# Vaccine Adverse Event Reporting System data mining

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Application of Pharmacovigilance to
U.S. FDA Regulatory Decisions for Vaccines
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# Overview

- Basic concepts
- FDA's vaccine data mining application:  Empirica
- Example:  Fluzone-febrile seizure signal from December 2010
- Limitations

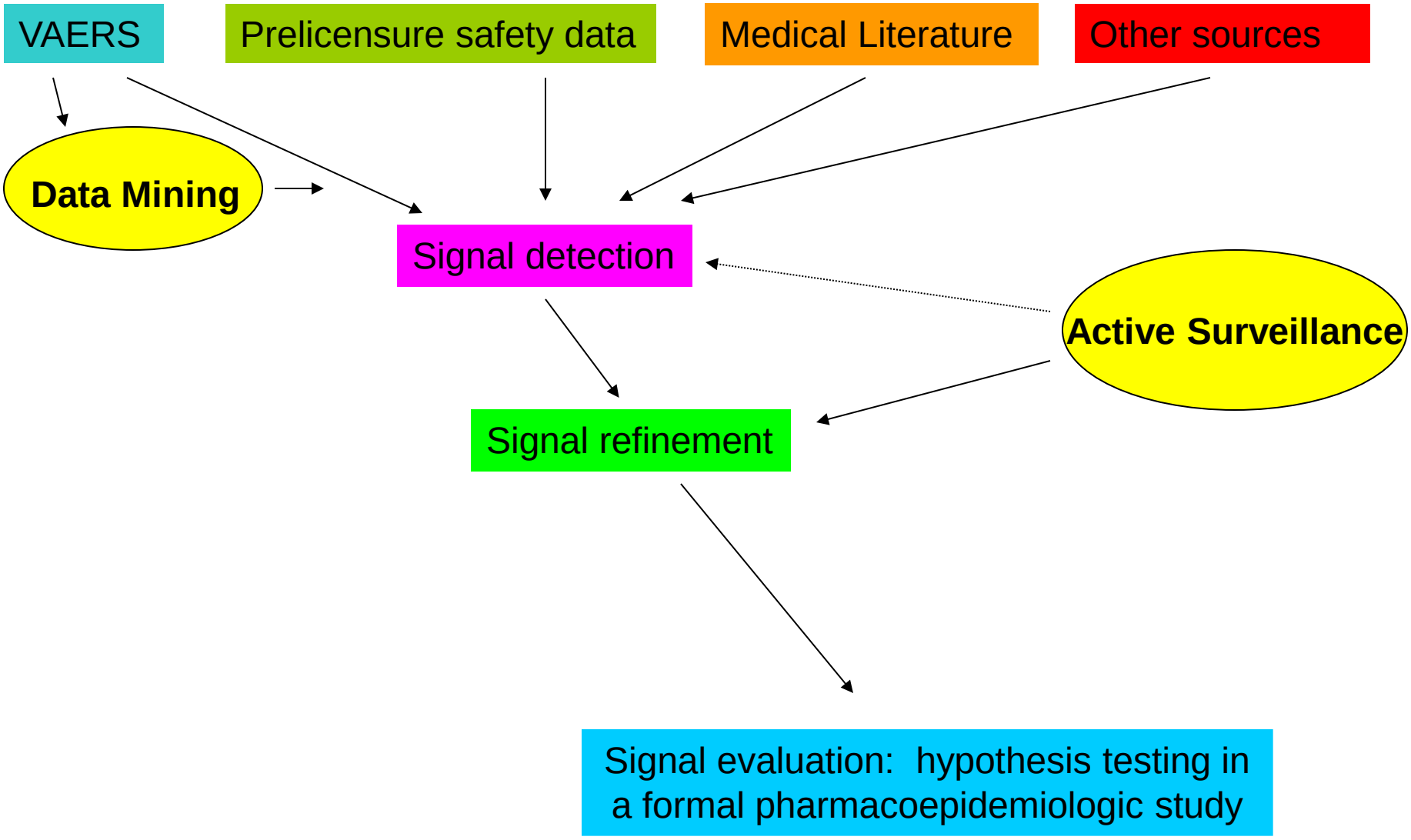
# Implementing FDA's definition of a "Signal" in VAERS

