Update: Rapid Cycle Analysis of RSV Vaccines in Older Adults

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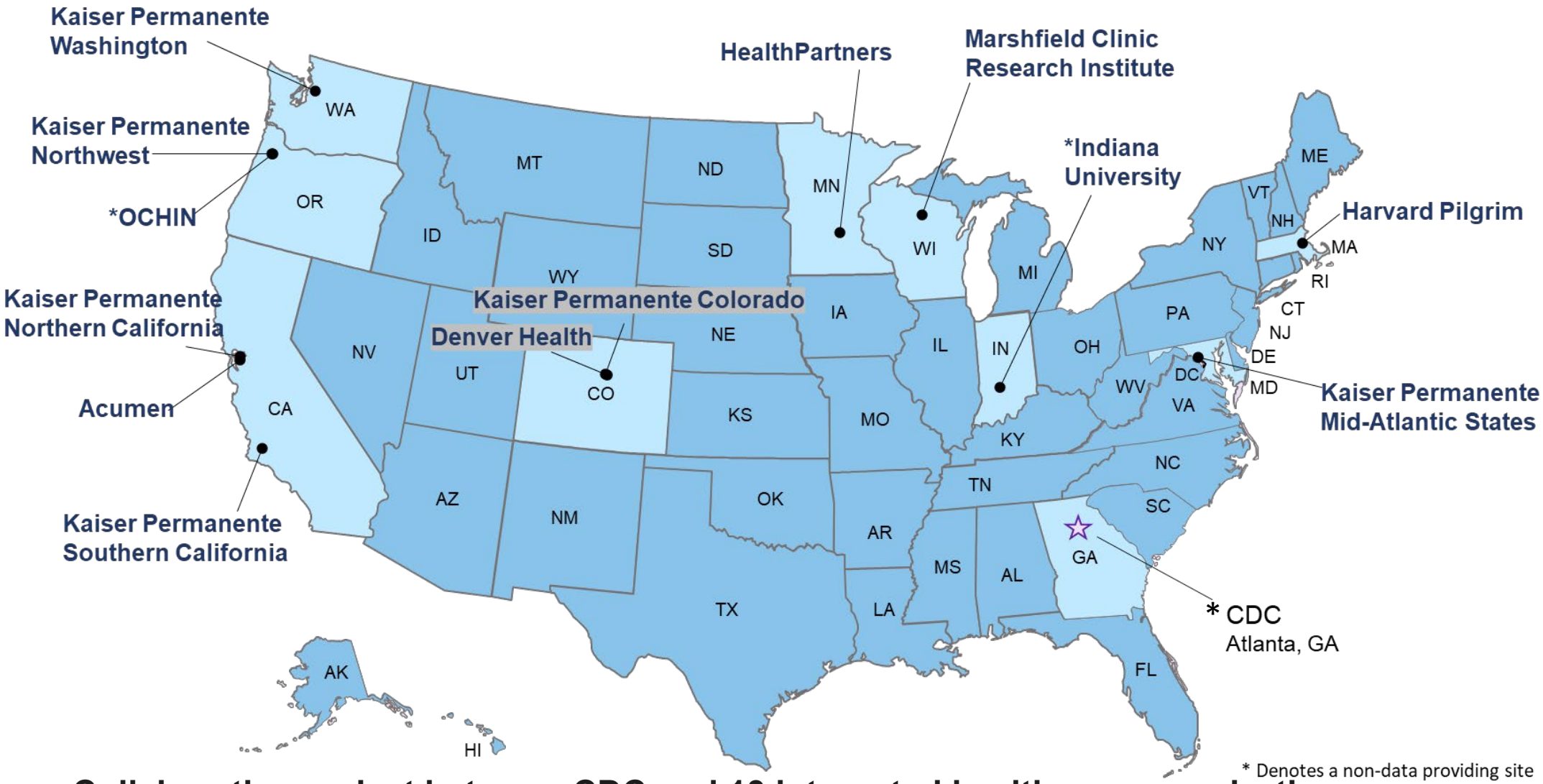
RSV RCA Interim Report – June 26, 2024

