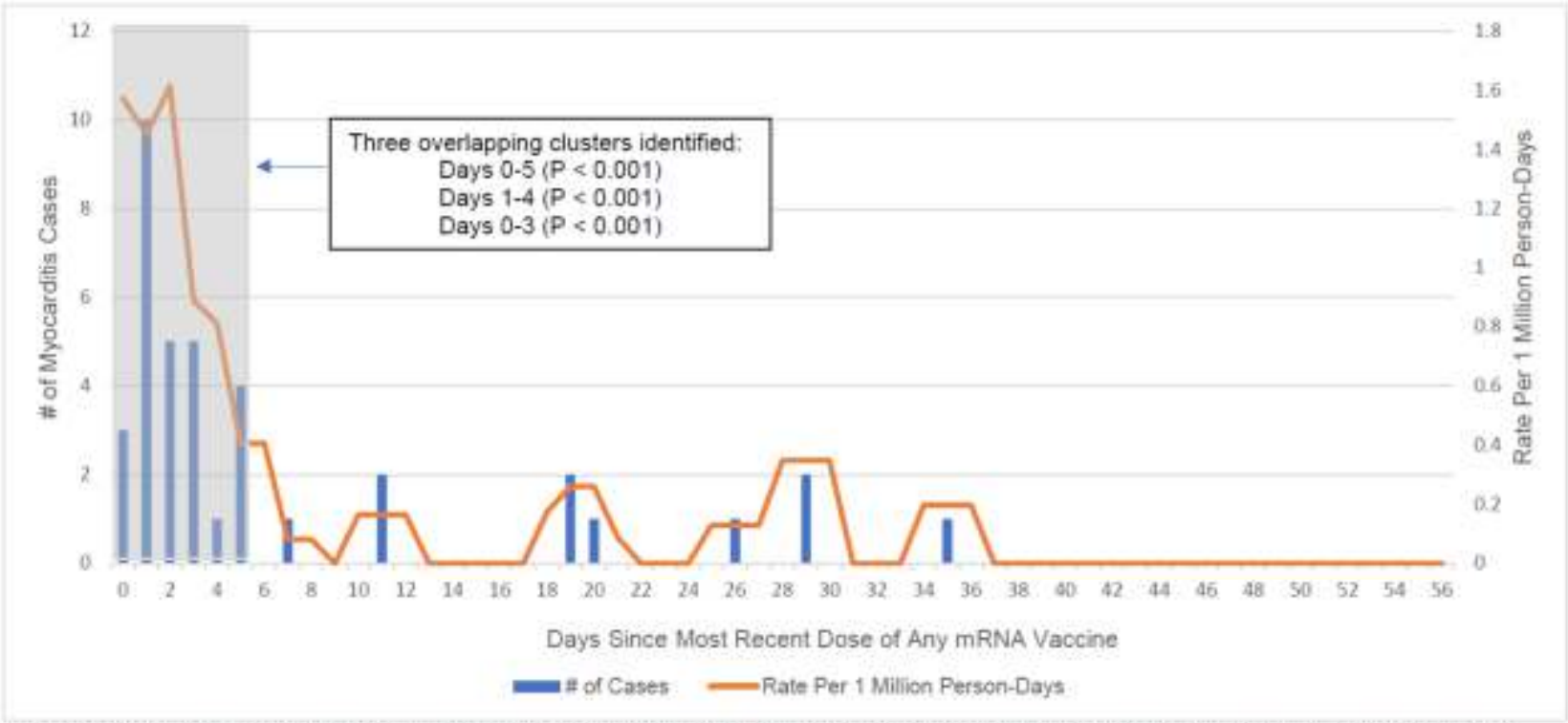
COVID-19 vaccine safety surveillance manual

Myocarditis / Pericarditis among subgroup <40 years of age

- **Chart reviews began May 2021**

- **All identified cases of myocarditis/pericarditis during the 98 days after vaccination were chart reviewed, followed by infectious disease clinician and/or a cardiologist adjudication to:**
  - Confirm case was incident following vaccination
  - Met CDC case definition (myocarditis, pericarditis, or myopericarditis)
  - Evaluated level of certainty for myocarditis

Clustering of Confirmed Myocarditis/pericarditis by Days Since Most Recent Dose of any mRNA Vaccine among 12-39 Year-Olds



Blue bars denote number of cases of medical-record confirmed myocarditis/pericarditis during days 0-56 after either dose of an mRNA vaccine. Orange line represents the rate of confirmed myocarditis/pericarditis per 1 million person-days. The rate is a moving 3 day mean. Clusters were identified using Kulldorff's scan statistic [17].

JAMA. Published online September 03, 2021. doi:10.1001/jama.2021.15072

Table 4. Confirmed Myocarditis/Pericarditis After Receipt of mRNA Vaccines Compared With Vaccinated Comparators Among Individuals Aged 12-39 Years by Dose and Risk Interval, December 14, 2020-June 26, 2021

Risk interval, d[a]	Dose	Events in risk interval (events/million person-years)[b]	Events in 21-d comparison interval[b,c] (events/million person-years)[b,c]	Adjusted rate ratio (95% CI)[d]	2-Sided *P* value	Excess cases in risk interval per million doses (95% CI)[e]
0-21	Both	34 (141.2)	4 (35.0)	3.75 (1.38 to 12.84)	.007	6.2 (2.3 to 7.8)
	1	9 (70.4)	4 (35.0)	3.67 (0.92 to 17.35)	.07	3.1 (-0.4 to 4.0)
	2	24 (221.3)	4 (44.6)	4.07 (1.45 to 14.18)	.005	10.1 (4.1 to 12.4)
0-7	Both	29 (320.8)	4 (35.0)	9.83 (3.35 to 35.77)	<.001	6.3 (4.9 to 6.8)
	1	5 (104.2)	3 (35.0)	7.27 (1.29 to 50.15)	.02	2.0 (0.5 to 2.2)
	2	23 (565.9)	4 (44.6)	10.4 (3.54 to 37.76)	<.001	11.2 (8.9 to 12.1)
8-14	Both	2 (25.7)	4 (35.0)	1.22 (0.14 to 7.74)	.82	0.1 (-3.0 to 0.4)
	1	2 (48.0)	3 (35.0)	3.25 (0.31 to 29.64)	.30	0.6 (-2.0 to 0.9)
	2	0	4 (44.6)	0 (0 to 3.22)	.28	-0.9 (-0.9 to 0)
15-21	Both	3 (41.3)	4 (35.0)	1.55 (0.28 to 7.78)	.58	0.3 (-2.0 to 0.7)
	1	2 (52.3)	4 (35.0)	2.58 (0.27 to 18.62)	.37	0.6 (-2.7 to 0.9)
	2	1 (29.1)	4 (44.6)	0.67 (0.03 to 5.64)	.79	-0.3 (-21.2 to 0.5)

Klein NP, Lewis N, et. al. *JAMA*. Published online September 03, 2021. doi:10.1001/jama.2021.15072

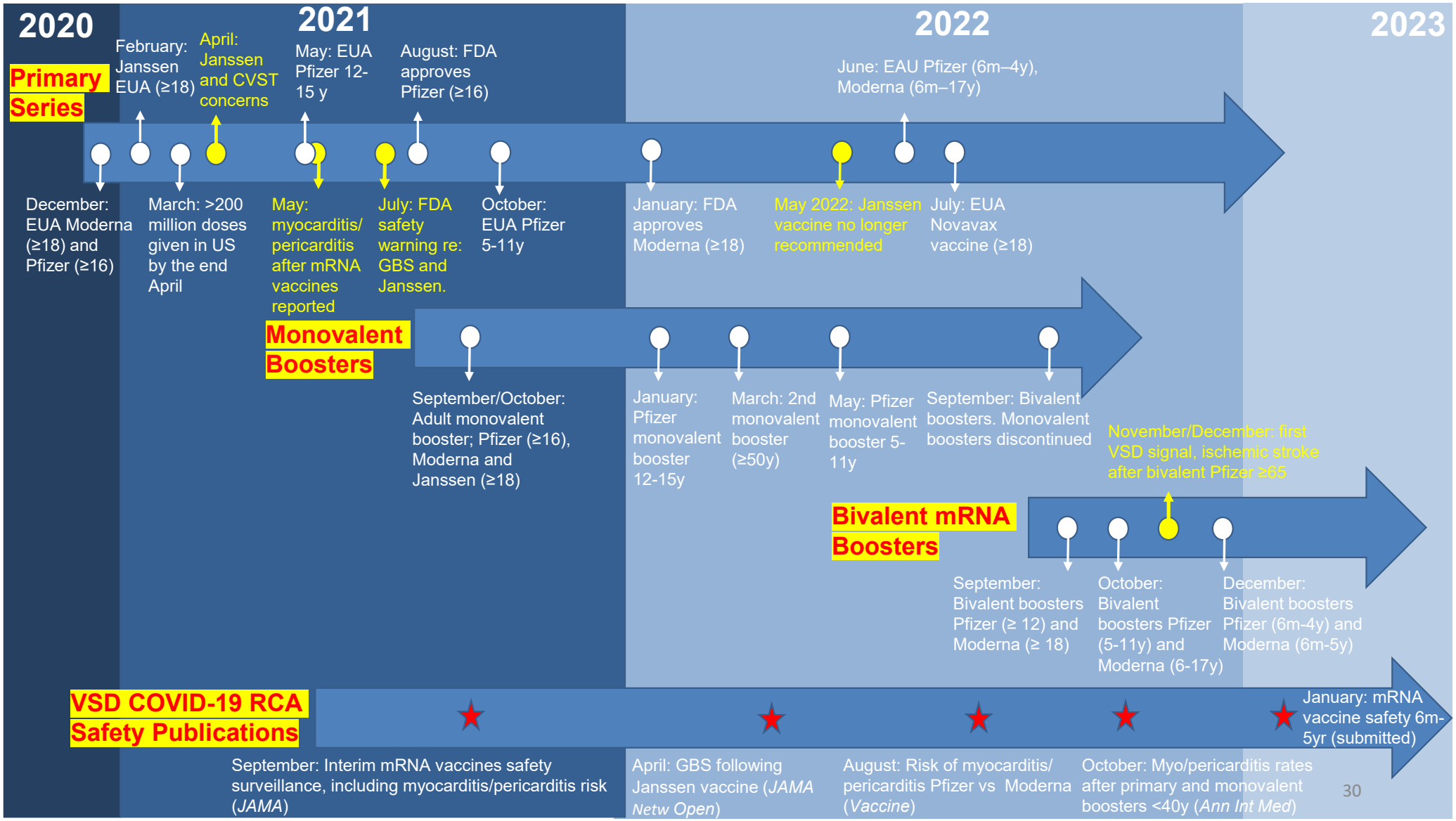
Outcomes monitored without comparators

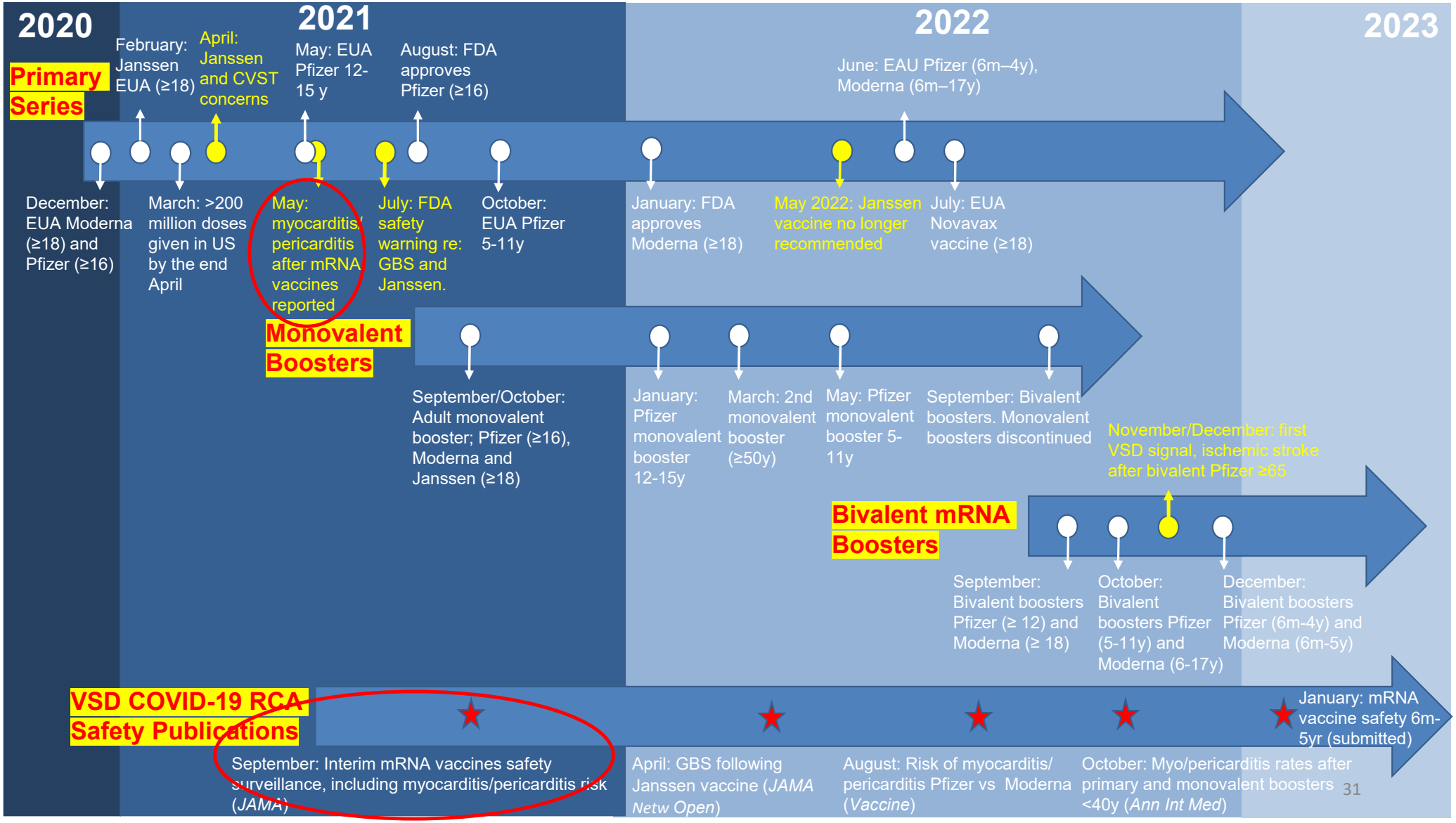
Table 5. Confirmed Anaphylaxis Cases After Medical Record Review Through May 29, 2021[a]

