COVID-19 Vaccine Safety Surveillance: Summary from VSD RCA

Nicola Klein, MD, PhD
Director, Kaiser Permanente Vaccine Study Center
Kaiser Permanente Northern California

Advisory Committee in Immunization Practices
September 12, 2023

KAISER PERMANENTE®
VACCINE STUDY CENTER

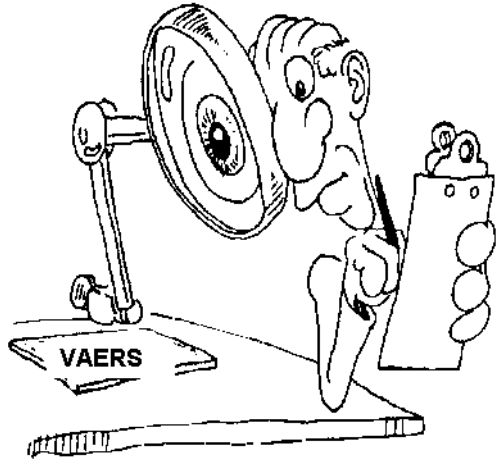
Vaccine Safety Datalink

- 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 methods for vaccine safety assessment

- Test hypotheses that emerge from elsewhere (e.g., VAERS, clinical trials, other platforms).



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 who are beyond their risk interval are expected to be similar to current vaccinees who are within their risk interval. They serve as better comparators than unvaccinated individuals, historical controls or non-concurrent self controls because they permit:
    - Careful adjustment for potential biases associated with calendar time, site, and demographic factors
    - Analyses that can begin sooner than alternative methods
  - *Supplemental analyses conducted weekly:* Unvaccinated/un-boosted comparators would also be available to provide context in real time

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: 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/enhanced 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

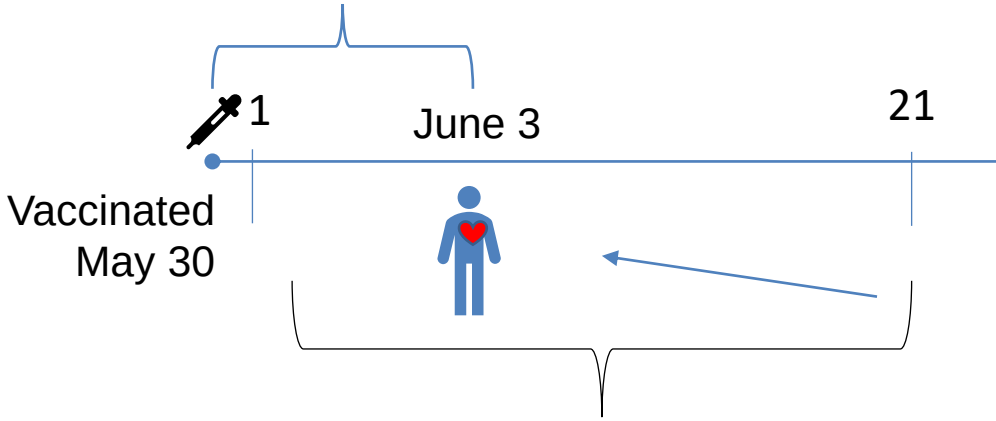
Imbalances in phase 3 COVID-19 vaccine clinical trials

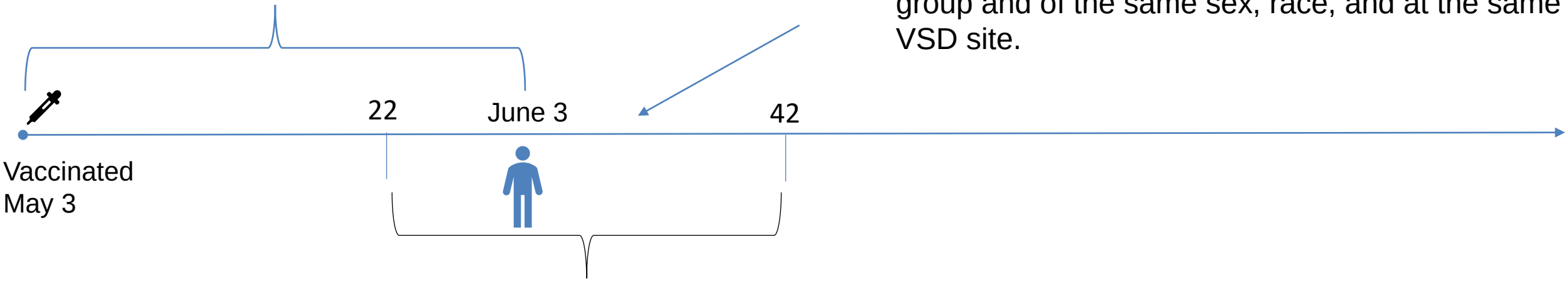
- Appendicitis
- Bell's palsy

✓ Only chart confirmed cases

*monitored without comparators

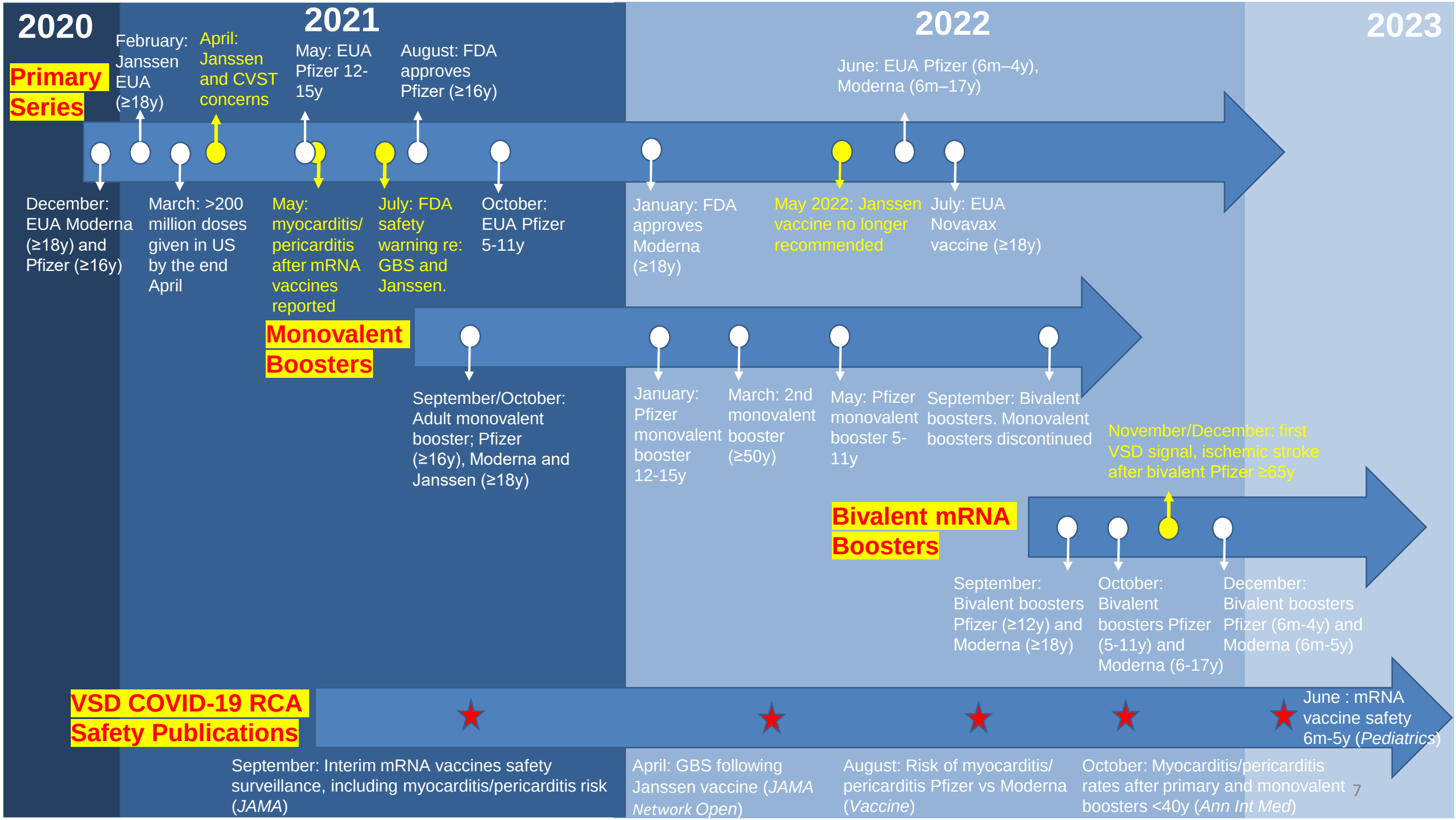
Vaccinee with Myocarditis in Risk Interval and a Concurrent Comparator





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.


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

JAMA | Original Investigation

Surveillance for Adverse Events After COVID-19 mRNA Vaccination

Nicola P. Klein, MD, PhD; Ned Lewis, MPH; Kristin Goddard, MPH; Bruce Fireman, MA; Ousseny Zerbo, PhD; Kayla E. Hanson, MPH; James G. Donahue, DVM, PhD; Elyse O. Kharbanda, MD, MPH; Allison Naleway, PhD; Jennifer Clark Nelson, PhD; Stan Xu, PhD; W. Katherine Yih, PhD, MPH; Jason M. Glanz, PhD; Joshua T. B. Williams, MD; Simon J. Hambidge, MD, PhD; Bruno J. Lewin, MD; Tom T. Shimabukuro, MD, MPH, MBA; Frank DeStefano, MD, MPH; Eric S. Weintraub, MPH

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.

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

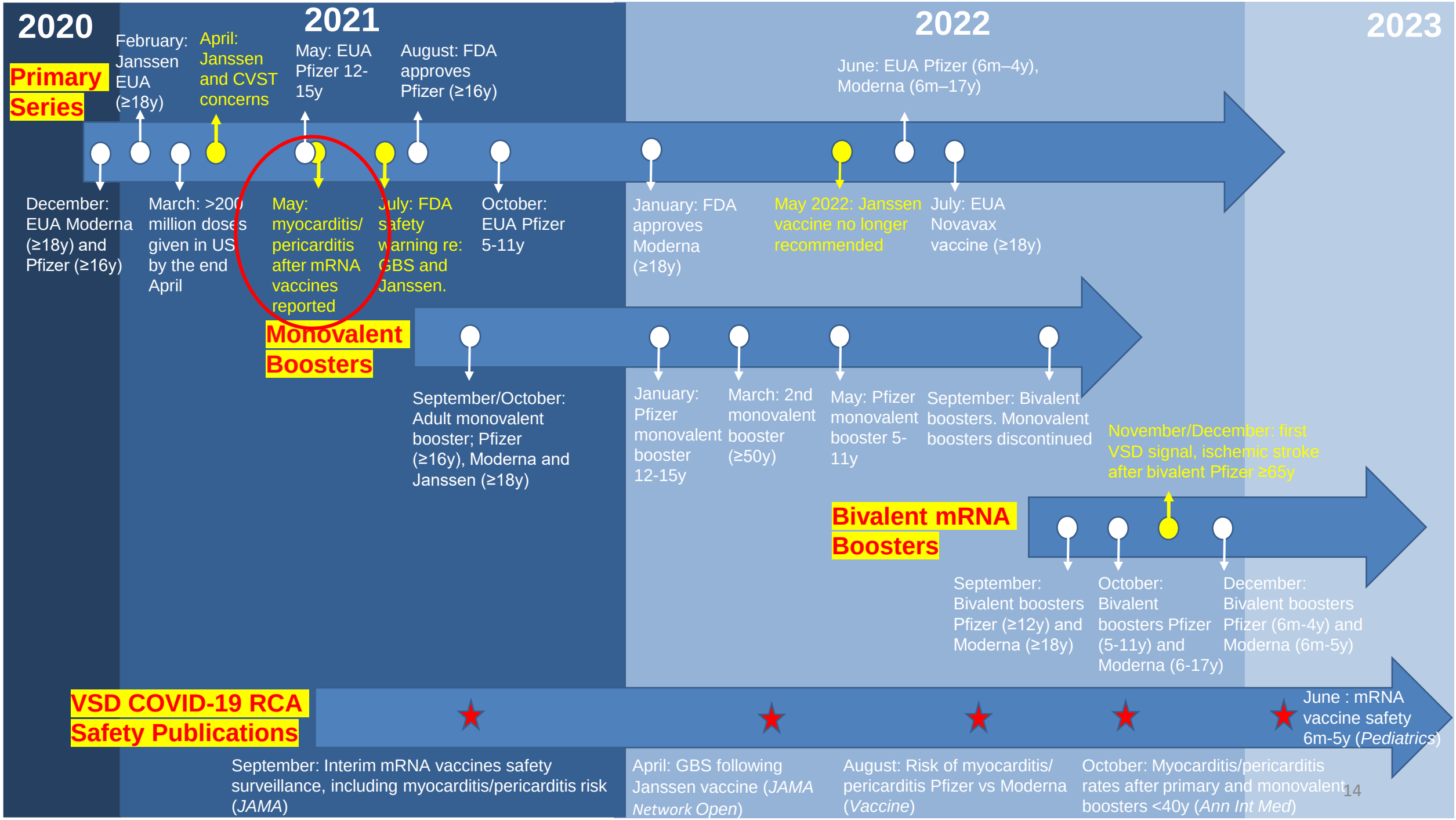
Outcomes Monitored Without Comparators

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)