- Description of Vaccine Safety Datalink and RCA
- Review of surveillance methods
- Descriptive analysis
- Sequential analysis
  - Immune thrombocytopenia (ITP)
  - Guillain-Barré syndrome (GBS)
  - Atrial fibrillation

Vaccine Safety Datalink 2024



* Denotes a non-data providing site

- **Collaborative project between CDC and 13 integrated healthcare organizations**
- **Data on ~13.5 million persons per year**
- **Conducts rigorous vaccine safety studies and near-real-time monitoring**

VSD Rapid Cycle Analyses (RCA)

- Permits rapid assessment of vaccine safety
  - Near real-time data for weekly, biweekly, or monthly analyses
- Outcome incidence in vaccinated persons compared to outcomes incidence in a comparator group
  - Outcomes are pre-specified
- Sequential analytic methods used to detect ‘statistical signals’ while maintaining a pre-defined type I error rate
  - Type I error = mistakenly reject the null hypothesis (“false positive”)
- Statistical signals are interpreted as **potential** associations

Objectives for RSV RCA in Older Adults

- Monitor RSV vaccine uptake
- Monitor the occurrence of pre-specified outcomes following RSV vaccination
- Conduct near real-time surveillance of pre-specified outcomes using RCA methods

Study Design and Population

- Near real-time surveillance among a prospective cohort of persons ≥60 years old who received an RSV vaccine
- Member of a participating VSD infrastructure site
- Data are extracted every week and analyses are biweekly
- Surveillance period: 8/1/2023 through 5/31/2025
  - Sequential analyses started in March 2024
- Project ends September 2025

Sequential Analysis Methods

- Biweekly analysis includes a sequential test of the one-sided null hypothesis that the vaccine does not increase the risk in the risk interval
- A ‘statistical signal’ occurs when the analysis produces a one-sided P value that is less than a pre-specified threshold
- The signal threshold is determined from an alpha-spending plan that keeps the overall chance of a Type 1 error <0.05 during the surveillance period
- Formal sequential analysis stops after a signal, but surveillance continues
- Design and analysis is analogous to that used in the VSD RCA of COVID-19 vaccines (Klein N, et al. JAMA 2021; 326:1390–9)