	No. (%)	
	BNT162b2 (n = 30)	mRNA-1273 (n = 25)
Age, mean (SD), y	42.8 (14.5)	45.7 (15.5)
Female sex	30 (100)	22 (88)
Time from vaccination to symptom onset, median (IQR) [N], min[b]	10.0 (5.0-20.0) [21]	10.0 (5.0-20.5) [20]
Time to symptom onset, min		
≤15[b]	19 (63)	17 (68)
≤30[b]	26 (87)	22 (88)
History		
Allergies[c]	24 (80)	19 (76)
Anaphylaxis[d]	15 (50)	5 (20)
Dose		
1	25 (83)	20 (80)
2	5 (17)	5 (20)
Brighton Collaboration case definition level[e]		
1, High certainty	13 (43)	6 (24)
2, Moderate certainty	17 (57)	18 (72)
3, Low certainty	0	1 (4)
Confirmed anaphylaxis cases per million doses (95% CI)[f]	4.8 (3.2-6.9)	5.1 (3.3-7.6)
Confirmed anaphylaxis cases per million doses among female individuals (95% CI)[f]	8.9 (6.0-12.7)	8.6 (5.2-12.5)

Interim Analyses Summary (9/21)

- No safety signals for any outcome in the 21 days after both mRNA doses in the overall VSD population, including all ages ≥12 years.
- In the subgroup aged 12–39 years, the rate ratio for myocarditis/pericarditis was elevated after both Pfizer and Moderna during days 0-21 after vaccination, and especially during days 0-7.
- In the VSD, rate of anaphylaxis after mRNA vaccines was ~ 5 cases / million doses.
- VSD surveillance was ongoing.


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18) and Pfizer (≥16)
February: Janssen EUA (≥18)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: EUA Pfizer 12-15 y
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18)
June: EAU Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16), Moderna and Janssen (≥18)
January: Pfizer monovalent booster 12-15y
March: 2nd monovalent booster (≥50y)
May: Pfizer monovalent booster 5-11y
September: Bivalent boosters. Monovalent boosters discontinued
Bivalent mRNA Boosters
November/December: first VSD signal, ischemic stroke after bivalent Pfizer ≥65
September: Bivalent boosters Pfizer (≥ 12) and Moderna (≥ 18)
October: Bivalent boosters Pfizer (5-11y) and Moderna (6-17y)
December: Bivalent boosters Pfizer (6m-4y) and Moderna (6m-5y)
VSD COVID-19 RCA Safety Publications
September: Interim mRNA vaccines safety surveillance, including myocarditis/pericarditis risk (JAMA)
April: GBS following Janssen vaccine (JAMA Netw Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myo/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
January: mRNA vaccine safety 6m-5yr (submitted)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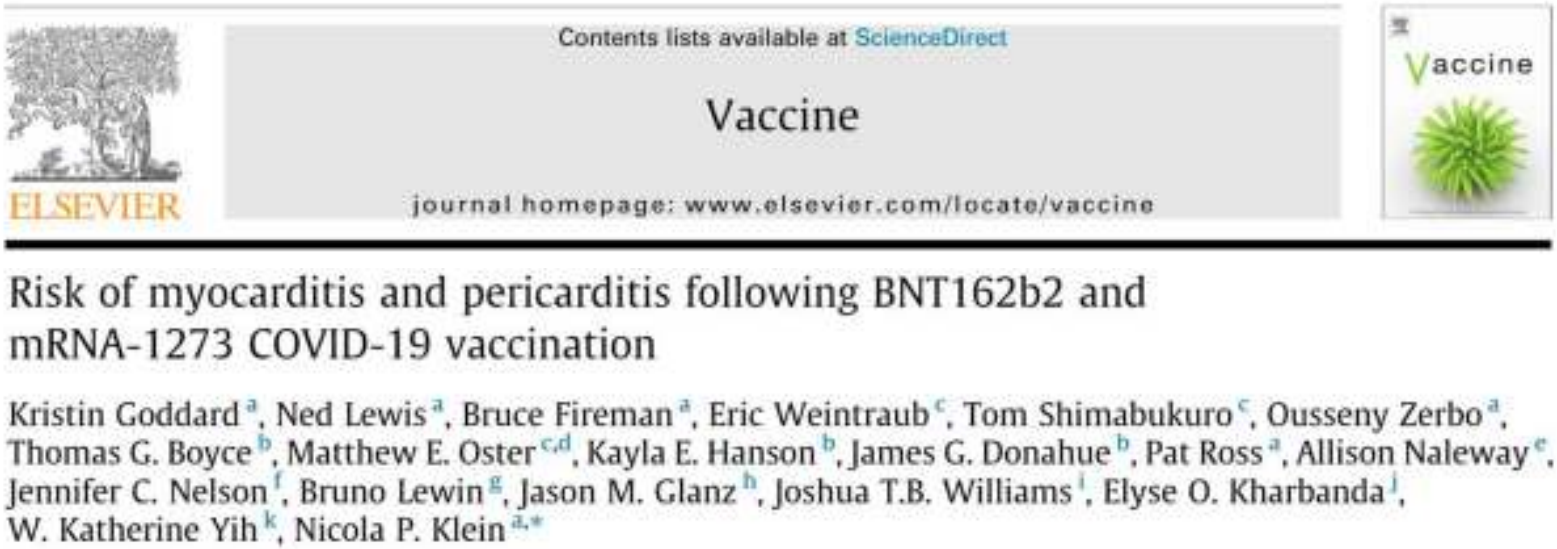
RCA Signal* for Myocarditis/Pericarditis in the 1-21 Day Risk Interval, all VSD population >12 years

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

			Sequential Test[1]	
Outcome	Event in Risk Interval	Adjusted Rate Ratio (95% CI)[2]	1-sided P-value	'Signal' 1-sided p <0.0048?
Myocarditis / pericarditis	138	1.72	<0.001	Yes

[1]Sequential test requires 1-sided p < 0.0048 (Fisher) for a signal. This keeps the probability of a false positive signal (due to chance alone) below 0.05 in 2 years of surveillance.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date. Comparison interval is 22–42 days after either dose.

*signal as of August 2021



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

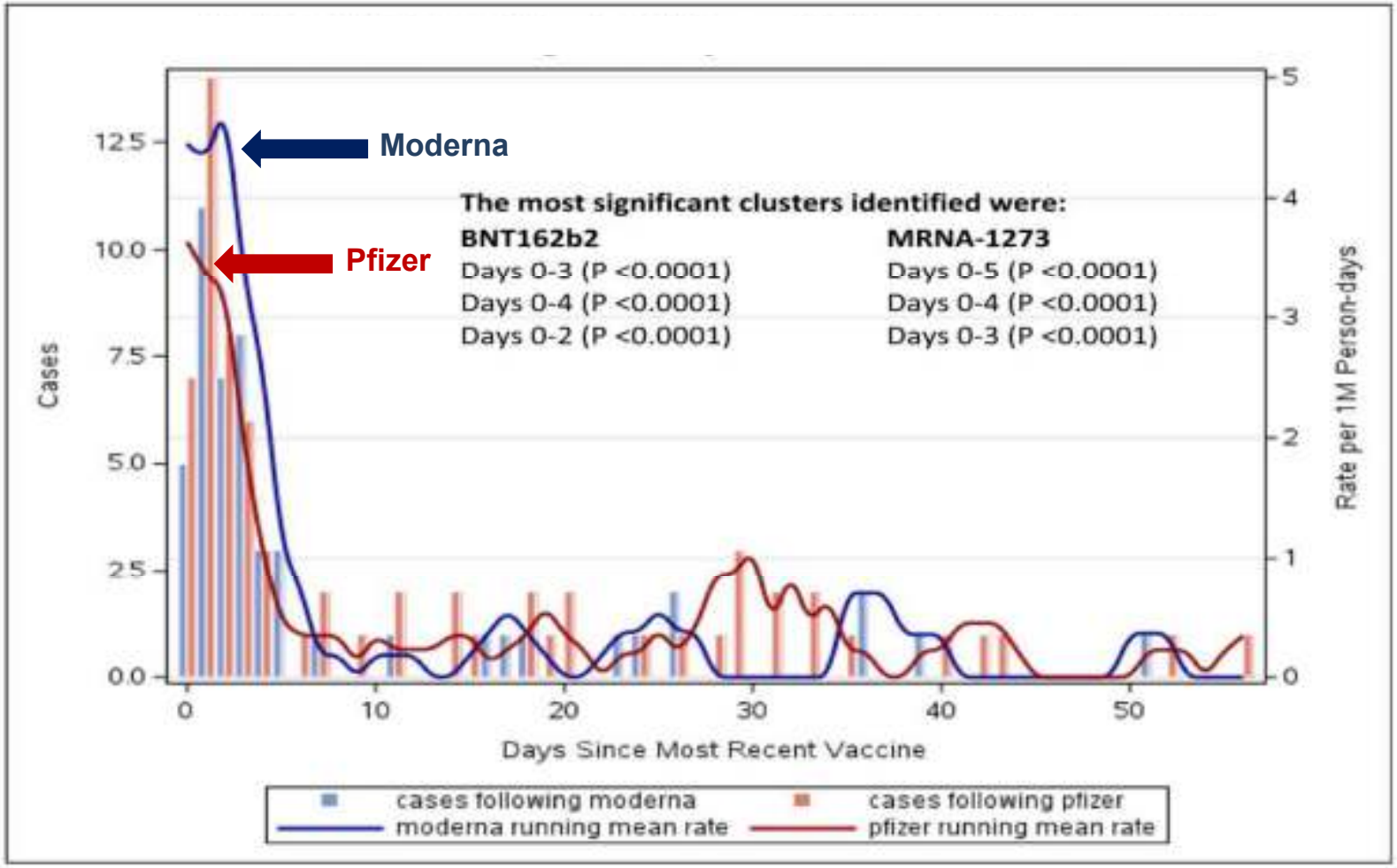
Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination

Kristin Goddard [a], Ned Lewis [a], Bruce Fireman [a], Eric Weintraub [c], Tom Shimabukuro [c], Ousseny Zerbo [a], Thomas G. Boyce [b], Matthew E. Oster [c,d], Kayla E. Hanson [b], James G. Donahue [b], Pat Ross [a], Allison Naleway [e], Jennifer C. Nelson [f], Bruno Lewin [g], Jason M. Glanz [h], Joshua T.B. Williams [i], Elyse O. Kharbanda [j], W. Katherine Yih [k], Nicola P. Klein [a,*]

- This study assessed whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer

- We conducted both indirect and direct head-to-head comparisons among 18–39-year-olds

Symptom Onset of 79 Verified Myocarditis and Pericarditis among 18–39-Year-Olds by Vaccine Product



Verified Myocarditis and Pericarditis in the 0-7 Day Risk Interval, among 18–39-Year-Olds by Product and Dose, December 14, 2020-January 14, 2022

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

Vaccine	Dose	Cases in 0–7 day risk interval (Rate of cases /million person years)	Cases in 22–42-day comparison interval (Rate of cases/million person years)	Adjusted rate ratio[2] (95% confidence interval)	2-Sided P-value	Cases in risk period per million doses	Excess cases in risk period per million doses[4]
Both mRNA	Either Dose[1]	79 (768.2)	20 (125.2)	7.55 (4.52–13.04)	<0.001	16.8	14.6
	Dose 1[1]	16 (303.9)	20 (125.2)	3.29 (1.52–7.07)	0.003	6.7	4.6
	Dose 2	63 (1255.2)	13 (99.4)	13.63 (7.39–26.55)	<0.001	27.5	25.5
BNT162b2	Either Dose[1]	41 (647.2)	13 (143.9)	6.94 (3.57–14.13)	<0.001	14.2	12.1
	Dose 1[1]	7 (216.0)	13 (144.2)	3.02 (1.03–8.33)	0.044	4.7	3.2
	Dose 2	34 (1099.1)	8[3] (111.5)	14.34 (6.45–34.85)	<0.001	24.1	22.4
mRNA-1273	Either Dose[1]	38 (962.4)	7 (100.2)	9.18 (4.12–22.89)	<0.001	21.1	18.8
	Dose 1[1]	9 (444.9)	7 (100.5)	3.46 (1.12–11.07)	0.031	9.7	6.9
	Dose 2	29 (1506.1)	4 (80.0)	18.75 (6.73–64.94)	<0.001	33.0	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.
[3] One case was non-informative in the BNT162b2, Dose 2 comparator interval.
[4] Excess cases are in addition to an estimated background rate of 2 cases/per million doses.

Goddard, et al. *Vaccine*.

Head-to-Head Comparison of Moderna versus Pfizer Regarding Myocarditis and Pericarditis During Days 0-7 Day Post-Vaccination in 18–39-Year-Olds

Dose	Sex	Myocarditis, myopericarditis, and pericarditis			Myocarditis and myopericarditis (pericarditis excluded)		
		Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]	Adjusted rate ratio[1] (95% CI)	2-sided p-value	Excess cases in risk period per 1 M doses of mRNA-1273 vs BNT162b2 [2]
Either Dose	All	1.61 (1.02–2.54)	0.041	8.0	1.35 (0.82–2.19)	0.237	4.3
	Male	1.52 (0.93–2.48)	0.097	13.4	1.32 (0.78–2.22)	0.288	8.1
	Female	2.34 (0.65–8.71)	0.188	3.5	1.57 (0.27–8.12)	0.585	1.1
Dose 2	All	1.48 (0.88–2.50)	0.141	10.7	1.24 (0.70–2.14)	0.454	5.2
	Male	1.50 (0.86–2.61)	0.152	21.9	1.31 (0.73–2.31)	0.361	13.6
	Female	1.35 (0.23–7.15)	0.714	1.6	0.53 (0.02–5.81)	0.658	–1.8

Abbreviation: CI = confidence interval.