- "A concern about an excess of adverse events compared to what would be expected to be associated with a product's use."*
- Two problems:
  - Because we do not know exactly how many individuals received each vaccine, we cannot define an "excess" based on rates
  - Every VAERS report does not provide new information that changes the safety profile of a product, and physician epidemiologists have other important surveillance and regulatory activities

* Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, USDHHS, FDA, CDER, CBER, March 2005

# Advantages of data mining

- **Triage**: data from large amounts of nonserious reports can be screened
- **Perspective**: the entire history of the VAERS database can be used, and relationships that may not have been apparent on a day to day basis might be detected
- **Logistics**: Reviewers for products change, and data mining output helps accelerate the familiarization process


VAERS
Prelicensure safety data
Medical Literature
Other sources
Data Mining
Signal detection
Active Surveillance
Signal refinement
Signal evaluation: hypothesis testing in a formal pharmacoepidemiologic study

# Basic data mining concepts

- The VAERS database is “coded” using MedDRA terms
- A vaccine product and an adverse event coding term form a “pair”
- An expected count for the pair is calculated based on the total number of vaccine reports (for the vaccine of interest) and the total number of adverse events in VAERS (for the adverse event of interest)
- The observed number of vaccine-adverse event pairs divided by the expected count yields the relative reporting ratio

# Calculation of the relative reporting ratio for Fluzone$_{2010\text{-}2011}$

| December 10, 2010 US VAERS analysis | Number of reports | | |
|---|---|---|---|
| | Reports with Fluzone$_{2010\text{-}2011}$ | All other reports | Total |
| **Febrile convulsion** | 41 | 2,532 | 2,573 |
| **All other adverse events** | 2,054 | 294,936 | 296,990 |
| **Total** | 2,095 | 297,468 | 299,563 |

The observed value (N) = 41, the expected value (E) = (2,573)(2,095)/299,563 = 17.9, and the crude relative reporting ratio = N/E = 41/17.9 = **2.28**

# VAERS data mining with Empirica®

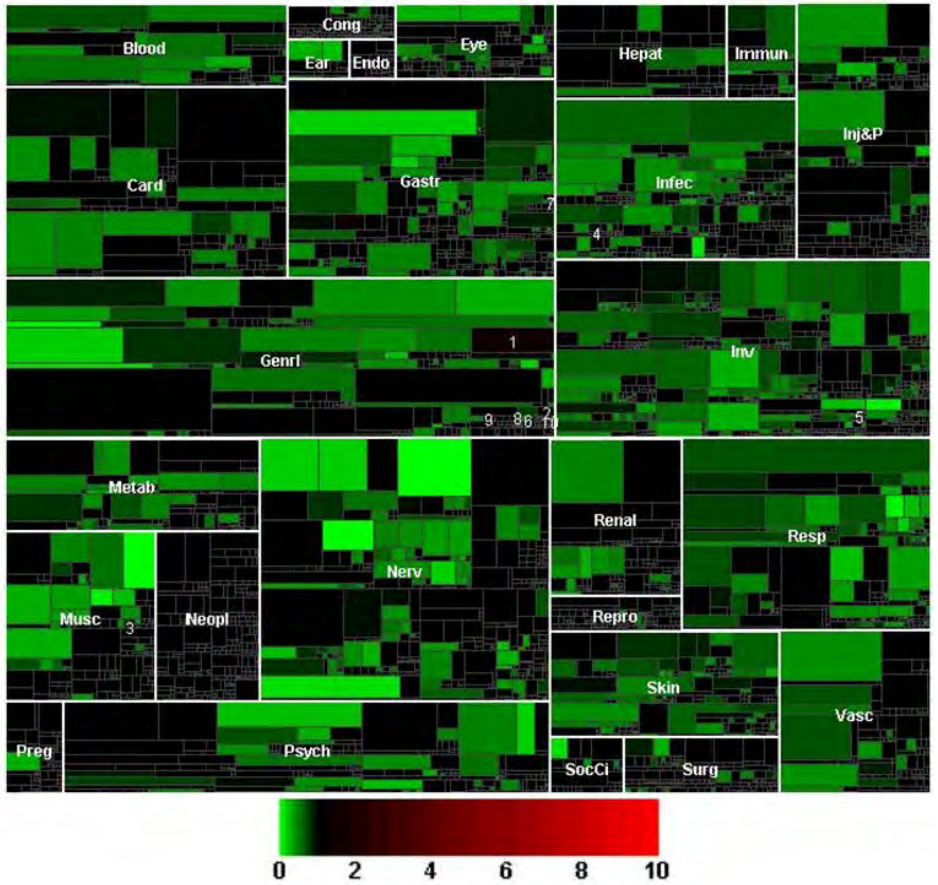
- **Relative Reporting Ratio**
  - Can be adjusted for one or more categorically defined potential confounders
    - CBER uses Age, Gender, and Year Received
  - Potentially unstable with low numbers
- **Empirical Bayesian Geometric Mean** (EBGM)
  - Calculated using a statistical model, the Multi-Item Gamma Poisson Shrinker (MGPS) which is fit to the entire database of observed and expected values
  - Quantifies disproportional reporting in the VAERS database