Risk and Comparison Intervals

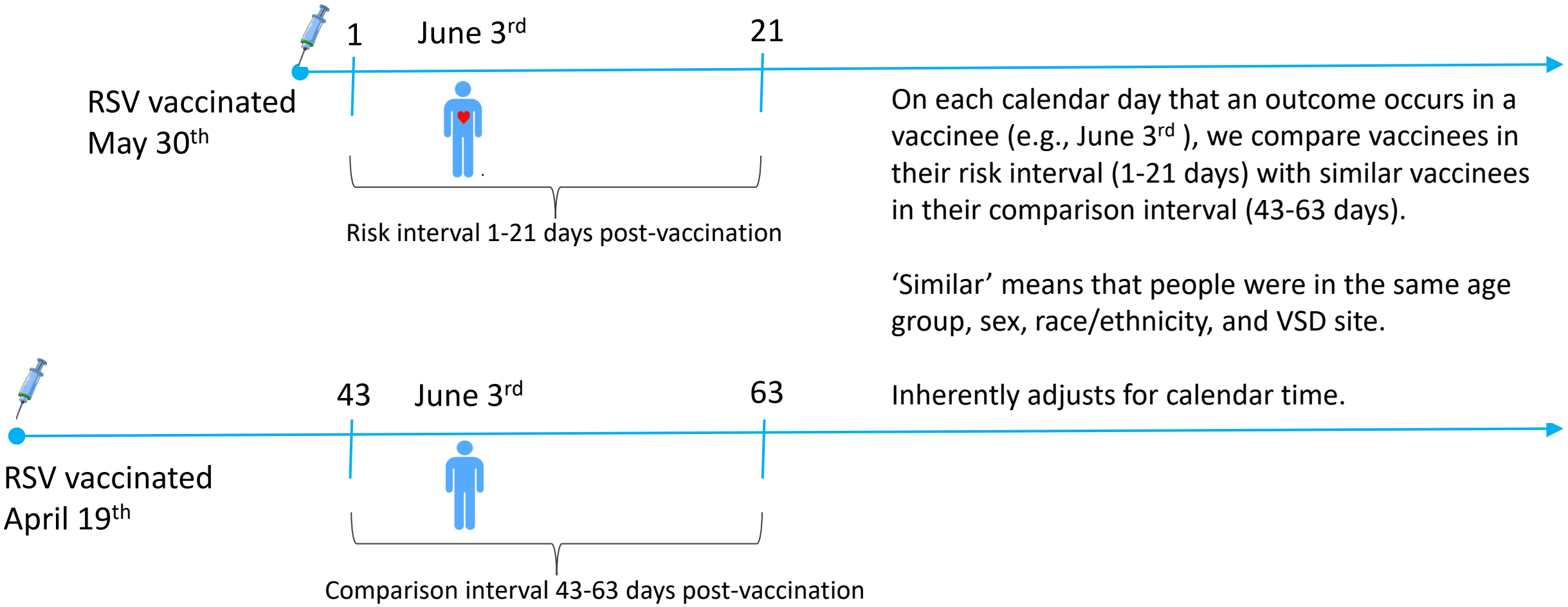
- Primary risk interval for all outcomes will be 1-21 days following RSV vaccination except anaphylaxis and CIDP*
  - Primary comparison interval of 43-63 days
  - Secondary comparison interval of 22-42 days
- Secondary risk interval of 1-42 days
  - Comparison interval of 43-84 days
- Anaphylaxis and CIDP will be descriptively monitored only
  - Anaphylaxis (0-1 days after RSV vaccination)
  - CIDP (1-84 days after RSV vaccination)

*chronic inflammatory demyelinating polyneuropathy

Analysis with Vaccinated Concurrent Comparators

- Comparators are RSV vaccinees, who on the same day as the exposed case in a risk interval, were in the same stratum (e.g., age, sex, race/ethnicity, VSD site), but in a comparison interval
- Outcome incidence is calculated during the risk interval and compared with incidence in the comparison interval
  - Relative risk estimates are computed with nominal 95% confidence intervals
  - Adjusted for calendar day, age group, sex, race/ethnicity, VSD site
- Advantages of vaccinated concurrent comparators compared to unvaccinated or historical comparators
  - Permits adjustment for potential biases due to calendar time, site, and demographic factors
  - Less confounding by indication (e.g., persons with chronic illness more likely to seek RSV vaccination **and** may be at increased risk of atrial fibrillation)

Vaccinated Concurrent Comparator Design



On each calendar day that an outcome occurs in a vaccinee (e.g., June 3rd), we compare vaccinees in their risk interval (1-21 days) with similar vaccinees in their comparison interval (43-63 days).

'Similar' means that people were in the same age group, sex, race/ethnicity, and VSD site.

Inherently adjusts for calendar time.

Ref: Klein N, et al. Kaiser Permanente Northern California

Four Exposure Groups

GSK	with simultaneous vaccination of another vaccine*
GSK	without simultaneous vaccination
Pfizer	with simultaneous vaccination of another vaccine*
Pfizer	without simultaneous vaccination

*Non-RSV vaccines typically include routine, age-appropriate vaccines such as COVID-19, influenza, RZV, PCV20/15, PPSV23, Td/Tdap

Pre-specified Outcomes (n=14)