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

VSD COVID-19 RCA Surveillance: Outcomes Monitored Due to Emerging Concerns


2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18y)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
August: FDA approves Pfizer (≥16y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18y) and Pfizer (≥16y)
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 (≥18y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

Myocarditis and Pericarditis Following mRNA Vaccines

COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) reviews cases of mild myocarditis reported with COVID-19 mRNA vaccines

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

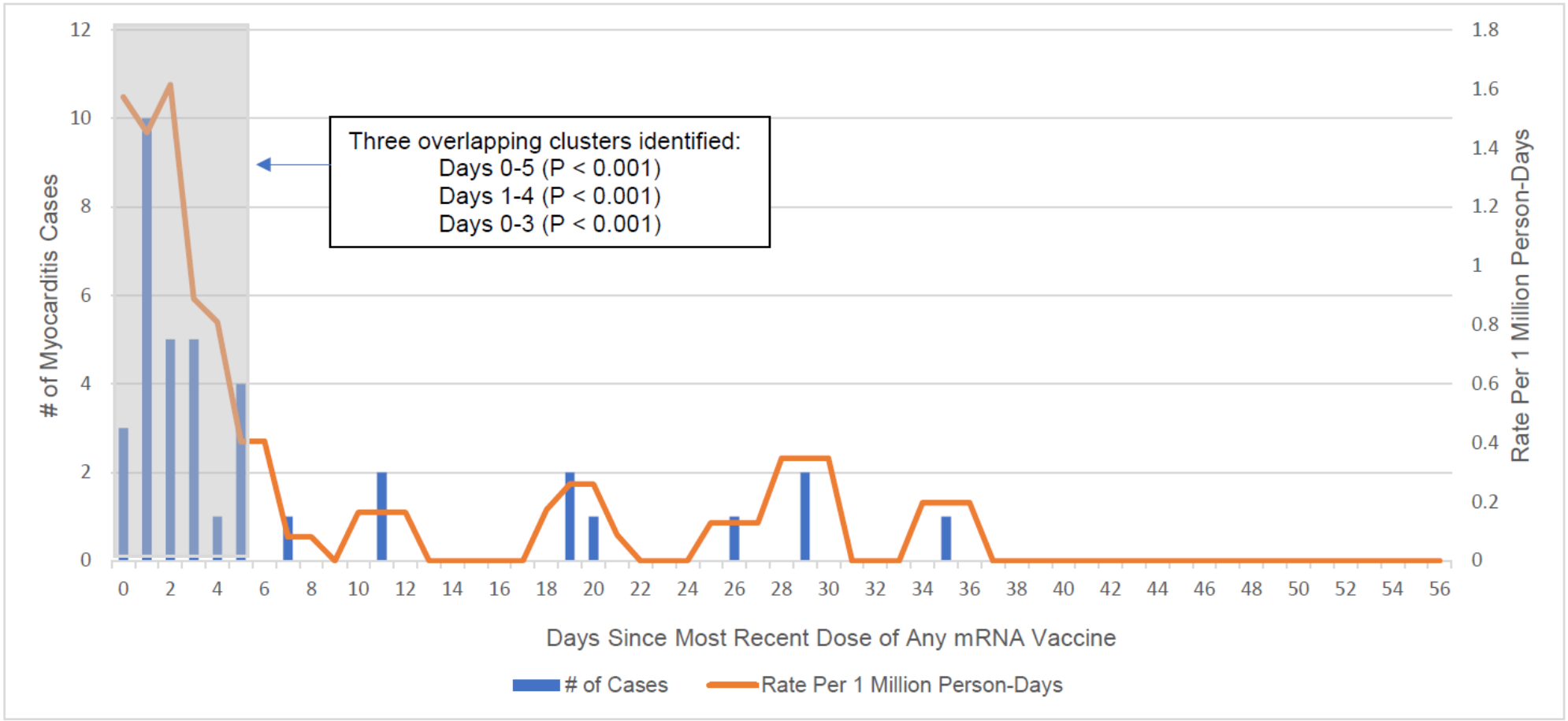
COVID-19 vaccine safety surveillance manual

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

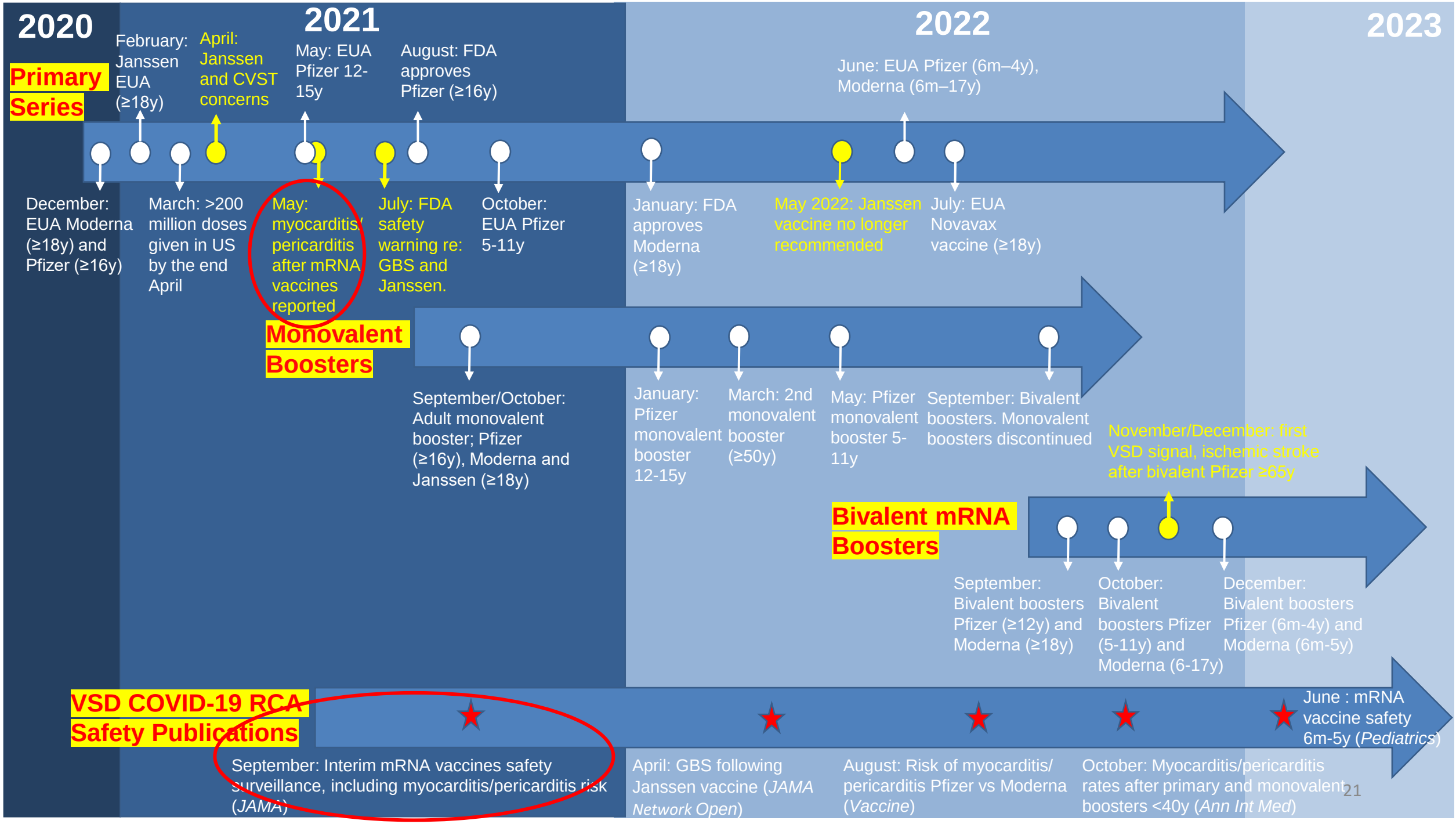
Summary
(data through June 2021)

- 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 subgroup analyses, both mRNA vaccines were associated with myocarditis/pericarditis in persons aged 12-39 years.

- In the VSD, rate of anaphylaxis after mRNA vaccines was ~ 5 cases / million doses.

- VSD surveillance was ongoing.


2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18y)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
August: FDA approves Pfizer (≥16y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18y) and Pfizer (≥16y)
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 (≥18y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

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 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

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.

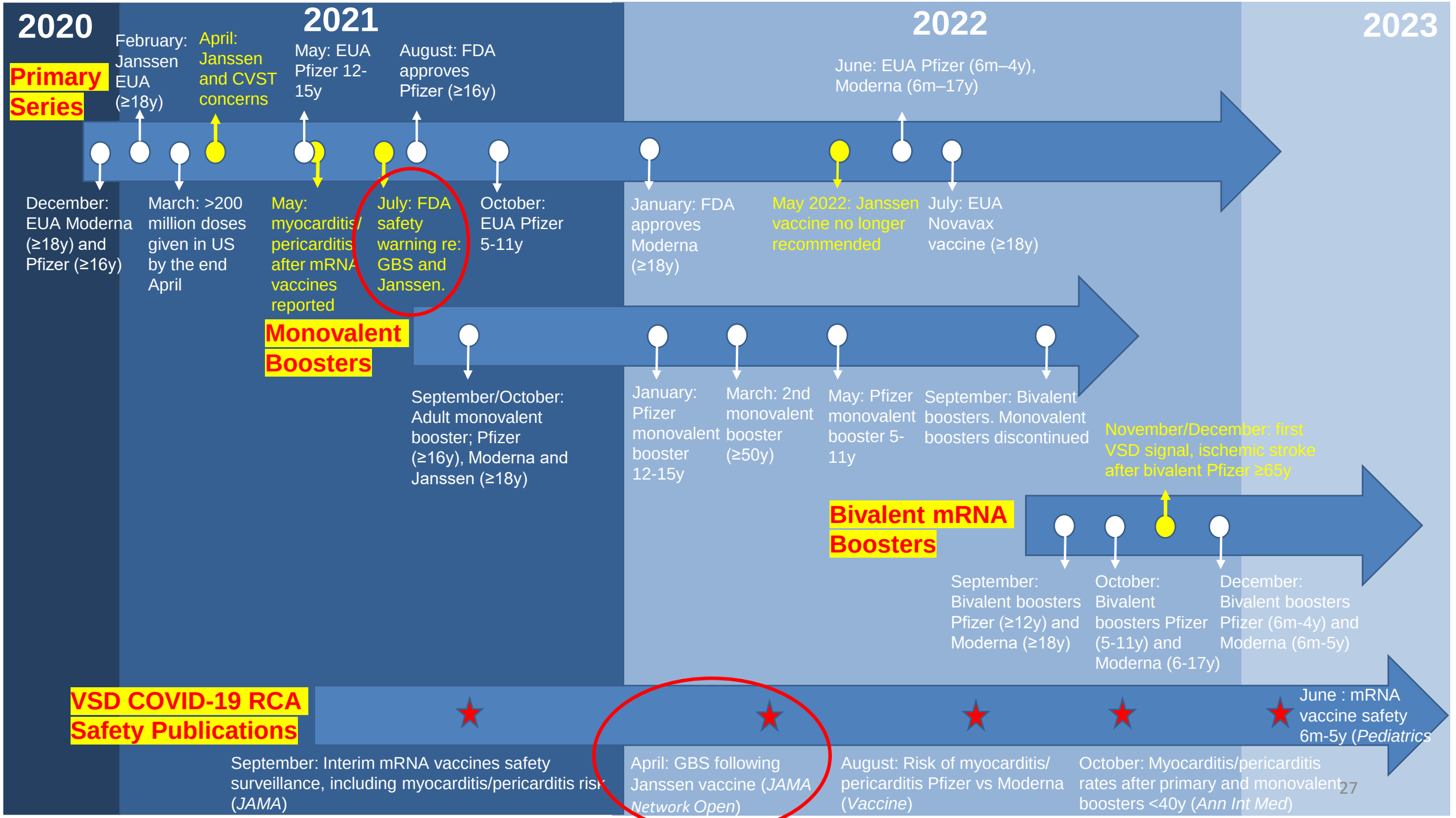
- Risk estimates of myocarditis/pericarditis in 18–39-year-olds during days 0-7 after 2 doses were modestly higher after Moderna than after Pfizer.

