

Vaccine Safety Signal Detection and Assessment

Karen R. Broder, MD

Claudia Vellozzi, MD, MPH

Frank DeStefano, MD, MPH

Immunization Safety Office

Centers for Disease Control and Prevention

Atlanta, Georgia

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National Center for Emerging and Zoonotic Infectious Diseases

Division of Healthcare Quality and Promotion



Disclaimer

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

Outline: Vaccine Safety Signal

- ❑ Background
- ❑ Detection
- ❑ Assessment
- ❑ Case examples – United States



Definition: Vaccine Safety Signal

- ❑ Different definitions for a “signal” in the pharmacovigilance field
- ❑ The Council for International Organizations of Medical Sciences (CIOMS) proposed a signal as:
 - “Information...from one or multiple sources ..., which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”*
- ❑ In practice efforts focus on detecting signals for “adverse” events

* Source: Report of CIOMS Working Group VIII, Practical Aspects of Signal Detection in Pharmacovigilance. Geneva 2010.



Detecting Signals

- ❑ Spontaneous reporting systems are cornerstone
 - Particularly for rare or unusual adverse events
- ❑ Other sources
 - Literature, expert reviews, inquires, media, internet
 - Large linked databases
- ❑ Two main US systems
 - Vaccine Adverse Event Reporting System (VAERS)
 - Vaccine Safety Datalink (VSD)



VAERS: Spontaneous Reporting System co-administered by the FDA and CDC

Strengths

- Rapid signal detection; national in scope
- Can detect rare adverse events
- Generates hypothesis
- Requires/encourages reports from manufacturers/healthcare providers and accepts reports from others
- Data available to the public

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event (AE)
- Lack of unvaccinated comparison group

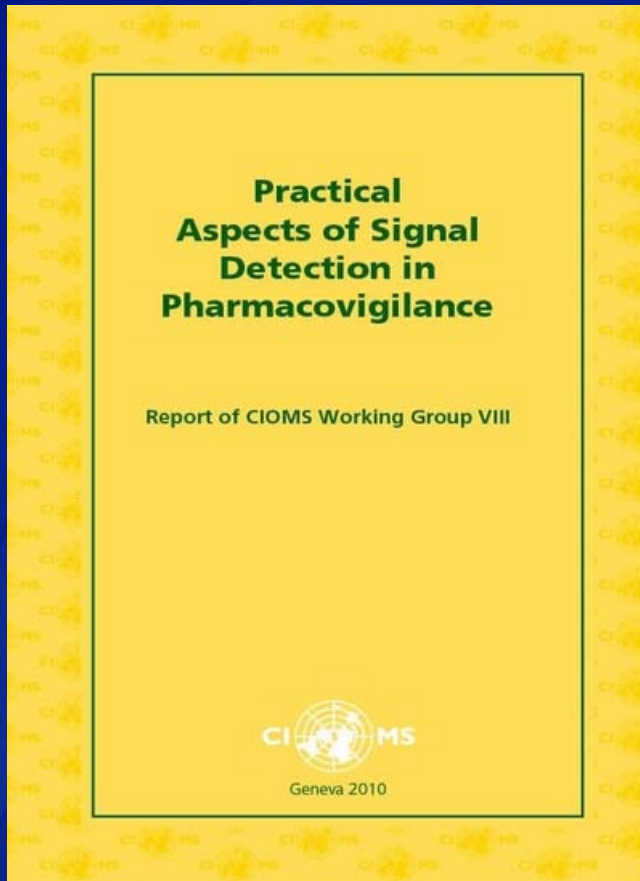
Vaccine Safety Datalink (VSD)

- ❑ Collaboration between CDC and 10 managed care organizations
 - Established in 1990
- ❑ Data on ~9.5 million persons
 - ~3% of U.S. population
- ❑ Used for planned vaccine safety studies to address hypotheses
- ❑ Conducts near real-time surveillance for adverse events after new vaccines using Rapid Cycle Analysis technique*

*Sources: Lieu et al. *Medical Care* 2007;45(10) Suppl 2:, October 2007.S89-S95.; Davis et al. *Epidemiology* 2005 (3)



Vaccine Safety Signal Management Guidance



Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and
Human Services

Food and Drug Administration
Center for Drug Evaluation and
Research (CDER)

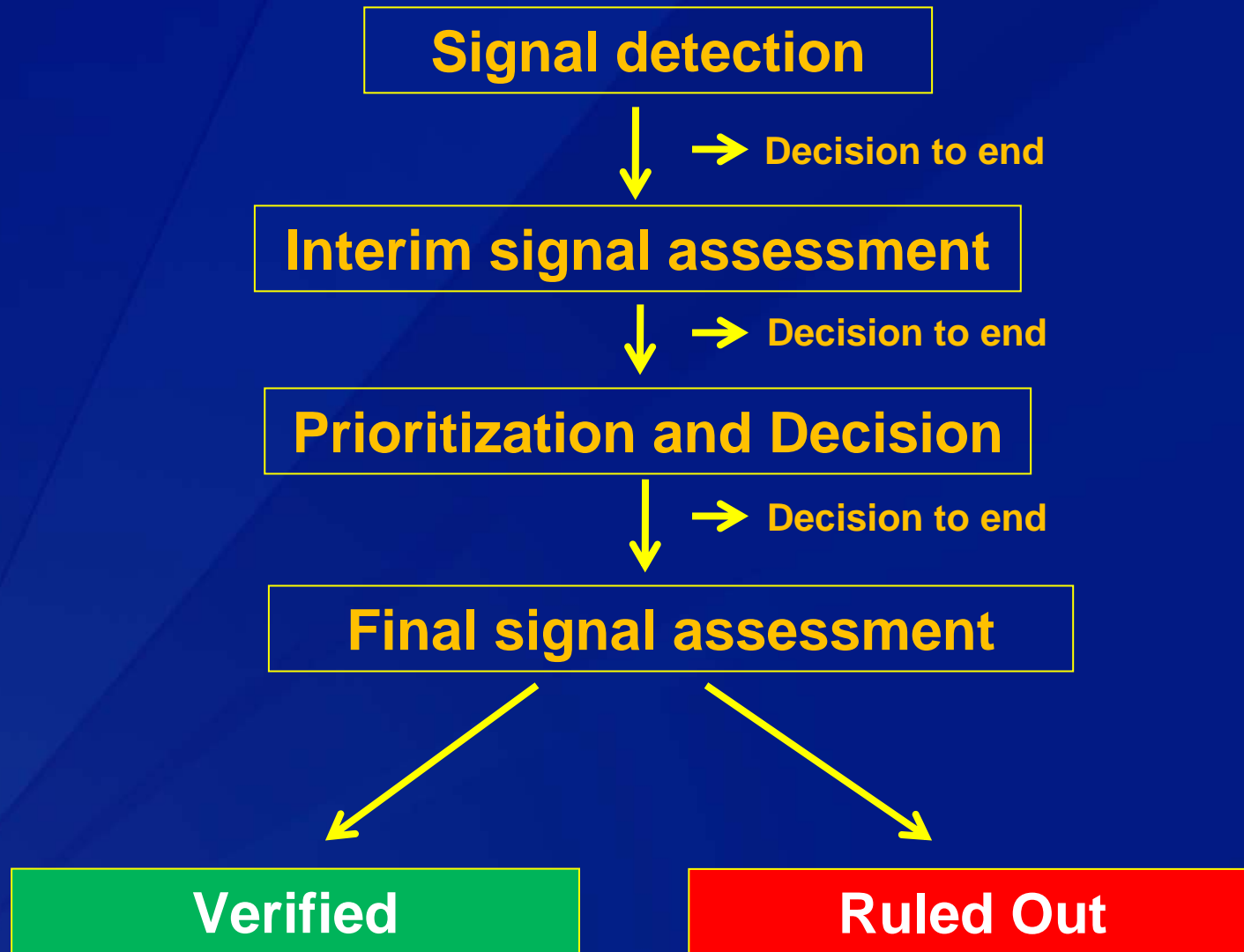
Center for Biologics Evaluation and
Research (CBER)