Outcome	Setting[1]	Primary risk interval (days)[2]
Acute disseminated encephalomyelitis (ADEM)[3]	E, I	1-21
Acute myocardial infarction (AMI)	E, I	1-21
Anaphylaxis[3]	E, I	0-1
Atrial fibrillation	E, I, O, T	1-21
Bell's palsy	E, I, O, T	1-21
Chronic inflammatory demyelinating polyneuropathy (CIDP)[3]	E, I, O, T	1-84
Deep vein thrombosis (DVT)	E, I, O, T	1-21
Encephalitis / myelitis / encephalomyelitis (not ADEM or TM)	E, I	1-21
Guillain-Barré syndrome (GBS)[3]	E, I	1-21
Immune thrombocytopenia (ITP)	E, I, O, T	1-21
Myocarditis / pericarditis	E, I	1-21
Pulmonary embolism (PE)	E, I	1-21
Stroke	E, I	1-21
Transverse myelitis (TM)[3]	E, I	1-21

[1]E=Emergency department; I=Inpatient; O=Outpatient; T=Telehealth

[2]All outcomes also have a secondary risk interval of 1-42 days after vaccination, except anaphylaxis and CIDP, which are descriptively monitored only.

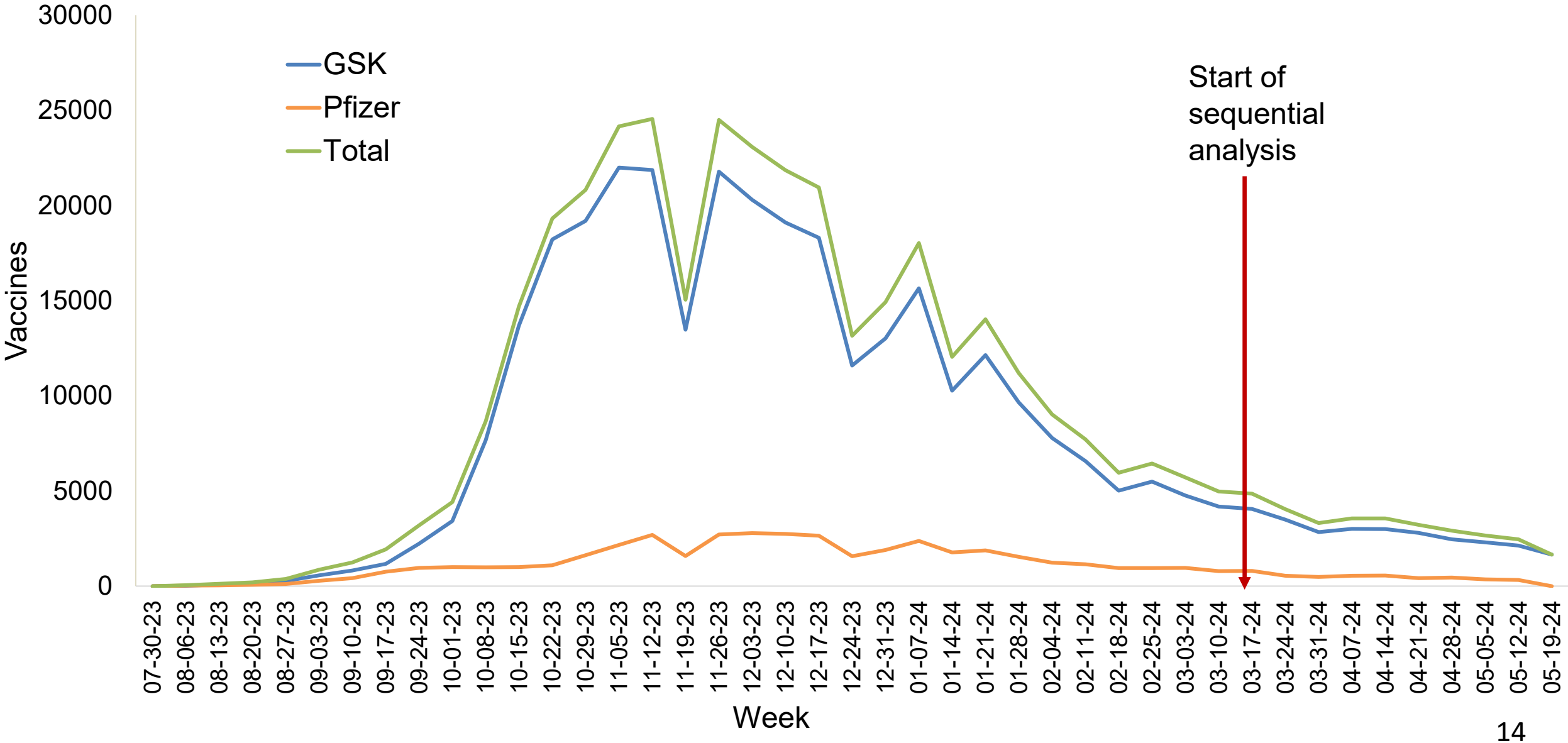
[3]Chart review regardless of whether there is a statistical signal; sequential analyses will use only chart-confirmed cases (ADEM, GBS, and TM).