- Theoretically, any EBGM value above one indicates disproportional reporting
- However, this yields a large number of data mining findings and leads to duplication of effort

Drug=[redacted]


| Rank | SOC | Term (PT) | EBGM |
|---|---|---|---|
| 1 | Infec | Injection site cellulitis | 4.114 |
| 2 | Skin | Skin striae | 3.007 |
| 3 | Infec | Cellulitis | 2.749 |
| 4 | Skin | Skin warm | 2.437 |
| 5 | Genrl | Oedema peripheral | 2.405 |
| 6 | Genrl | Local reaction | 2.328 |
| 7 | Blood | Leukocytosis | 2.323 |
| 8 | Inv | White blood cell count increased | 2.205 |
| 9 | Infec | Necrotising fasciitis | 2.177 |
| 10 | Genrl | Injection site swelling | 2.170 |

To increase specificity, FDA ranks vaccine-event pairs by the lower 5% bound (EB05) of the confidence interval surrounding the EBGM and applies a threshold of 2.0 to identify pairs of interest




| Rank | SOC | Term (PT) | EB05 |
|---|---|---|---|
| 1 | Genrl | Gait disturbance | 1.600 |
| 2 | Genrl | Injection site pain | 1.554 |
| 3 | Musc | Weight bearing difficulty | 1.552 |
| 4 | Infec | Injection site cellulitis | 1.516 |
| 5 | Inv | X-ray abnormal | 1.508 |
| 6 | Genrl | Injection site swelling | 1.496 |
| 7 | Gastr | Intussusception | 1.478 |
| 8 | Genrl | Injection site haematoma | 1.463 |
| 9 | Genrl | Injection site erythema | 1.438 |
| 10 | Genrl | Injection site warmth | 1.409 |

# Background for the Fluzone-febrile seizure signal (December 2010)

- Febrile seizures: seizures that occur in febrile children who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures[1,2]
  - Affects 2-5% of young children in the United States[1]
  - Usually occurs at ages 6-60 months
  - Peak age 14-18 months

- Australia suspended 2010 seasonal trivalent influenza vaccination for all children < 5 years old in April 2010
  - In the US, the CSL influenza vaccine (Afluria) was not recommended for children <9 years for the 2010-11 influenza season due to these findings[3]

[1]AAP. Pediatrics. 2008;121:1281-6. [2]Johnston M. Nelson Textbook of Pediatrics. 2007.