March 2005

Clinical Medical



Vaccine Safety Signal Management Framework



Approaches for Detecting Signals in VAERS

❑ Traditional methods

- Clinical review of individual reports
- Aggregate report review: e.g., cases counts, frequencies of adverse event coding terms, reporting trends

❑ Statistical data mining methods

- Detect disproportionate reporting of specific vaccine-event combinations in VAERS database
- A statistically significant result does NOT demonstrate an increased risk for an adverse event after vaccination or causality



Proportional Reporting Ratio (PRR)*

	Specific outcome	All other outcomes
Vaccine of interest	A	B
All other vaccines	C	D

$$PRR = \frac{a / (a + b)}{c / (c + d)}$$

Criteria: $PRR \geq 2$, $\text{Chi}^2 \geq 4$ and number of reports in A ≥ 3 *

*Evans SJW, Waller PC, Davis S (2001). *Pharmacoepidemiology and Drug Safety* 10:483-6.
Banks D, Woo J, Burwen DR, et al (2005). *Pharmacoepidemiology and Drug Safety* 14:601-609.

Empirical Bayesian Data Mining

- Assess for adverse events reported more frequently than expected after vaccine product X compared with other vaccines in the VAERS database
 - Vaccine product X – event pairs with reporting proportions at least twice that of all other vaccines (i.e. lower bound of the 90% confidence interval of the Empirical Bayesian Geometric Mean (EBGM) ($EB_{05} \geq 2$)) are further evaluated
- Shrinkage toward the null based on a prior distribution derived from the entire database
 - Limits finding signals based on small numbers of reports that might represent chance data fluctuations

Sources: Bate, A. Pharmacoepidemiology and Drug Safety. 2009;18: 427-436



Detecting Signals in VSD Using Rapid Cycle Analysis

- ❑ For each vaccine, choose specific outcomes to monitor
 - Hypothesis testing, not data mining
- ❑ Each week, evaluate the number of outcomes in specified risk window in persons who received vaccine X and compare it to the expected number of outcomes based on a comparison group
 - Controls receiving another vaccine (historical or concurrent)
 - Self-control
 - Background rates in VSD

*Sources: Lieu et al. *Medical Care* 2007;45(10) Suppl 2:, October 2007.S89-S95.
Davis et al. *Epidemiology* 2005 (3); Eric Weintraub, personal communication



Interim Assessment: VAERS Safety Signal

- ❑ Review the reports of the adverse event after the vaccine product
 - Verify diagnoses
 - Characterize clinical and laboratory features
 - Assess other potential risk factors (e.g., co-administration of vaccine, underlying health conditions)
 - Evaluate the interval between vaccination and the adverse event
 - Assess for positive re-challenge
- ❑ Calculate crude reporting rate if denominator data available (e.g., doses distributed)
 - Compare with background rates for the health outcome if available; interpret with caution



Interim Assessment: VSD Safety Signal

- ❑ Check data quality
- ❑ Check background incidences
- ❑ Check whether comparison groups are defined appropriately
- ❑ Conduct the analysis using a different control group (e.g., concurrent vs. historical) or different vaccine
- ❑ Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
- ❑ Review charts to confirm or exclude cases as true cases

Interim Assessment for Signal from any Source

- ❑ Review the literature
- ❑ Assess for similar findings in other data sources
- ❑ Consider the biological plausibility of a causal relationship between the vaccine and adverse event
- ❑ Consider need for definitive study or expert review

Signal Prioritization: Questions to Consider

- ❑ Severe clinical event?
- ❑ Unexpected or new event?
- ❑ Large number of people impacted?
- ❑ Evidence of temporal clustering of the adverse event?
- ❑ Potential to mitigate risk (alternative options, feasible strategies, including reducing medical errors)?
- ❑ High level of stakeholder and public interest?
- ❑ Suggestion of high magnitude of association?
- ❑ Suggestion of special population being impacted more than general population?

