Vaccine Safety Monitoring in the United States

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Disclosure

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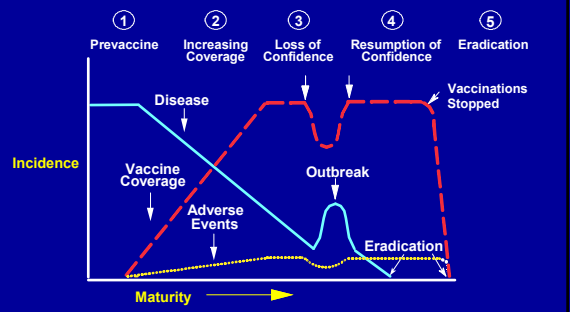
Presentation Overview

- Why Safety Monitoring Matters
- Vaccine Safety Monitoring
  - Clinical Trials
  - Licensure
  - Post Licensure
    - Passive Surveillance
    - Active Surveillance
    - Clinical Assessment
  - Causality Assessment
- Influenza Vaccine Safety

Why Safety Monitoring Matters

- Ensure that benefits of vaccines outweigh the risks for individuals and populations
  - High standards as often for healthy children and prevention
- Optimize the use of limited resources
- Improve and maintain public confidence in vaccines – high vaccine coverage

Evolution of Immunization Program and Prominence of Vaccine Safety



Chen & Hibbs, Pediatr Ann. , 1998

Post hoc ergo propter hoc

after this, therefore because of this", is a logical fallacy ...since that event *followed* this one, that event must have been *caused* by this one.

The fallacy lies in coming to a conclusion based *solely* on the order of events, rather than taking into account other factors that might rule out the connection.

http://dictionary.sensagent.com/post+hoc+ergo+propter+hoc/en-en/

Adverse Events Following Immunization (AEFI) will occur

- Important to differentiate between coincidental events and events causally related to vaccination
  - 2,500 miscarriages and 3,000 heart attacks each day in US
- Important to rapidly identify and follow-up vaccine safety signals
- Robust scientific follow up takes time

Other Contemporary Issues Impacting Vaccine Safety

- Trust in corporations and gov't low
- Fear of 'pharmaceutical industrial complex'
- Growing interest in natural products - "green our vaccines"
- Changing medical model
  - Shared decision making > paternalism
  - More patients in less time
- The role of the media
- Internet

Parental Vaccine Behaviors

- Social Norm is to vaccinate
  - Nationally, infant coverage (19-35 months) at or near all time highs
- Rates of parents claiming exemptions to school immunization requirements
  - Increasing in many states
  - Geographically clustered
  - Associated with outbreaks of measles and pertussis
- Increasingly parents are delaying or refusing vaccines
  - 23% of parents of children <5 delay
  - 16.7% of parents refused 1 or more vaccine

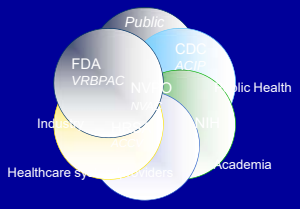
Hill HA, MMWR, 2015; Omer SB, NEJM, 2012; Atwell JE, Pediatrics, 2013; Hough-Telford C, Pediatrics, 2016; Nowak GJ, Human Vaccines and Immunotherapeutics, 2017.

77% of Parents Reported Vaccine Concerns

- 38% - painful to receive so many shots
- 36% - too many vaccines at one doctors visit
- 34% - too many vaccines if first two years of life
- 32% - may cause fevers
- 30% - may cause learning disabilities, such as autism
- 26% - ingredients unsafe
- 17% - not tested enough for safety
- 16% - may cause chronic disease
- 11% - unlikely to get diseases
- 9% - not enough vaccine supply
- 8% - diseases not serious

Kennedy, Health Affairs, 2011

The Vaccine Safety System



Other federal contributors: AHRQ, CMS, DoD, VA

Phase I Clinical Trials - Safety

- No Gross Toxicity
- Gather safety data on dose-related immune response

20-100 Healthy Subjects

Phase II Clinical Trials - Safety

- Assess common, short-term side effects
- Explore reactions between investigational drug and already licensed drug