[3]http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm

# Fluzone – febrile seizure signal detection process

Data mining finding/Signal of disproportionate reporting in screening analysis

- FDA VAERS data mining finding noted for the combination of Fluzone and the coding term febrile convulsion in December 2010:
  - EB05>2 with no stratification of the database

# Initial Review of Data Mining Results: Alternative Explanations*

| Symptom: PT | N | EB05 | Known Labeled Event | Reporting Artifact | Confounding by Indication | Confounding by Healthcare Setting | Known Effects of a Confounding Product | No Pattern Identified After Case Review | Not an Adverse Effect |
|---|---|---|---|---|---|---|---|---|---|
| Abortion induced | 115 | 2.8 | | | | X | | | |
| Acne | 61 | 2.1 | | | X | | | | |
| Alopecia | 201 | 2.2 | | | | | | X | |
| Myocarditis | 90 | 2.7 | | | | | X | | |
| Syncope | 2709 | 2.2 | X | | | | | | |
| Foetal exposure during pregnancy | 33 | 2.0 | | X | | | | | |
| Incorrect storage of drug | 71 | 2.1 | | | | | | | X |
| Vaccine positive | 515 | 2.2 | | | | | | X | |

*Note: Results presented are notional*

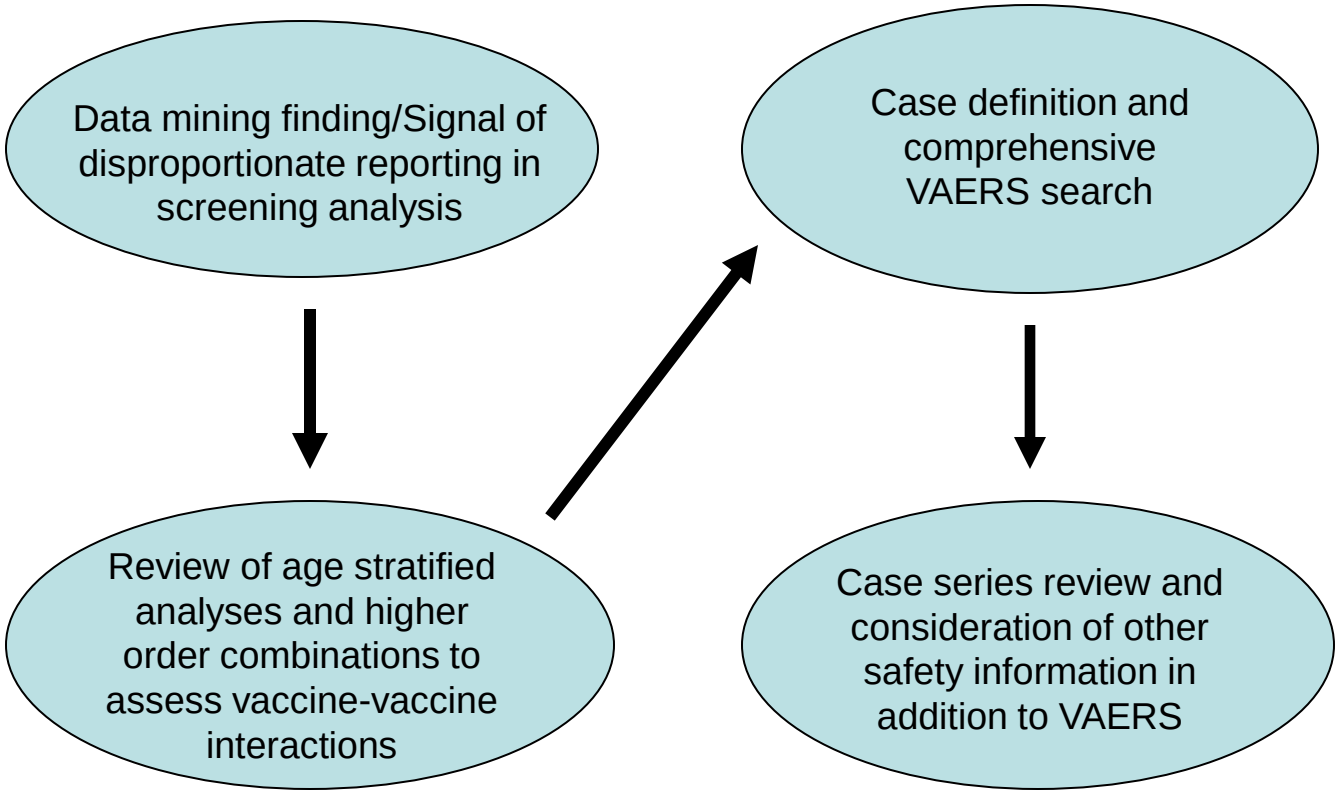
# Fluzone – febrile seizure signal detection process