Final Signal Assessment

- ❑ Conduct carefully designed observational or clinical studies using appropriate comparison groups
 - May require more than one study
- ❑ Convene expert advisory group to review evidence (e.g., Institute of Medicine)



Case Examples - United States

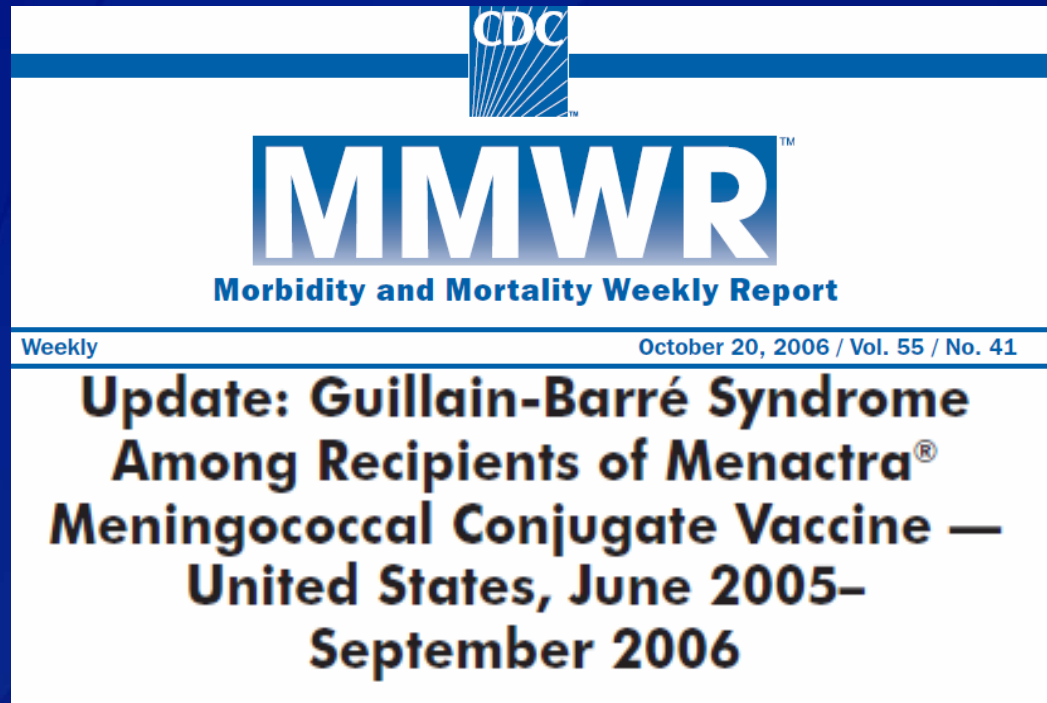


Example 1: Guillain-Barré Syndrome (GBS) after Meninogococcal Conjugate Vaccine (MCV4, Menactra®)

- ❑ MCV4 licensed for ages 11-55 years for disease caused by Neisseria meningitidis serogroups A, C, Y and W-135; recommended for adolescents (2005)
 - Prelicensure studies conducted by sanofi pasteur of approximately 7,000 recipients of MCV4: no GBS cases
- ❑ Signal detected in VAERS: 5 reports of GBS after MCV4 in VAERS (2005) (~2.5 million doses distributed) (2005)
- ❑ Interim Assessment
 - Review of VAERS reports
 - Brighton GBS case definition developed
 - Comparison VAERS reporting rate vs. background rate
 - Conducted VSD RCA (2005-2006)



Example 1: GBS after MCV4 (continued)

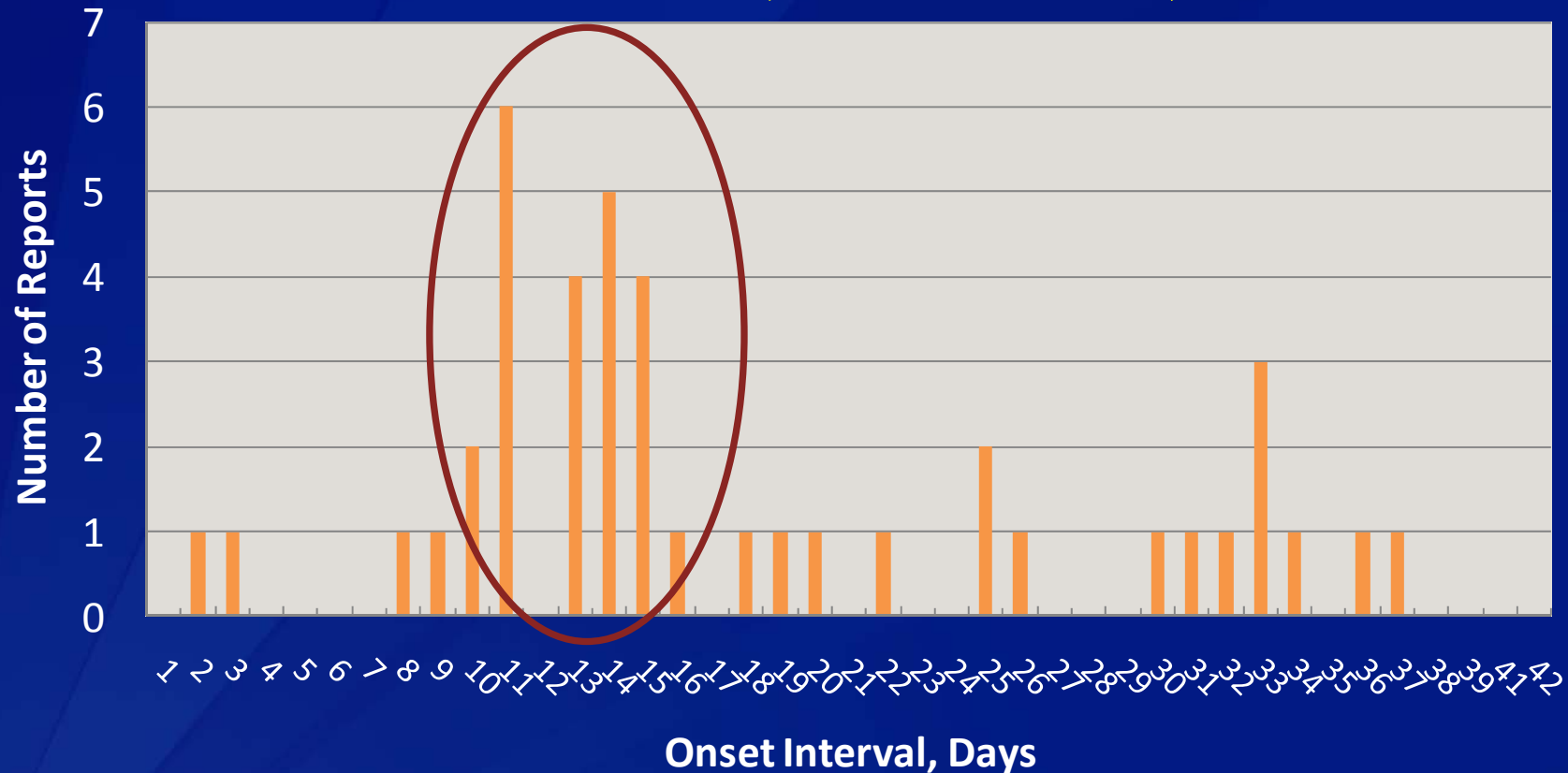


- “...Although these data suggest a small increased risk for GBS after MCV4 vaccination, the inherent limitations of VAERS and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution”
- No change in CDC recommendations for MCV4