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)

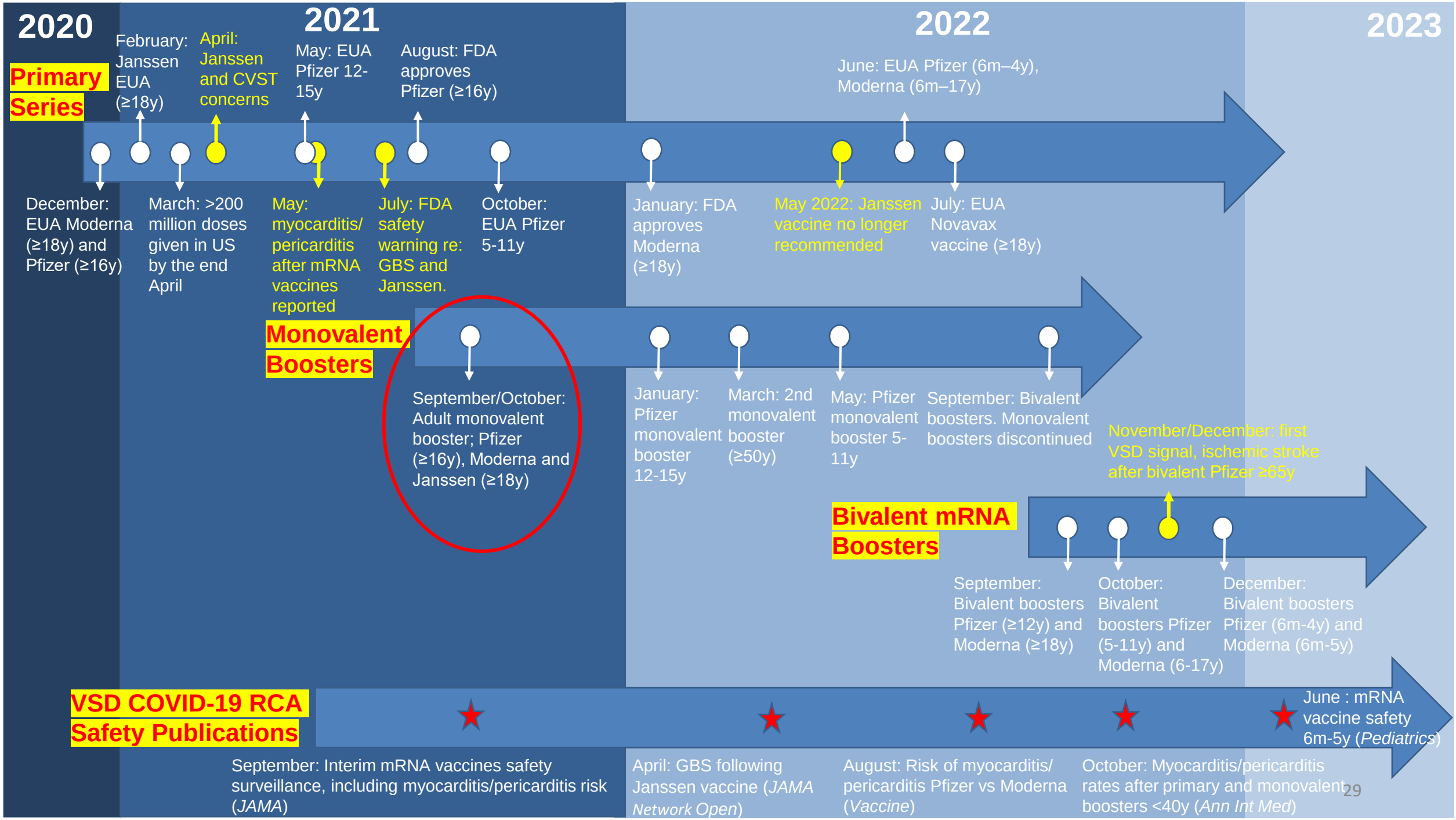
* Data through August 20, 2022

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

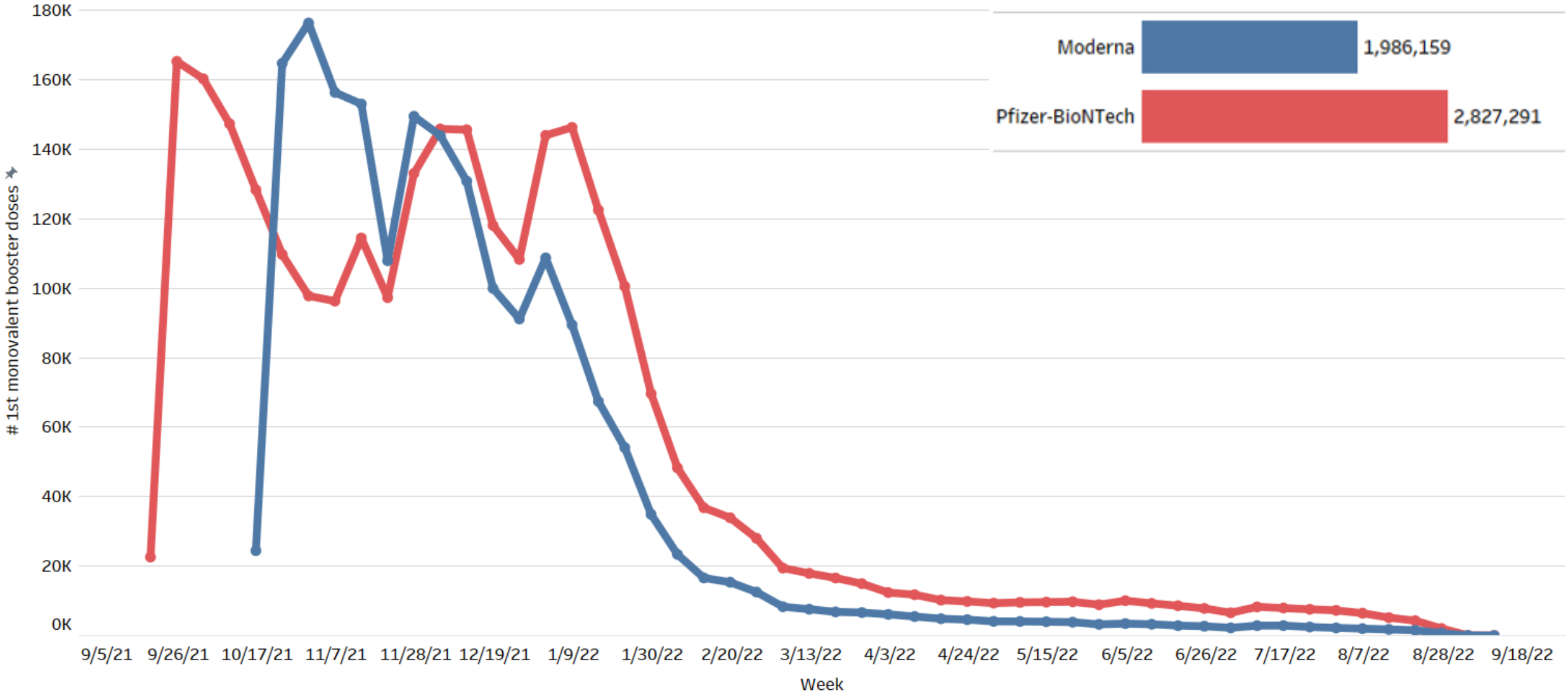

2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18y)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
August: FDA approves Pfizer (≥16y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18y) and Pfizer (≥16y)
March: >200 million doses given in US by the end April
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics

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. *(JAMA Netw Open.* 2022;5(4):e228879.https://doi.org/10.1001/jamanetworkopen.2022.8879)
  - When directly compared with mRNA vaccines, the risk of GBS after Janssen vaccine was 21 times higher.
- 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
- Since publication and through February 2023, VSD identified 5 additional confirmed cases of GBS: 4 after mRNA vaccines and 1 after Janssen.
  - 2 were in 1-21 risk interval (1 mRNA, 1 Janssen), 1 in 22–42 day interval, and 2 in 43–84 day interval.
  - All new cases were among males aged 55-65 years, except one case in a 4-year-old male.
- ACIP preferentially recommended mRNA-based COVID-19 vaccines over Janssen vaccine in December 2021. (https://www.cdc.gov/mmwr/volumes/71/wr/pdfs/mm7103a4-H.pdf)
  - FDA revoked Janssen EUA as of June 2023. (https://www.fda.gov/vaccines-blood-biologics/coronavirus-covid-19-cber-regulated-biologics/janssen-covid-19-vaccine)


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

Monovalent Booster Uptake Among Persons Aged ≥12 Years in the VSD, Over Time*



* Data through September 10, 2022 when monovalent booster were discontinued in favor of bivalent boosters.

Summary of RCA Findings in the 1-21 Day Risk Interval After Monovalent Boosters ≥12 Years

Compared with Outcome Events 22-42 Days After in Vaccinated Comparators*

		Either mRNA	Pfizer	Moderna	Janssen		
Risk Period Days	Outcome Event	Either mRNA Signal?**	Pfizer Signal?**	Moderna Signal?**	Pfizer Signal?**	Moderna Signal?**	Janssen Signal?**
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

- **Following <u>mRNA primary series and monovalent booster</u>, only myocarditis/pericarditis met the signaling criteria in the 21 days among ages ≥12 years in the VSD population.**

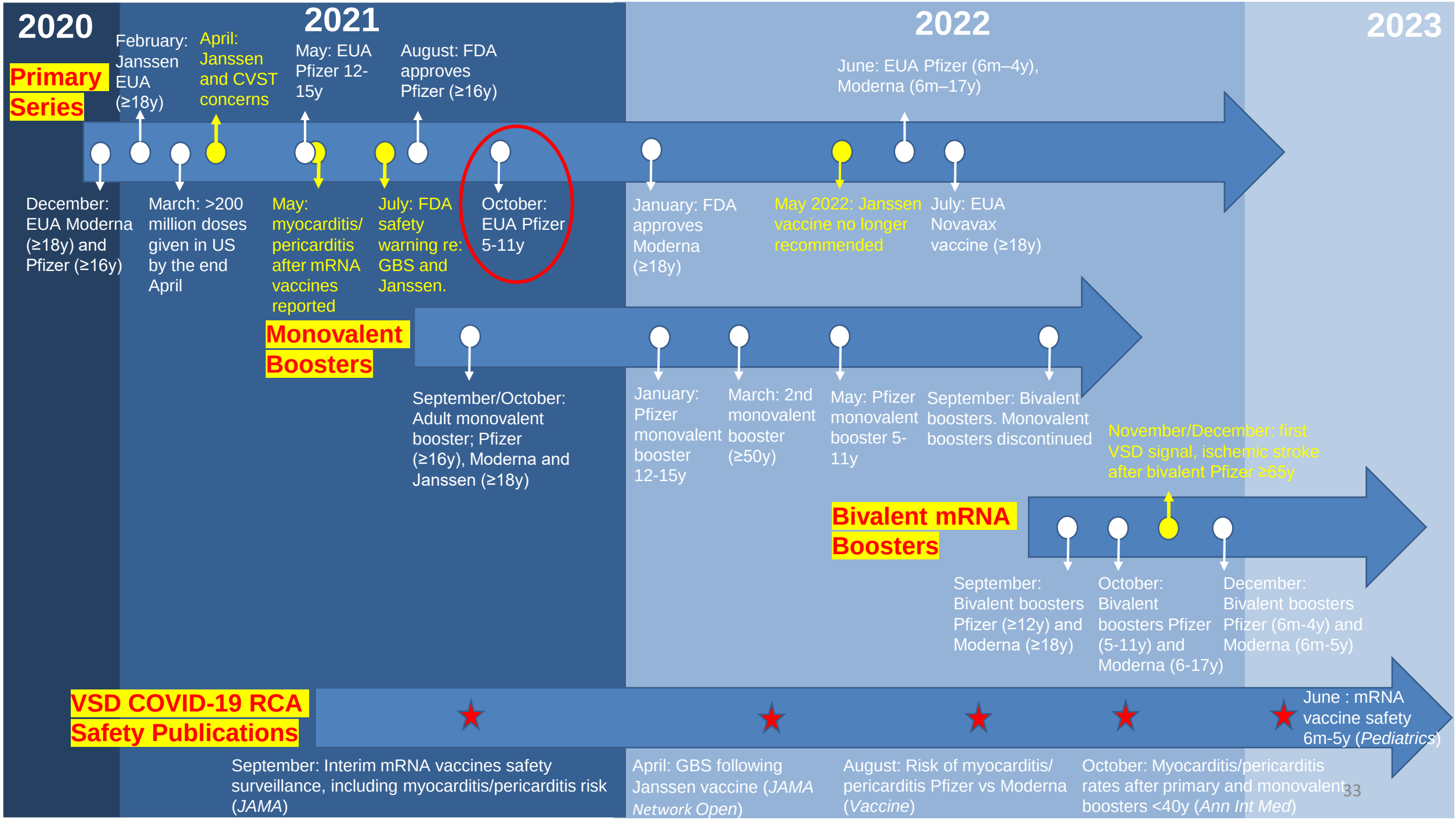
*Final analyses through September 2022
**Signaling threshold P<0.01 (one-sided)

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
Monovalent 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.