100-100 (up to 1,000) Healthy Subject

Phase III Clinical Trials - Safety

- Confirm safety
- Define risk/benefit relationship
- Gather information for licensure application and package insert

1,000-20,000+ Persons

Pro's of Clinical Trials

- The Gold Standard - Double blind, randomized trials
  - Reduce Confounding
  - Reduce Bias
- Strict inclusion and exclusion criteria
  - Reduces risk to participants
  - Reduces Confounding
- Incremental phases to minimize risk and optimize information obtained

Limitations of Clinical Trials

- Inclusion/Exclusion criteria
  - Can not evaluate AEs in persons excluded from studies (medicated, concurrent medical conditions)
  - Can not evaluate delayed AEs
- Small sample size
  - Can not evaluate rare AEs
  - Can not evaluate AEs in sub-populations

Sample Sizes Needed to Detect Rare Adverse Events

Rates (%)	Sample Size *	No. Potentially Affected
0.1 vs. 0.2	50,000	4,000
0.1 vs. 0.3	17,500	8,000
0.05 vs. 0.1	100,000	2,000
0.01 vs. 0.02	500,000	400
0.01 vs. 0.03	175,000	800

* Two-arm trial, power 80%, alpha (2 sided) = 5%

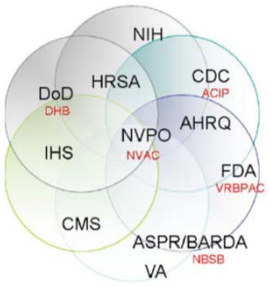
Source: Ellenberg 2001

Post-Licensure Studies (Phase IV)

- Expand safety profile to include:
  - Intermediate or rare AEs
  - Subpopulations
- Address emerging safety issues

US Federal Vaccine System

- NIH – basic research, vaccine development & evaluation incl. clinical trials
- FDA – licensure, inspection, post-licensure surveillance
- CDC – post-licensure surveillance, clinical assessment, communication
- HRSA - compensation
- NVPO – coordination



Advisory Committees in Red

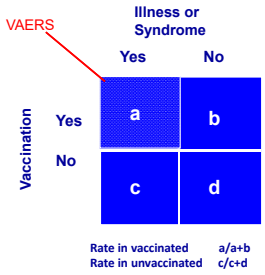
Passive Surveillance

- Purpose: to detect signals of unanticipated events that may deserve further follow-up
- Primary Limitation: Usually can not determine if event is caused by vaccine or coincidental
  - Lack of good denominator and comparison (unvaccinated) group
  - Potential Bias (under-reporting, incomplete reporting, over-reporting, etc).

Vaccine Adverse Event Reporting System (VAERS)

- Co-administered by CDC and FDA
- Accepts reports from anyone
- Limitations
  - Under reporting
  - Incomplete data
- Designed for detecting signals or generating hypothesis
  - Can not assess causality

Establishing Causal Link: Adverse Event and Vaccine



Rate in vaccinated a/a+b
Rate in unvaccinated c/c+d

Source: R T Chen

Perception of VAERS

"There have been estimates that fewer than 10 percent, even as low as 1 to 4 percent, of adverse events which occur after prescription drug or vaccine use are ever reported to government adverse event reporting systems….If only 1 to 4 percent of all adverse events associated with GARDASIL vaccination are being reported to VAERS, there could have been up to 38,000 health problems after GARDASIL vaccination in 2006 which were never reported"

Barbara Loe Fisher, National Vaccine Information Center (NVIC)
http://www.nvic.org/nvic-archives/pressrelease/hpvfeb212007.aspx

Assessing Associations between Vaccines & Adverse Events: Active Surveillance

- Vaccine Safety Datalink (VSD)
- Post-licensure Rapid Immunization Safety Monitoring (PRISM) Network
- Centers for Medicare & Medicaid Services (CMS)
- Department of Defense (DoD)
- Department of Veterans Affairs (VA)
- Indian Health Service (IHS)

Vaccine Safety Datalink (VSD)