Example 1: GBS after MCV4 (continued)

Confirmed GBS Reports (n=42) by Onset Interval Following Menactra Administration, 11-19 Year Olds, VAERS Data



Onset Interval 2-37 days

Mean 16.7 Days

Temporal Scan Statistic Cluster 10-15 days (p=.002)

Example 1: GBS after MCV4 (continued)

Final Signal Assessment

- New MCV4 safety study implemented: Harvard (PI: R. Platt; funded sanofi pasteur)
- Combining the 2 studies (VSD and Harvard), there is over 2.3 million MCV4 (Menactra[®]) vaccinations and 0 confirmed cases of GBS occurred within 1-42 days following vaccination of adolescents
- Using exact statistics, the upper 95% confidence limit for the attributable risk of GBS associated with MCV4 ~1 case per million doses
- **The two studies provide no evidence of an increased risk of GBS associated with MCV4 (June 2010)**



Signal Ruled Out

Example of VAERS signal for rare, unexpected adverse event ruled out

Example 2: Febrile Seizures after 2010-11 Trivalent Inactivated Influenza Vaccine (TIV)

- ❑ 2010 Southern Hemisphere CSL TIV associated with a transient increased risk for febrile seizures in young children*
 - In the US, TIV before 2010-11 season not previously associated with increased risk for febrile seizure
 - ACIP recommended for US 2010-11 season not using CSL vaccine for children aged <9 years; Fluzone® was the only recommended US 2010-11 TIV product for children aged 6-23 months
- ❑ Because of the CSL product association, US monitoring enhanced for febrile seizures after 2010-11 TIV

*CDC. *MMWR* Aug. 13, 2010. Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding Use of CSL Seasonal Influenza Vaccine (Afluria) in the United States During 2010--11

Available at:

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm?s_cid=mm5931a4_w



Example 2: Febrile Seizures after 2010-11 TIV (continued)



[Home](#) > [Vaccines, Blood & Biologics](#) > [Safety & Availability \(Biologics\)](#) > [Vaccine Safety & Availability](#)

Vaccines, Blood & Biologics

Fluzone Vaccine Safety

FDA and CDC Update on Fluzone Influenza Vaccine and VAERS Reports of Febrile Seizures in Children
January 20, 2011

- ❑ “FDA and CDC have recently detected an increase in the number of reports to VAERS of febrile seizures following vaccination with Fluzone TIV... reported febrile seizures have primarily been seen in children younger than 2 years of age” *
- ❑ Clinical review showed VAERS reports had typical features of febrile seizures and all children recovered †

*<http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm>

†http://vaers.hhs.gov/resources/VAERSupdate_FebrileSeizures_Children.pdf



Example 2: Febrile Seizures after 2010-11 TIV

- ❑ VSD also detected signal for seizure after 2010-11 TIV
- ❑ Interim VSD assessment showed statistically significant excess risk for febrile seizures in 12-23 month old children after receiving TIV + PCV13** vaccines (+/- other vaccines) during 0-1 days after vaccination
 - Attributable risk of 61/100,000 doses***
 - No excess risk seen for TIV* or PCV13* vaccinees§

*As of 2/2011 VSD data from Grace Lee)

**PCV13 - pneumococcal 13-valent conjugate vaccine

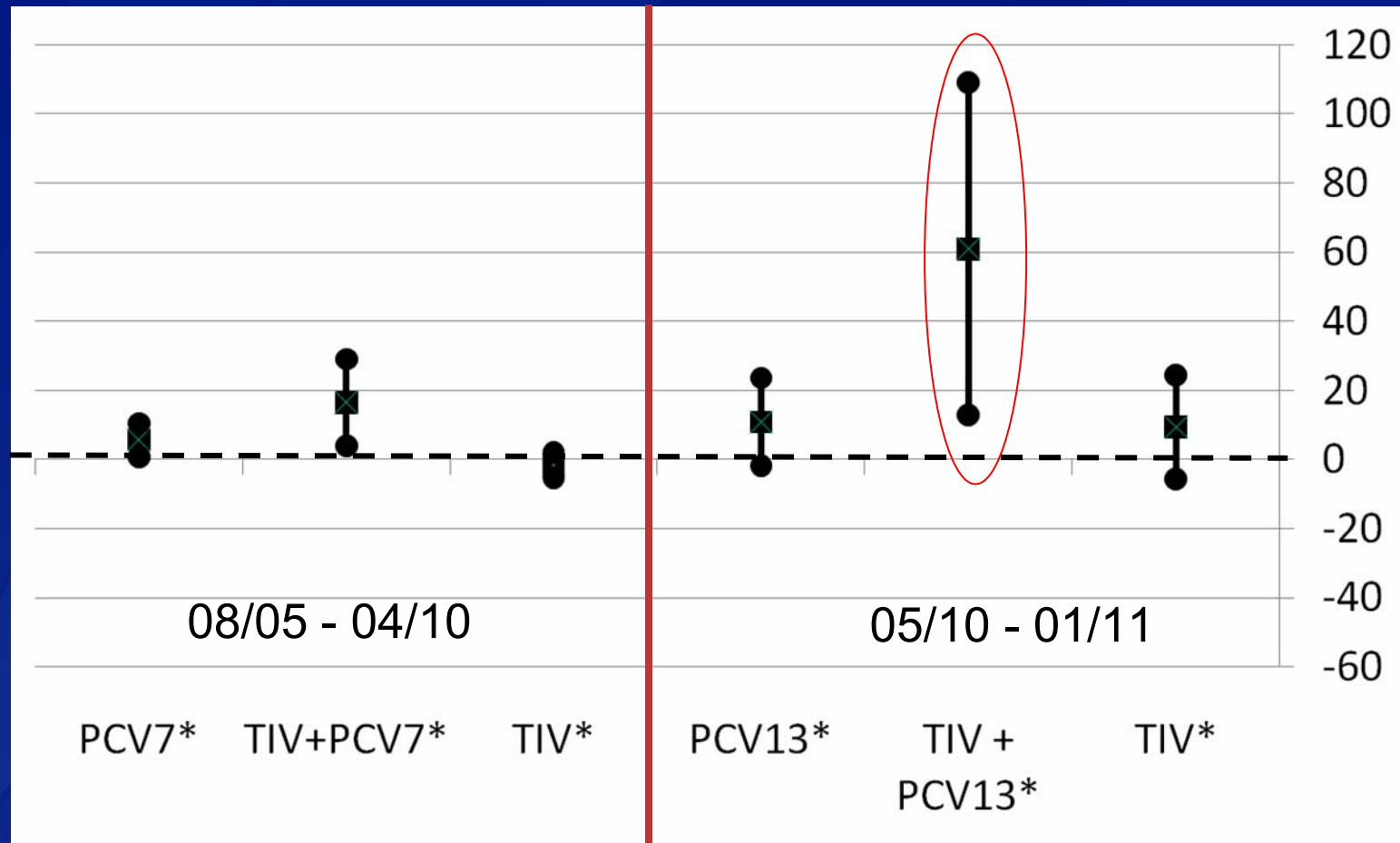
***<http://www.cdc.gov/vaccines/recs/acip/slides-feb11.htm#immunsafety>