Data mining finding/Signal of disproportionate reporting in screening analysis

Review of age stratified analyses and higher order combinations to assess vaccine-vaccine interactions

- Larger EB05 in the 0-18 months age stratum
- No other independent vaccine product - febrile convulsion findings to date
- No interaction with other vaccines

# Fluzone – febrile seizure signal detection process

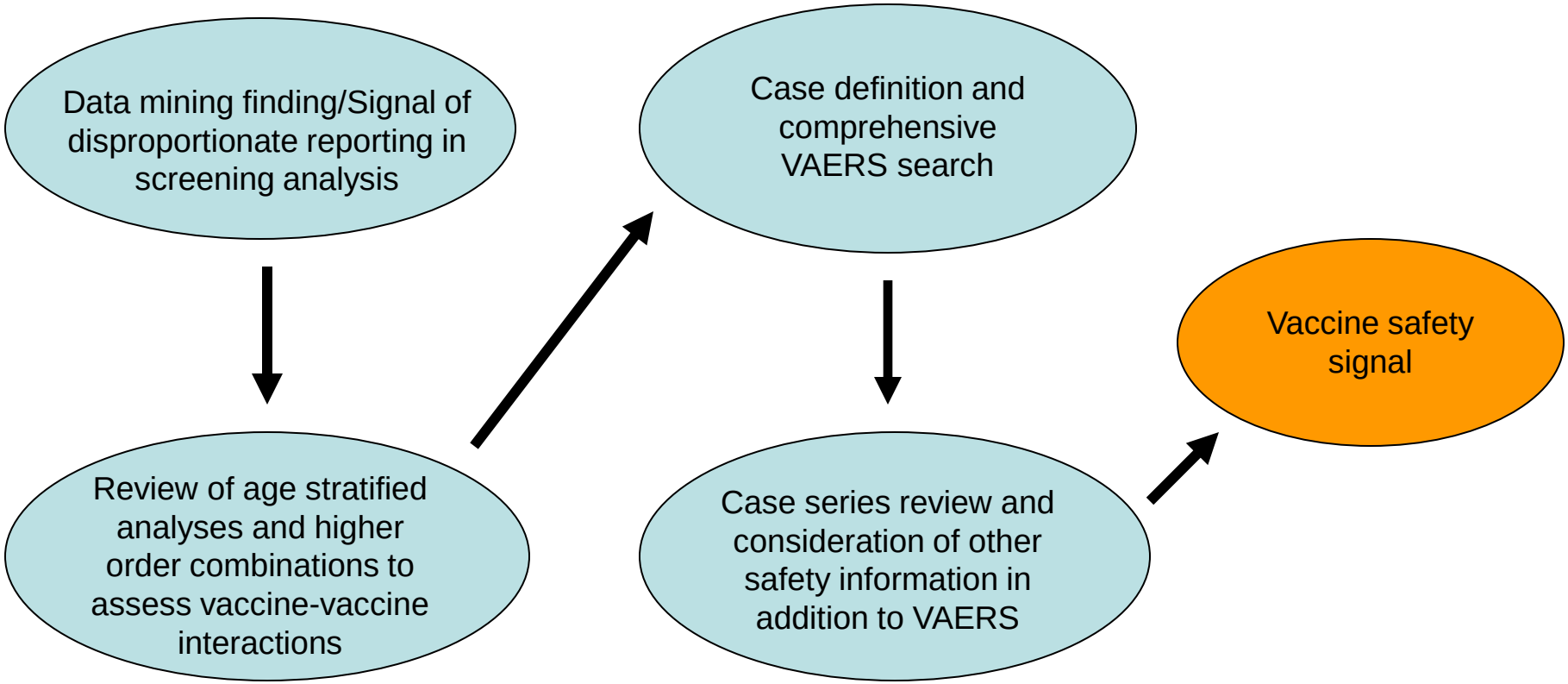


# Joint FDA/CDC VAERS descriptive analysis: December 13, 2010

- Forty-two febrile seizure cases after Fluzone
  - All recovered
  - Ten (24%) serious*; most hospitalized overnight and released
- Vaccination to onset interval
  - Median: 10 hours
  - Range: 3 hours to 10 days
    - 86% occurred on the same day or day after administration
- Concomitant vaccination reported in 27 (64%) of cases.
- Medical history
  - Family history of seizure in 7 (17%) cases
  - Concurrent illness (URI or GI) in 6 (8%) of cases
  - Temperature elevation: 100.4 to 104°F
- No apparent geographic or product lot clustering

*Regulatory definition: Any adverse experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

# Fluzone – febrile seizure signal detection process




- FDA and CDC reviewed available VAERS data mining and VSD rapid cycle analysis findings
  - FDA and VAERS public communication issued on January 20, 2011
    http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm
    http://vaers.hhs.gov/resources/updates

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**Safety & Availability (Biologics)**

**Vaccine Safety & Availability**

# Fluzone Vaccine Safety

## FDA and CDC Update on Fluzone Influenza Vaccine and VAERS Reports of Febrile Seizures in Children

January 20, 2011

The Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) routinely monitor the safety of all U.S. vaccines by using several vaccine safety surveillance systems, including the Vaccine Adverse Event Reporting System (VAERS). VAERS collects and analyzes information from reported adverse events (health problems or possible side effects) that occur after vaccination.

