FDA CBER:
Safety Assessment of 20-valent Pneumococcal Conjugate Vaccine (PCV20)

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Disclaimer

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- There are no potentially conflicting relationships to disclose
- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, the Centers for Medicare & Medicaid Services, or Acumen, LLC

Is there an elevated risk for the listed health outcomes* following PCV20 vaccination?

- Acute Myocardial Infarction
- Myocarditis/Pericarditis
- Anaphylaxis
- Atrial Fibrillation
- Bell's Palsy
- Cardiomyopathy; Heart Failure
- Cellulitis and Infection
- Cholecystitis or Cholelithiasis
- Guillain-Barré syndrome
- Immune Thrombocytopenia
- Thrombocytopenia
- Transient Ischemic Attack

* The list of health outcomes were identified via literature review

Near Real-Time Monitoring: Medicare Fee-for-Service (FFS) Population (Age ≥ 65 years)

Design	Concurrent Comparator Cohort Design[1] for Near Real-Time Sequential Analysis Self-controlled case series planned to verify detected signals
Data Sources	Centers for Medicare & Medicaid Services (CMS) – Shared Systems Data (SSD)
Study Population	Medicare FFS beneficiaries (age ≥ 65 years) receiving one dose of PCV 15 or PCV 20 on or after the licensing date for the product - Two product populations analyzed separately
Study Period	Licensing date (PCV 15 = July 16, 2021 and PCV 20 = July 1, 2021) through the end of each calendar month (most recent update through November 30, 2023)
Health Outcomes	The 12 pre-specified health outcomes identified by claims algorithms and monitored within the follow-up window for each vaccinated beneficiary

1. Klein, N.P., et al., Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA, 2021. 326(14): p. 1390-1399.

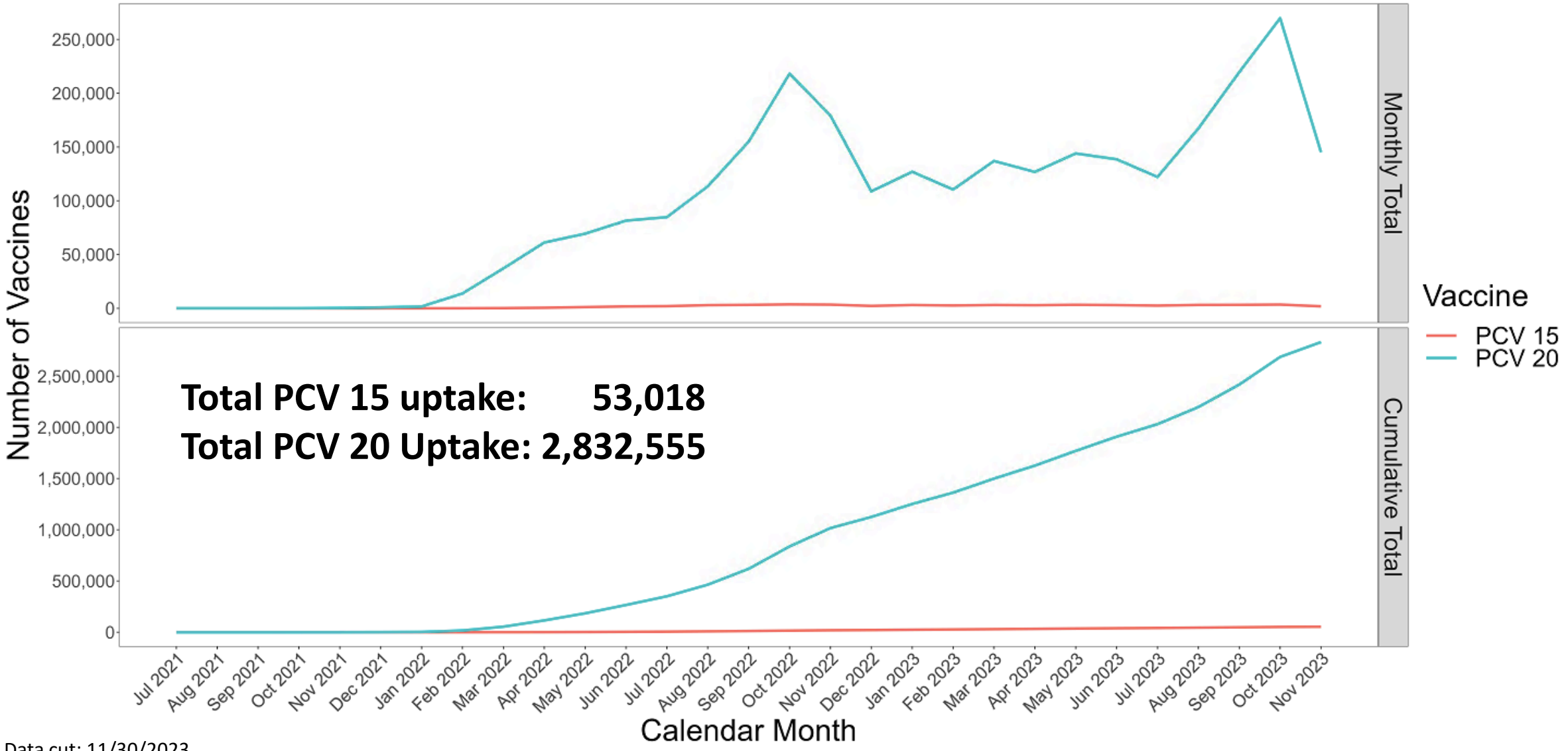
Near Real-Time Monitoring: Medicare Fee-for-Service (FFS) Population (Age ≥ 65 years)