[1] Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the mRNA-1273 rate divided by the BNT162b2 rate.

[2] Excess cases is an estimate of the mRNA-1273 rate minus the BNT162b2 rate. Excess cases per million doses were estimated by dividing the mRNA-1273 incidence rate by the rate ratio estimate and subtracting the result from the mRNA-1273 rate.

Annals of Internal Medicine

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after mRNA vaccination in 5–39-year-olds, by product, age groups, sex and dose number*

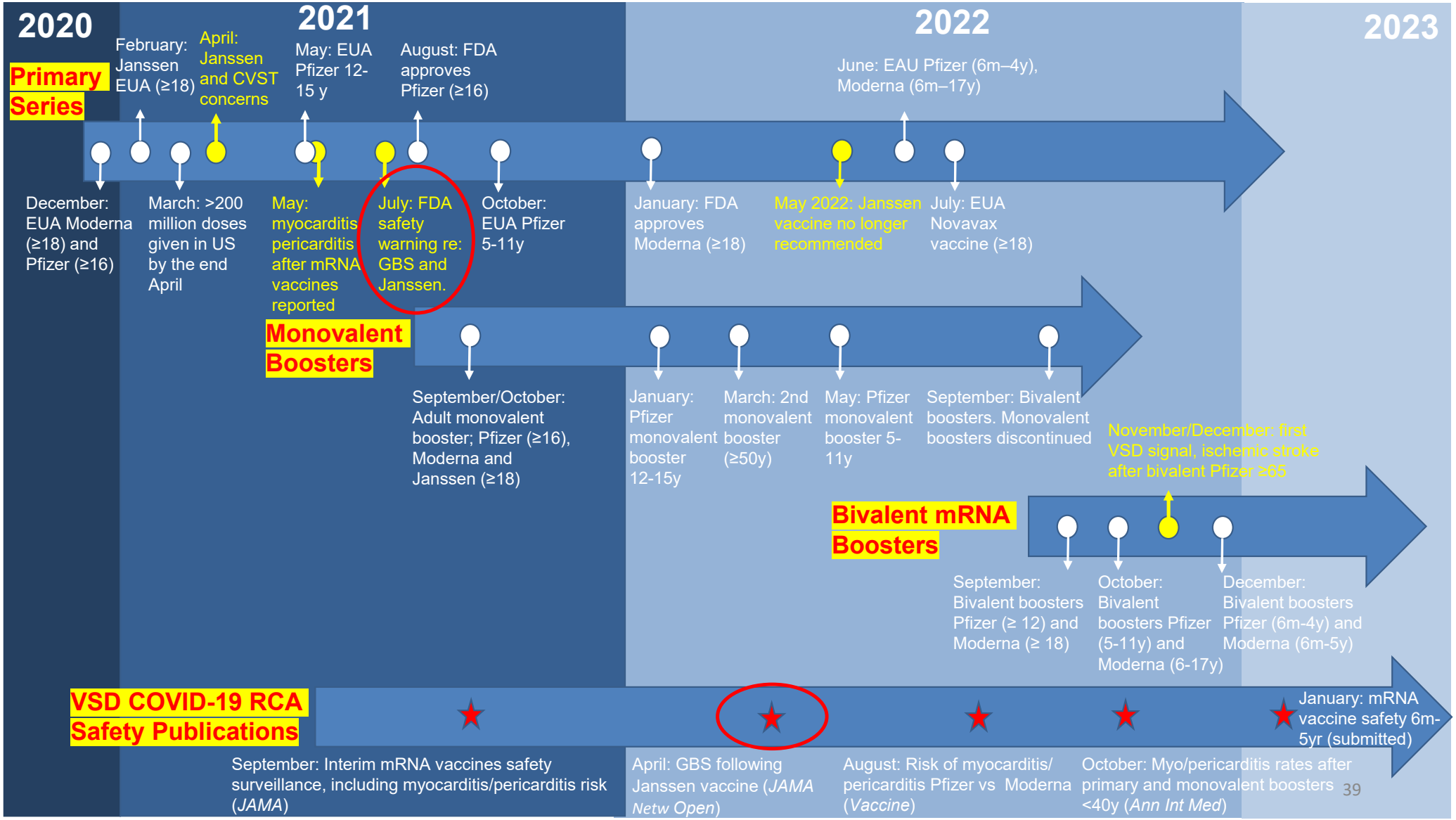
Product and Patient Group	Dose 1		Dose 2		First Booster	
	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)	Cases/Doses Administered†	Incidence Rate/ Million Doses (95% CI)
Pfizer‡						
Male, age						
5–11 y	0/221 975	0.0 (0.0–13.5)	3/207 958	14.4 (3.0–42.2)	0/50 415	0.0 (0.0–59.4)
12–15 y§	2/212 977	9.39 (1.1–33.9)	31/205 955	150.5 (102.3–213.6)	5/81 613	61.3 (19.9–143.0)
16–17 y	1/105 147	9.51 (0.2–53.0)	14/102 091	137.1 (75.0–230.1)	9/47 874	188.0 (86.0–356.9)
18–29 y	4/348 080	11.5 (3.1–29.4)	27/331 889	81.4 (53.6–118.4)	7/166 973	41.9 (16.9–86.4)
30–39 y	1/352 403	2.8 (0.1–15.8)	5/341 527	14.6 (4.8–34.2)	3/197 554	15.2 (3.1–44.4)
Female, age						
5–11 y	0/215 986	0.0 (0.0–13.9)	0/202 596	0.0 (0.0–14.8)	0/49 261	0.0 (0.0–60.8)
12–15 y	0/210 741	0.0 (0.0–14.2)	5/204 074	24.5 (8.0–57.2)	0/84 114	0.0 (0.0–35.6)
16–17 y	1/110 066	9.1 (0.2–50.6)	1/107 173	9.3 (0.2–52.0)	2/55 004	36.4 (4.4–131.3)
18–29 y	1/414 730	2.4 (0.1–13.4)	2/400 321	5.0 (0.6–18.0)	1/240 226	4.2 (0.1–23.2)
30–39 y	0/420 934	0.0 (0.0–7.1)	3/410 713	7.3 (1.5–21.3)	1/268 412	3.7 (0.1–20.8)
Moderna‖¶						
Male, age						
18–29 y	5/207 073	24.2 (7.8–56.3)	19/195 809	97.0 (58.4–151.5)	7/109 337	64.0 (25.7–131.9)
30–39 y	1/223 064	4.5 (0.1–25.0)	8/216 583	36.9 (15.9–72.8)	1/149 468	6.7 (0.2–37.3)
Female, age						
18–29 y	1/253 773	3.9 (0.1–22.0)	0/243 560	0.0 (0.0–12.3)	1/156 707	6.4 (0.2–35.6)
30–39 y	1/265 362	3.8 (0.1–21.0)	1/259 780	3.9 (0.1–21.4)	2/191 765	10.4 (1.3–37.7)

* Data through August 20, 2022

Goddard K, et al. . *Ann Intern Med*. 2022;175:1169-1771.

Summary: Myocarditis/Pericarditis in the VSD after COVID-19 Primary Series and Monovalent Boosters

- Myocarditis/pericarditis subsequently signaled among ≥12 years during days 1-21 after the primary series.
- During days 0-7 post vaccination, both mRNA vaccines were associated with increased risk of myocarditis and pericarditis in 12–39-year-olds.
- Risk estimates of myocarditis and pericarditis in 18–39-year-olds during days 0-7 after 2 doses were modestly higher after Moderna than after Pfizer.
- For persons ages 12–39 years, rates of myocarditis/pericarditis 0–7 days after primary and monovalent boosters were highest among male 12-15 and 16–17-year-olds.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2021
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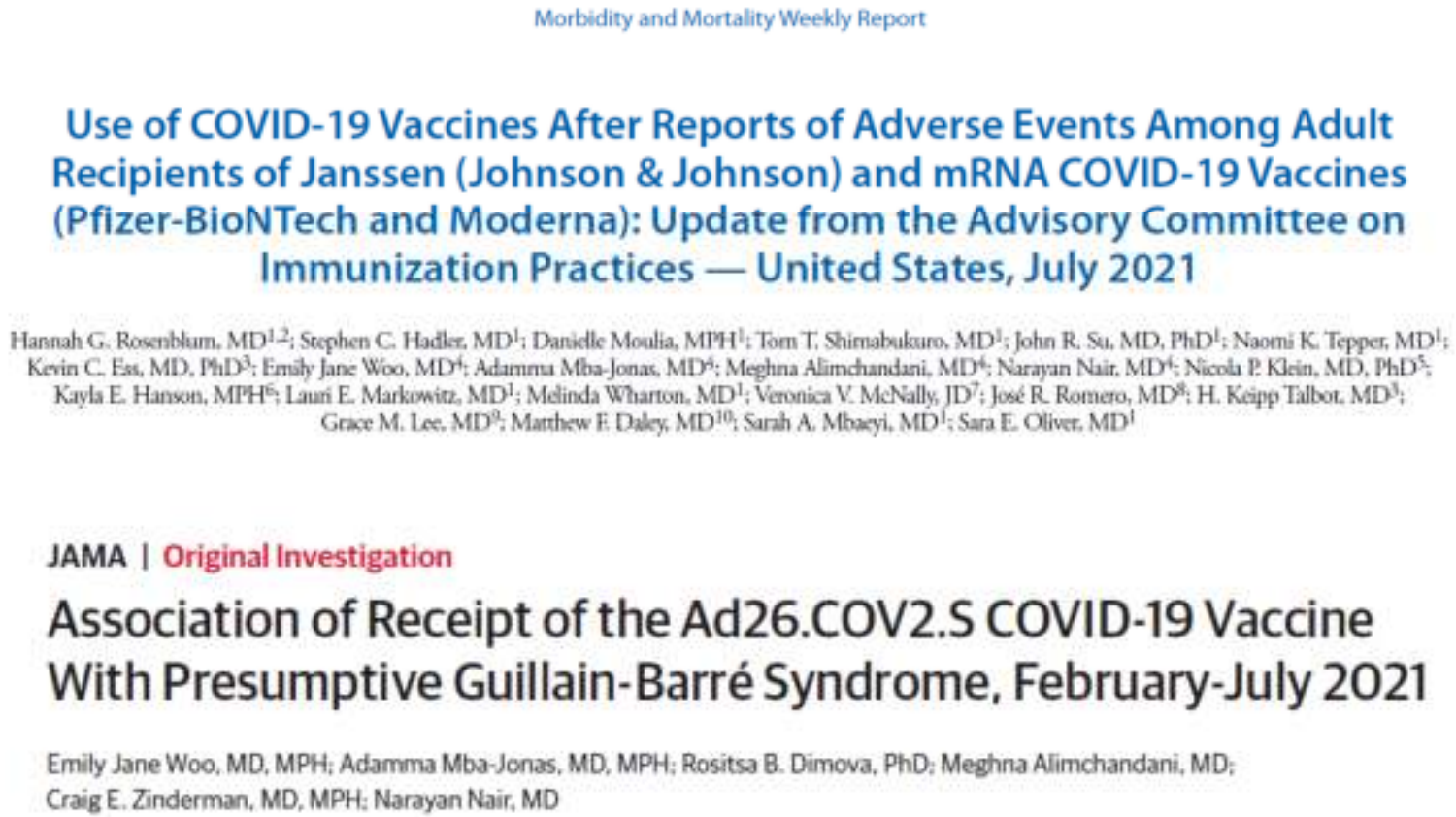


Morbidity and Mortality Weekly Report

Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices — United States, July 2021

Hannah G. Rosenblum, MD[1,2]; Stephen C. Hadler, MD[1]; Danielle Moulia, MPH[1]; Tom T. Shimabukuro, MD[1]; John R. Su, MD, PhD[1]; Naomi K. Tepper, MD[1]; Kevin C. Ess, MD, PhD[3]; Emily Jane Woo, MD[4]; Adamma Mba-Jonas, MD[4]; Meghna Alimchandani, MD[4]; Narayan Nair, MD[4]; Nicola P. Klein, MD, PhD[5]; Kayla E. Hanson, MPH[6]; Lauri E. Markowitz, MD[1]; Melinda Wharton, MD[1]; Veronica V. McNally, JD[7]; José R. Romero, MD[8]; H. Keipp Talbot, MD[3]; Grace M. Lee, MD[9]; Matthew F. Daley, MD[10]; Sarah A. Mbaeyi, MD[1]; Sara E. Oliver, MD[1]

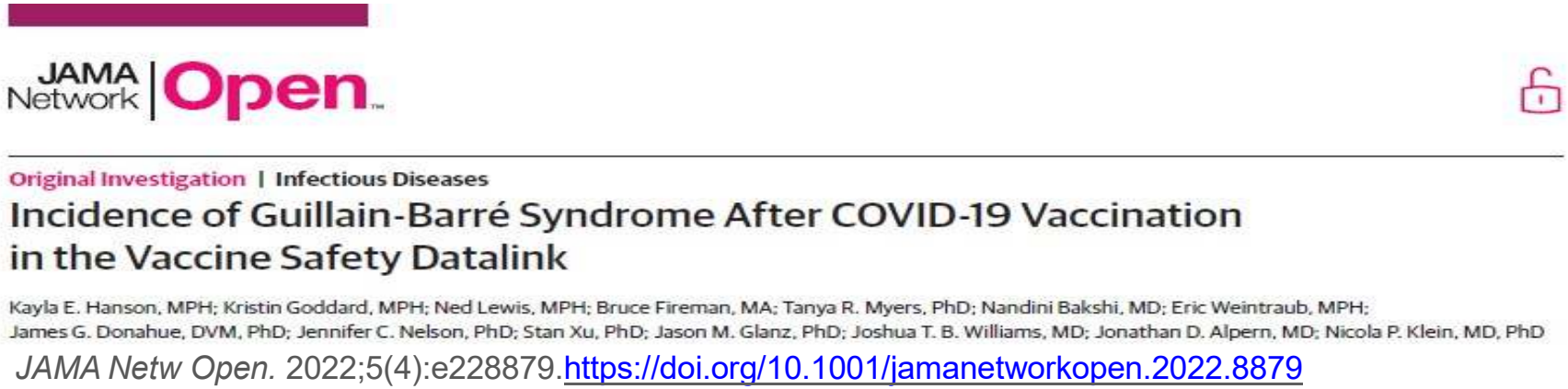
JAMA | Original Investigation

Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021

Emily Jane Woo, MD, MPH; Adamma Mba-Jonas, MD, MPH; Rositsa B. Dimova, PhD; Meghna Alimchandani, MD; Craig E. Zinderman, MD, MPH; Narayan Nair, MD

- FDA added safety warning about GBS to Janssen vaccine fact sheet in July 2021

Guillain-Barre Syndrome following Janssen vaccine



JAMA Network | Open

Original Investigation | Infectious Diseases

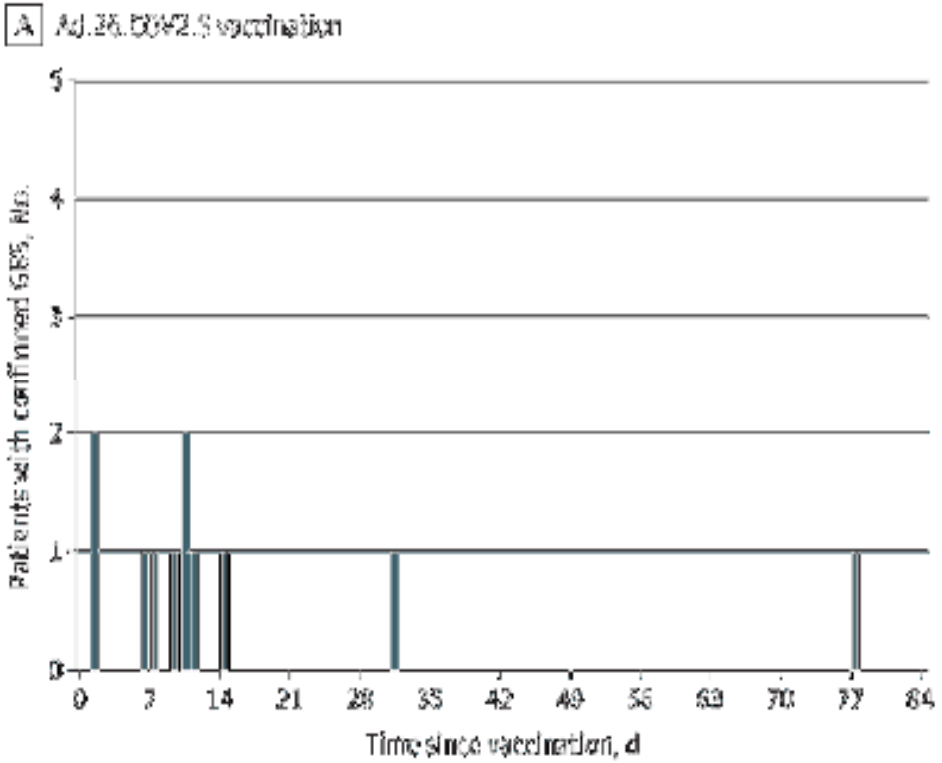
Incidence of Guillain-Barré Syndrome After COVID-19 Vaccination in the Vaccine Safety Datalink

Kayla E. Hanson, MPH; Kristin Goddard, MPH; Ned Lewis, MPH; Bruce Fireman, MA; Tanya R. Myers, PhD; Nandini Bakshi, MD; Eric Weintraub, MPH; James G. Donahue, DVM, PhD; Jennifer C. Nelson, PhD; Stan Xu, PhD; Jason M. Glanz, PhD; Joshua T. B. Williams, MD; Jonathan D. Alpern, MD; Nicola P. Klein, MD, PhD

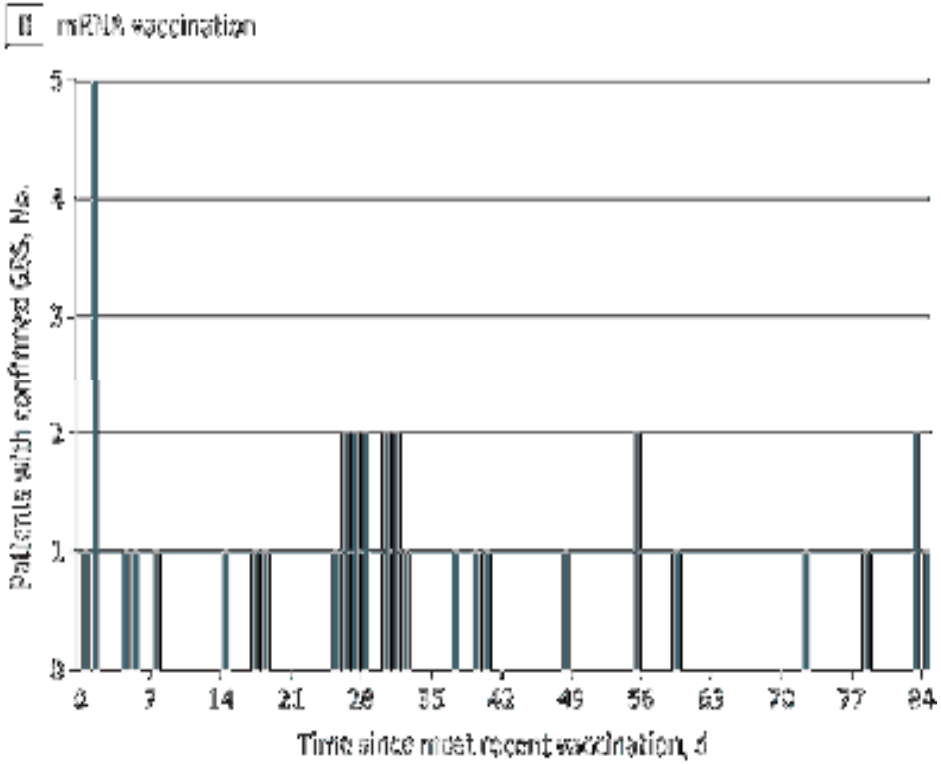
JAMA Netw Open. 2022;5(4):e228879.https://doi.org/10.1001/jamanetworkopen.2022.8879

- Describe GBS cases and incidence following COVID-19 vaccine primary series in the VSD
- Assess the risk of GBS after vaccination with Janssen and mRNA vaccines in the VSD

Timing of GBS Symptom Onset after COVID-19 Vaccination, December 13, 2020-November 14, 2021



- 11/22 (50%) GBS cases confirmed after review and adjudication
  - 9/11 (82%) cases had symptom onset within 1-21 days
- Cases temporally clustered days 1-14 (*P*=0.003)



- 36/78 (50%) cases confirmed after review and adjudication
  - 11/36 (31%) cases had symptom onset within 1-21 days
  - 15/36 (42%) cases had symptom onset within 22-42 days
  - 9/36 (25%) cases had symptom onset within 43-84 days

Hansen, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

Table 3. Incidence Rate of Confirmed GBS in the 1 to 21 Days and 1 to 42 Days After COVID-19 Vaccination

Vaccine type	Risk window, d	Including BL 4 cases[a]	No. GBS cases	Vaccine doses	Person-years[b]	Unadjusted incidence rate (95% CI) Per million doses	Per 100 000 person-years	P value, 2-sided[c]
Ad.26.COV2.S	1-21	Yes	9	483 053	27 773	18.6 (8.5-35.4)	32.4 (14.8-61.5)	<.001
		No	8	483 053	27 773	16.6 (7.3-32.8)	28.8 (12.4-56.8)	<.001
	1-42	Yes	10	483 053	55 546	20.7 (9.9-38.1)	18.0 (8.6-33.1)	<.001
		No	9	483 053	55 546	18.6 (8.5-35.4)	16.2 (7.4-30.8)	<.001
mRNA vaccine	1-21	Yes	11	14 637 020	821 790	0.8 (0.4-1.3)	1.3 (0.7-2.4)	.20
		No	9	14 637 020	821 790	0.6 (0.3-1.2)	1.1 (0.5-2.1)	.06
	1-42	Yes	26	14 637 020	1 929 813	1.8 (1.2-2.6)	2.0 (1.3-2.9)	.09
		No	23	14 637 020	1 929 813	1.6 (1.0-2.4)	1.7 (1.1-2.5)	.06

Abbreviations: BL, Brighton level; GBS, Guillain-Barré syndrome.

[a] Sensitivity analyses were conducted excluding Brighton level 4 cases (suspected cases).

[b] Follow-up time after dose 1 of either mRNA vaccine was censored after receipt of dose 2.

[c] The background rate of GBS is 1 to 2 per 100 000 person-years.[14,15] Exact Poisson regression was used to compare the observed number of GBS cases with the expected number of cases, which was derived from a background rate of 2 per 100 000 person-years and the observed number of person-years.

Hansen, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

- Unadjusted incidence rates of confirmed GBS per 100,000 person-years after Janssen vaccination were significantly higher than background rate of 2 per 100,000 person-years.*

*Sejvar, et. al. *Neuroepidemiology*. 2011;36(2):123-133. https://doi.org/10.1159/000324710

Table 4. Head-to-Head Comparisons of Confirmed GBS Incidence After Ad.26.COV2.S vs mRNA Vaccination

Risk window, d	No.		Adjusted RR (95% CI)[b]	*P* value, 2-sided	Excess cases in risk interval per million doses
	GBS cases after Ad.26.COV2.S	GBS cases after mRNA vaccination[a]			
1-21	9	8	20.56 (6.94-64.66)	<.001	15.5
1-42	10	21	11.46 (4.83-26.16)	<.001	17.5

Abbreviations: GBS, Guillain-Barré syndrome; RR, rate ratio.

[a] Not all confirmed cases of GBS after mRNA vaccination are included in this analysis, such as cases that occurred prior to the authorization of Ad.26.COV2.S.

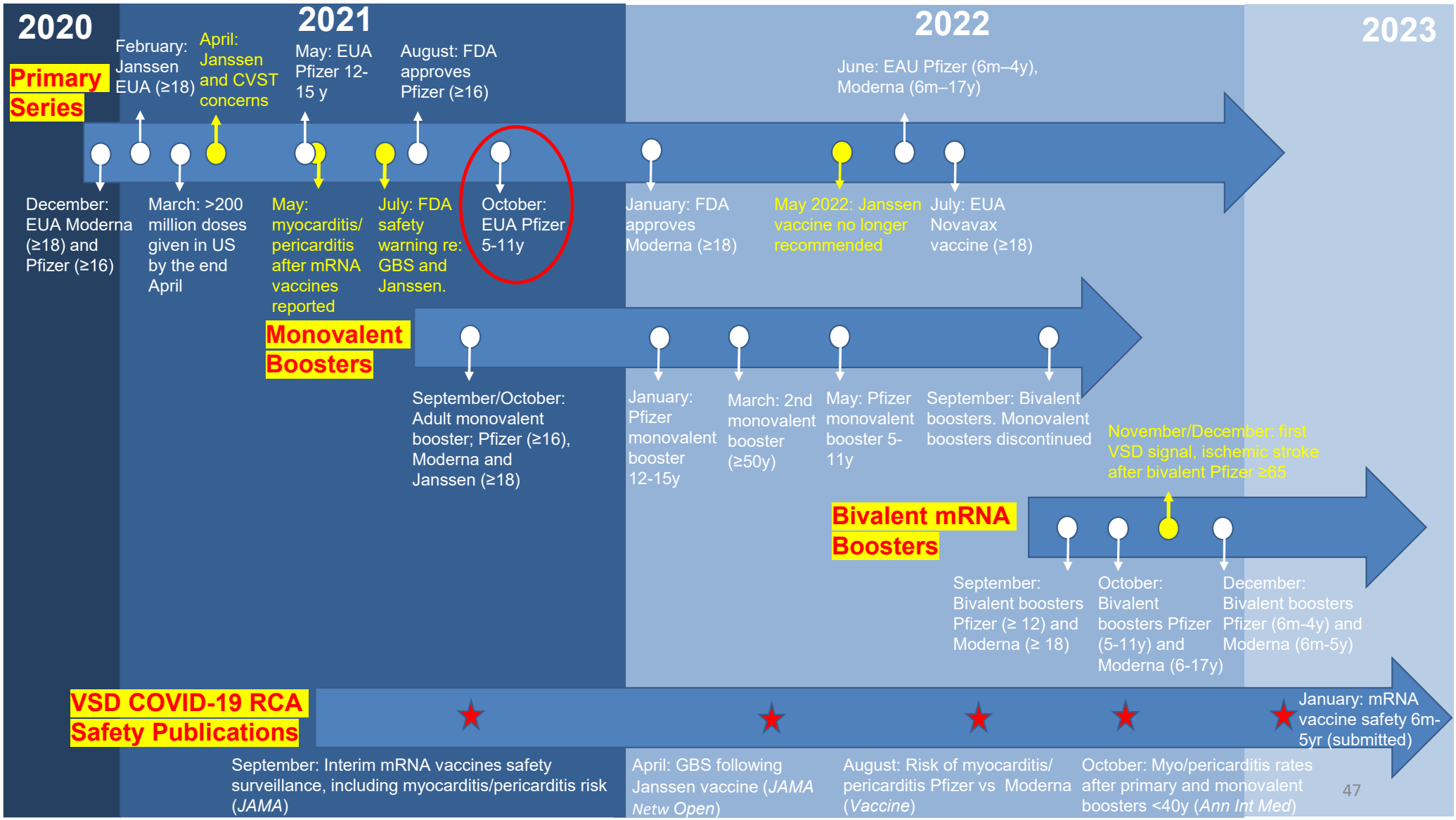
[b] Adjusted for 5-year age group, sex, race and ethnicity, site, and calendar day.

- When directly compared with mRNA vaccines, the risk of GBS after Janssen vaccine was significantly higher.

Hansen, K, et al. JAMA Netw Open. 2022;5(4):e228879. doi:10.1001/jamanetworkopen.2022.8879

Summary: Guillain-Barre after COVID-19 Vaccination in the VSD

- Findings were consistent with an association between increased risk of GBS and Janssen COVID-19 vaccine.
  - Incidence after Janssen vaccine was 21 times higher than after mRNA vaccines.
- No evidence of association between GBS and mRNA-based COVID-19 vaccines
  - Incidence of GBS in the 21 days after mRNA vaccines was similar to the expected background rate
  - No statistical signals in weekly surveillance with vaccinated concurrent comparators
- ACIP preferentially recommended mRNA-based COVID-19 vaccines over Janssen vaccine in December 2021.
- Since May 2022, Janssen vaccine has no longer been recommended.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Summary of RCA Findings in the 1-21 Day Risk Interval, 5–11-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

		Pfizer		
Risk Interval	Outcome Event	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses
1 -21	Appendicitis	No	No	No
	Bell's palsy	No	No	No
	Encephalitis / myelitis / encephalomyelitis	No	No	No
	Stroke, hemorrhagic	No	No	No
	Stroke, ischemic	No	-	No
	Immune thrombocytopenia	No	No	No
	Kawasaki disease	No	No	No
	Myocarditis / pericarditis	No	No	No
	Seizures	No	No	No
	Thrombotic thrombocytopenic purpura	No	-	No

- **No monitored outcomes after Pfizer vaccine met the signaling criteria in the 21 days after primary series vaccination among children aged 5-11 years in the VSD population.**

*Final analyses through January 2023

**Signaling threshold was one sided P<0.061.

Safety of COVID-19 Vaccination in United States Children Ages 5 to 11 Years

Anne M Hause [1], David K Shay [1], Nicola P Klein [2], Winston E Abara [1], James Baggs [1], Margaret M Cortese [1], Bruce Fireman [2], Julianne Gee [1], Jason M Glanz [3], Kristin Goddard [2], Kayla E Hanson [4], Brandon Hugueley [1], Tat'Yana Kenigsberg [1], Elyse O Kharbanda [5], Bruno Lewin [6], Ned Lewis [2], Paige Marquez [1], Tanya Myers [1], Allison Naleway [7], Jennifer C Nelson [8], John R Su [1], Deborah Thompson [9], Babatunde Olubajo [1], Matthew E Oster [1,10], Eric S Weintraub [1], Joshua T B Williams [11], Anna R Yousaf [1], Ousseny Zerbo [2], Bicheng Zhang [1], Tom T Shimabukuro [1]

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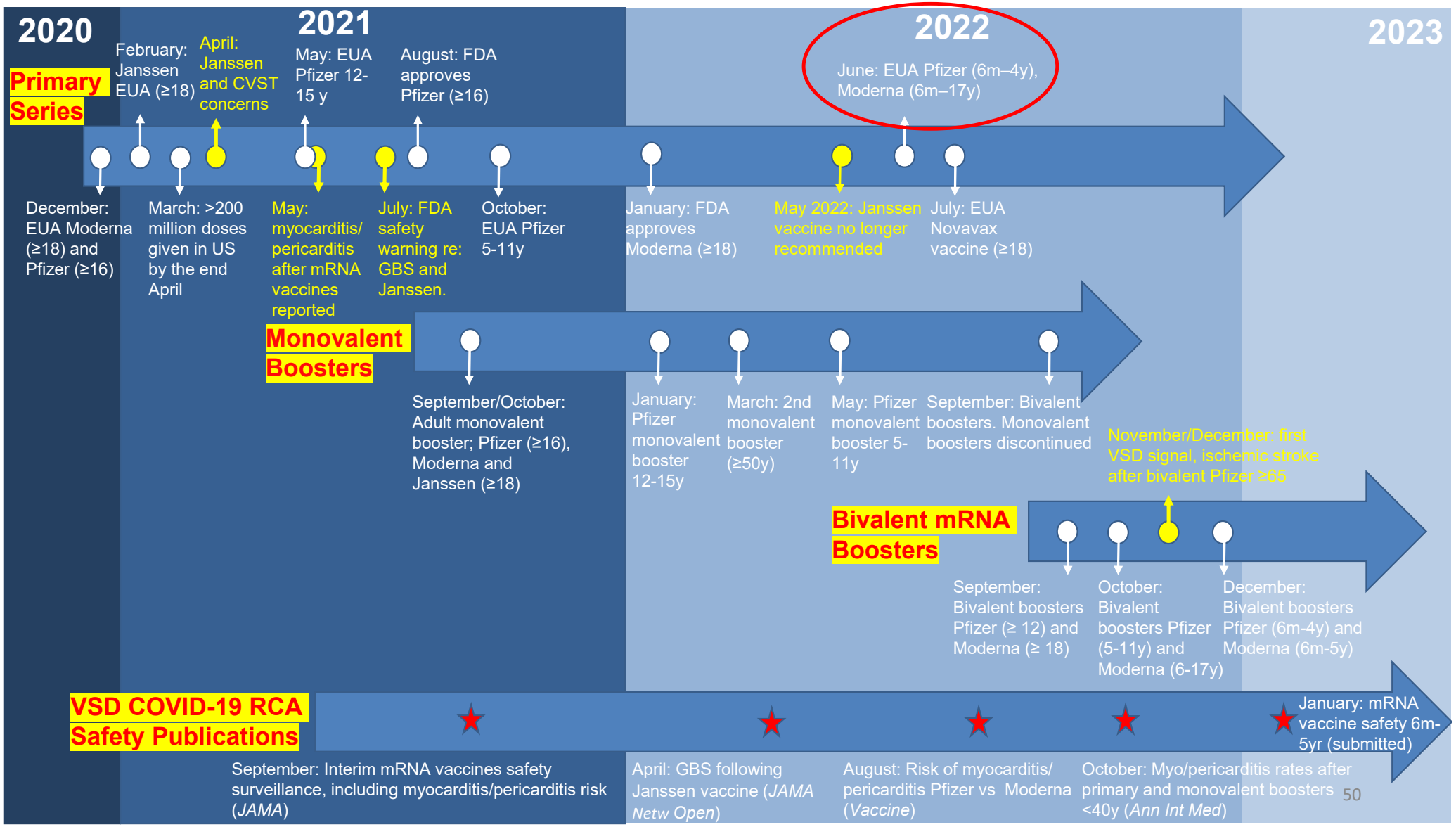
Abstract

Background and objectives: Limited postauthorization safety data for the Pfizer-BioNTech coronavirus disease 2019 vaccination among children ages 5 to 11 years are available, particularly for the adverse event myocarditis, which has been detected in adolescents and young adults. We describe adverse events observed during the first 4 months of the United States coronavirus disease 2019 vaccination program in this age group.

Methods: We analyzed data from 3 United States safety monitoring systems: v-safe, a voluntary smartphone-based system that monitors reactions and health effects; the Vaccine Adverse Events Reporting System (VAERS), the national spontaneous reporting system comanaged by the Centers for Disease Control and Prevention and Food and Drug Administration; and the Vaccine Safety Datalink, an active surveillance system that monitors electronic health records for prespecified events, including myocarditis.

Results: Among 48 795 children ages 5 to 11 years enrolled in v-safe, most reported reactions were mild-to-moderate, most frequently reported the day after vaccination, and were more common after dose 2. VAERS received 7578 adverse event reports; 97% were nonserious. On review of 194 serious VAERS reports, 15 myocarditis cases were verified; 8 occurred in boys after dose 2 (reporting rate 2.2 per million doses). In the Vaccine Safety Datalink, no safety signals were detected in weekly sequential monitoring after administration of 726 820 doses.

Conclusions: Safety findings for Pfizer-BioNTech vaccine from 3 United States monitoring systems in children ages 5 to 11 years show that most reported adverse events were mild and no safety signals were observed in active surveillance. VAERS reporting rates of myocarditis after dose 2 in this age group were substantially lower than those observed among adolescents ages 12 to 15 years.


2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15 y
August: FDA approves Pfizer (≥16)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18) and Pfizer (≥16)
March: >200 million doses given in US by the end April
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16), Moderna and Janssen (≥18)
January: Pfizer monovalent booster 12-15y
March: 2nd monovalent booster (≥50y)
May: Pfizer monovalent booster 5-11y
September: Bivalent boosters. Monovalent boosters discontinued
November/December: first VSD signal, ischemic stroke after bivalent Pfizer ≥65
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥ 12) and Moderna (≥ 18)
October: Bivalent boosters Pfizer (5-11y) and Moderna (6-17y)
December: Bivalent boosters Pfizer (6m-4y) and Moderna (6m-5y)
VSD COVID-19 RCA Safety Publications
January: mRNA vaccine safety 6m-5yr (submitted)
September: Interim mRNA vaccines safety surveillance, including myocarditis/pericarditis risk (JAMA)
April: GBS following Janssen vaccine (JAMA Netw Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myo/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)

RCA in the 1-21 Day Risk Interval, 6 months-4/5-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators on the Same Calendar Days, June 18, 2022-Feb 25, 2023[a]

Outcome*	Risk interval (days)	Vaccine type	Events in risk interval	Events in comparison interval (22-42 days)	Adjusted rate ratio (95% CI)**	1-sided p-value	Signal? P<0.011
Appendicitis	1 – 21	Pfizer-BioNTech	1	1	0.48 (0.01 – 26.31)	0.91	No
		Moderna	0	1	0.00 (0.00 – 12.67)	0.40	No
Bell's Palsy	1 – 21	Pfizer-BioNTech	0	1	0.00 (0.00 – 38.00)	0.67	No
		Moderna	1	0	NE (0.06 - ∞)	0.49	No
Encephalitis/myelitis/ encephalomyelitis	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	1	0	NE (0.02 - ∞)	0.74	No
Guillain-Barre Syndrome	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 26.56)	0.58	No
Immune thrombocytopenia	1 – 21	Pfizer-BioNTech	0	1	0.00 (0.00 – 19.00)	0.50	No
		Moderna	1	1	1.13 (0.03 – 44.21)	0.72	No
Kawasaki disease	1 – 21	Pfizer-BioNTech	2	1	2.05 (0.15 – 60.78)	0.49	No
		Moderna	0	3	0.00 (0.00 – 1.10)	0.06	No
Pulmonary embolism	1 – 21	Pfizer-BioNTech	1	0	NE (0.08 – ∞)	0.41	No
		Moderna	-	-	-	-	-
Seizures	0-7	Pfizer-BioNTech	9	23	0.68 (0.26 – 1.60)	0.86	No
		Moderna	5	19	0.85 (0.17 – 2.31)	0.71	No
	0-21	Pfizer-BioNTech	38	23	1.02 (0.58 – 1.80)	0.53	No
		Moderna	23	19	1.09 (0.57 – 2.11)	0.46	No
Stroke, hemorrhagic	1 – 21	Pfizer-BioNTech	1	1	1.12 (0.03 – 44.64)	0.72	No
		Moderna	-	-	-	-	-
Transverse Myelitis	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No
Venous thromboembolism	1 – 21	Pfizer-BioNTech	-	-	-	-	-
		Moderna	0	1	0.00 (0.00 – 38.00)	0.67	No

CI=confidence intervals; NE=not estimable. -: analysis not yet possible

*Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type, making analyses possible.

**Stratified by Vaccine Safety Datalink site, age (year), sex, race/ethnicity, and calendar date

RCA in the 1-21 Day Risk Interval, 6 months-4/5-year-olds

Compared with Outcome Events 22-42 days after in Vaccinated Comparators on the Same Calendar Days, June 18, 2022-Feb 25, 2023[a]

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no cases of myocarditis or pericarditis within the risk interval

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**Stratified by Vaccine Safety Datalink site, age (year), sex, race/ethnicity, and calendar date

Summary of RCA Safety Monitoring in Children <12 years in the VSD

- Among 5–11-year-olds, there were no safety signals after the primary mRNA series, nor the monovalent booster (not shown).
  - There were no signals for myocarditis/pericarditis after the primary series or the monovalent booster
- Among children aged 6 months to 4/5 years, there were no safety signals after the primary mRNA series
  - There were no cases of myocarditis/pericarditis during the 21 days after vaccination in this age group.
- RCA surveillance in children aged 6 months to 4/5 years is ongoing.

Summary of Safety Findings after COVID-19 Vaccines in the VSD

Anaphylaxis

- Rate of anaphylaxis after primary series was ~ 5 cases / million doses

Myocarditis/Pericarditis after mRNA vaccines

- During days 0-7 post vaccination, both mRNA vaccines were associated with increased risk of myocarditis and pericarditis in 12–39-year-olds.
  - Myocarditis/pericarditis signaled in RCA surveillance both after the primary series and monovalent booster (not shown).
- Risk estimates of myocarditis and pericarditis in 18–39-year-olds during days 0-7 after 2 doses were modestly higher after Moderna than after Pfizer.
- Rates of myocarditis/pericarditis 0–7 days after primary and monovalent boosters were highest among male 12-15- and 16–17-year-olds.

GBS after Janssen vaccine

- Findings consistent with an association between increased risk of GBS and Janssen vaccine.

Challenges and lessons in Rapidly Generating Vaccine Safety Evidence During the Pandemic

Challenges in Rapidly Generating Vaccine Safety Evidence During the Pandemic

1. Vaccine uptake was early & unpredictable.
   - One rationale for using vaccinated concurrent comparators
   - Most RCA findings from the primary series in adults came early and have been mostly unchanged since fall 2021.

2. The VSD COVID-19 RCA analytic methods have been hard to understand.
   - Important features of this RCA differed from traditional sequential analyses, and from how we have framed past RCAs.

3. Our vaccine safety research questions have continually changed and expanded, with requirements to rapidly adapt our surveillance to include new outcomes and age groups
   - Focus switched from primary series in adults to boosters to younger ages, etc.
   - Flexibility in routinely accommodating (sometime substantial) changes has been critical.

4. We have large amounts of interesting data/results “on the shelf” (e.g., comparisons with unvaccinated people), which were available should a concern/signal arises (from VSD or elsewhere)

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4. We have large amounts of interesting data/results “on the shelf” (e.g., comparisons with unvaccinated people), which were available should a concern/signal arises (from VSD or elsewhere), but rarely examined due to time and other constraints.

#2. Our methods have been hard to understand.

- Vaccinated concurrent comparators is an unfamiliar approach and difficult to explain how the follow up in the comparison interval is concurrent (i.e., on the same calendar day) with the follow up in the risk interval

- Vaccinated concurrent comparators are advantageous because they adjust for potential biases associated with calendar time, site, and demographic factors.

- For this reason, we believe that vaccinated concurrent comparators are better than the alternatives.

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- However, our publications and talks have been occasioned by intense public/media focus on COVID vaccine safety (rather than by safety signals or pre-specified endpoints) and were mainly driven by the need to communicate
  - with the ACIP (both WG and public meetings) and other government stakeholders
  - about emerging safety concerns
- Thus, since we were frequently communicating preliminary results on short notice, methods that are hard to concisely explain and understand posed substantial challenges.

#3. Our research questions continue to expand…

Vaccinees

- Changing age groups
  - Primary series: adults → to adolescent 12-15 years → to children 5-11 years → to youngest children < 5 years.

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  - Now Omicron-specific bivalent boosters
- Vaccines that use different technology (e.g., Janssen, Novavax)

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  - Now Omicron-specific bivalent boosters (but only >12-year-olds)
- Vaccines that use different technology (e.g., Janssen)

Outcomes

- Originally pre-specified 21 outcomes → 23 outcomes
  - Revised ICD codes and adding new age subgroups for specific outcomes (e.g., myocarditis/pericarditis).
  - Expanded outcomes to add emerging concerns (i.e., cerebral venus sinus thrombosis, thrombosis with thrombocytopenia syndrome).

Lessons Learned and Next Steps

- VSD is very well-situated to respond to vaccine safety needs in a pandemic and features.
  - Analyses that are updated weekly, are population based and are geographically diverse.
  - Flexible structure with access to comprehensive medical record data, including charts to conduct rapid case confirmation when needed.
  - Ability to rapidly add new outcomes in response to emerging concerns.
- VSD RCA surveillance complements other vaccine safety monitoring systems in the US.
- During a pandemic, an RCA protocol is a living document and may rapidly evolve as surveillance needs change.
  - Surveillance we plan today will not necessarily be the same population or vaccines we monitor in several months
  - Surveillance (and associated protocol) has to focus on doing work that adds value.
- VSD RCA surveillance is ongoing in children aged < 5 years and after bivalent booster doses.

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  - Kaiser Permanente Colorado, Denver, Colorado
  - Kaiser Permanente Northwest, Portland, Oregon
  - Kaiser Permanente Southern California, Los Angeles, California
  - Kaiser Permanente Washington, Seattle, Washington
  - Denver Health, Denver, Colorado

Backup Slides

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

Code List[+] (based on cardiologist and VSD feedback)
• 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

[+]Individuals with COVID-19 diagnosis or positive PCR 30 days prior to myocarditis/pericarditis were excluded. Those with COVID diagnosis or positive PCR >30 days prior were included.

- All identified cases 98 days after vaccination were chart reviewed, followed by infectious disease clinician and/or a cardiologist adjudication to:
  - Confirm case was incident following vaccination
  - Met CDC case definition (myocarditis, pericarditis, or myopericarditis)
  - Evaluated level of certainty for myocarditis

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

Myocarditis and Pericarditis after an mRNA Vaccine Among 18-39 year olds: Chart Review Summary

- 95 potential cases were identified during days 0-7 after mRNA vaccination
- Chart review and adjudication verified 79/95 (83%) myocarditis and pericarditis cases
  - 16 cases were after dose 1 of either vaccine
  - 63 cases were after dose 2 of either vaccine
- 41/79 (51.9%) verified cases were after either dose of Pfizer
- 38/79 (48.1%) verified cases were after either dose of Moderna

eTable 4. Medical record review of 34 confirmed myocarditis/pericarditis cases 0-21 days after mRNA vaccines among individuals aged 12-39 years, December 14, 2021 - June 19, 2021.

	Confirmed Myocarditis/Pericarditis N=34 (%)
Age, median (range)	24 years (13 – 39 years)
12-15 years	1 (3)
16-19 years	7 (21)
20-24 years	10 (29)
25-29 years	3 (9)
30-34 years	7 (21)
35-39 years	6 (18)
Male sex	29 (85)
Race/Ethnicity	
Hispanic/Latino	7 (21)
White, Non-Hispanic	17 (50)
Black, Non-Hispanic	0 (0)
Asian, Non-Hispanic	5 (15)
Native Hawaiian/Pacific Islander, Non-Hispanic	0 (0)
American Indian/Alaskan Native, Non-Hispanic	0 (0)
Multiple/Other	2 (6)
Unknown	3 (9)
History of COVID-19 infection	3 (9)
History of myocarditis/pericarditis	3 (9)
Time from vaccination to symptom onset, median (range)	2 days (0 – 20 days)
Signs and symptoms	
Chest pain/pressure/discomfort	34 (100)
Dyspnea/Shortness of breath	15 (44)
Palpitations	4 (12)
Pericardial rub	1 (3)
Other (fever, fatigue, chills, numbness, tingling nausea, etc)	20 (59)
Diagnostic testing	
Troponin level obtained	34 (100)
Abnormal troponin Level	28 (82)
ECG obtained	34 (100)
Abnormal ECG	30 (88)
Echocardiogram obtained	30/34 (88)
Abnormal echocardiogram	15/30 (50)
Cardiac MRI obtained	9/34 (26)
Abnormal cardiac MRI	8/9 (89)
Diagnosis after adjudication	
Acute myocarditis	7 (21)
Acute pericarditis	6 (18)
Myopericarditis	21 (62)
Highest level of care	
Outpatient	1 (3)
Emergency department	5 (14)
Admitted to hospital	26 (76)
Admitted to ICU	7 (6)
Length of hospital stay, median (range)	1 day (0 – 13 days)
Status at time of medical record review	
Discharged to home	34 (100)
Follow-up visit[1]	31 (91)

[1]Nearly all follow-up notes indicated resolution of symptoms time of follow-up visit. Of those that had follow-up ECG/echo or lab testing, most had returned to normal or baseline. Most patients were noted to be tapering off some medications (nonsteroidal anti-inflammatory drug, prednisone, etc). Follow-up notes also indicated use of colchicine maintenance and recommendations for reduced activity for 3-6 months.

Assessing GBS in the VSD COVID-19 RCA

- Potential cases of GBS in the emergency department or inpatient setting in the 1-98 days after COVID-19 vaccination
  - Potential cases were identified using ICD-10 codes
  - Individuals with a history of GBS (G61.0) since 10/1/2015 excluded
- All potential cases of GBS underwent medical record review and adjudication according to the Brighton Collaboration criteria*
  - Analyses include Brighton level 1-4 cases
- Cases of GBS identified among unvaccinated individuals did not undergo medical record review

*Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre Syndrome and Fisher Syndrome: Case Definitions and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data. *Vaccine.* 2011;29(3):599-612. https://doi.org/10.1016/j.vaccine.2010.06.003

RCA Analyses Verified GBS after mRNA Vaccines, December 13, 2020-Novemer 16, 2021

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

Comparators	Risk Interval	Comparison Interval	Adjusted Rate Ratio (95% CI)[a]	2-sided P-value	1-sided P-value[b]	Signal?[c]
Vaccinated	1-21 days	22-42 days	0.56 (0.21-1.48)	0.25	0.93	No
Unvaccinated[d]	1-21 days	22-42 days	0.83 (0.50-1.33)	0.45	N/A	N/A
Unvaccinated[d]	1-42 days	43-84 days	0.85 (0.57-1.27)	0.44	N/A	N/A

[a]Adjusted for 5-year age group, sex, race/ethnicity, site, and calendar day.
[b]1-sided sequential testing was only conducted for primary weekly analyses with vaccinated concurrent comparators.
[c]Signal threshold is 1-sided *P*-value<0.0048.
[d]Unvaccinated concurrent comparator analyses are conducted using unverified electronic data.

- Rate ratios not elevated; no statistical signals

RCA Analyses Verified GBS after Janssen Vaccine, December 13, 2020-Novemer 16, 2021

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

Comparators	Risk Interval	Comparison Interval	Adjusted Rate Ratio (95% CI)[a]	2-sided P-value	1-sided P-value[b]	Signal?[c]
Vaccinated	1-21 days	22-42 days	6.03 (0.79-147.79)	0.09	0.08	No
Vaccinated	1-42 days	43-84 days	8.64 (1.18-207.32)	0.03	0.03	No
Unvaccinated[d]	1-21 days	22-42 days	10.57 (5.15-20.16)	<0.001	N/A	N/A
Unvaccinated[d]	1-42 days	43-84 days	10.05 (5.75-16.96)	<0.001	N/A	N/A

[a]Adjusted for 5-year age group, sex, race/ethnicity, site, and calendar day.
[b]1-sided sequential testing was only conducted for primary weekly analyses with vaccinated concurrent comparators.
[c]Signal threshold is 1-sided *P*-value<0.0048.
[d]Unvaccinated concurrent comparator analyses are conducted using unverified electronic data.

- Vaccinated concurrent comparator analyses did not signal, though rate ratios were elevated compared with unvaccinated comparators

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people ages 12–39 years*

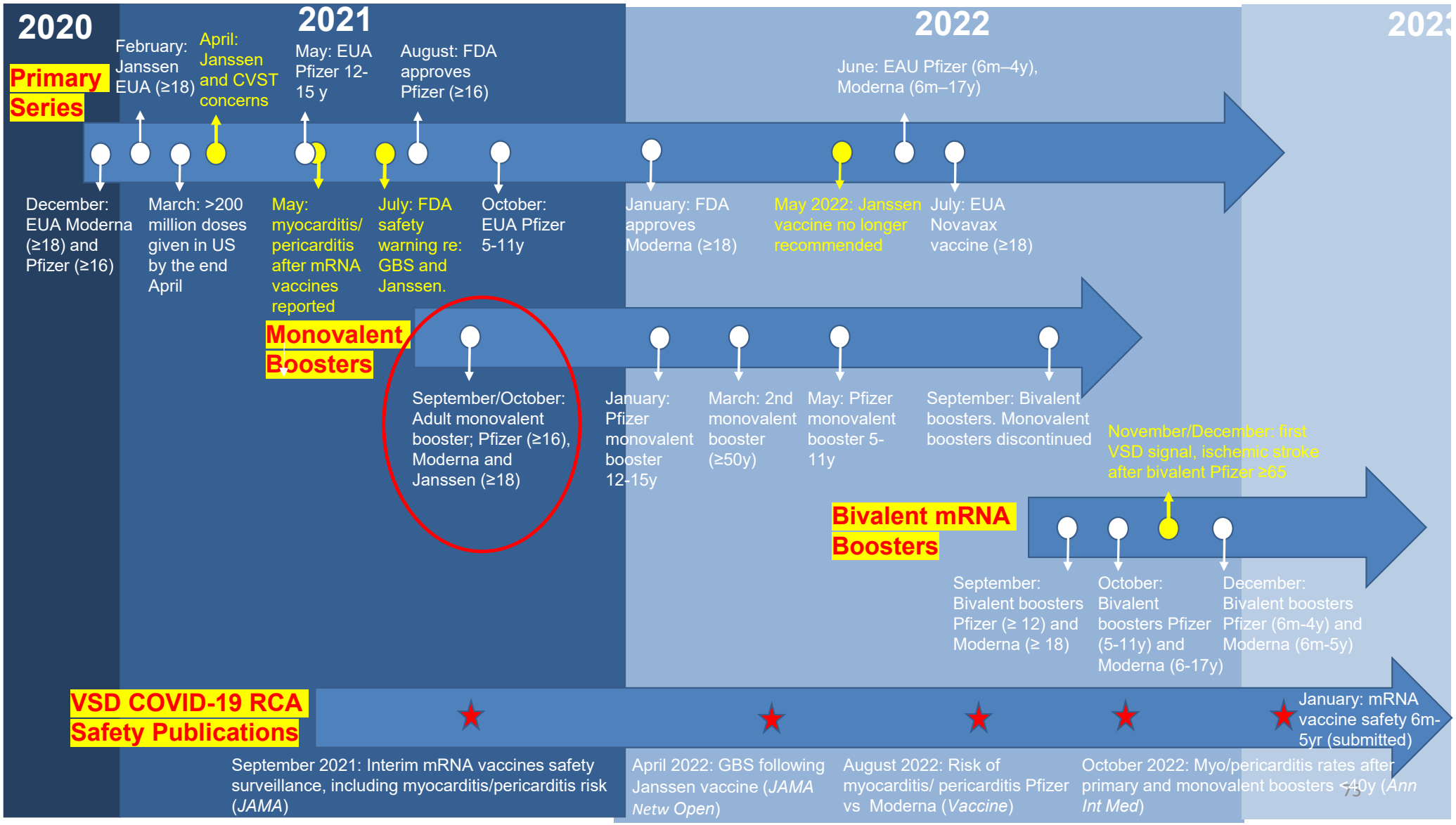
	Dose 2 primary series Pfizer-BioNTech			Monovalent booster dose Pfizer-BioNTech			Bivalent booster dose Pfizer-BioNTech		
Age Group (yrs)	**Cases**	**Dose 2 total**	**Incidence rate/ million doses (95% CI)**	**Cases**	**1st booster total**	**Incidence rate/ million doses (95% CI)**	**Cases**	**Bivalent booster total**	**Incidence rate/ million doses (95% CI)**
12–17 Males Females	 45 6	 308,046 311,247	 146.1 (106.6–195.5) 19.3 (7.1–42.0)	 14 2	 129,487 139,118	 108.1 (59.1–181.4) 14.4 (1.7–51.9)	 0 0	 48,066 49,725	 0.0 (0.0–62.3) 0.0 (0.0–60.2)
18–29 Males Females	 27 2	 331,889 400,321	 81.4 (53.6–118.4) 5.0 (0.6–18.0)	 7 1	 166,973 240,226	 41.9 (16.9–86.4) 4.2 (0.1–23.2)	 1 0	 50,687 80,211	 19.7 (0.5–53.1) 0.0 (0.0–37.3)
30–39 Males Females	 5 3	 341,527 410,713	 14.6 (4.8–34.2) 7.3 (1.5–21.3)	 3 1	 197,554 268,412	 15.2 (3.1–44.4) 3.7 (0.1–20.8)	 0 0	 82,191 115,014	 0.0 (0.0–36.4) 0.0 (0.0–26.0)

* Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; Source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. *Ann Intern Med*. 2022;175:1169-1771.

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Moderna vaccination in people ages 18–39 years*

	Dose 2 primary series Moderna			Monovalent booster dose Moderna			Bivalent booster dose Moderna		
Age Group (yrs)	**Cases**	**Dose 2 total**	**Incidence rate/ million doses (95% CI)**	**Cases**	**Monovalent booster total**	**Incidence rate/ million doses (95% CI)**	**Cases**	**Bivalent booster total**	**Incidence rate/ million doses (95% CI)**
18–29 Males Females	19 0	195,809 243,560	97.0 (58.4 – 151.5) 0.0 (0.0 – 12.3)	7 1	109,337 156,707	64.0 (25.7 – 131.9) 6.4 (0.2 – 35.6)	0 0	18,499 29,561	0.0 (0.0–161.9) 0.0 (0.0–101.3)
30–39 Males Females	8 1	216,583 259,780	36.9 (15.9 – 72.8) 3.9 (0.1 – 21.4)	1 2	149,468 191,765	6.7 (0.2 – 37.3) 10.4 (1.3 – 37.7)	0 0	35,318 47,620	0.0 (0.0–84.8) 0.0 (0.0–62.9)

* Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771.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August 2022: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October 2022: Myo/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)

VSD RCA Safety Surveillance

Final signaling table for monovalent 1st boosters in the 12+ years of age population - (mid- September 2022)

Signaling threshold was 0.01.

Only myocarditis/pericarditis after either mRNA vaccine met the signaling criteria in the 21 days after 1st booster vaccines among all ages ≥12 years in the VSD population.

		Either mRNA	Pfizer	Moderna	Janssen		
Risk Period Days	Outcome Event	Either mRNA	Pfizer	Moderna	Pfizer	Moderna	Janssen
1-21	Acute disseminated encephalomyelitis	No	No	-	-	-	-
	Acute myocardial infarction	No	No	No	No	No	No
	Appendicitis	No	No	No	No	No	No
	Bell's palsy	No	No	No	Yes	No	No
	Cerebral venous sinus thrombosis	No	No	No	-	-	No
	Disseminated intravascular coagulation	No	No	No	No	-	-
	Encephalitis / myelitis / encephalomyelitis	No	No	No	-	-	-
	Guillain-Barre syndrome	No	No	No	No	-	No
	Stroke, hemorrhagic	No	No	No	No	No	No
	Stroke, ischemic	No	No	No	No	No	No
	Immune thrombocytopenia	No	No	No	No	No	-
	Myocarditis / pericarditis	Yes	No	No	No	No	No
	Seizures	No	No	No	No	No	No
	Transverse myelitis	No	No	No	-	-	-
	Thrombotic thrombocytopenic purpura	No	No	No	-	-	No
	Thrombosis with thrombocytopenia syndrome	No	No	No	-	No	-
	Venous thromboembolism	No	No	No	No	No	No
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No

- = analyses not possible

Verified Myocarditis and Pericarditis in 0 –7 Days following Monovalent Booster in 12–39-year-olds

Compared with Events on the Same Calendar Days Among Boosted Comparators

					Analysis			
	Ages	Vaccine	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Events/Million Doses
1st Booster[3]	**12 - 17**	**Pfizer[4]**	15	4	**7.21**	**2.04 – 29.66**	**0.002**	59.9 (34.3 – 97.3)
	18–39	**Either**	22	10	**4.46**	**2.02 – 10.37**	**<0.001**	15.8 (9.9 – 23.9)
	18–39	**Pfizer**	11	5	**4.81**	**1.55 – 16.81**	**0.006**	14.3 (7.1 – 25.5)
	18–39	**Moderna[5]**	6	4	3.27	0.82 – 14.23	0.093	16.8 (7.3 – 33.1)

[1]Comparison interval is 22–42 days after booster dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, calendar date, and time since primary series.
[3]"Either" includes heterologous and homologous primary -> booster doses. Product specific analyses include only homologous primary->booster doses.
[4]One additional case was in the risk interval but not included because there were no appropriate comparators. This case is included in the events/million dose calculation.
[5]Two additional cases were in the risk interval but were not included because there were no appropriate comparators. These cases are included in the events/million dose calculation.

VSD RCA Safety Surveillance

Final signaling table for monovalent boosters in the 5-11 years of age population (end of January 2023)

Signaling threshold was 0.011.

No monitored outcomes met the signaling criteria in the 21 days after monovalent 1st booster vaccines among 5-11 years in the VSD population. However, uptake was low.

		Either mRNA	Pfizer	Moderna	Janssen		
Risk Period Days	Outcome Event	Either mRNA	Pfizer	Moderna	Pfizer	Moderna	Janssen
1-21	Appendicitis	-	No	-	-	-	-
	Bell's palsy	-	No	-	-	-	-
	Immune thrombocytopenia	-	No	-	-	-	-
	Seizures	-	No	-	-	-	-

- = analyses not yet possible

VSD RCA Safety Surveillance

Current signaling table for *bivalent boosters* in the 5-64 years of age population - (early March 2023)

Signaling threshold was 0.01.

No monitored outcomes met the signaling criteria in the 21 days after bivalent vaccines among all ages ≥5 - 64 years in the VSD population.

Risk Interval Days	Age Group	Outcome Event	Either mRNA	Pfizer	Moderna
1 -21	**0-4y**	Kawasaki disease	No	No	-
	5-11y	Appendicitis	No	No	-
		Bell's palsy	No	No	-
		Stroke, hemorrhagic	No	No	-
		Immune thrombocytopenia	No	No	-
		Seizures	No	No	-
	12-17y	Appendicitis	No	No	No
		Bell's palsy	No	No	-
		Encephalitis / myelitis / encephalomyelitis	No	No	-
		Immune thrombocytopenia	No	No	-
		Seizures	No	No	-
		Venous thromboembolism	No	No	-
	18-64y	Acute disseminated encephalomyelitis	No	No	-
		Acute myocardial infarction	No	No	No
		Appendicitis	No	No	No
		Bell's palsy	No	No	No
		Cerebral venous sinus thrombosis	No	No	No
		Disseminated intravascular coagulation	No	-	No
		Encephalitis / myelitis / encephalomyelitis	No	No	No
		Guillain-Barre syndrome	No	No	-
		Stroke, hemorrhagic	No	No	No
		Stroke, ischemic	No	No	No
		Immune thrombocytopenia	No	No	No
		Myocarditis / pericarditis	No	No	No
		Seizures	No	No	No
		Transverse myelitis	No	No	-
		Thrombotic thrombocytopenic purpura	No	No	No
		Thrombosis with thrombocytopenia syndrome	No	No	No
		Venous thromboembolism	No	No	No
		Pulmonary embolism (subset of VTE)	No	No	No

- = analyses not yet possible

VSD RCA Safety Surveillance

Current signaling table for *bivalent boosters* in the 65+ years of age population - (early March 2023)

Signaling threshold was 0.01.

Only ischemic stroke has met the signaling criteria in the 21 days after bivalent vaccines among those 65+ years of age in the VSD population.

Risk Interval Days	Age Group	Outcome Event	Either mRNA	Pfizer	Moderna
1 -21	65+	Acute myocardial infarction	No	No	No
		Appendicitis	No	No	No
		Bell's palsy	No	No	No
		Cerebral venous sinus thrombosis	No	No	-
		Disseminated intravascular coagulation	No	No	No
		Guillain-Barre syndrome	No	No	No
		Stroke, hemorrhagic	No	No	No
		Stroke, ischemic	Yes	Yes	No
		Immune thrombocytopenia	No	No	No
		Myocarditis / pericarditis	No	No	No
		Seizures	No	No	No
		Thrombotic thrombocytopenic purpura	No	No	No
		Thrombosis with thrombocytopenia syndrome	No	No	No
		Venous thromboembolism	No	No	No
		Pulmonary embolism (subset of VTE)	No	No	No

- = analyses not yet possible

Ischemic Stroke following Pfizer bivalent booster vaccination in 65+ years of age

CDC & FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older

Updated Jan. 13, 2023 Español | Other Languages Print

Transparency and vaccine safety are top priorities for the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). U.S. government agencies use multiple, complementary safety monitoring systems to help detect possible safety signals for vaccines and other medical countermeasures as early as possible and to facilitate further investigation, as appropriate. Often these safety systems detect signals that could be due to factors other than the vaccine itself.

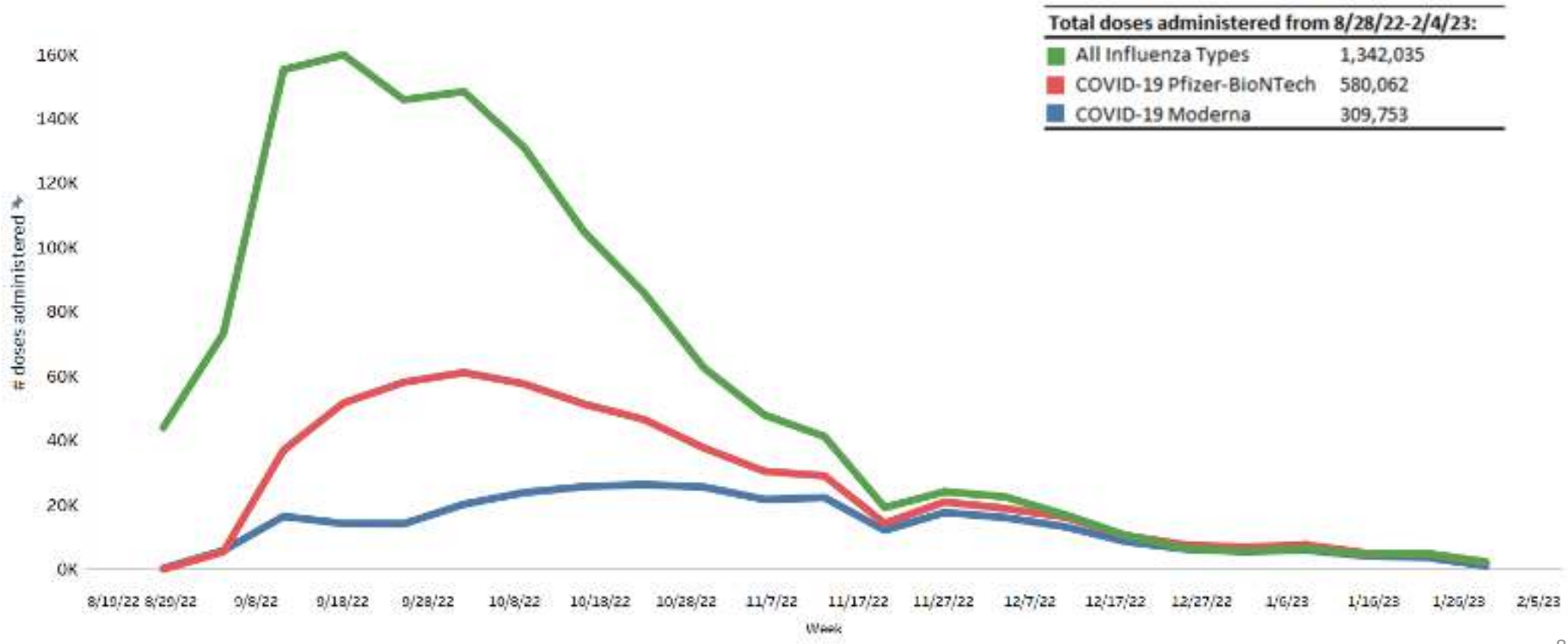
All signals require further investigation and confirmation from formal epidemiologic studies. When one system detects a signal, the other safety monitoring systems are checked to validate whether the signal represents an actual concern with the vaccine or if it can be determined to be of no clinical relevance.

Following the availability and use of the updated (bivalent) COVID-19 vaccines, CDC's Vaccine Safety Datalink (VSD), a near real-time surveillance system, met the statistical criteria to prompt additional investigation into whether there was a safety concern for ischemic stroke in people ages 65 and older who received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent. Rapid-response investigation of the signal in the VSD raised a question of whether people 65 and older who have received the Pfizer-BioNTech COVID-19 Vaccine, Bivalent were more likely to have an ischemic stroke in the 21 days following vaccination compared with days 22-42 following vaccination.