RSV Vaccines Administered in VSD, 8/1/2023–5/25/2024

GSK		Pfizer		Unspec		Total
N	%	N	%	N	%	
338,290	87.7	47,287	12.3	152	0.0	385,729

- NOTE: All subsequent analyses and slides **exclude** RSV vaccines in the ‘Unspecified’ manufacturer category

RSV Vaccinations by Manufacturer and Week of Administration



Results of Sequential Analysis

Six runs—data through 5/25/2024

RSV RCA Vaccine Statistical Signals in VSD (5/25/2024)

VSD Outcomes	Setting[1]	Signal (Y/N)
Acute disseminated encephalomyelitis (ADEM)	E, I	N
Acute myocardial infarction (AMI)	E, I	N
Atrial fibrillation (AF)	E, I, O, T	N
Bell's palsy (BP)	E, I, O, T	N
Deep vein thrombosis (DVT)	E, I	N
Encephalitis / myelitis / encephalomyelitis (ENCEPH)	E, I	N
Guillain-Barré syndrome (GBS)	E, I	N
Immune thrombocytopenia (ITP)	E, I, O, T	Y
Myocarditis / pericarditis (MYOC)	E, I	N
Stroke (STK)	E, I	N
Transverse myelitis (TM)	E, I	N
Pulmonary embolism (PE)	E, I	N

[1]E = ED, I = Inpatient, O = Outpatient, T=Telehealth

VSD RCA of RSV Vaccine in Older Adults
Surveillance Initiated on 01AUG2023, Analyses Based on Data Through 16MAR2024 (run #1, week #1836)
Concurrent Comparator Sequential Analysis Signal Assessment for Immune Thrombocytopenia
---Age:60+ yrs---

Analysis Parameters				Signal Information and Informative Counts					Nominal Analysis			Sequential Test
Outcome Event	Risk Interval Days	Comp Interval Days	Vaccine Type	Signaled in a Prior Run[1]	New Sequential Analysis Signal[2]	Events in Risk Interval	Events in Comp Interval	Adjusted Expected Events in Risk Interval	Adjusted Rate Ratio[3]	95% Confidence Interval[4]	2-sided P Value	1-sided P Value[5]
ITP	1-21	43-63	GSK w simul	n/a	No	2	1	0.6	3.08	0.23-92.44	0.408	0.347
			GSK wo simul	n/a	No	19	8	8.1	2.35	0.99-5.97	0.054	0.040
			Pfizer w simul	n/a	No	0	1	0.2	0.00	0.00-81.18	0.810	0.810
			Pfizer wo simul	n/a	No	2	2	1.8	1.10	0.11-11.27	0.931	0.659
		22-42	GSK w simul	n/a	No	3	2	1.4	2.21	0.31-19.61	0.432	0.340
			GSK wo simul	n/a	Yes	19	6	6.3	3.04	1.22-8.47	0.016	0.012
			Pfizer w simul	n/a	No	0	1	1.1	0.00	0.00-16.74	0.468	0.468
			Pfizer wo simul	n/a	No	2	1	0.7	2.67	0.20-78.89	0.472	0.394
	1-42	43-84	GSK w simul	n/a	No	4	7	4.3	0.93	0.22-3.42	0.931	0.662
			GSK wo simul	n/a	No	25	14	15.6	1.60	0.80-3.28	0.186	0.121
			Pfizer w simul	n/a	No	1	3	3.5	0.29	0.01-4.25	0.428	0.957
			Pfizer wo simul	n/a	No	3	3	3.4	0.88	0.14-5.47	0.888	0.718