§ +/- other non-TIV, non-PCV vaccines



Example 2: Febrile Seizures after 2010-11 TIV

Attributable Risk for Febrile Seizure 0-1 Days after Vaccination per 100,000 TIV Doses, aged 12-23 mo in VSD



* +/- other non-TIV, non-PCV vaccines; assuming chart confirmation rate of 80%;
Source: G Lee presentation to ACIP February 2011

Example 2: Febrile Seizures after TIV (continued)

Prioritization and Decision

- Further assessment needed; high priority (2011)
 - VSD 2010-11 TIV assessment in progress
- New VSD study of febrile seizure after vaccination to be planned
- No change in TIV policy; information communicated to public
- Policy aspects under consideration by ACIP General Recommendations Working Group



Final Signal Assessment

- In progress



Example of VAERS and VSD signal for adverse event under enhanced monitoring -- Interim assessment suggests signal partially verified with likely vaccine interaction (TIV and PCV-13)

Example 3: Febrile Seizures after Measles, Mumps, Rubella and Varicella Vaccine (ProQuad®)

- ❑ FDA licensed MMRV (ProQuad®) for use in children 12 months to 12 years of age (2005)
- ❑ ACIP recommended use of MMRV vaccine (2006)
 - MMRV preferred over separate administration of MMR and varicella vaccines as part of general preference for combination vaccines
- ❑ In pre-licensure trials, higher rates of fever observed 5–12 days after vaccination in children who received the first dose of MMRV vs. measles, mumps and rubella (MMR) vaccine and varicella vaccine at the same visit (MMR+V).
 - Not enough subjects to detect risk for febrile seizures
 - ❑ MMRV safety monitoring for febrile seizures after MMRV
 - 2 studies implemented (VSD RCA and Merck-sponsored)
 - **Signal for febrile seizure detected VSD 2007**



Example 3: Febrile Seizures after MMRV (cont)

Results from Preliminary VSD and Final Merck-sponsored Studies of Dose 1 MMRV and Febrile Seizure

Post-vaccination Interval	<u>Preliminary</u> VSD: All aged 12–23 months PI: N. Klein	Final Merck-sponsored 99% aged 12–23 months PI: S. S. Jacobsen
	MMRV: N=43,353 MMR+V N=314,599	MMRV: N=31,298 MMR+V: N=31,298
Weeks 1–2	<u>7–10 days</u> [†] OR: 2.3 (95% CI: 1.6, 3.2) AR: 5.2 per 10,000 (95% CI: 2.2, 8.1)	<u>5–12 days</u> [†] RR: 2.2 (95% CI: 1.0, 4.7) AR: 3.8 per 10,000 (95% CI: 0.3, 7.4)
Weeks 3–4	No chart review done	<u>13–30 days</u> RR: 0.6 (95% CI: 0.3, 1.1) AR: -3.2 per 10,000 (95% CI: -7.0, 0.6)
Weeks 1–4	No chart review done	<u>0–30 days</u> RR: 1.1 (95% CI: 0.7, 1.7) AR: 1.3 per 10,000 (95% CI: -4.5, 7.0)

* Sources: 2008 ACIP presentations; CDC. *MMWR* March 14, 2008.

[†]Significant at p<0.05 OR= odds ratio; RR = relative risk; AR= attributable risk

Example 3: Febrile Seizures after MMRV (cont)

Interim signal assessment:

- New study question: Is there a decreased risk for febrile seizures after dose 1 MMRV compared with MMR+V in the 13 to 30 days after vaccination that might compensate for the increased risk after MMRV in the 5 to 12 (or 7-10) day period? (“shift hypothesis”)