Statistical Analyses	• Descriptive and Sequential analyses were performed monthly
	
	• Bayesian Poisson Regression was used to estimate the posterior distribution of incidence rate ratio (IRR) between pre-specified post-vaccination risk and comparison windows for each outcome
	  • Age, Sex, Immunocompromised Conditions*, Concomitant Influenza Vaccination**, and Months Post-Surveillance Start Date were included as adjustment covariates
	  • Adjustment for claims delay was made
	
	• Safety signal was assessed by evaluating if:
	  • The 95% Credible Interval (CI) exceeds 1 – Weak Signal
	  • The 98% Credible Interval (CI) exceeds 1 – Strong Signal

* Immunocompromised conditions was identified using administrative codes indicating presence of immunocompromising conditions or use of immunosuppressive therapies[2]
** Concomitant influenza vaccination is defined as seasonal influenza vaccination events that happened on or within 42 days prior to PCV 20 vaccination date

2. Greenberg JA, et al., Validation of a Method to Identify Immunocompromised Patients with Severe Sepsis in Administrative Databases. Ann Am Thorac Soc. 2016;13(2):253-258.

Uptake of PCV15 or PCV20 Vaccines in the Medicare FFS 65+ years Population; Monthly (top) and Cumulative (bottom) Counts*



* Data cut: 11/30/2023

Descriptive Characteristics of PCV 20 Vaccinees (N = 2,832,555)

Beneficiary Characteristics	Number of Vaccinees	% of Vaccinees
Race/Ethnicity		
Asian	70,416	2.49%
Black	155,878	5.50%
Hispanic	41,611	1.47%
Alaska Native/American Indian	6,964	0.25%
White	2,410,290	85.09%
Other	57,163	2.02%
Missing/Unknown	90,233	3.19%
Age (years)		
65-69	1,242,140	43.85%
70-74	599,077	21.15%
75-79	461,978	16.31%
80-84	291,753	10.30%
85-89	154,499	5.45%
90-94	64,176	2.27%
95+	18,932	0.67%

Beneficiary Characteristics	Number of Vaccinees	% of Vaccinees
Sex		
Female	1,614,235	56.99%
Male	1,218,320	43.01%
Urban/Rural		
Urban	2,375,807	83.88%
Rural	455,787	16.09%
Missing/Unknown	961	0.03%
Immunocompromised Status		
Yes	144,510	5.10%
No	2,688,045	94.90%
Medicare-Medicaid Dual Eligibility Status**		
Yes	264,266	9.33%
No	2,568,289	90.67%
Concomitant Influenza Vaccination***		
Yes	496,007	17.51%
No	2,336,548	82.49%

* Data cut: 11/30/2023

** Medicare-Medicaid dual eligibility status is defined as ever being dual eligible within the 3 months prior to the vaccination date

*** Concomitant influenza vaccination is defined as seasonal influenza vaccination events that happened on or within 42 days prior to PCV 20 vaccination date