(1) n/a = not applicable
(2) No prior signal, at least 2 events in the risk interval, 1-sided P value < 0.014
(3) Adjusted for calendar date, VSD site, age category, sex, and race/ethnicity
(4) ne = not estimable
(5) Red: new sequential analysis signal, Yellow: 1-sided P value < 0.014 but already signaled in a prior run

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ITP Statistical Signal and Rapid Review

- ITP signal for GSK vaccine without simultaneous vaccination in 1-21 day risk interval versus 22-42 day comparison interval
- Quick medical record reviews
  - Of the 19 cases in the risk interval, 4 were incident ITP*
  - Of the 14 cases in comparison intervals, 2 were incident ITP, 1 in the 22-42 day interval and 1 in the 43-63 day interval
- After quick review: 4 cases of ITP in the primary risk interval, 1 case each in the 22-42 and 43-63 day comparison intervals
- Plan to do more detailed chart review of ITP cases going forward

*New cases of ITP relative to RSV vaccination.

GBS Cases Following RSV Vaccination
--No Statistical Signal--

GBS Cases 1-84 Days after RSV Vaccination

Automated Cases	Completed Chart Review	Chart Confirmed Cases	Not GBS	Cases Pending Review
12	11	9	2	1

- GBS cases identified electronically, then receive medical record review, and presumptive cases are adjudicated by two reviewers
- Cases defined using Brighton Level (BL) criteria*
- 7 cases of GBS (BL 1-3) following any RSV vaccination
  - 5 following GSK – onset days 6, 10, 31, 54, 76
  - 2 following Pfizer – onset days 9, 46
- 2 BL 4 cases following GSK

*Sejvar J, et al. Vaccine. 2011;29(3):599-612.

VSD RCA of RSV Vaccine in Older Adults
Surveillance Initiated on 01AUG2023, Analyses Based on Data Through 25MAY2024 (run #6, week #1846)
Concurrent Comparator Sequential Analysis Signal Assessment for Guillain-Barre Syndrome

---Age:60+ yrs---

Analysis Parameters				Signal Information and Informative Counts					Nominal Analyses			Sequential Test
Outcome Event	Risk Interval Days	Comp Interval Days	Vaccine Type	Signaled in a Prior Run[2]	New Sequential Analysis Signal[3]	Events in Risk Interval	Events in Comparison Interval	Adjusted Expected Events in Risk Interval	Adjusted Rate Ratio[4]	95% Confidence Interval[5]	2-sided P value	1-sided P value[6]
GBS[1]	1-21	43-63	GSK wo simul	No	No	2	1	0.9	2.33	0.10-93.95	0.603	0.515
			Pfizer wo simul	No	No	1	0	0.0	ne	0.05-ne	0.496	0.496
		22-42	GSK wo simul	No	No	2	1	1.3	1.55	0.11-47.77	0.775	0.600
			Pfizer wo simul	No	No	1	0	0.0	ne	0.07-ne	0.439	0.439
	1-42	43-84	GSK wo simul	No	No	3	1	1.4	2.17	0.16-74.98	0.605	0.501
			Pfizer wo simul	No	No	1	0	0.0	ne	0.04-ne	0.557	0.557

(1) Chart-confirmed cases only, Brighton level 1-3
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(3) No prior signal, at least 2 events in the risk interval, 1-sided P value < 0.014
(4) Adjusted for calendar date, VSD site, age category, sex, and race/ethnicity
(5) ne = not estimable
(6) Red: new sequential analysis signal, Yellow: 1-sided P value < 0.014 but already signaled in a prior run

Crude GBS Incidence Rates after RSV Vaccination[1]