FDA and CDC have recently detected an increase in the number of reports to VAERS of febrile seizures following vaccination with Fluzone (trivalent inactivated influenza vaccine or TIV, manufactured by Sanofi Pasteur, Inc.). Fluzone is the only influenza vaccine recommended for use for the 2010-2011 flu season in infants and children 6-23 months of age. These reported febrile seizures have primarily been seen in children younger than 2 years of age. Data from VAERS are preliminary and serve as a sign or indication that further investigation is warranted. Further investigations are under way to assess whether there could be an association between influenza vaccination and febrile seizures, or if other factors could be involved. FDA and CDC have seen no increase in VAERS reports of febrile seizures in people older than 2 years of age following vaccination with TIV, and no increase after live attenuated influenza vaccine (FluMist, the nasal spray vaccine). In the cases reported, all children recovered and no lasting effects have been seen. Recommendations for the use of flu vaccine in children have **not** changed.

FDA and CDC will continue to conduct studies and provide additional information to the public and health care providers as it becomes available.

Full text available at
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm

# Limitations of VAERS Data Mining

- Underlying weaknesses of VAERS
- Data mining relies on a coding hierarchy
  - Some pathophysiologic processes do not fit neatly into the hierarchy
  - Readily identifiable diagnoses are easier to code; diagnoses that come after lengthy clinical evaluations might require updated VAERS reports or submission of clinical records
- Threshold identification (e.g., EB05 > 0) is a subjective decision
- Database restrictions, adjustment (stratification), and subsets operate upstream from the MGPS algorithm and must be considered carefully
- Data mining findings in one database using a particular data mining method cannot be directly compared to those from another database using another method