Outcome Count and Incidence Rate (IR) among PCV20 vaccinated population*

Health Outcome	Risk Window** (days)	Comparison Window (days)	Total N (IR***)	Risk Window N (IR****)	Comparison Window N (IR****)
Acute Myocardial Infraction	1-28	29-56	3,274 (970)	1,699 (965)	1,575 (975)
Myocarditis/Pericarditis	1-21	22-42	80 (31)	43 (32)	37 (29)
Anaphylaxis	0-1	3-16	25 (20)	- (26)	- (20)
Atrial Fibrillation	1-42	43-84	17,925 (3,879)	9,709 (3,908)	8,216 (3,845)
Bell's Palsy	1-42	43-84	1,090 (207)	624 (220)	466 (191)
Cardiomyopathy; Heart Failure	1-42	43-84	16,263 (3,503)	8,778 (3,518)	7,485 (3,486)
Cellulitis and Infection	1-7	8-14	3,187 (3,548)	1,660 (3,685)	1,527 (3,410)
Cholecystitis or Cholelithiasis	1-28	29-56	665 (195)	323 (182)	342 (210)
Guillain-Barré Syndrome	1-42	43-84	29 (6)	- (8)	- (4)
Immune Thrombocytopenia	1-42	43-84	49 (10)	30 (11)	19 (8)
Thrombocytopenia	1-28	29-56	3,552 (1,053)	1,787 (1,015)	1,765 (1,093)
Transient Ischemic Attack	1-28	29-56	621 (182)	318 (179)	303 (186)

* Data cut: 11/30/2023, # of PCV 20 total uptake: 2,832,555
** Risk and comparison windows are defined as the number of days post vaccination
*** All IRs expressed as IR per 100,000 person-years
**** For the health outcome that has risk or comparison windows count less than 11, the counts for both windows are masked by "-"

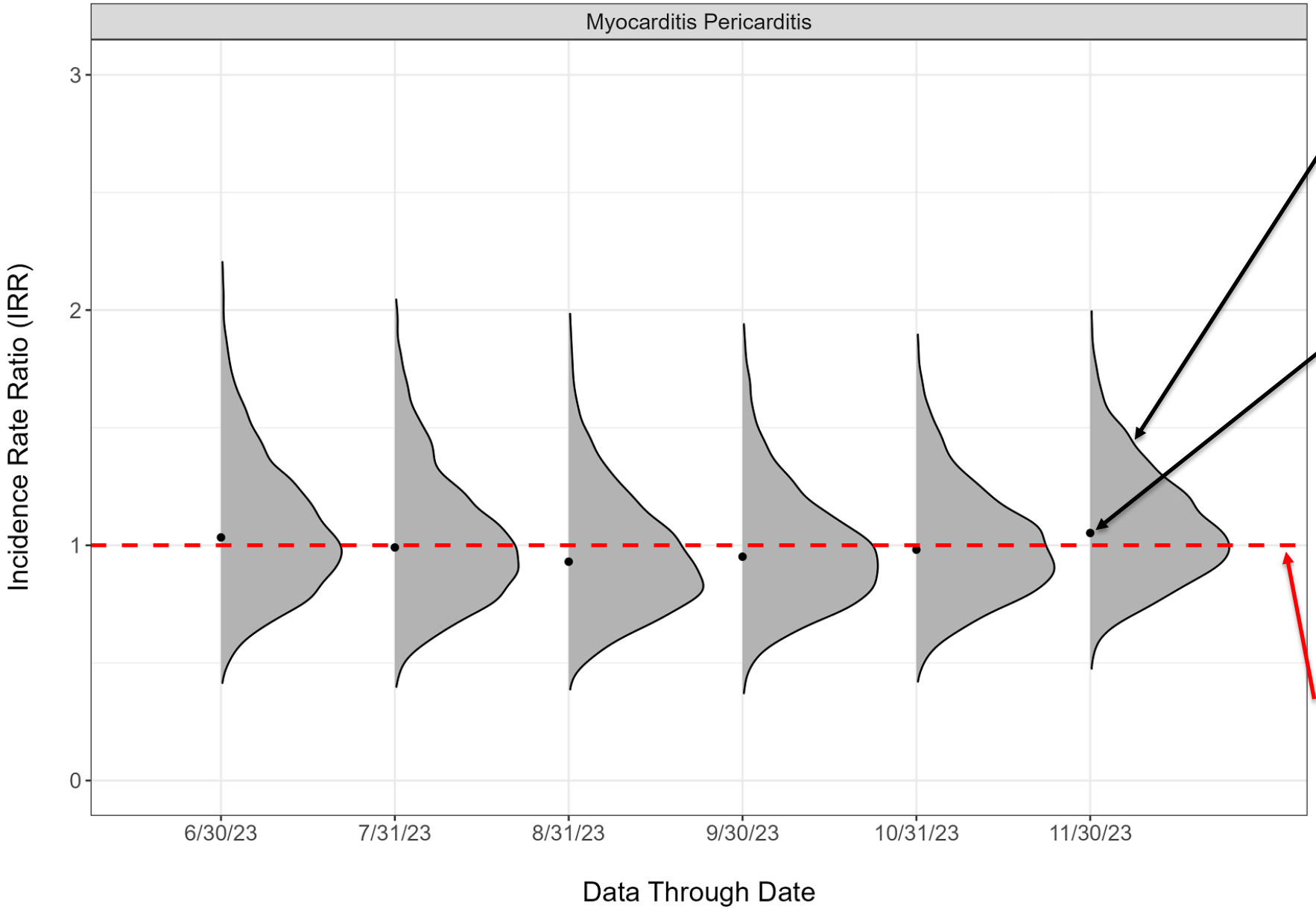
IRR between Risk and Comparison Windows with 95% and 98% CI among PCV20 Vaccinated Population*