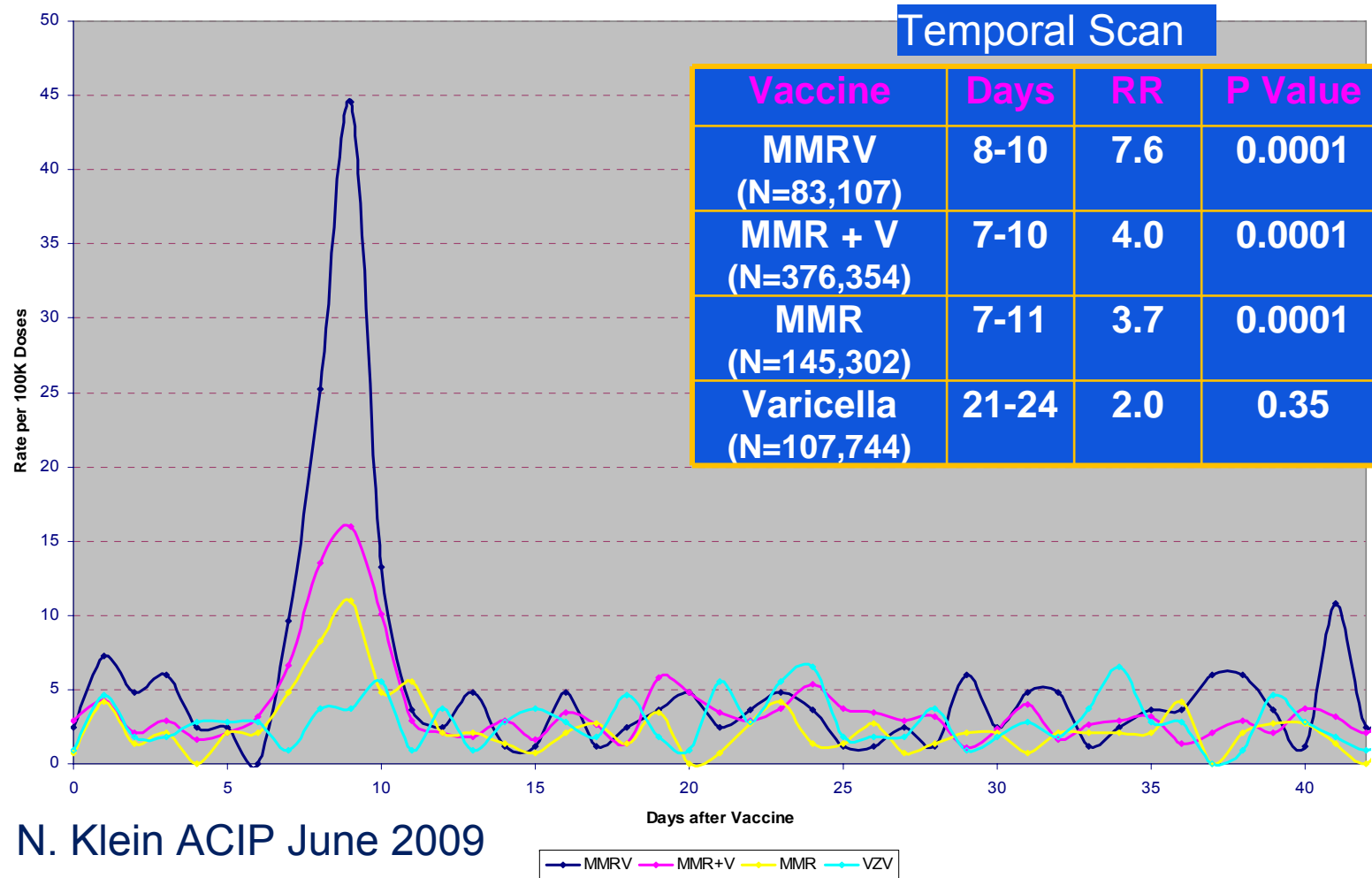


Public Health Action

- ACIP removed the preference for MMRV over MMR and varicella vaccines in response to the findings (2/2008)
- New ACIP MMRV Vaccine Safety Working Group (WG) established to assess the risk data and review MMRV policy
- VSD implemented a study to assess risk of FS in 42 days after dose 1 MMRV

Example 3: Febrile Seizure after MMRV (continued) Seizures after Dose 1 Vaccine in Children Aged 12-23 Months in VSD

Seizures Days 0-42 after Vaccine, 2000-11/2008

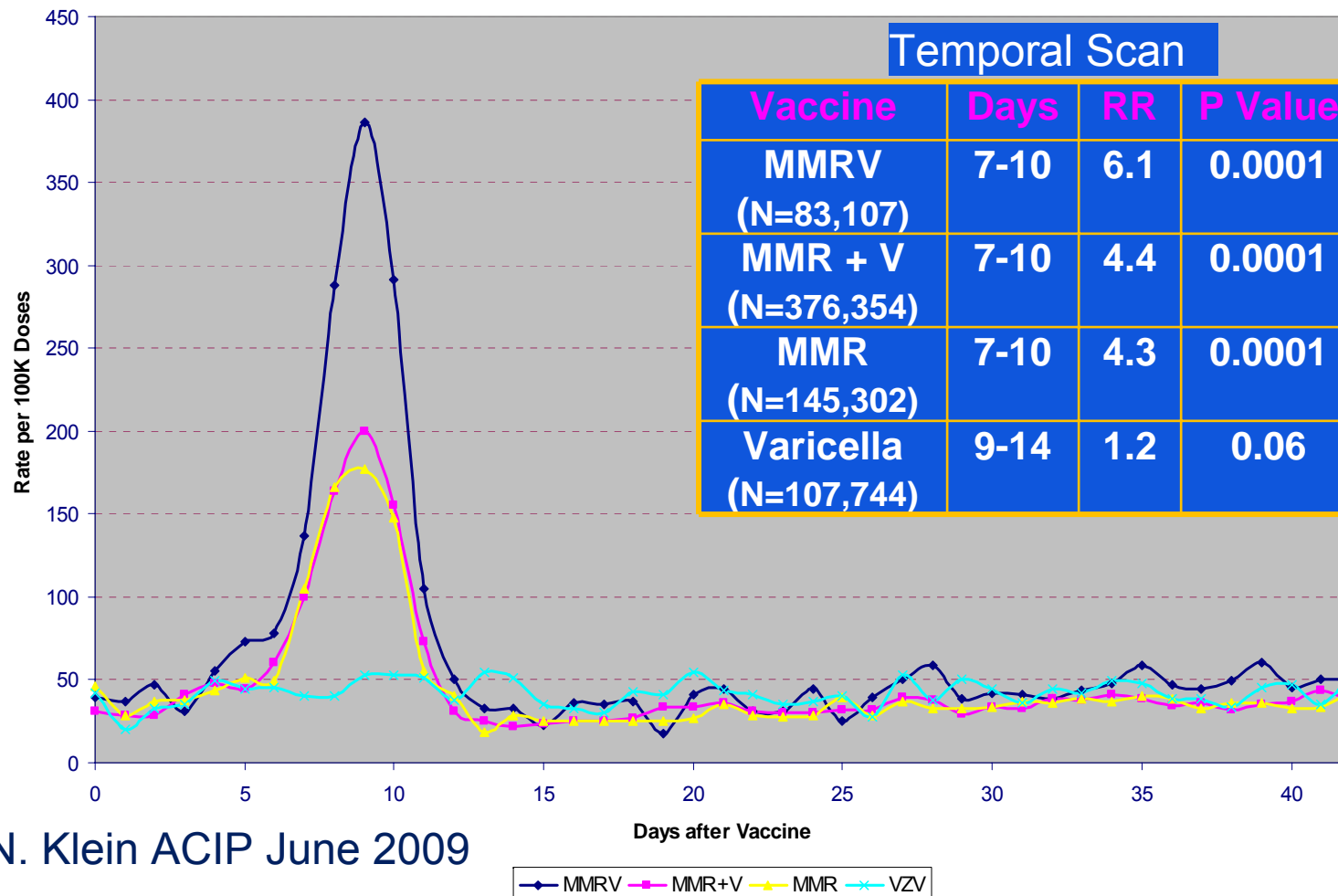


N. Klein ACIP June 2009

Example 3: Febrile Seizures after MMRV (continued)

Outpatient Fever Visits after Dose 1 Vaccine in Children Aged 12-23 Months in VSD

Fever 0-42 days after Vaccine, 12-23 Months of Age, 2000-11/2008



N. Klein ACIP June 2009

Example 3: Febrile Seizures after MMRV (cont)

Results from Final VSD and Final Merck-sponsored Studies of Dose 1 MMRV and Febrile Seizure*

Post-vaccination Interval	Final VSD: All aged 12–23 months PI: N. Klein	Final Merck-sponsored 99% aged 12–23 months PI: S. S. Jacobsen
	MMRV: N= 83,107 MMR+V: N= 376,354	MMRV: N=31,298 MMR+V: N=31,298
Weeks 1–2	<u>7–10 days</u> [†] RR: 2.0 (95% CI: 1.4, 2.9) AR: 4.3 per 10,000 (95% CI: 2.6, 5.6)	<u>5–12 days</u> [†] RR: 2.2 (95% CI: 1.0, 4.7) AR: 3.8 per 10,000 (95% CI: 0.3, 7.4)
Weeks 3–4	<u>13–30 days</u> RR: 0.9 (95% CI: 0.6, 1.5) AR: -0.4 per 10,000 (95% CI: -2.9, 1.2)	<u>13–30 days</u> RR: 0.6 (95% CI: 0.3, 1.1) AR: -3.2 per 10,000 (95% CI: -7.0, 0.6)
Weeks 1–6	<u>0-42 day</u> RR: 1.5 (95% CI: 1.1, 2.0) [†] AR: 6.2 per 10,000 (95% CI: 2.0, 9.5)	<u>0–30 days</u> RR: 1.1 (95% CI: 0.7, 1.7) AR: 1.3 per 10,000 (95% CI: -4.5, 7.0)

* Sources: 2008-09 ACIP presentations; Jacobsen, Vaccine 2009;27(34):4656-61 and Klein N. Pediatrics 2010
 RR = relative risk; AR= attributable risk; CI: confidence interval †Significant p<0.05

Final Quality of Evidence Grading Assessment: Risk for Febrile Seizures after Dose 1 MMRV vs. MMR and Varicella Vaccines MMRV WG Assessment on 6-17-2009*

Evidence Category	Weeks 1–2 post vaccination (7–10 and 5–12 days) <u>Increased risk</u> after MMRV vs. MMR+V	Weeks 3–4 post vaccination (13–30 days) <u>Decreased risk</u> after MMRV vs. MMR+V
Population-based Risk	HIGH	LOW
Biological Plausibility	HIGH	LOW



Verified

Example of VSD signal for adverse event; not unexpected– final assessment verified

*K. Broder ACIP June 2009

Conclusion

- ❑ Systematic approach to vaccine safety signal detection and assessment important
- ❑ Signal management is challenging; combines science, statistics and sound clinical judgment
- ❑ Signals may generate high levels of concern; need to maintain logic and focus
- ❑ Much that glitters is not gold; most signals are not verified
- ❑ Future efforts should focus on strengthening vaccine safety infrastructures and maintaining talented vaccine safety workforce



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- Jonathan Temte

□ Vaccine Safety Datalink

□ Clinical Immunization

Safety Assessment Network

□ ACIP MMRV Vaccine Safety WG

Additional Slides



VAERS Report Processing

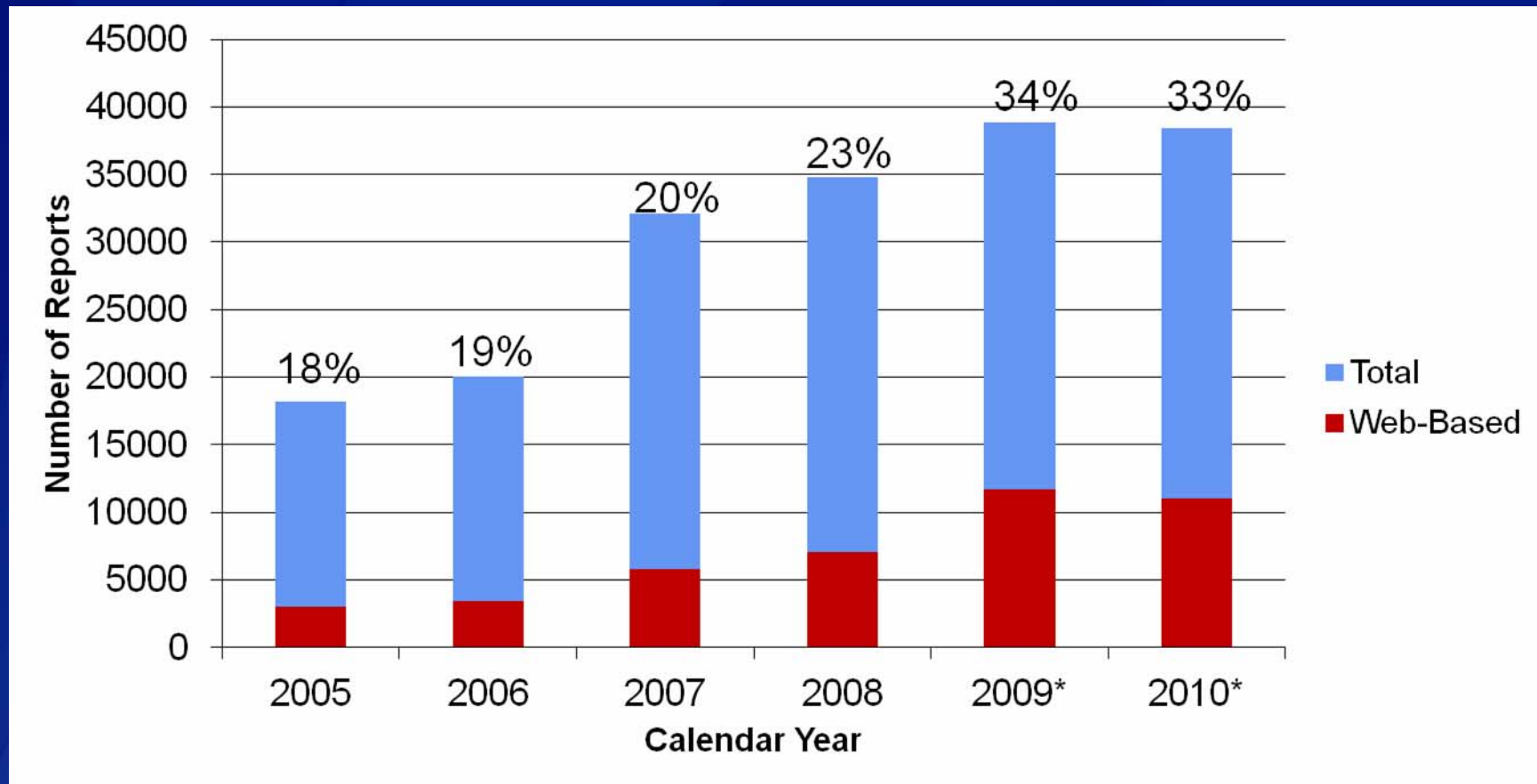
- ❑ **VAERS report received by contractor**
 - Received by web, mail, and/or fax
- ❑ **Data entered into database and adverse events coded using MedDRA terms***
- ❑ **Data sent to CDC and FDA**
- ❑ **Follow-up procedures implemented**
 - Medical records requested for serious** and special interest report (except manufacturer reports)