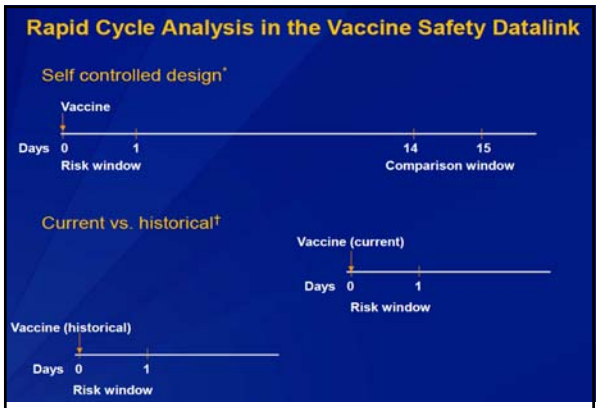
- Developed by CDC >20 years ago
- ~9 million people in 9 linked MCOs
- Includes vaccination, hospital, outpatient, and laboratory data
- Rapidly conduct chart review if needed

Rapid Cycle Analysis

- Developed by VSD to monitor pre-specified outcomes in near real-time
- Every week, compares rates of pre-specified outcomes in pre-specified time windows

Pre-specified Outcomes Example: 2009-10 H1N1

- Guillain-Barré Syndrome
- Demyelinating disease
- Disorders of the peripheral nervous system and neuropathies
- Seizures (epilepsy, convulsions)
- Narcolepsy/cataplexy
- Select pregnancy outcomes (SAb, pre-eclampsia, stillbirth)
- Encephalitis, myelitis, encephalomyelitis
- Bell's Palsy
- Other cranial nerve disorders (Facial/Trigeminal nerve disorders)
- Ataxia (other cerebellar ataxia, ataxia)
- Anaphylaxis
- Angioneurotic edema, Allergic Reaction, Urticaria
- Myocarditis and pericarditis (LAIV only)
- Hemorrhagic stroke
- Ischemic stroke (excludes transient ischemic attack)
- Wheezing (LAIV only)
  - Asthma, wheezing, respiratory distress/insufficiency, other diseases of trachea/bronchi
  - Multiple definitions with and without bronchiolitis
- TP/ITP
- Other non-fatal serious adverse events
- Death



Shimabukuro, ACIP, June 24, 2015

Signal Evaluation Steps Rapid Cycle Analysis

- Check data quality
- Check whether comparison groups are defined appropriately
- Repeat analysis with different control group (e.g., concurrent vs. historical) or different vaccine
- Check for temporal clustering of outcomes during a post-vaccination time window
- Adjust for confounding, e.g., stratified and multivariate analyses
- Review charts to confirm/exclude cases and obtain additional information on potential confounders
- Historically, 90% of signals turn out to be spurious

Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Developed by National Vaccine Program Office (NVPO) & Harvard Pilgrim for 2009-10 H1N1
  - 8 State Immunization Registries captured exposures
  - 4 large Health Plans captured some exposures and outcomes
- Ongoing FDA Activity as a part of Sentinel
- 170 million people under active surveillance
- Chart review capable (but not quickly)
- Rapid Cycle Analysis (RCA) and ad hoc studies

Salmon et al, Health Affairs, 2013; Baker et al, Vaccine, 2013; Baker et al, Am J Epidemiol, 2015.

Centers for Medicare & Medicaid Services (CMS)

- ~14 million vaccinations annually
- Predominantly ages 65 years and older
- Chart review capable (but not quickly)
- Focus on influenza vaccine

Defense Medical Surveillance System (DoD)

- 2.6 million persons
- Healthy adults, limited ages represented
- Chart-review capable
- Predominantly focused on influenza vaccine

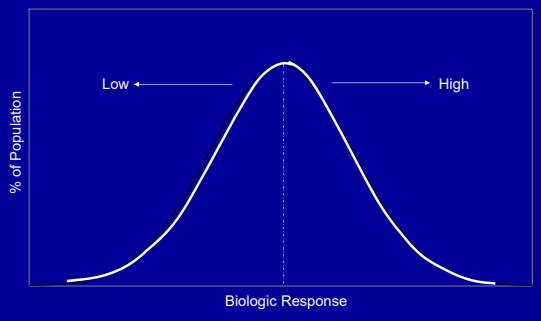
Dept. of Veterans Affairs

- ~5 million persons
- Captures elderly and Federal employees (other than DoD)
- Chart-review capable
- Predominantly focused on influenza vaccine

Influenza Awareness System (IHS)

- ~350,000 people from all life phases of the American Indian and Alaska Native community
- Chart-review capable
- Predominantly focused on influenza vaccine

Distribution of Biologic Response* to Immunizations in the Population



* e.g., Immunogenicity, Reactogenicity

Source: R T Chen

CISA Clinical Immunization Safety Assessment Network

- The Need:
  - Vaccine adverse events occur rarely for each clinician
  - Medical "outliers" difficult to advance science on, like orphan disease (leukemia)
- The Solution:
  - Academic centers of excellence
  - Vaccine safety clinicians
  - Clinical subspecialty for referrals
  - Laboratory research capabilities

Source: R T Chen

CISA Clinical Immunization Safety Assessment Network

- Tasks:
  - Standardized assessment/management of persons with:
    - Known reaction (e.g., intussusception)
    - Suspect new vaccine adverse event syndrome
    - Next dose in patient with prior vaccine adverse event ? (e.g., HHE, limb swelling)
  - Real time consult for clinicians + F/U for compliance & outcome
- Goal:
  - Increase scientific understanding of "outliers"
    - Immunology
    - Pathophysiology
    - Genetic or other predisposing risk factors
  - Maximize utility of VAERS as "disease registry".
  - Disseminate protocols and findings
  - Create new subspecialty of "Immunization Safety"

Source: R T Chen

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Federal Immunization Safety Task Force (ISTF)

- Includes representatives from all agencies within HHS with assets in vaccine safety, DoD, and VA

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SIGNAL ≠ ASSOCIATION ≠ CAUSALITY

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Institute of Medicine (IOM)
Immunization Safety Review Committee

- Causality assessment
- Developed in response to
  - Increasing number of vaccine safety hypotheses
  - Increasingly polarized climate
- Provides a mechanism for timely, objective, and expert review of vaccine safety hypotheses
  - Evaluate evidence for causality, biologic plausibility, and strength of competing hypotheses
  - Conduct significance assessment
  - Guide public health response
    - Research, surveillance, communications, policy review

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Existing sources of vaccine safety information inadequate for needs of clinicians

- helpful, but not based on comprehensive systematic lit reviews
- often lack clear causality conclusions for clinician audience

- extraordinarily comprehensive but need updating
- requested by Health and Human Services for updating the National Vaccine Injury Compensation Program, not for clinicians
  - not succinct
  - "evidence is inadequate to accept or reject a causal relationship" for 135 of 158 (85%) of adverse events following immunization (AEFIs) studied

The State of Vaccine Safety Science: Systematic Reviews of the Evidence

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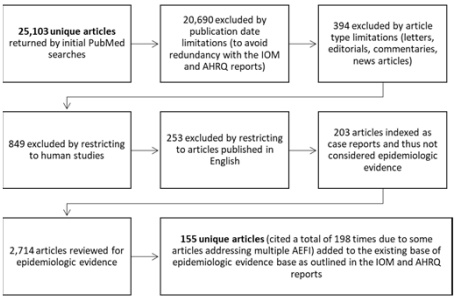
Methods

- Started with their lists of adverse events following immunization (AEFI), then added more recent AEFI of interest:
  - Narcolepsy
  - Primary Ovarian Insufficiency
  - Spontaneous Abortion
- Searched PubMed using MeSH indexing and free text terms for each AEFI
  - limited to articles published after final AHRQ search for all AEFI they included

Literature Review Diagram



Categories of Causality Conclusions

- The evidence shows a clear association between the event and at least one vaccine routinely recommended in the US.
- The evidence showed a clear association between the event and at least one previously recommended vaccine. However, these vaccine(s) are no longer used in the US, if they ever were.

Categories of Causality Conclusions

- The evidence of an association between the event and vaccines currently routinely recommended to the general population in the US is insufficient or non-existent.
- The evidence shows clear lack of association between the event and vaccines currently routinely recommended to the general population in the US.

Frequency Categories[1]

Categories	Definitions
Very common	≥ 1/10 (≥ 10%)
Common	≥ 1/100 and < 1/10 (~1%-10%)
Uncommon	≥ 1/1,000 and < 1/100 (~0.1-1%)
Rare	≥ 1/10,000 and < 1/1,000 (~0.01-0.1%)
Very rare	< 1/10,000 (< 0.01%)

Results

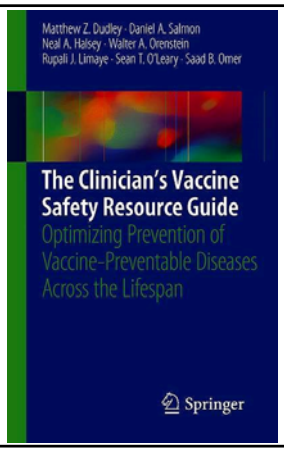
- Anaphylaxis (very rare)
- Arthralgia/Arthritis (mild, acute, and transient – not chronic)
- Deltoid Bursitis (only from incorrect administration)
- Disseminated Varicella Infection (only in immune deficient individuals)
- Encephalitis (very rare)
- Febrile Seizures (scary to witness but rare and no long-term sequelae)
- Guillain-Barré Syndrome (very rare)
- Hepatitis (only in immune deficient individuals)
- Herpes Zoster (rare)
- Immune Thrombocytopenic Purpura (very rare)
- Meningitis (very rare)
- Syncope (rare)

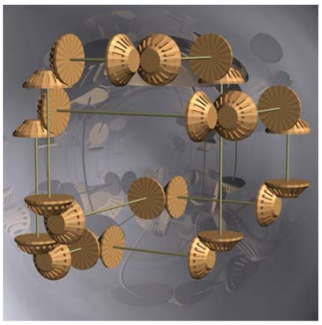
Results

- No causal relationship established for other 35 AEFI
- Clear lack of association established for some AEFI/vaccines:
  - influenza vaccines do not cause asthma
  - childhood vaccines do not cause autism
  - vaccines do not cause diabetes
  - vaccines given to immunocompetent persons do not cause hepatitis
  - influenza vaccines do not cause MS in adults
  - DTP and hepatitis B vaccines do not cause SIDS

Conclusions

Although vaccines currently recommended for the general population in the U.S. do cause some adverse reactions, vaccines have an excellent safety profile overall and provide protection against infectious diseases to individuals and the general population.





National Center for Emerging and Zoonotic Infectious Diseases

CDC

Update on post-licensure safety monitoring of recombinant zoster vaccine (RZV, Shingrix)

February 2019 Advisory Committee on Immunization Practices (ACIP) meeting

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

February 28, 2019

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Recombinant Zoster Vaccine (RZV)

- Adjuvanted ($AS01_B$) glycoprotein vaccine
- Licensed by FDA in October 2017
- Preferentially recommended by ACIP for adults ≥50 years in October 2017
  - Previously-licensed live-attenuated zoster vaccine (ZVL, Zostavax) is recommended for adults ≥60 years
- 85% of vaccinated study participants in pre-licensure clinical trials reported local or systemic reactions
  - 17% experienced grade 3 reactions*
- Rates of serious adverse events similar between RZV and placebo groups

*Erythema or induration >3.5 inches or systemic symptoms that interfere with normal activity

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Pre-specified outcomes (based on pre-licensure trials and ZVL reports)

- Acute myocardial infarction
- Amyotrophic lateral sclerosis
- Anaphylaxis
- Autoimmune disorders
- Autoimmune vasculitis
- Bell's Palsy
- Co-administration with another adjuvanted vaccine
- Death
- Gout
- Guillain-Barré syndrome
- Herpes zoster
- Idiopathic thrombocytopenia
- Inflammatory eye disease
- Lymphadenitis
- Meningitis
- Neuropathy
- Optic ischemic neuropathy
- Osteonecrosis
- Post-herpetic neuralgia
- Seizures / convulsions
- Stroke / CVA
- Supraventricular tachyarrhythmias

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Reports to VAERS following RZV

- Reporting rates (based on 8.59 million doses distributed)
  - All reports: 167 per 100,000 doses distributed
  - Serious reports*: 4 per 100,000 doses distributed

Report characteristics	N (%)
Total reports	14,381
Female	9694 (67.4)
Non-serious	14,029 (97.6)
Type of reporter	
Manufacturer	5196 (36.1)
Healthcare professional	5179 (36.0)
Patient	3201 (22.3)
Other	805 (5.6)
Age groups (years)	
<50†	72 (0.5)
50-59	2919 (20.3)
60-69	4947 (34.3)
70-79	3166 (22.0)
80+	873 (6.1)
Not reported or unknown	2404 (16.7)
RZV given alone	13,465 (93.6)

*Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability (FDA routinely reviews all serious reports)

†RZV not approved for use in <50 y/o

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Most common signs and symptoms in reports to VAERS following RZV and review of pre-specified outcomes

Signs and symptoms (MedDRA Preferred Terms)*	14,381 total reports n (%)
Pyrexia (fever)	3619 (25.2)
Chills	3005 (20.9)
Injection site pain	2973 (20.7)
Pain	2864 (19.9)
Headache	2681(18.6)
Injection site erythema	2432 (16.9)
Pain in extremity	2301 (16.0)
Fatigue	2300 (16.0)
Myalgia	1705 (11.9)
Injection site swelling	1666 (11.6)

*Not mutually exclusive; a report may contain more than one MedDRA Preferred Term

- Systemic signs and symptoms and injection site reactions were the most commonly reported AEs
- No unexpected patterns detected by physician reviewers of reports of the 22 pre-specified outcomes

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Data mining

- Empirical Bayesian (EB) data mining identifies AEs that are reported more frequently than expected, adjusting for age, sex, and the year in which reports are received
  - Identifies AEs that are reported at least twice as frequently as would be expected by chance following a given vaccine (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2)
- One empirical Bayesian data mining finding to date for RZV for the MedDRA PT:
  - "Product administered to patient of inappropriate age" when looking at individuals aged 19-44.9 years old

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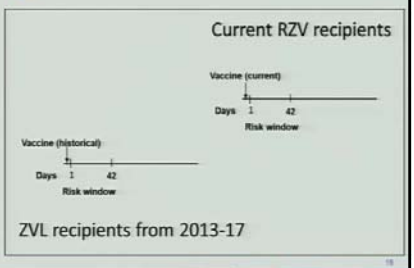
Primary analysis for RZV RCA is a historical comparator design

- Monthly near real-time sequential monitoring of pre-specified outcomes
- 18 planned monthly analyses (1st at 6 months), with an 18 week data lag
- Uses ICD-10/9 coded diagnoses
- 3rd analysis has been completed
- **Test statistic:** Adjusted likelihood ratio test (H_0: RR=1 versus H_A: RR>1)



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10 pre-specified RZV RCA outcomes*

High priority pre-specified outcomes	Risk interval (days)
Acute myocardial infarction	1-42
Anaphylaxis	0-1
Bell's palsy	1-42
Convulsion	1-42
Giant cell arteritis	1-42
Guillain-Barré syndrome	1-42
Optic ischemic neuropathy	1-42
Polymyalgia rheumatica	1-42
Stroke	1-42
Supraventricular tachycardia	1-42

*Other outcomes for descriptive analysis only include: gout, keratitis, local reactions, non-specific adverse effects, pneumonia, systemic reactions, uveitis and retinitis, and zoster ocular disease

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Secondary analyses for RZV RCA in the VSD uses 2 concurrent comparators

1. Had an ICD-10 coded well-visit during the RZV uptake period
2. Received some other vaccine (e.g., for pneumonia, Td, Tdap, IIV) during the RZV uptake period

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RZV RCA results: statistical signal for GBS detected

High priority outcomes	Obs events	Exp events	Obs rate (per 100K)	RR	Prelim statistical signal
Stroke	61	63	57.5	0.97	No
Acute MI	56	62	52.8	0.90	No
Polymyalgia rheumatic	16	27	15.1	0.60	No
Supraventricular tachycardia	19	20	17.9	0.94	No
Convulsion assoc. terms	20	20	18.8	0.99	No
Bell's palsy	23	15	21.7	1.52	No
Anaphylaxis	4	3	3.8	1.39	No
Giant cell arteritis	3	8	2.8	0.36	No
Optic ischemic neuropathy	5	8	4.7	0.59	No
Guillain-Barré syndrome (GBS)	4	0.8*	3.8	5.06	Yes**

*Based on 5 historical GBS events
**GBS had 1st preliminary statistical signal at 2nd analysis (3 events vs 0.6 expected; RR=5.25)

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Signal assessment: short chart review of automated cases

Description of the four ICD-10 coded cases of GBS	Adjudication
65 y/o with a history of GBS diagnosed years prior, no recurrence or exacerbation after RZV	Historical case, not a true incident (i.e., 'new') case
72 y/o with a history of GBS diagnosed years prior, no recurrence or exacerbation after RZV	Historical case, not a true incident (i.e., 'new') case
68 y/o female who received concurrent PCV13 and had ZVL 7 years prior, had GBS symptom onset 13 days post-vaccination and was hospitalized 15 days post-vaccination	Short chart review confirmed case, Brighton Criteria level 2*
59 y/o female who received concurrent hepatitis B vaccination had chart documented GBS onset no later than 1 day post-vaccination, but sx may have started prior to vaccination. Patient had some signs and sx in the month prior and in the days leading up to vaccination suggestive of an infection (i.e., vague sx and respiratory and GI sx prior to GBS admission)	Short chart review confirmed case, Brighton Criteria level 1*, actual GBS symptom onset uncertain

*Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

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Signal assessment:
2 cases ruled out, 1 confirmed, 1 confirmed with uncertain onset

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Summary of VSD RCA for RZV (3rd analysis of 18 planned)

- 106,121 doses of RZV administered in VSD, Jan-Aug 2018
- No evidence of increased risk for any of the pre-specified outcomes except GBS (in automated, ICD-10/9 analyses)
- Detected a statistical signal* for GBS in primary (ZVL historical comparator) analysis and consistently elevated RR across other comparators
  - RR=5.06 for ZVL comparators*
  - RR=2.95 for well-visit comparators†
  - RR=3.25 for 'received some other vaccine' comparators†

*Likelihood ratio exceeded critical value; †adjusted likelihood ratio test not conducted on secondary analyses

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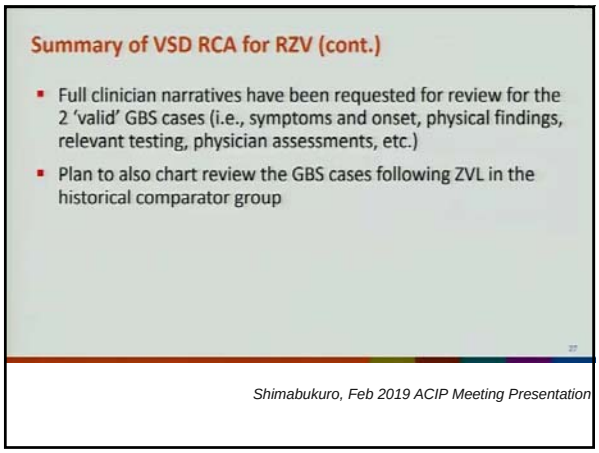

Shimabukuro, Feb 2019 ACIP Meeting Presentation

Take Home Messages

- Very robust vaccine safety system
- Involves a broad range of Federal agencies and non-Federal partners
- Vaccine safety concerns will not go away, so we need timely data

Vaccine Safety Monitoring in the US

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