Health Outcome	IRR**	95% CI	98% CI
Acute Myocardial Infraction	0.95	(0.89, 1.02)	(0.87, 1.03)
Myocarditis/Pericarditis	1.05	(0.69, 1.64)	(0.64, 1.77)
Anaphylaxis	1.11	(0.31, 3.12)	(0.22, 3.78)
Atrial Fibrillation	0.98	(0.95, 1.01)	(0.95, 1.02)
Bell's Palsy	1.13	(1.00, 1.29)	(0.97, 1.32)
Cardiomyopathy; Heart Failure	0.96	(0.93, 0.99)	(0.92, 1.00)
Cellulitis and Infection	1.06	(0.99, 1.14)	(0.97, 1.15)
Cholecystitis or Cholelithiasis	0.85	(0.73, 1.00)	(0.71, 1.03)
Guillain-Barré Syndrome	2.19	(0.97, 5.42)	(0.82, 6.50)
Immune Thrombocytopenia	1.35	(0.75, 2.50)	(0.67, 2.78)
Thrombocytopenia	0.89	(0.83, 0.95)	(0.82, 0.97)
Transient Ischemic Attack	0.94	(0.80, 1.11)	(0.78, 1.14)

No statistically significant elevated risk was detected

* Data cut: 11/30/2023, # of PCV 20 total uptake: 2,832,555
** IRR = Incidence rate ratio

Estimated Posterior Distributions of IRR from Sequential Analyses at Different Data Cuts – Myocarditis/Pericarditis