Risk interval estimates

Vaccine	Risk interval	# of Cases	# of Doses[2]	Rate Per Million (95% CI)	Rate per 100,000 PY (95% CI)
GSK	1-21 days	2	323929	6.2 (0.7 – 22.3)	10.7 (1.3 – 38.8)
GSK	1-42 days	3	323929	9.3 (1.9 – 27.1)	8.1 (1.7 – 23.5)
Pfizer	1-21 days	1	45162	22.1 (0.6 – 123.4)	38.5 (1.0 – 214.6)
Pfizer	1-42 days	1	45162	22.1 (0.6 – 123.4)	19.3 (0.5 – 107.3)

Comparison interval estimates

Vaccine	Comparison interval	# of Cases	# of Doses[3]	Rate Per Million (95% CI)	Rate per 100,000 PY (95% CI)
GSK	43-84 days	2	301547	6.6 (0.8 – 24.0)	5.8 (0.7-20.9)
Pfizer	43-84 days	1	41031	24.4 (0.6 – 135.8)	21.2 (0.5 – 118.1)

- Background rate for GBS in persons 60+ years old: 1.4-3.7 per 100,000 PY (Sejvar, J., et al. Neuroepidemiol, 2011)

[1]Cases restricted to chart confirmed, Brighton Level 1-3
[2]Vaccines administered 8-1-23 through 4-13-24
[3]Vaccines administered 8-1-23 through 3-2-24

Atrial Fibrillation Following RSV Vaccination
--No Statistical Signal--

VSD RCA of RSV Vaccine in Older Adults
Surveillance Initiated on 01AUG2023, Analyses Based on Data Through 25MAY2024 (run #6, week #1846)
Concurrent Comparator Sequential Analysis Signal Assessment for Atrial Fibrillation

---Age:60+ yrs---

Analysis Parameters				Signal Information and Informative Counts					Nominal Analysis			Sequential Test
Outcome Event	Risk Interval Days	Comp Interval Days	Vaccine Type	Signaled in a Prior Run[1]	New Sequential Analysis Signal[2]	Events in Risk Interval	Events in Comp Interval	Adjusted Expected Events in Risk Interval	Adjusted Rate Ratio[3]	95% Confidence Interval[4]	2-sided P value	1-sided P value[5]
AFIB	1-21	43-63	GSK w simul	No	No	81	75	76.7	1.06	0.75-1.49	0.756	0.411
			GSK wo simul	No	No	198	232	222.3	0.89	0.72-1.10	0.282	0.871
			Pfizer w simul	No	No	7	15	11.9	0.59	0.21-1.51	0.282	0.910
			Pfizer wo simul	No	No	23	33	38.7	0.59	0.32-1.09	0.093	0.968
		22-42	GSK w simul	No	No	91	109	106.9	0.85	0.63-1.14	0.282	0.876
			GSK wo simul	No	No	211	222	209.8	1.01	0.83-1.22	0.954	0.497
			Pfizer w simul	No	No	8	17	13.8	0.58	0.22-1.41	0.238	0.924
			Pfizer wo simul	No	No	25	30	29.9	0.84	0.48-1.46	0.530	0.781
	1-42	43-84	GSK w simul	No	No	190	155	166.7	1.14	0.90-1.44	0.267	0.146
			GSK wo simul	No	No	422	441	444.2	0.95	0.82-1.10	0.496	0.764
			Pfizer w simul	No	No	23	27	23.3	0.99	0.54-1.79	0.966	0.577
			Pfizer wo simul	No	No	52	60	71.3	0.73	0.48-1.10	0.137	0.945

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VSD RSV RCA Summary and Next Steps

- VSD initiated surveillance in older adults in January 2024
- 385,729 doses of RSV vaccines have been administered to older adults (88% GSK)
- Statistical signal for ITP in persons 60+ years old who received the GSK RSV vaccine without simultaneous vaccination
  - Most were not incident ITP cases with onset after RSV vaccination
  - Plan for more detailed chart review of ITP in the fall
- No GBS signal, but few observed cases
- No other statistical signals observed to date
- Surveillance will continue for all outcomes, including GBS, through May 2025

RCA Study Team and Acknowledgments

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention