

Vaccine Safety Datalink (VSD) update on post-licensure safety monitoring of recombinant zoster vaccine (RZV, Shingrix)

**October 2020 Advisory Committee on
Immunization Practices (ACIP) meeting**

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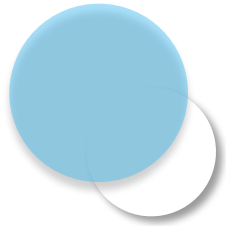
Kaiser Permanente Washington Health Research Institute

Acknowledgements

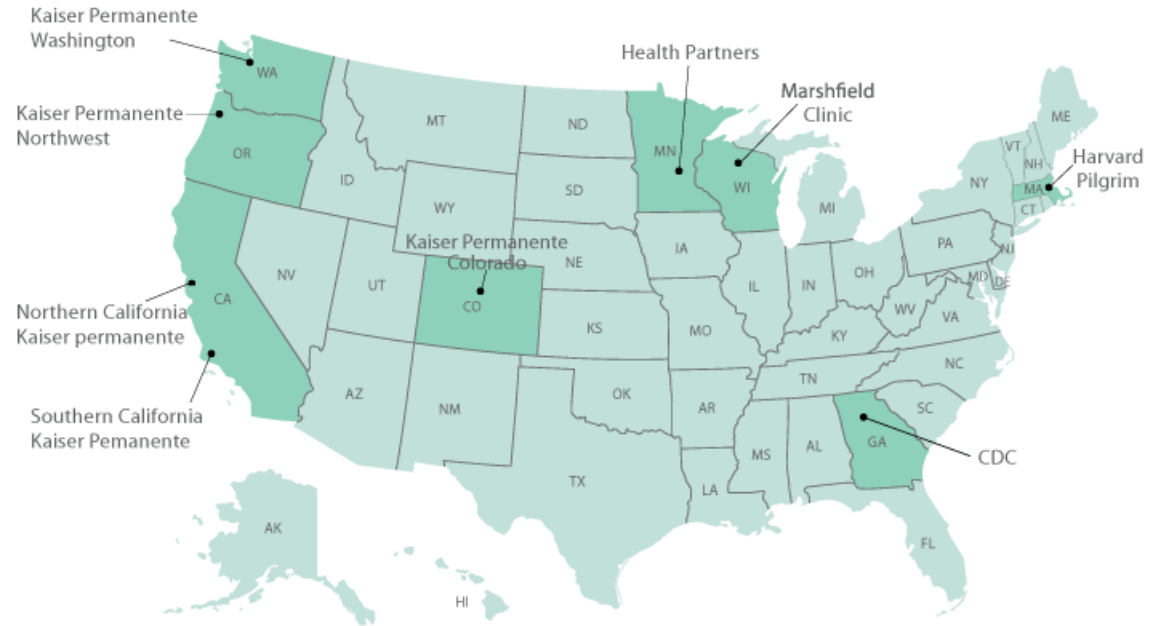
- KPWHRI team
 - Onchee Yu, Ernesto Ulloa, Rachel Burganowski, Andrea Cook, Mike Jackson, Erika Kiniry
- CDC team members
 - Frank DeStefano, Jonathan Duffy, Mike McNeil, Tanya Myers, Tom Shimabukuro, Lakshmi Sukumaran, Eric Weintraub
- Other VSD team members
 - Ed Belongia, Matt Daley, Elyse Kharbanda, Nicky Klein, Allison Naleway, Hung-Fu Tseng, Katherine Yih



VSD

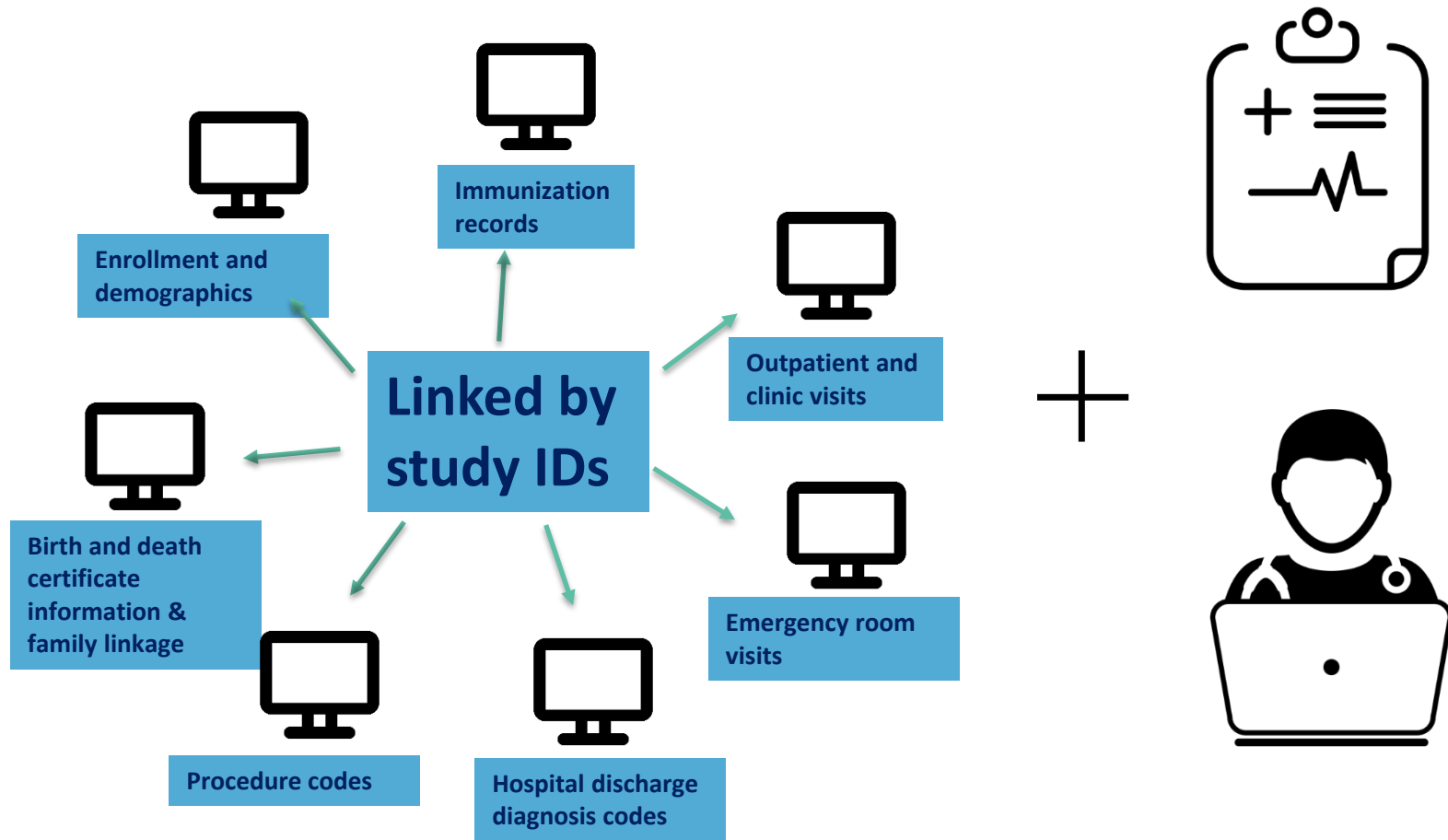


Vaccine Safety Datalink



- Collaboration established in 1990
- CDC and **8** participating integrated healthcare organizations
- Medical care and demographic data on over **12.1** million persons per year (~**3.7** % of U.S. population)

VSD links electronic files + manual chart review



Images created by Wilson Joseph, Megan Mitchell, Ananth, and Iga from the noun project

Slide courtesy of Dr. Tom Shimabukuro at the Centers for Disease Control and Prevention

VSDs targeted active surveillance methodology

- Also referred to as Rapid Cycle Analysis (RCA)
- Established in 2006 for near real-time vaccine safety monitoring
- Like a traditional epidemiologic study, we pre-specify:
 - ✓ Primary vaccine exposure and comparator populations
 - ✓ Adverse event (AE) outcome targets of interest (about 5-10)
 - ✓ Potential confounding factors
- Unlike a traditional epidemiologic study, it involves:
 - ✓ Routine & cumulative updating of study data (e.g., monthly)
 - ✓ Repeated interim analyses over time to compare risks
- Statistically significant findings are preliminary “signals”
- Signals are fully investigated with numerous follow-up activities (e.g., chart validation to confirm true incident cases)

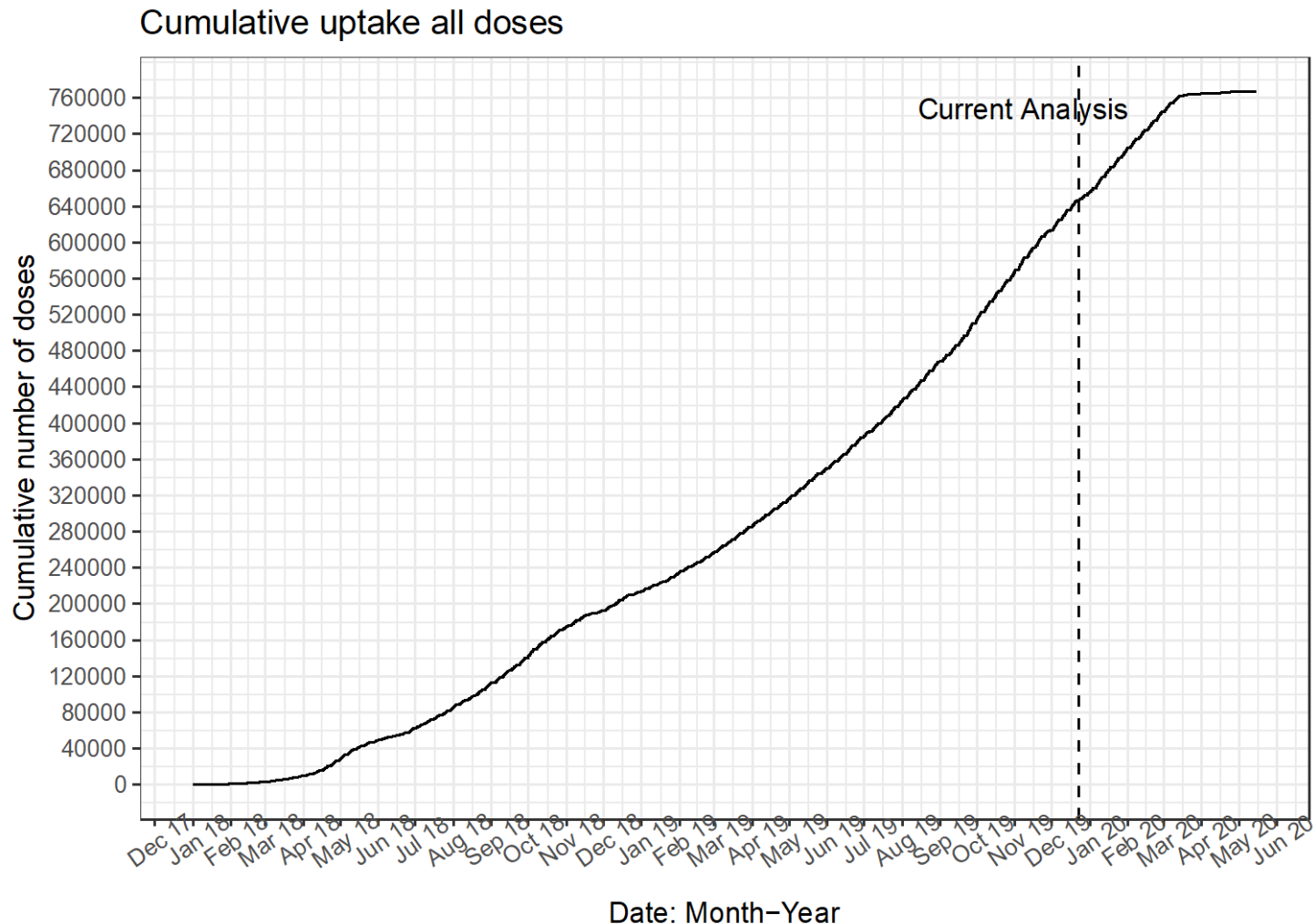
Design for RZV safety surveillance

- **Aim:** To sequentially monitor RZV safety among adults 50+ years
- **Surveillance period:** January 2018 – December 2019
- **Primary analysis:** historical Zostavax (ZVL) vaccine comparators
 - Compared adverse event risks among 50-65 year-old RZV recipients with 60-65 year-old ZVL vaccinees (2013-2017)
- **Secondary analyses:** age-comparable concurrent comparators
 - Had a well-visit or other vaccine during RZV uptake period
- **Measured baseline covariates (selected)**
 - Dose (1 or 2), concomitant vaccines, prior receipt of ZVL, health care utilization measures, chronic medical conditions
- **Sequential interim analysis plan**
 - 1st analysis in June 2018 then 18 more monthly analyses

Pre-specified health outcomes of interest (HOIs)

- **Formal sequential analyses for 10 high priority outcomes (incident events occurring 1-42 days post-vaccination)**
 - Acute myocardial infarction (MI), stroke
 - Convulsion, polymyalgia rheumatica, supraventricular tachycardia, Bell's palsy
 - Anaphylaxis (days 0-1), giant cell arteritis, optic ischemic neuropathy, GBS
- **Exploratory analyses for other post-vaccination outcomes**
 - 1-42 days: gout, pneumonia, non-specific adverse effects, stroke subtypes, pericarditis, myocarditis, and eye-related outcomes (e.g., keratitis)
 - 1-7 days: systemic reactions, local reactions, urgent care or ED visit

RZV Uptake across all VSD sites (647,833 doses)



Sequential analysis results for RZV

N = 647,833	Observed Events	Expected Events	Observed rate/100K	RR	Preliminary signal¹?
Stroke	287	376.2	44.3	0.76	No
Acute MI	320	379.8	49.4	0.84	No
Polymyalgia rheumatica	134	152.7	20.7	0.88	No
Supraventricular tachycardia	151	125.5	23.3	1.20	No
Convulsion Assoc. terms	112	123.6	17.3	0.91	No
Bell's Palsy	86	95.72	13.3	0.90	Yes ²
Anaphylaxis	20	15.15	3.1	1.32	No
Giant Cell Arteritis	35	49.20	5.4	0.71	No
Optic Ischemic Neuropathy	37	52.61	5.7	0.70	No
GBS	6	4.83	0.9	1.24	Yes ³

1. Statistical significance is based on an adjusted sequential likelihood ratio test of $H_0: RR=1$ vs $H_A: RR>1$

2. Signaled preliminarily at Analysis #5 (36 events vs 24 expected; $RR=1.51$, adj $p=0.03$) but effect attenuated.

3. Signaled preliminarily at Analysis #2 (3 vs 0.6 expected; $RR=5.25$, adj $p=0.02$)

Validation of GBS cases via medical chart review

- Among the 6 presumptive RZV GBS cases (i.e., ICD-9/10 based)
 - 3 were ruled out (had symptoms prior to vaccination)
 - 3 were confirmed (2 as Brighton level 2, 1 as Brighton level 3)
- Among the 5 presumptive ZVL-GBS cases (i.e., ICD-9/10 based)
 - 2 cases were ruled out
 - 1 case was unable to be validated (chart data were missing)
 - 2 confirmed (both Brighton level 2)
- Based on chart validated outcomes, our best estimates are:
 - RR = 1.55 (95% CI: 0.17, 18.60) [assuming 2 ZVL cases]
 - RR = 1.03 (95% CI: 0.14, 7.73) [assuming 3 ZVL cases]

Summary

- 647,833 RZV doses were received in VSD, Jan 2018 - Dec 2019
- A preliminary signal was observed for Bell's Palsy (RR=1.51), but this effect did not persist as more doses accrued (RR = 0.90)
- A preliminary signal was observed for GBS (RR=5.25) based on ICD-9/10 codes, and this effect waned over time (RR=1.24)
 - Chart review was conducted to confirm true GBS case status
 - In the final chart-confirmed analysis, VSD has insufficient evidence to determine if there is an increased risk of GBS
 - RR = 1.55 (95% CI: 0.17, 18.60)
- There is no sustained evidence of increased risk among RZV recipients for any of the pre-specified outcomes
- Subgroup & secondary analyses provide further reassurance (data not shown)