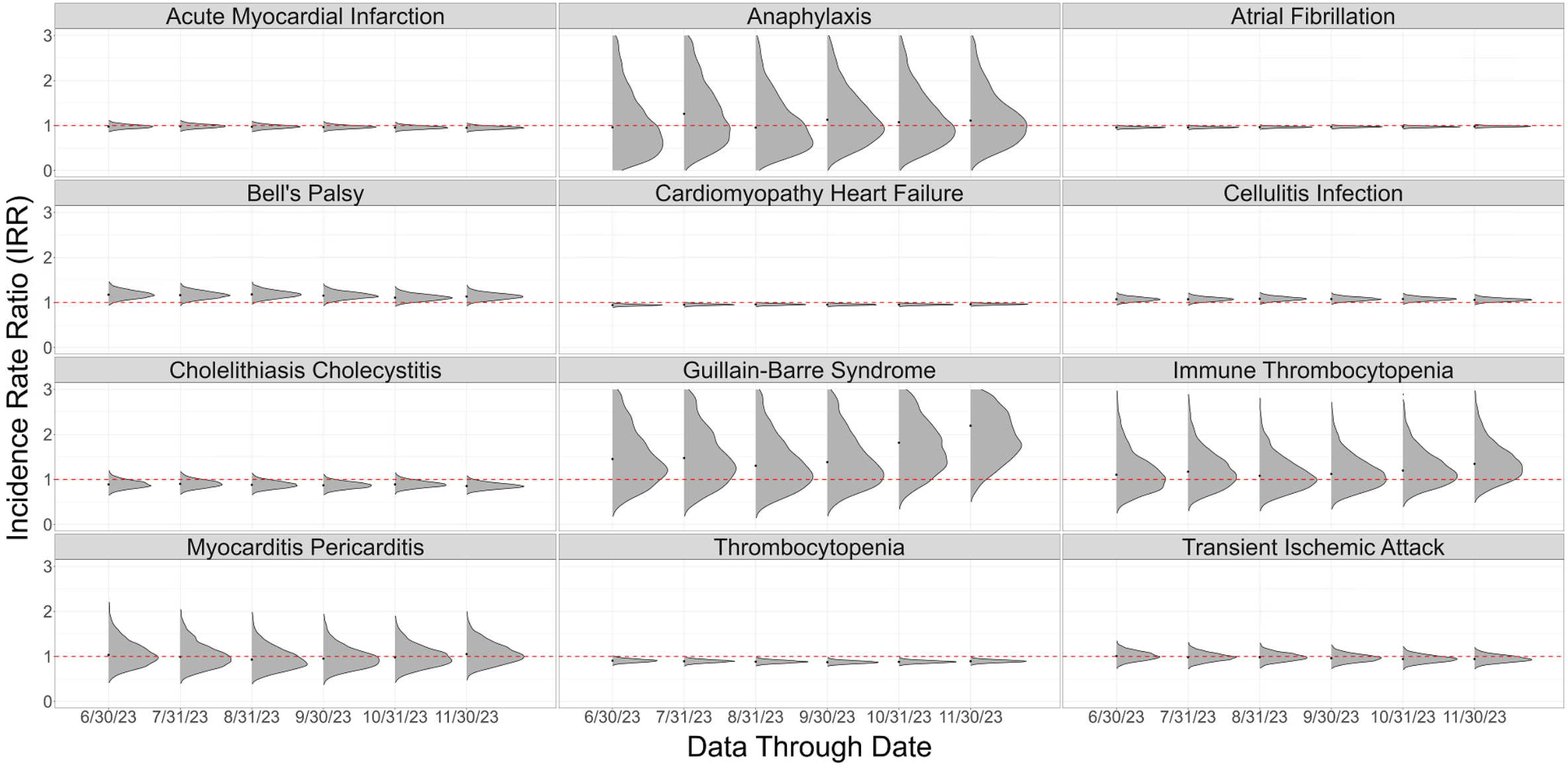


IRR posterior distribution from Bayesian model using data through November 2023

Median of the Posterior Distribution (IRR = 1.05)

IRR = 1, meaning no rate difference in the health outcome between risk and comparison windows

Estimated Posterior Distributions of IRR from Sequential Analyses at Different Data Cuts – All Health Outcomes



Summary

- Incidence rates post PCV 20
  - Incidence rates for Myocarditis/Pericarditis, Anaphylaxis, Guillain-Barré Syndrome and Immune Thrombocytopenia are less than 100 cases per 100,000 person-years

- Signal detection
  - The estimated IRRs and CIs did not identify statistically significant risk elevation following PCV 20 vaccination for any of the outcomes (no significant evidence that IRR > 1)
    - We continue to monitor and evaluate the health outcomes

Note: Summary based on results from data cut: 11/30/2023

Limitations for Sequential Monitoring

- Statistically significant results may appear and disappear from month to month due to use of Bayesian methods.
- Events were not chart-confirmed and the Positive Predictive Value (PPV) for some outcomes are likely low, e.g. The PPV for Bell's Palsy was 12.66% and the PPV for ITP was 4.00% in a recent study.
- Residual confounding may still exist given the limited number of variables being adjusted in the regression model
- Large uncertainty of incidence rate ratios for certain outcomes
  - Small number of events, wide credible intervals

Future Planning

- Active monitoring to continue monthly
- End of surveillance analysis may be performed using the self-controlled case series (SCCS) method for each outcome where there is sufficient sample size for a powered analysis

Summary of Evidence

- No GBS signal in clinical trials
- GBS signal for PCV20 in VAERS
- Currently no GBS signal in Medicare sequential monitoring. Monitoring is ongoing.
- Significant uncertainty because of the small number of cases observed
- Limitations in VAERS and Medicare studies

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