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

Primary Series uptake among persons aged 5-11 years in the VSD, over time*

* Data through February 4, 2023

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

- **Among children aged 5-11 years in the VSD, no outcome met the signaling criteria in the 21 days after primary series vaccination.**

*Final analyses through January 2023
**Signaling threshold P<0.061 (one-sided)

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]

Affiliations + expand

PMID: 35581698 PMCID: PMC9706403 DOI: 10.1542/peds.2022-057313

Free PMC article

www.pediatrics.org/cgi/doi/10.1542/peds.2022-057313

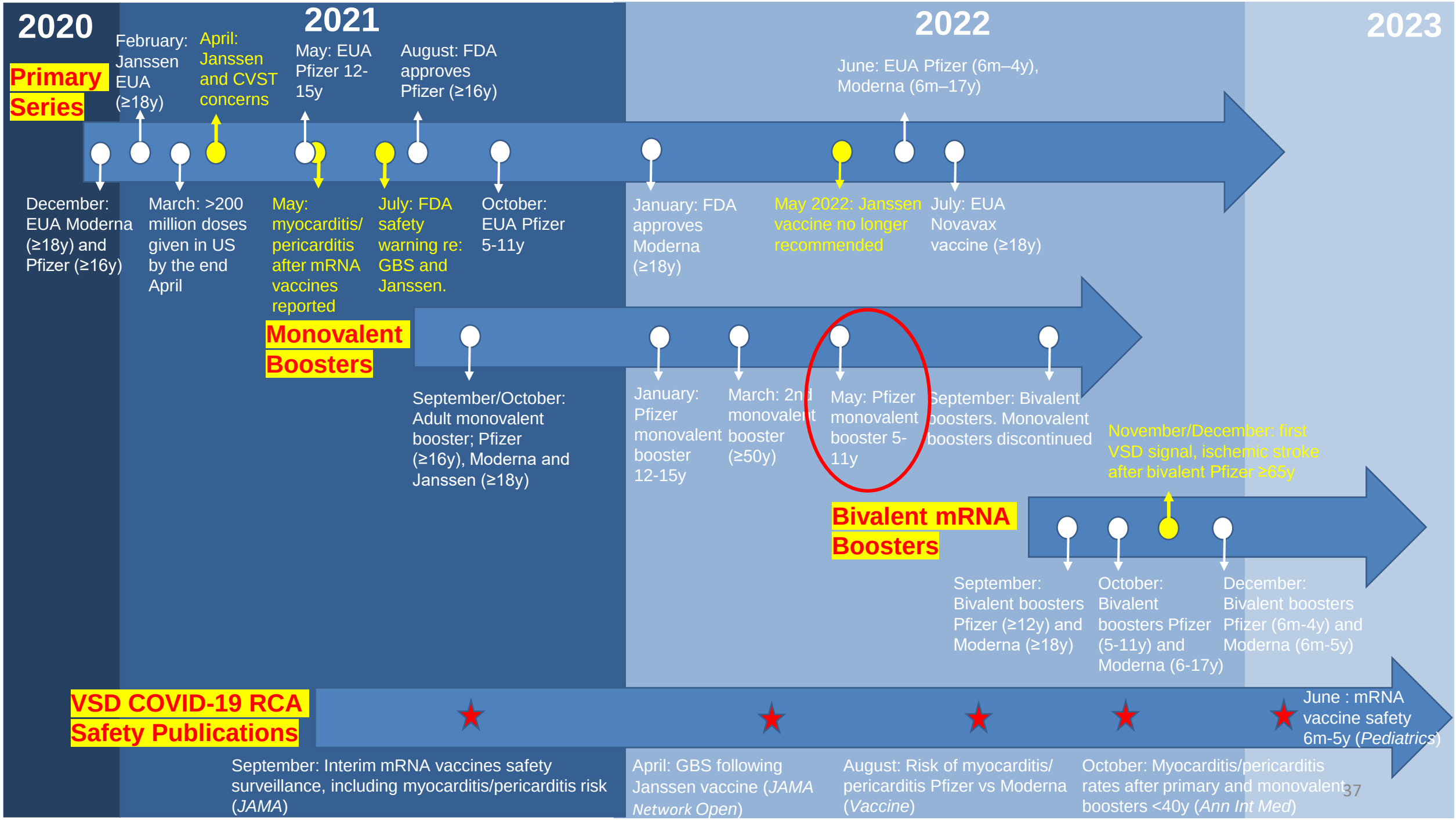
Abstract

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.

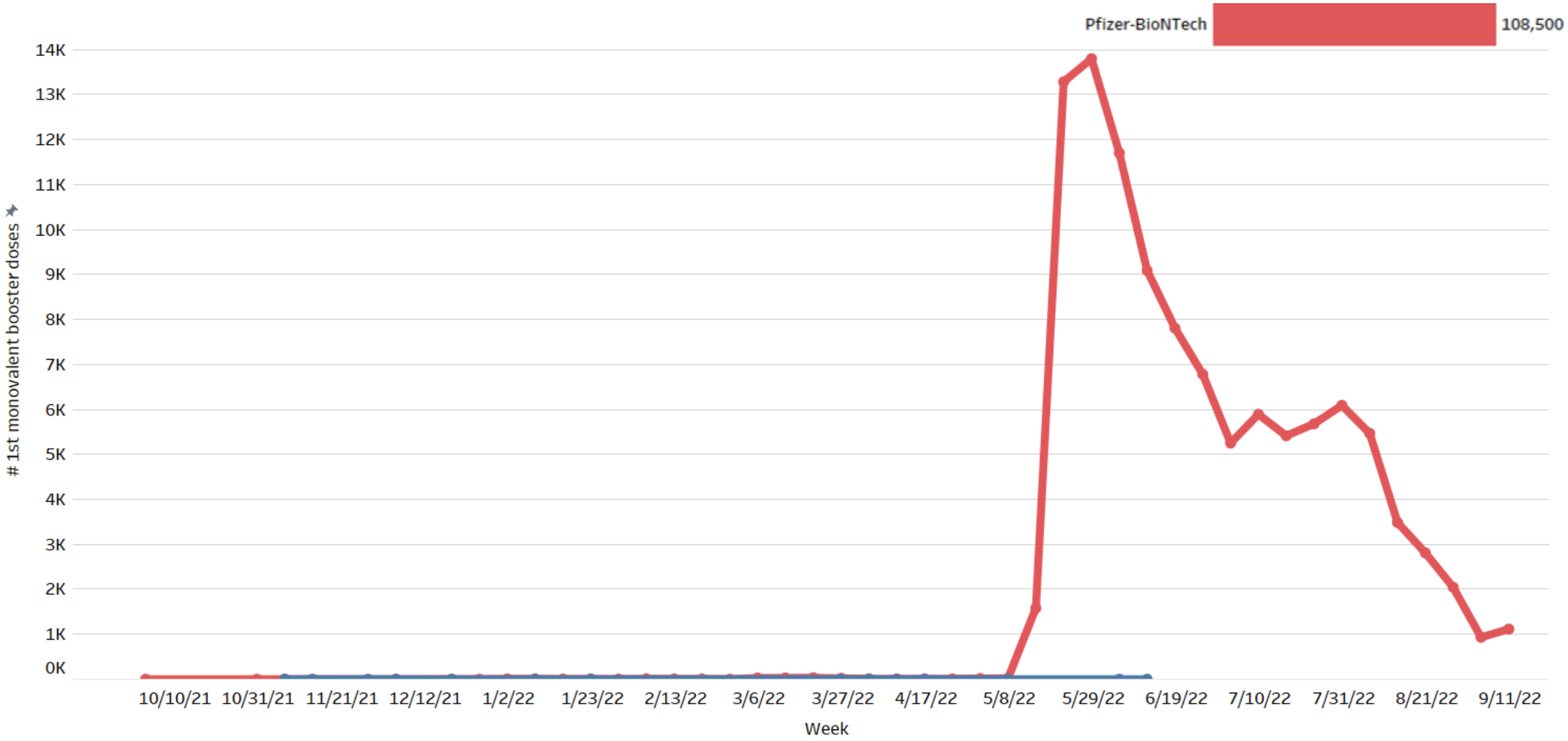
Methods: We analyzed data from 3 United States safety monitoring systems: v-safe, a voluntary smartphone-based system that monitors reactions and health effects; the Vaccine Adverse Events Reporting System (VAERS), the national spontaneous reporting system comanaged by the Centers for Disease Control 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
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
May: myocarditis/ pericarditis after mRNA vaccines reported
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

Monovalent Booster Uptake Among Persons Aged 5-11 Years in the VSD, Over Time*



* Data through September 10, 2022

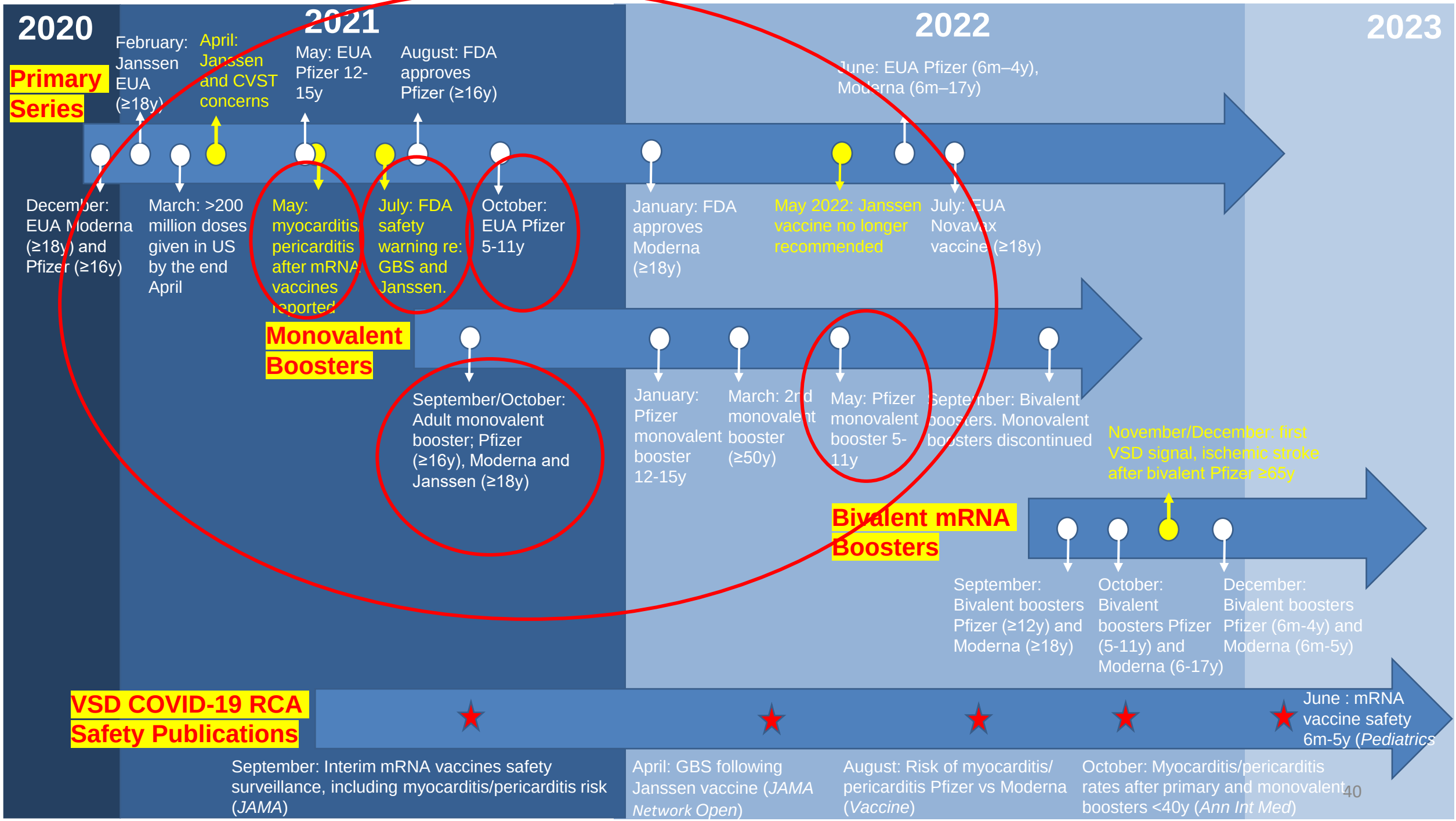
Summary of RCA Findings in the 1-21 Day Risk Interval after Monovalent Booster, 5–11-year-olds Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