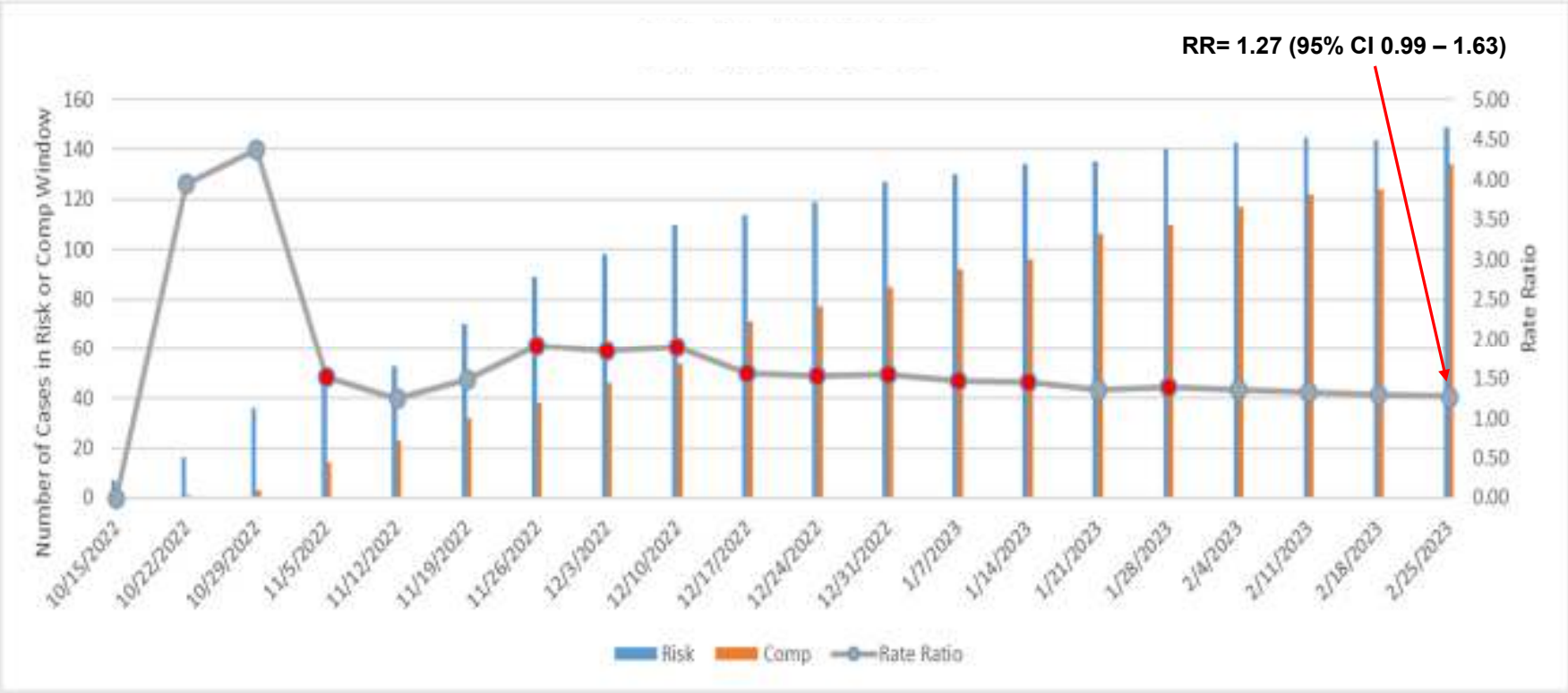
This preliminary signal has not been identified with the Moderna COVID-19 Vaccine, Bivalent. There also may be other confounding factors contributing to the signal identified in the VSD that merit further investigation. Furthermore, it is important to note that, to date, no other safety systems have shown a similar signal and multiple subsequent analyses have not validated this signal:

- A large study of updated (bivalent) vaccines (from Pfizer-BioNTech and Moderna) using the Centers for Medicare and Medicaid Services database revealed no increased risk of ischemic stroke
- A preliminary study using the Veterans Affairs database did not indicate an increased risk of ischemic stroke following an updated (bivalent) vaccine
- The Vaccine Adverse Event Reporting System (VAERS) managed by CDC and FDA has not seen an increase in reporting of ischemic strokes following the updated (bivalent) vaccine

Number of COVID-19 bivalent booster doses and influenza vaccine doses administered over time among persons aged ≥65 years, by vaccine type in VSD

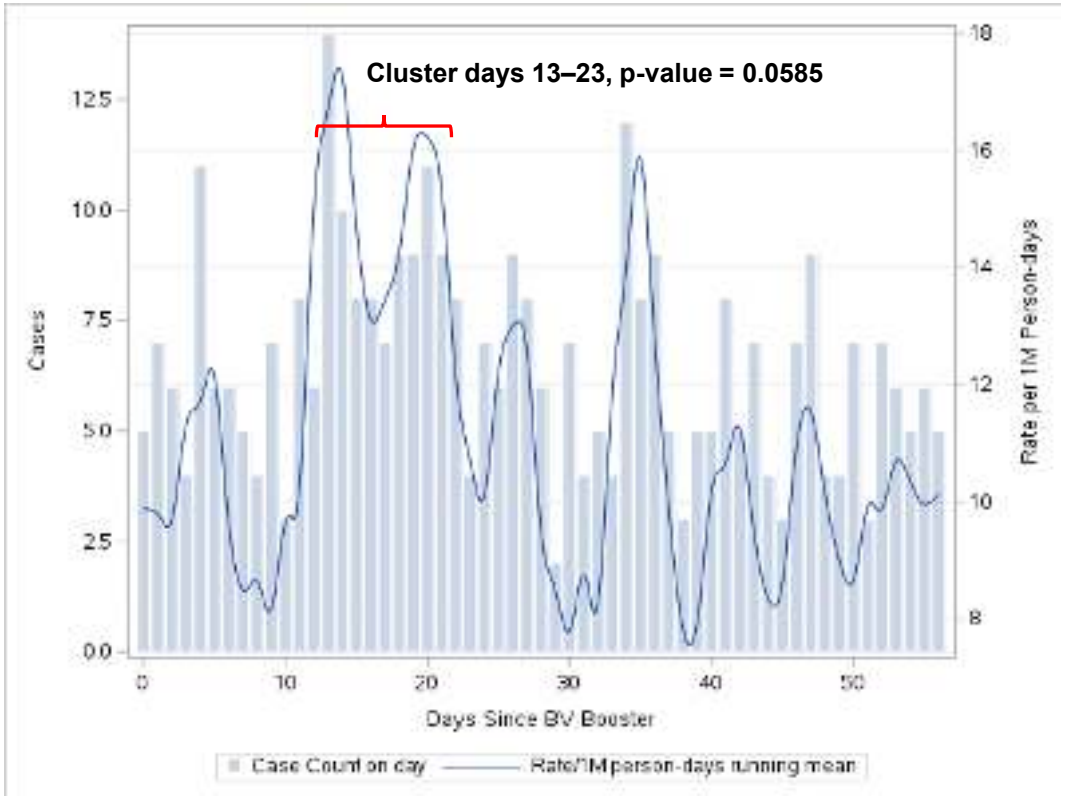


Ischemic stroke after Pfizer-BioNTech bivalent booster, age ≥65 years, counts and adjusted rate ratios (Oct 16, 2022 – Feb 25, 2023)



- Red dot represents sequential signal: p-value <0.01 (1-sided)

Ischemic stroke by day after Pfizer-BioNTech bivalent boosters, people ages ≥65 Years*



* Data cutoff 3 weeks prior

Post-signal analyses*: Ischemic stroke incidence during days 1–21 compared with days 22–42, among ≥65 years with and without simultaneous influenza vaccination

Analytic population	Cases in 1–21-day Risk Interval (N=139)	Cases in 22–42-day Comparison Interval (N=108)	Adjusted Rate Ratio** (95% CI)	P-value
Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine	43	26	**1.65 (1.02 – 2.72)**	**0.04**
Bivalent Pfizer + same day standard dose flu vaccine	8	8	1.00 (0.36 – 2.76)	1.00
Bivalent Pfizer without any same day flu vaccine	88	74	1.19 (0.87 – 1.62)	0.27

* Analyses only include vaccination data through December 3, 2022, and stroke outcome data through January 14, 2023
** Adjusted by 5-year age groups

Additional considerations for stroke outcome

- **Small numbers of strokes and imprecise rate ratios limit some analyses**
  - Reduced follow-up time after Moderna booster due to distribution delays
  - Simultaneous flu vaccine analyses limited by small numbers
- **Difficult to interpret temporal clustering during risk and comparison intervals**
- **Possible unmeasured confounding**
  - Results may be influenced by confounders that vary over time
  - Do early adopters of bivalent booster vaccine have greater risk of near-term cardiovascular events?
    - Same trend has not been observed for acute myocardial infarctions
    - Potential impact of differential vaccine availability after EUA (Pfizer-BioNTech > Moderna)
- **Possible role of SARS-CoV-2 infection before booster?**
  - Background incidence of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake
    - Analysis excluded cases with COVID-19 diagnosis or positive test in prior 30 days, although asymptomatic infections and home antigen tests are not consistently documented in EHR; however, KPNC chart reviews did not find recent SARS-CoV-2 infection or exposure

Add in uptake for Novovax and Moderna 6-17 years (just to show they are both very minimal)

Placeholder for MIS descriptives table

VSD RCA Safety Surveillance

Final signaling table for primary series in the 12+ years of age population - (end of May 2022)

Signaling threshold was 0.01.

		Moderna			Pfizer			Both mRNA Vaccines			Janssen
Risk Period Days	Outcome Event	Dose 1	Dose 2	Both Doses	Dose 1	Dose 2	Both Doses	Dose 1	Dose 2	Both Doses	Dose 1
1-21	Acute disseminated encephalomyelitis	-	No	No	No	-	No	No	No	No	-
	Acute myocardial infarction	No	No	No	No	Yes	No	No	Yes	No	No
	Appendicitis	No	No	No	No	No	No	No	No	No	No
	Bell's palsy	No	No	No	No	No	No	No	No	No	No
	Cerebral venous sinus thrombosis	No	No	No	No	No	No	No	No	No	-
	Disseminated intravascular coagulation	No	No	No	No	No	No	No	No	No	No
	Encephalitis / myelitis / encephalomyelitis	No	No	No	No	No	No	No	No	No	-
	Guillain-Barre syndrome	No	No	No	No	No	No	No	No	No	No
	Stroke, hemorrhagic	No	No	No	No	No	No	No	No	No	No
	Stroke, ischemic	No	No	No	No	No	No	No	No	No	No
	Immune thrombocytopenia	No	No	No	No	No	No	No	No	No	No
	Kawasaki disease	No	No	No	-	-	-	No	No	No	-
	Myocarditis / pericarditis	No	No	No	No	Yes	Yes	No	Yes	Yes	No
	Seizures	No	No	No	No	No	No	No	No	No	No
	Transverse myelitis	No	No	No	No	No	No	No	No	No	No
	Thrombotic thrombocytopenic purpura	No	No	No	No	No	No	No	No	No	No
	Thrombosis with thrombocytopenia syndrome	No	No	No	No	No	No	No	No	No	No
	Venous thromboembolism	No	No	No	No	Yes	Yes	No	Yes	Yes	No
	Pulmonary embolism (subset of VTE)	No	No	No	No	No	No	No	No	No	No

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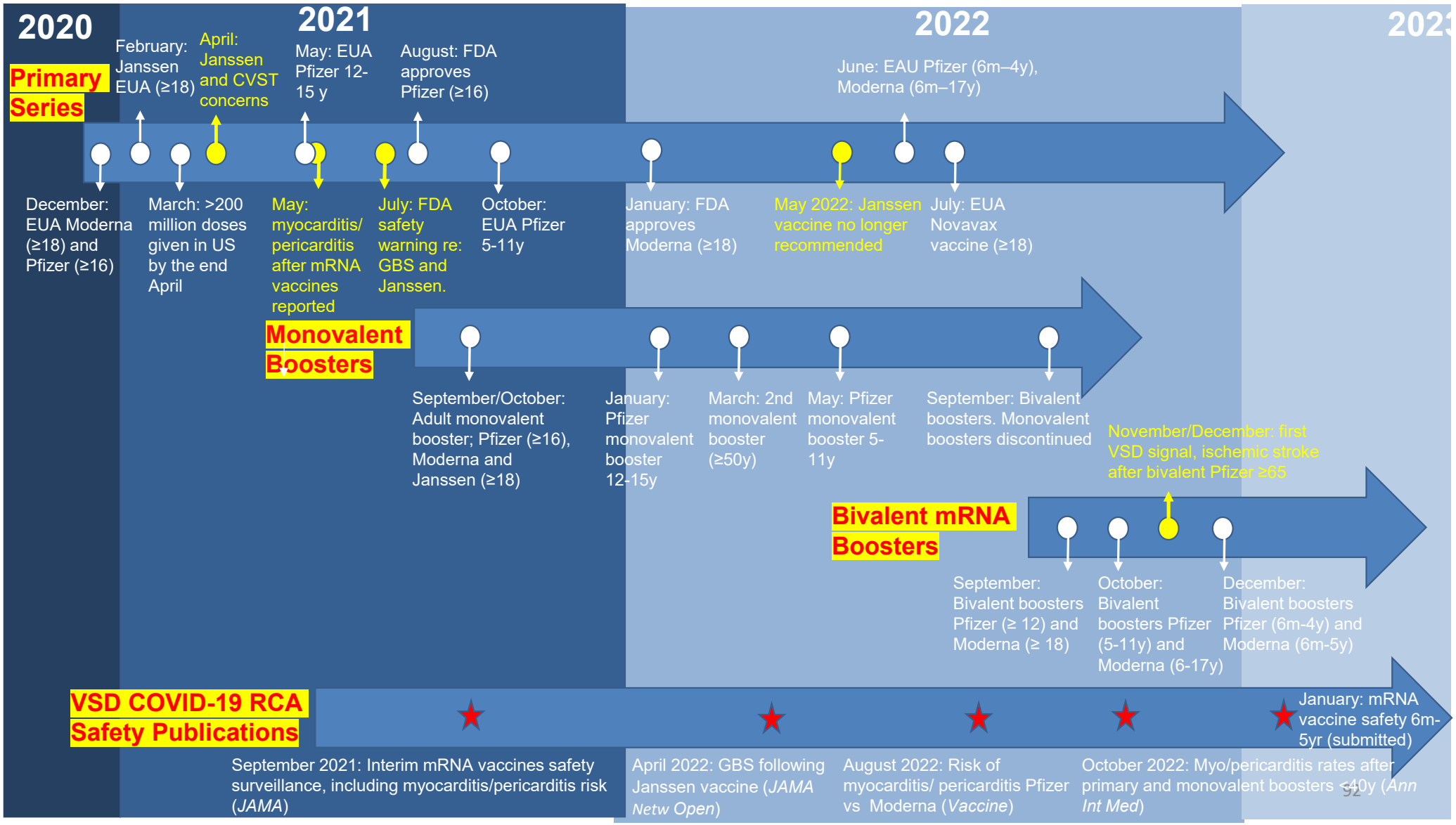
Summary: Safety Monitoring after COVID-19 Bivalent Booster Vaccines in the VSD

Ischemic stroke after Pfizer bivalent booster among ≥65 years

- Rate ratio met signaling criteria consistently for 8 weeks but slowly attenuated and now no longer meets signaling criteria
- Temporal clustering evaluation found a significant cluster 13–22 days after vaccination
- Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.07 (95% CI 0.89–1.28)
- Analyses evaluating simultaneous high-dose or adjuvanted flu vaccine showed a rate ratio RR=1.65 (95% CI 1.02–2.72; p-value 0.04)
  - Separate analyses did not detect an elevated RR for stroke after flu vaccine alone (data not shown)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