* Medical Dictionary for Regulatory Activities <http://www.meddransso.com/>

**A serious report is defined as death, life-threatening illness, hospitalization, prolongation of hospitalization, permanent disability and 'other medically important conditions.



Initiative to Improve Reporting Efficiency and Data Quality: Trends of Total and Web-based VAERS Reports Following U.S. Licensed Vaccines, 2005 - 2010

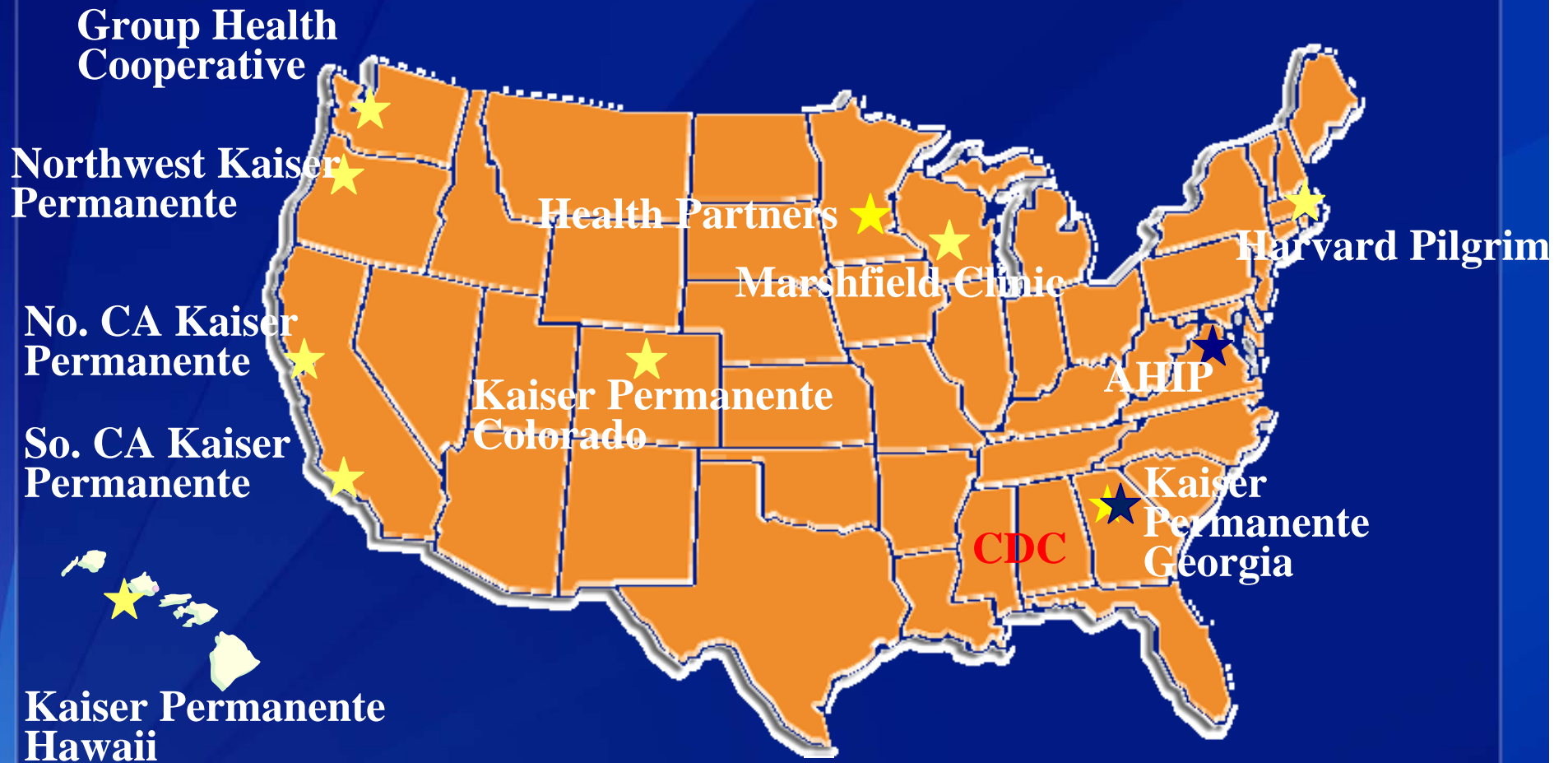


Percentages above bars represent web-based percents of total report (primary and secondary US reports)

*Includes 2009-2010 H1N1 vaccine reports



VSD Sites: 2011



Resources

- VAERS data publicly available on VAERS website <http://vaers.hhs.gov> or CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) <http://wonder.cdc.gov/vaers.html>