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

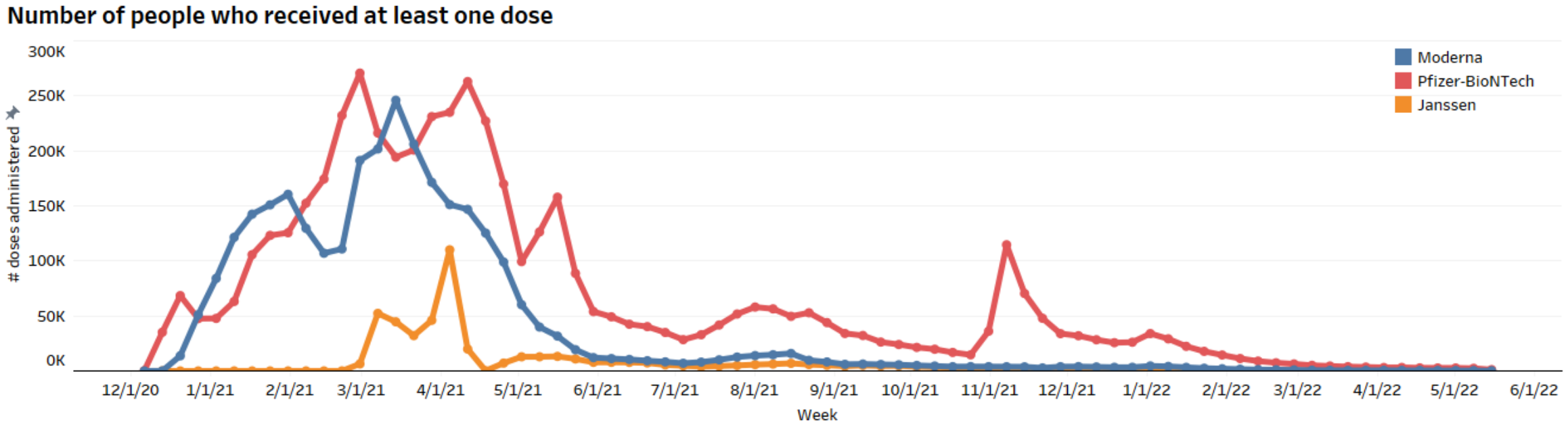
- = analyses not yet possible

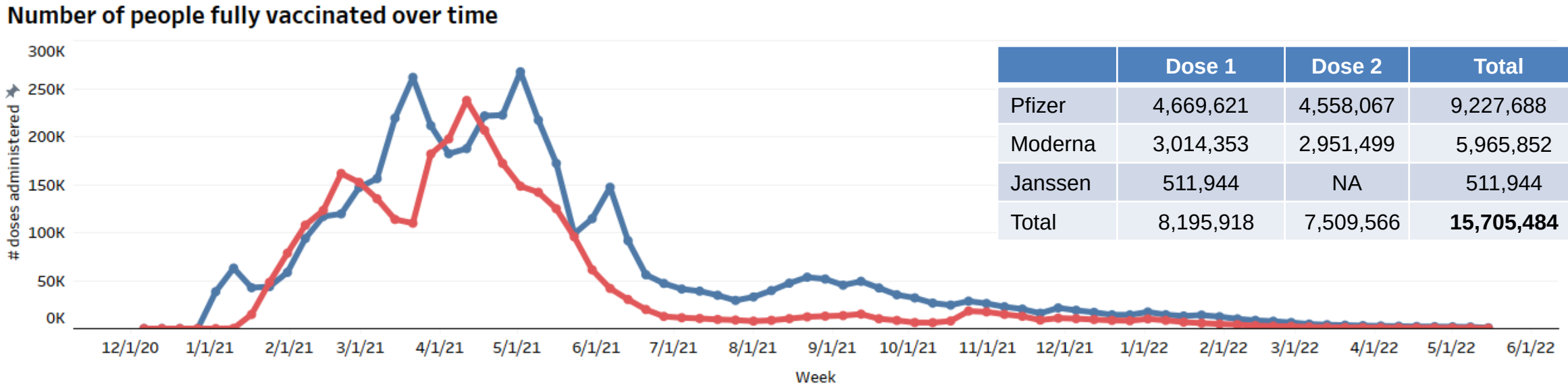
- **Among children aged 5-11 years in the VSD, no outcome met the signaling criteria in the 21 days after monovalent booster vaccination. However, vaccine uptake was low.**

*Final analyses through January 2023
**Signaling threshold P<0.011 (one-sided)


2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18y)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
August: FDA approves Pfizer (≥16y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18y) and Pfizer (≥16y)
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 (≥18y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics

Primary Series Uptake Among Persons Aged ≥12 Years in the VSD, Over Time*





	Dose 1	Dose 2	Total
Pfizer	4,669,621	4,558,067	9,227,688
Moderna	3,014,353	2,951,499	5,965,852
Janssen	511,944	NA	511,944
Total	8,195,918	7,509,566	**15,705,484**

* Data through May 21, 2022

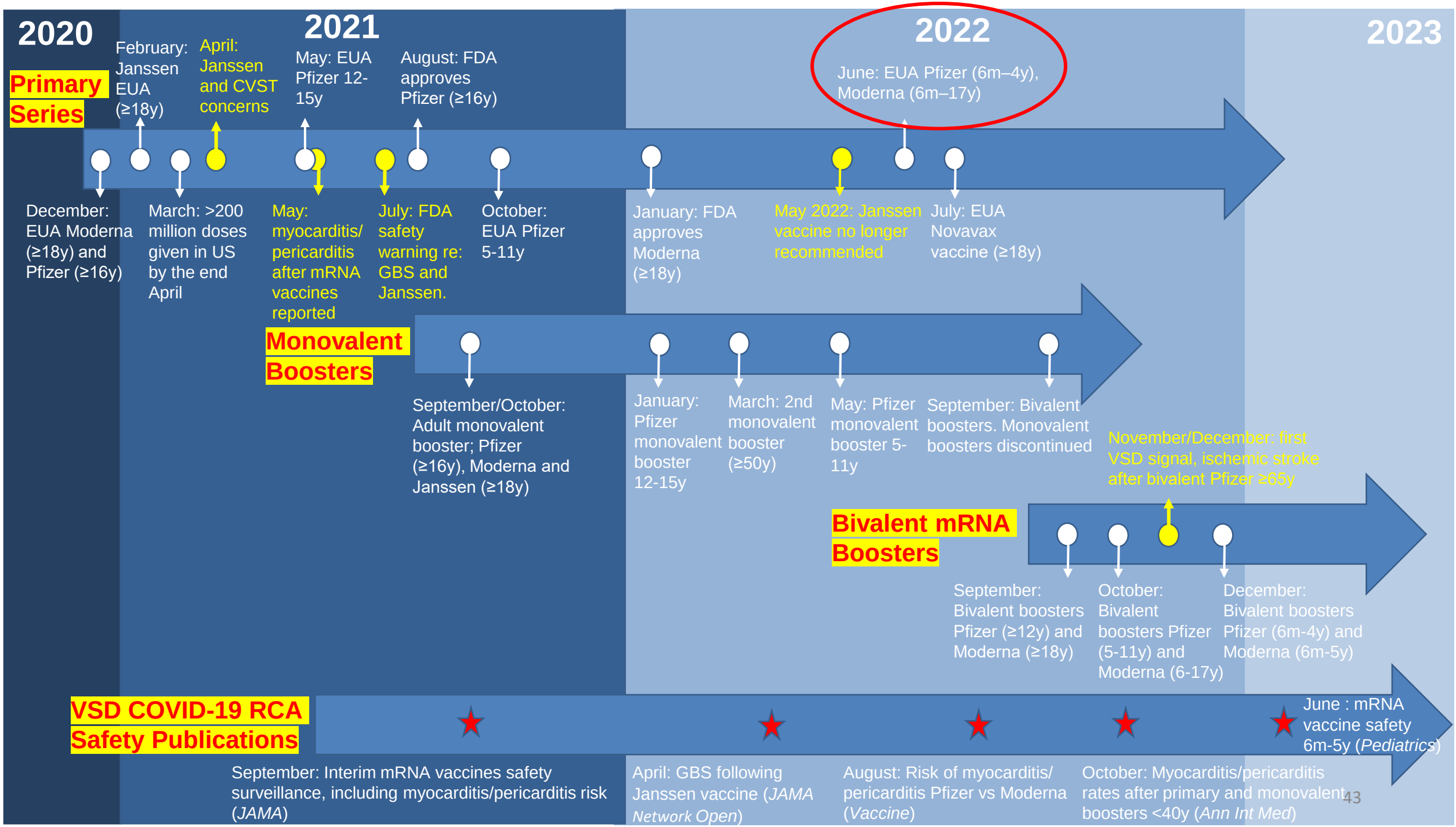
Final RCA Findings in the 1-21 Day Risk Interval After Primary Series ≥12 Years

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

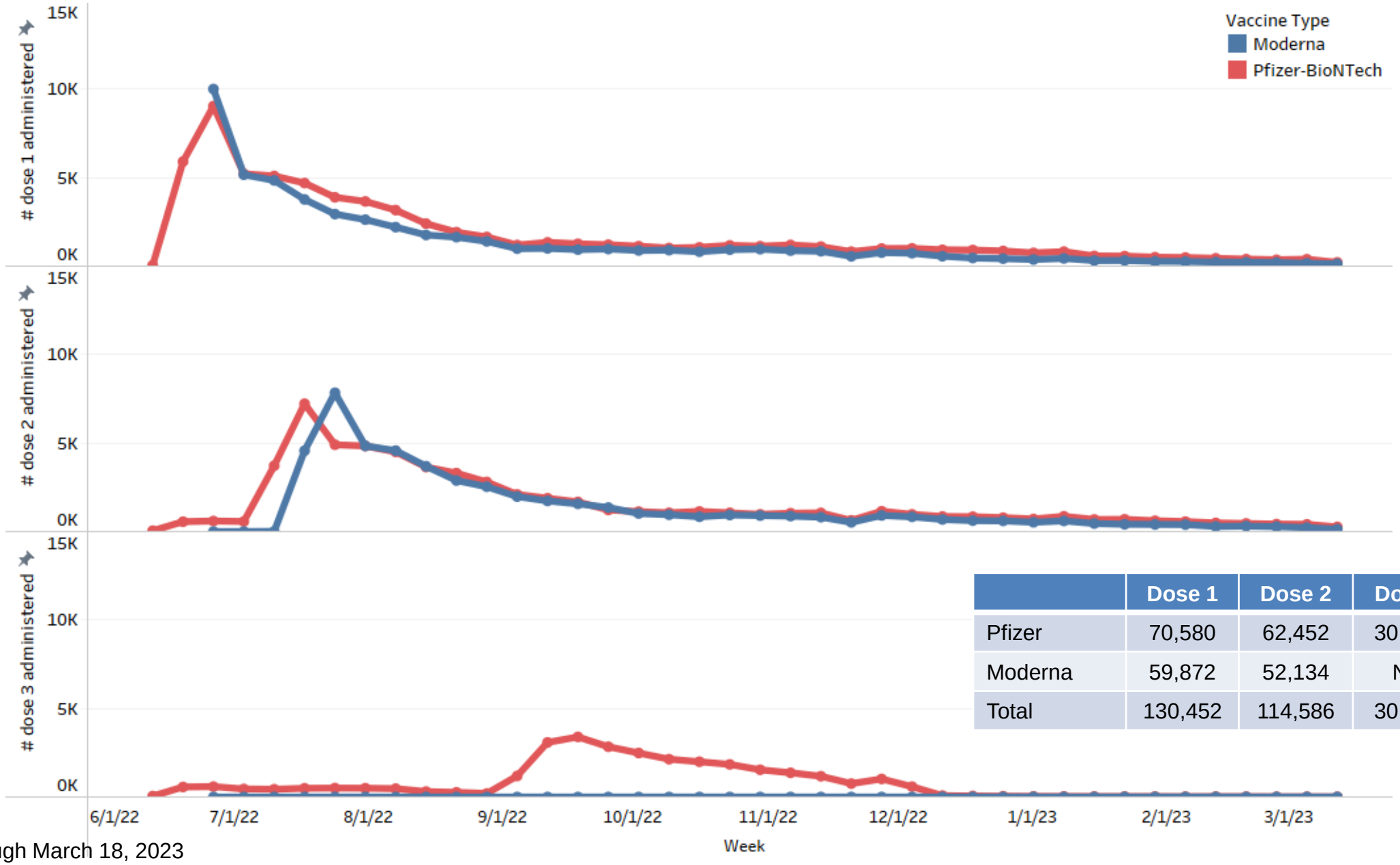
		Moderna			Pfizer			Both mRNA Vaccines			Janssen
Risk Period Days	Outcome Event	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**	Dose 2 Signal?**	Both Doses	Dose 1 Signal?**
1-21	Acute disseminated encephalomyelitis	-	No	No	No	-	No	No	No	No	-
	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