# Reserve slides

# No disproportional reporting identified for concomitantly administered vaccines, US VAERS December 10, 2010

| Vaccine | EB05 | EBGM |
|---|---|---|
| FLUZONE (2010-2011) | 2.44 | 3.36 |
| PREVNAR 13 | 1.00 | 1.29 |
| MMR II | 1.64 | 1.72 |
| ACTHIB | 0.94 | 1.03 |
| RECOMBIVAX HB | 0.57 | 0.66 |
| VAQTA | 1.39 | 1.68 |
| PROQUAD | 1.64 | 1.98 |
| VARIVAX | 1.00 | 1.07 |
| HAVRIX | 1.31 | 1.52 |
| DAPTACEL | 1.02 | 1.17 |
| PEDVAXHIB | 0.90 | 1.03 |
| INFANRIX | 0.82 | 0.93 |
| TRIPEDIA | 0.94 | 1.05 |
| PREVNAR | 1.05 | 1.12 |
| PENTACEL | 0.55 | 0.70 |

# Examination of potential interactions

- US VAERS three dimensional analysis
  - $Fluzone_{2010\text{-}2011}$ – concomitant vaccine- *Febrile convulsion* combination
  - Adjusted for age group, gender, year received
  - Interaction Signal Score (INTSS) is the EB05 from the triple divided by the EB95 from the highest pair
  - INTSS > 1 indicates that the confidence interval for the triple does not overlap with the confidence interval for either pair
- US VAERS as of December 10, 2010
  - No product concomitantly administered with $Fluzone_{2010\text{-}2011}$ had an INTSS > 1

## Three dimensional febrile convulsion PT results for vaccines given concomitantly with Fluzone$_{2010\text{-}2011}$, December 10, 2010

| Vaccine | N | INTSS |
|---|---|---|
| PREVNAR 13 | 13 | 0.59 |
| MMR II | 7 | 0.53 |
| ACTHIB | 7 | 0.53 |
| RECOMBIVAX HB | 3 | 0.49 |
| VAQTA | 4 | 0.48 |
| PROQUAD | 2 | 0.46 |
| VARIVAX | 6 | 0.46 |
| HAVRIX | 4 | 0.45 |
| DAPTACEL | 2 | 0.43 |
| PEDVAXHIB | 2 | 0.43 |
| INFANRIX | 2 | 0.42 |
| TRIPEDIA | 1 | 0.40 |
| PREVNAR | 3 | 0.39 |
| PENTACEL | 1 | 0.29 |

# Fluzone$_{2010\text{-}2011}$ crude relative reporting ratio

| December 10, 2010 US VAERS analysis | Number of reports | | |
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The observed value (N) = 41, the expected value (E) = (2,573)(2,095)/299,563 = 17.9, and the **crude relative reporting ratio = N/E = 41/17.9 = 2.28**

# Prevnar 13 crude relative reporting ratio

| December 10, 2010 US VAERS analysis | Number of reports | | |
|---|---|---|---|
| | Reports with Prevnar 13 | All other reports | Total |
| **Febrile convulsion** | 42 | 2,531 | 2,573 |
| **All other adverse events** | 1,262 | 295,728 | 296,990 |
| **Total** | 1,304 | 298,259 | 299,563 |

The observed value (N) = 42, the expected value (E) = (2,573)(1,304)/299,563 = 11.2, and the **crude relative reporting ratio = N/E = 41/17.9 = 3.75**

# Comparison of the December 10 US VAERS analysis for Fluzone$_{2010\text{-}2011}$ and Prevnar 13

| | Crude E | Crude Rel Rep Ratio | Adjusted E | Adjusted Rel Rep Ratio | EBGM | EB05 |
|---|---|---|---|---|---|---|
| **Fluzone** $_{2010\text{-}2011}$ | 17.9 | 2.28 | 10.7 | 3.84 | 3.36 | 2.44 |
| **Prevnar 13** | 11.2 | 3.75 | 31.3 | 1.34 | 1.29 | 1.00 |