- = analyses not yet possible

*Final analyses through May 2022
**Signaling threshold P<0.01 (one-sided)


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: myocarditis/ pericarditis after mRNA vaccines reported
May: EUA Pfizer 12-15y
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
May 2022: Janssen vaccine no longer recommended
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics)

Primary Series Uptake Among Persons Aged 6 Months- 5 Years in the VSD, Over Time*



	Dose 1	Dose 2	Dose 3	Total
Pfizer	70,580	62,452	30,641	163,673
Moderna	59,872	52,134	NA	112,006
Total	130,452	114,586	30,641	**275,679**

* Data through March 18, 2023

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 – March 18, 2023

TABLE 2 Outcomes Among Vaccinees During the 1 Through 21 Day Risk Interval After Any Dose of COVID-19 mRNA Vaccine, Compared on the Same Calendar Day With Outcomes Among Vaccinated Individuals 22 to 42 Days After Their Most Recent Dose, June 18, 2022 Through March 18, 2023

Outcome[b]	Risk Interval	Vaccine Type	Events in Risk Interval	Events in Comparison Interval (22–42 d)	Crude/ Adjusted Expected Counts[a]	Adjusted Rate Ratio (95% CI)[c]	1-Sided *P*	Signal[d]
Appendicitis	1–21 d	Pfizer-BioNTech	1	1	0.9/2.1	0.49 (0.01–26.53)	.91	No
		Moderna	0	1	1.5/NE	0.00 (0.00–12.67)	.40	No
Bell's Palsy	1–21 d	Pfizer-BioNTech	0	1	0.5/NE	0.00 (0.00–38.00)	.67	No
		Moderna	1	0	0.0/NE	NE (0.06–∞)	.49	No
Encephalitis, myelitis, or encephalomyelitis	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	1	0	0.0/NE	NE (0.02–∞)	.74	No
Guillain-Barre syndrome	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	0	1	0.7/NE	0.00 (0.00–26.75)	.59	No
Immune thrombocytopenia	1–21 d	Pfizer-BioNTech	0	1	1.0/NE	0.00 (0.00–18.77)	.50	No
		Moderna	1	1	0.8/0.9	1.14 (0.03–44.34)	.72	No
Kawasaki disease	1–21 d	Pfizer-BioNTech	2	1	1.1/1.0	2.05 (0.15–60.69)	.49	No
		Moderna	0	3	5.8/NE	0.00 (0.00–1.09)	.06	No
Pulmonary embolism	1–21 d	Pfizer-BioNTech	1	0	0.0/NE	NE (0.08–∞)	.41	No
		Moderna	—	—	—	—	—	—
Seizures	0–7 d	Pfizer-BioNTech	9	24	9.5/14.0	0.64 (0.25–1.51)	.89	No
		Moderna	5	19	5.4/5.9	0.85 (0.27–2.32)	.70	No
	0–21 d	Pfizer-BioNTech	38	24	25.0/38.9	0.98 (0.56–1.71)	.59	No
		Moderna	23	19	20.9/21.0	1.09 (0.57–2.11)	.46	No
Stroke, hemorrhagic	1–21 d	Pfizer-BioNTech	1	1	1.1/0.9	1.12 (0.03–44.64)	.72	No
		Moderna	—	—	—	—	—	—
Transverse myelitis	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	0	1	0.5/NE	0.00 (0.00–38.00)	.67	No
Venous thromboembolism	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	0	1	0.5/NE	0.00 (0.00–38.00)	.67	No

NE, not estimable. —, analysis not yet possible.

[a] Expected counts: crude estimate via indirect standardization and maximum likelihood estimate.

[b] Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type after any dose, making analyses possible. All outcomes under surveillance are listed in Supplemental Table 3. Safety monitoring by individual dose is ongoing, however, since very few outcomes have cases in either the risk or comparison interval only combined analyses are presented here.

[c] Stratified by Vaccine Safety Datalink site, age (year), sex, race and ethnicity, and calendar date.

[d] Signal defined as 1-sided $P < 0.011$.

Goddard K, Donahue JG, Lewis N, Hanson KE, Weintraub ES, Fireman B, Klein NP. Safety of COVID-19 mRNA Vaccination Among Young Children in the Vaccine Safety Datalink. Pediatrics. 2023 Jul 1;152(1):e2023061894. doi: 10.1542/peds.2023-061894.

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 – March, 2023

TABLE 2 Outcomes Among Vaccinees During the 1 Through 21 Day Risk Interval After Any Dose of COVID-19 mRNA Vaccine, Compared on the Same Calendar Day With Outcomes Among Vaccinated Individuals 22 to 42 Days After Their Most Recent Dose, June 18, 2022 Through March 18, 2023

Outcome[b]	Risk Interval	Vaccine Type	Events in Risk Interval	Events in Comparison Interval (22–42 d)	Crude/ Adjusted Expected Counts[a]	Adjusted Rate Ratio (95% CI)[c]	1-Sided *P*	Signal[d]
Appendicitis	1–21 d	Pfizer-BioNTech	1	1	0.9/2.1	0.49 (0.01–26.53)	.91	No
		Moderna	0	1	1.5/NE	0.00 (0.00–12.67)	.40	No
Stroke, hemorrhagic	1–21 d	Pfizer-BioNTech	1	1	1.1/0.9	1.12 (0.03–44.64)	.72	No
		Moderna	—	—	—	—	—	—
Transverse myelitis	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	0	1	0.5/NE	0.00 (0.00–38.00)	.67	No
Venous thromboembolism	1–21 d	Pfizer-BioNTech	—	—	—	—	—	—
		Moderna	0	1	0.5/NE	0.00 (0.00–38.00)	.67	No

NE, not estimable. —, analysis not yet possible.

[a] Expected counts: crude estimate via indirect standardization and maximum likelihood estimate.

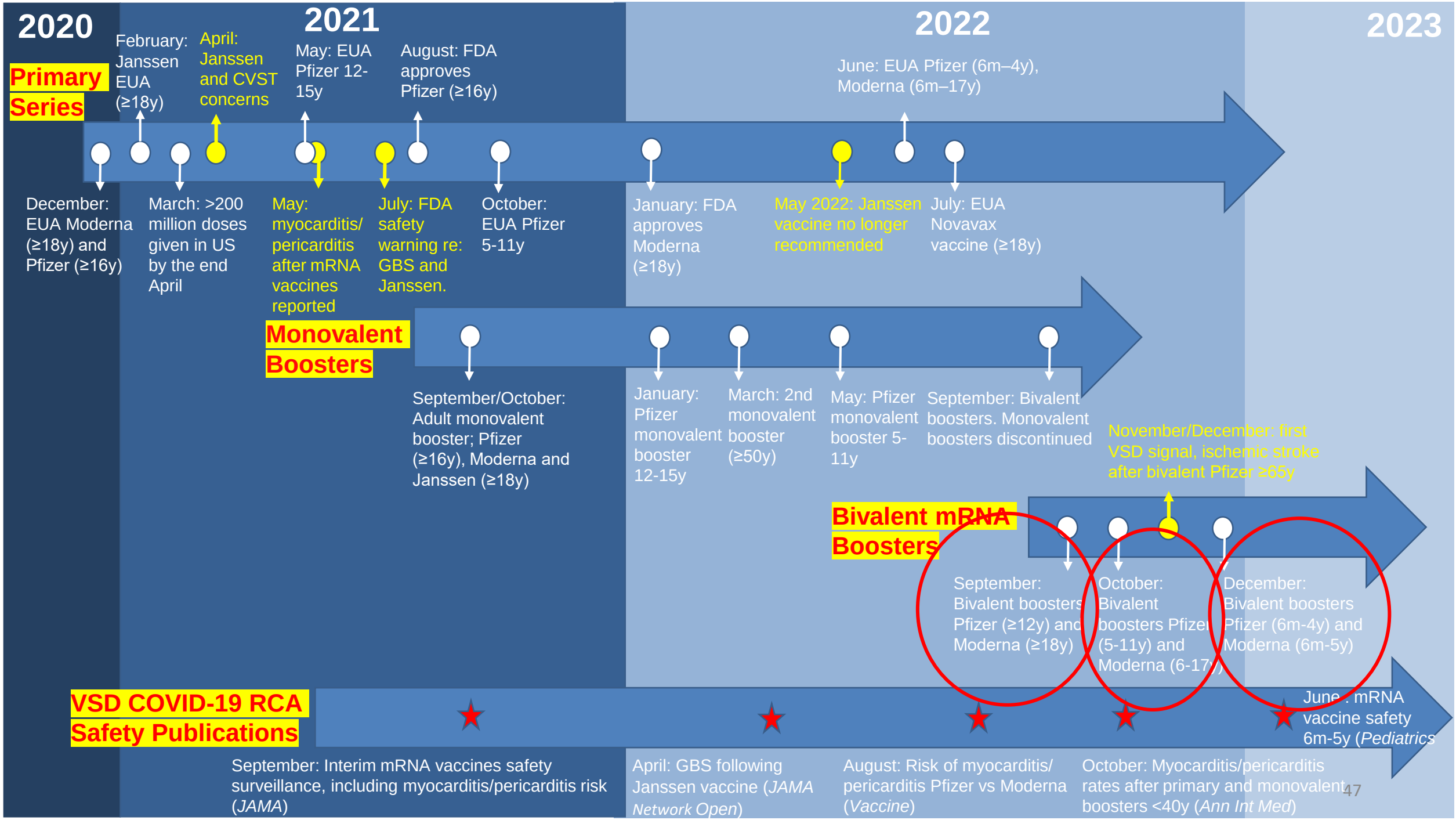
[b] Outcomes were only included in this table if there were events in either the risk or comparison interval for either vaccine type after any dose, making analyses possible. All outcomes under surveillance are listed in Supplemental Table 3. Safety monitoring by individual dose is ongoing, however, since very few outcomes have cases in either the risk or comparison interval only combined analyses are presented here.

[c] Stratified by Vaccine Safety Datalink site, age (year), sex, race and ethnicity, and calendar date.

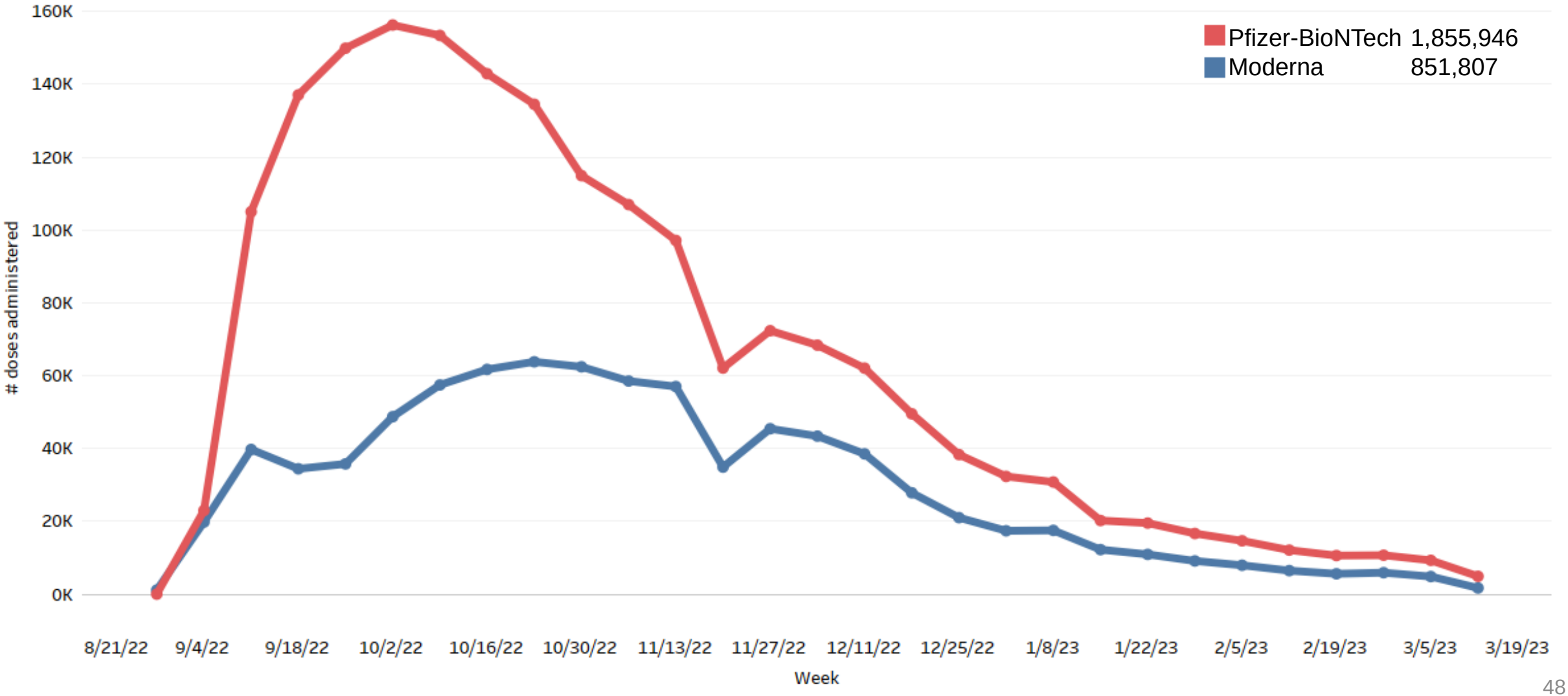
[d] Signal defined as 1-sided $P < 0.011$.

- Among children 6 month-4/5 years, no outcome met the signaling criteria in the 21 days after primary series.
- No cases of myocarditis or pericarditis within the risk interval
- However, vaccine uptake has been low

Goddard K, Donahue JG, Lewis N, Hanson KE, Weintraub ES, Fireman B, Klein NP. Safety of COVID-19 mRNA Vaccination Among Young Children in the Vaccine Safety Datalink. Pediatrics. 2023 Jul 1;152(1):e2023061894. doi: 10.1542/peds.2023-061894.


2020
2021
2022
2023
Primary Series
February: Janssen EUA (≥18y)
April: Janssen and CVST concerns
May: EUA Pfizer 12-15y
August: FDA approves Pfizer (≥16y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
December: EUA Moderna (≥18y) and Pfizer (≥16y)
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 (≥18y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics

Bivalent Booster Uptake Among Persons Aged ≥12 Years, Over Time*



* Data through March 18, 2023

Summary RCA Findings in the 1-21 Day Risk Interval after Bivalent Booster 6 months - 64 years

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

Risk Interval Days	Age Group	Outcome Event	Either mRNA	Pfizer Signal?**	Moderna Signal?**
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

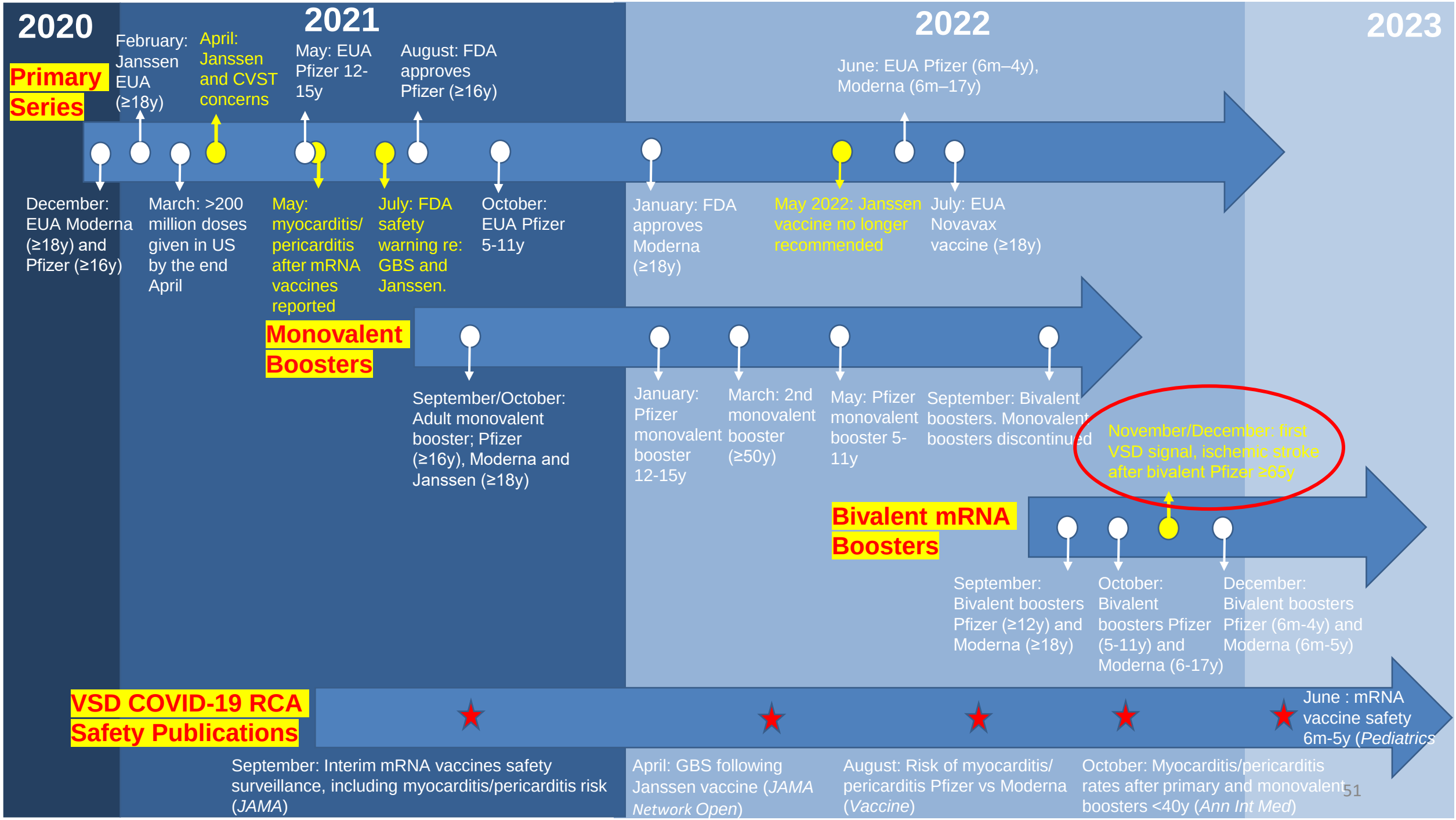
- Among ages 5 - 64 years in the VSD, no outcomes have met the signaling criteria in the 21 days after bivalent booster vaccine.

*Analyses through March 2023
**Signaling threshold P<0.01 (one-sided)

VSD Incidence Rates of Verified Myocarditis or Pericarditis in the 0–7 Days After Bivalent Booster in Ages 12–39 years*

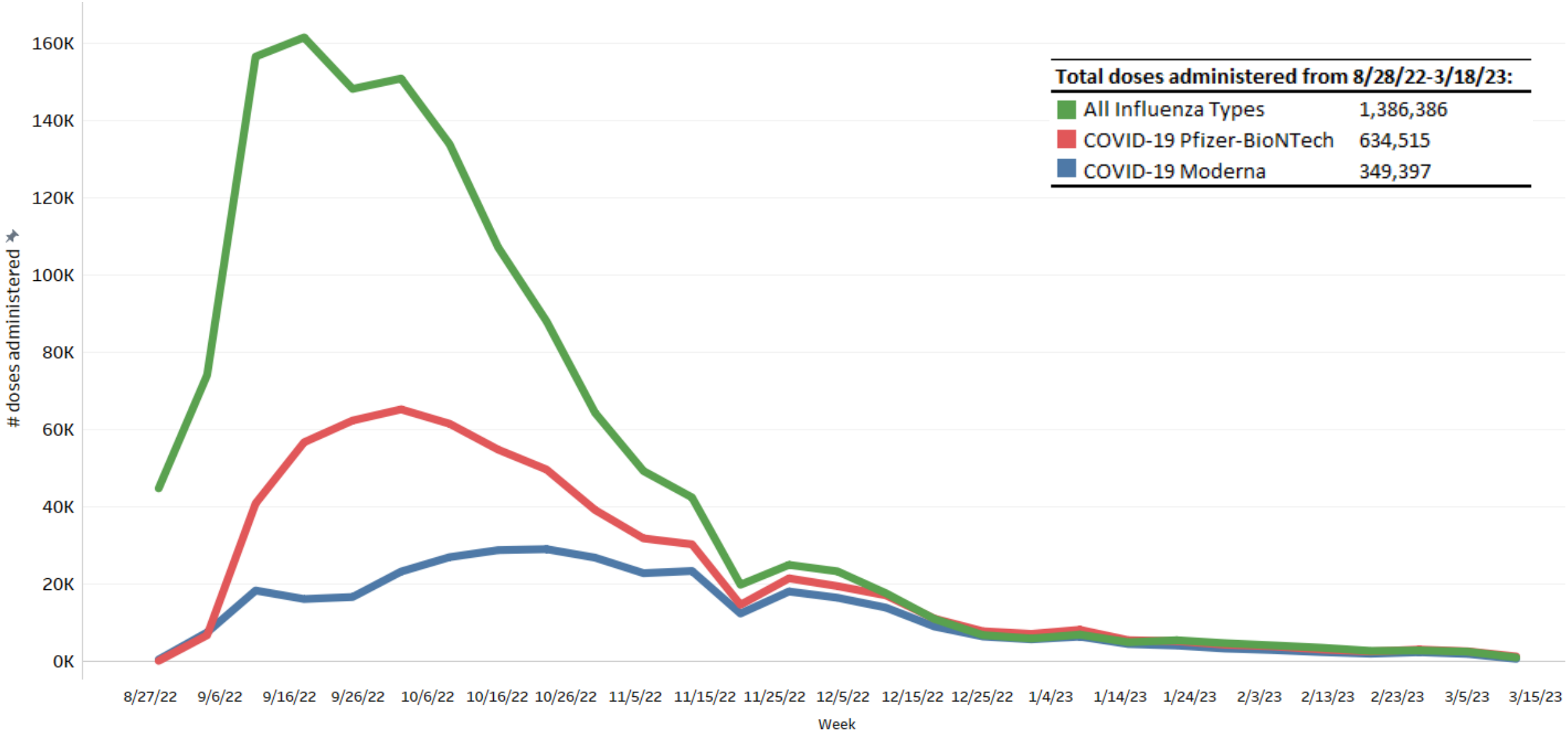
	Dose 2 primary series Pfizer-BioNTech			Monovalent booster dose Pfizer-BioNTech			Bivalent Booster Doses (Pfizer and Moderna)		
Age Group (yrs)	Cases	Total Dose 2 (N)	Incidence rate/ million doses (95% CI)	Cases	Total Doses (N)	Incidence rate/ million doses (95% CI)	Cases	Total Doses (N)	Incidence rate/ million doses (95% CI)
Pfizer									
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	55,649 57,776	0.0 (0.0–53.8) 0.0 (0.0–51.9)
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	60,338 95,162	16.6 (0.4 – 92.3) 0.0 (0.0–31.5)
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	97,171 133,305	0.0 (0.0–30.8) 0.0 (0.0–22.5)
Moderna									
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	22,247 35,393	0.0 (0.0–134.7) 0.0 (0.0–84.6)
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)	1 0	41,820 55,816	23.9 (0.6–133.2) 0.0 (0.0–53.7)

* Primary series and monovalent booster data through August 20, 2022;; 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. **Bivalent booster data through March 11, 2023**


2020
2021
2022
2023
Primary Series
December: EUA Moderna (≥18y) and Pfizer (≥16y)
February: Janssen EUA (≥18y)
March: >200 million doses given in US by the end April
April: Janssen and CVST concerns
May: myocarditis/ pericarditis after mRNA vaccines reported
May: EUA Pfizer 12-15y
July: FDA safety warning re: GBS and Janssen.
August: FDA approves Pfizer (≥16y)
October: EUA Pfizer 5-11y
January: FDA approves Moderna (≥18y)
June: EUA Pfizer (6m–4y), Moderna (6m–17y)
May 2022: Janssen vaccine no longer recommended
July: EUA Novavax vaccine (≥18y)
Monovalent Boosters
September/October: Adult monovalent booster; Pfizer (≥16y), Moderna and Janssen (≥18y)
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 ≥65y
Bivalent mRNA Boosters
September: Bivalent boosters Pfizer (≥12y) and Moderna (≥18y)
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 Network Open)
August: Risk of myocarditis/ pericarditis Pfizer vs Moderna (Vaccine)
October: Myocarditis/pericarditis rates after primary and monovalent boosters <40y (Ann Int Med)
June : mRNA vaccine safety 6m-5y (Pediatrics

Ischemic Stroke Following Pfizer Bivalent Booster Vaccination in 65+ Years of Age

Number of COVID-19 Bivalent Booster Doses and Influenza Vaccine Doses Administered Over Time Among Persons Aged ≥65 years, by Vaccine Type



Summary RCA Findings in the 1-21 Day Risk Interval After Bivalent Booster ≥65 years

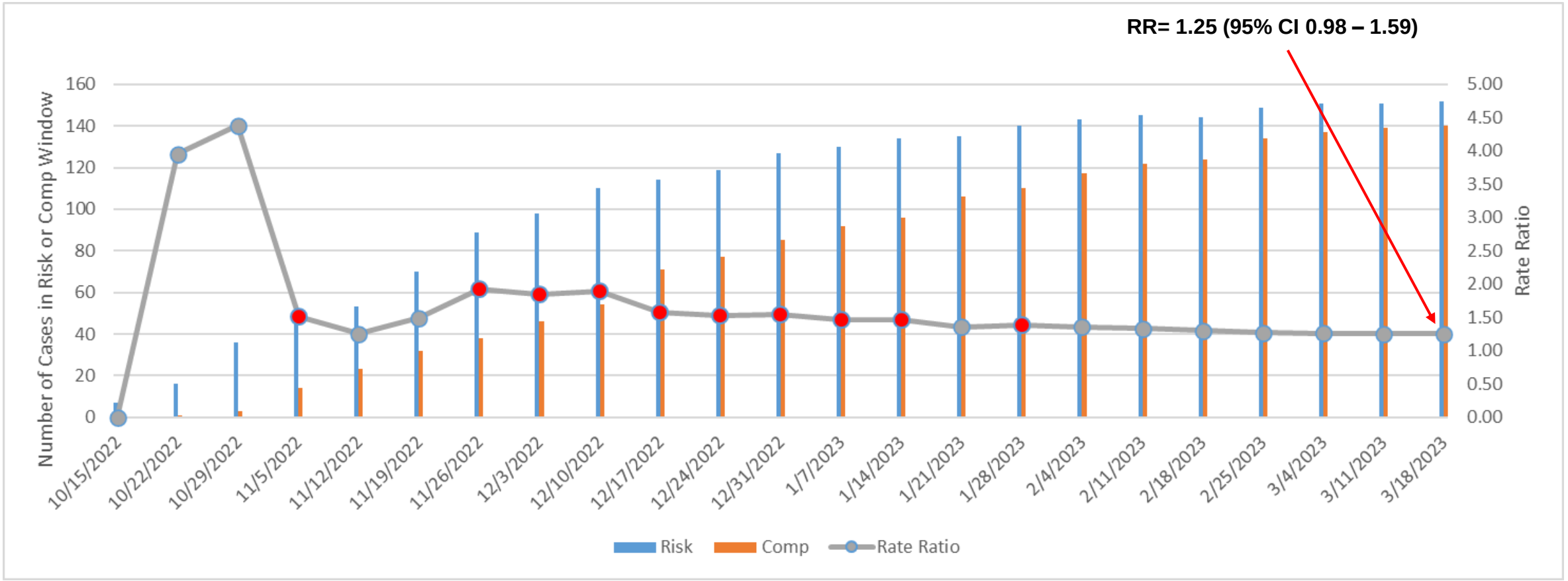
Compared with Outcome Events 22-42 days after in Vaccinated Comparators*

Risk Interval Days	Age Group	Outcome Event	Either mRNA Signal?**	Pfizer Signal?**	Moderna Signal?**
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

- Ischemic stroke signaled in the 21 days after bivalent booster vaccine among ≥65 years in the VSD.

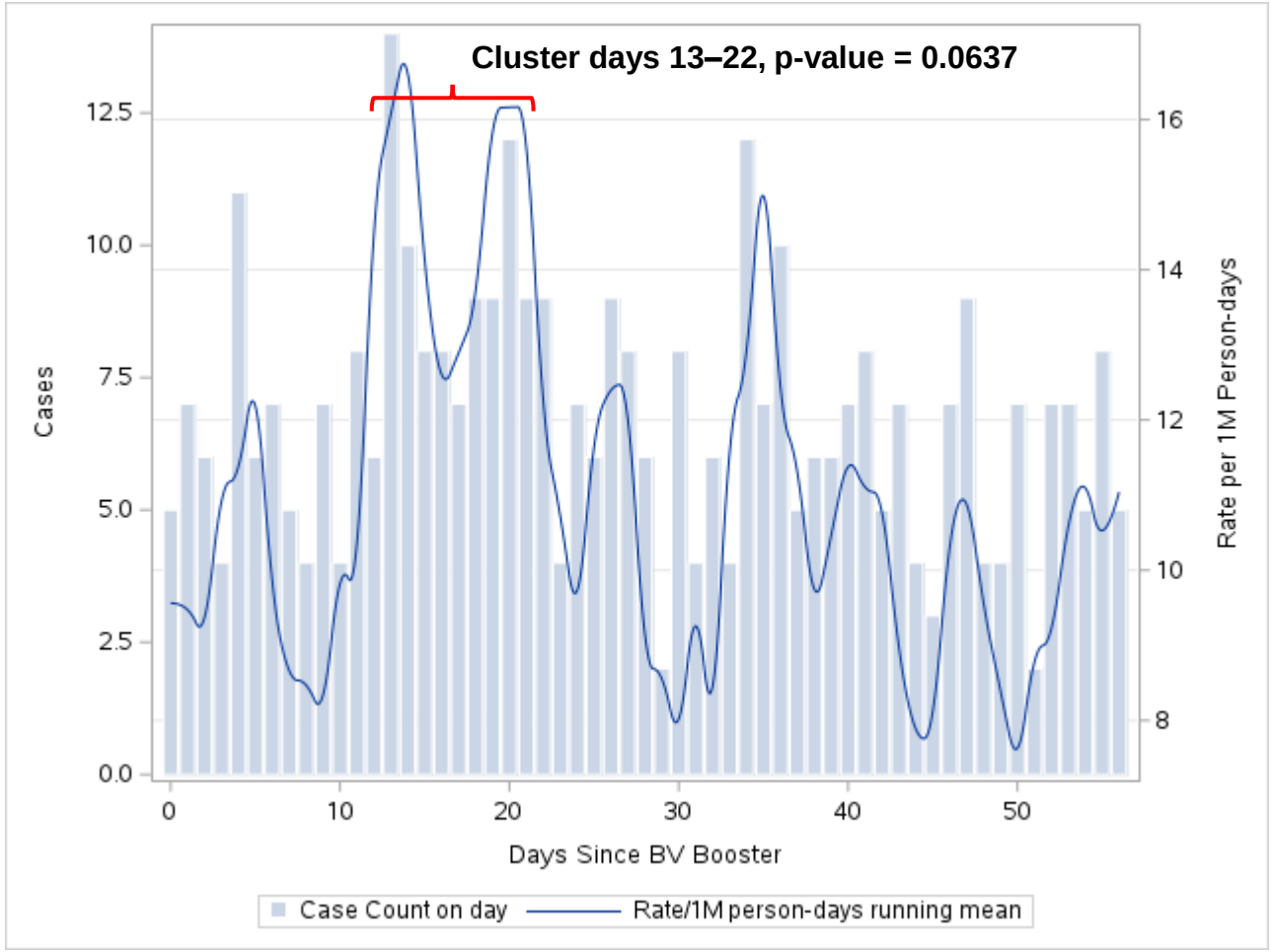
*Analyses through March 2023
**Signaling threshold P<0.01 (one-sided)

Ischemic Stroke After Pfizer-BioNTech Bivalent Booster, Age ≥65 years, Counts and Adjusted Rate Ratios (Oct 15, 2022 – March 18, 2023)



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

Ischemic Stroke by Day after Pfizer-BioNTech Bivalent Booster, People Aged ≥65 Years*



* Data cutoff 2/28/2023

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	27	1.59 (0.99 – 2.61)	0.06
Bivalent Pfizer + same day standard dose flu vaccine	8	11	0.73 (0.28 - 1.83)	0.50
Bivalent Pfizer without any same day flu vaccine	107	99	1.08 (0.82 – 1.42)	0.58

* Analyses only include vaccination data through January 14, 2023, and stroke outcome data through February 25, 2023
** Adjusted by 5-year age groups

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

Additional Considerations for Stroke Outcome

- **Small numbers of strokes and imprecise rate ratios limit some analyses**
  - Uptake of Moderna booster was delayed and reduced due to distribution delays
  - Follow-up of individuals concurrently given bivalent booster + hi-dose flu was limited by small numbers
- **Difficult to interpret temporal clustering which attenuated as rate ratio attenuated**
- **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

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

Anaphylaxis

- The rate of anaphylaxis was ~ 5 cases/million doses for the mRNA primary series.
  - The rate of anaphylaxis was <5 cases/million doses for mRNA booster doses.

Myocarditis/Pericarditis after mRNA vaccines

- During days 0-7 post vaccination, both mRNA vaccines were associated with increased risk of myocarditis/pericarditis in 12–39-year-olds.
- Risk estimates of myocarditis/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.
  - Evidence suggests there was an increased risk for myocarditis/pericarditis following monovalent booster dose for some age groups.
  - No current evidence for an increased rate of myocarditis/pericarditis following bivalent boosters. Uptake was low in age groups expected to be at highest risk.

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

Ischemic stroke after Pfizer bivalent booster

- Rate ratio met signaling criteria consistently for 8 weeks but slowly attenuated and now does not meet signaling criteria
- Temporal clustering 13–22 days after vaccination (significant at time of initial signal but attenuated as the rate ratio estimate attenuated)
- Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.07 (95% CI 0.89–1.28) (data not shown)
- Analyses evaluating simultaneous high-dose or adjuvanted flu vaccine showed a rate ratio RR=1.59 (95% CI 0.99 – 2.61)
  - Separate analyses did not detect an elevated RR for stroke after flu vaccine alone (data not shown)

GBS after Janssen vaccine

- Findings were consistent with an association between increased risk of GBS and Janssen COVID-19 vaccine.

Summary of VSD COVID RCA chart review

Vaccine	Outcome										
	Acute disseminated encephalo-myelitis (ADEM) N=9	Anaphylaxis N=342	Cerebral venous sinus thrombosis (CVST) N=98	Guillain-Barré syndrome (GBS) N=130	Ischemic Stroke N=100	Multisystem Inflammatory Syndrome – Child/Adult (MIS-C/A) N=33	Myocarditis/ Pericarditis N=935	Thrombosis with thrombo-cytopenia syndrome (TTS) N=32	Transverse myelitis (TM) N=43	Venous thrombo-embolism (VTE) N=186	TOTAL N=1908
Primary series (mRNA and Janssen)	9	300	98	130	NR	33	342 (6 months-39 yrs)	32	43	186	1173
Monovalent Booster (mRNA)	NR	30	NR	NR	NR	NR	362 (all ages)	NR	NR	NR	392
Bivalent Booster (mRNA)	NR	12	NR	NR	100 (65+ yrs)	NR	231 (all ages)	NR	NR	NR	343

*Counts are included per individual; however, most outcomes underwent multiple reviews (i.e., quick review, full review, clinical adjudication)
NR= not reviewed

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 came early and have been mostly unchanged since fall 2021.

2. The VSD COVID-19 RCA analytic methods have been hard to understand.
   - We believe that vaccinated concurrent comparators are less vulnerable to bias, but it is an unfamiliar approach that is 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.
   - However, intense public attention on COVID vaccine safety meant we frequently communicated preliminary results on short notice, and methods that are hard to concisely explain and understand posed substantial challenges.

3. Our vaccine safety questions have frequently changed and expanded, requiring us to rapidly adapt our surveillance to include new outcomes and age groups.
   - Flexibility in routinely accommodating (sometime substantial) changes has been critical.

4. Challenging to digest and interpret the large amounts of potentially relevant data and results that we put “on the shelf” weekly (e.g., comparisons with unvaccinated people).
   - Supplementary analyses were available should a safety concern arise from VSD or elsewhere.

Future Considerations

- 2020-2023 VSD COVID-19 RCA surveillance is complete.

- Future Studies - VSD may consider further investigating:
  - mRNA vaccine primary series signals of VTE and AMI
  - Bell's palsy after Janssen primary and mRNA monovalent booster (limited data since neither vaccine is currently available or used)
  - Ischemic stroke after concomitant bivalent boosters and flu vaccines in ≥65-year-olds in future season

It takes a village…

Acknowledgements

- Kaiser Permanente Northern California:
  - Ned Lewis, Kristin Goddard, Bruce Fireman, Ousseny Zerbo, Karen Nunley, Pat Ross, Nandini Bahkshi, Laurie Aukes, Berwick Chan, Arnold Yee, Varun Shah
- Marshfield Clinic Research Institute:
  - Jim Donahue, Kayla Hanson, Ed Belongia, Tom Boyce, Burney Kieke, Dave McClure, Erica Scotty
- CDC Immunization Safety Office:
  - Eric Weintraub, Tom Shimabukuro, Matt Oster, Tat'Yana Kenigsberg, Jonathan Duffy, Frank Destefano, Tanya Myers
- VSD Sites
  - HealthPartners Institute, Minneapolis, Minnesota
  - 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