Framework for Evaluating Passive Reporting

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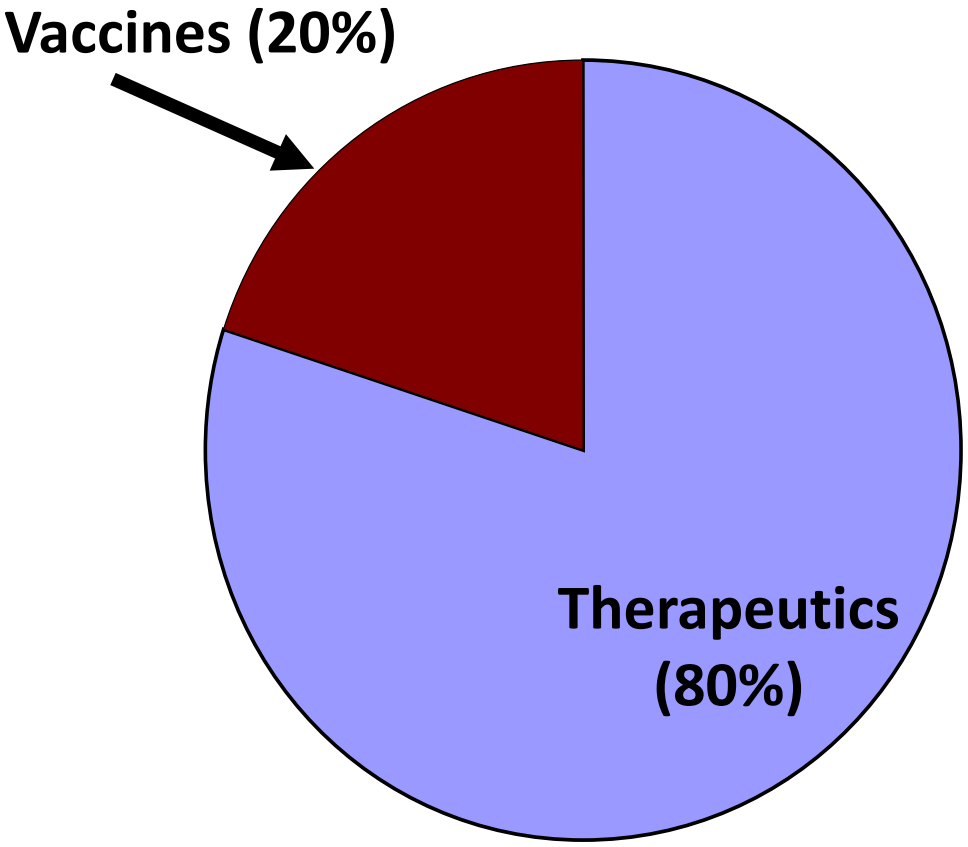
Objectives

- Present an overview of CBER's adverse event report review for therapeutics and vaccines
- Discuss product-based monitoring and the methods used to conduct periodic safety review
- Discuss features which suggest a product-event association and provide relevant examples

Volume and Variety of CBER Marketed Medical Products

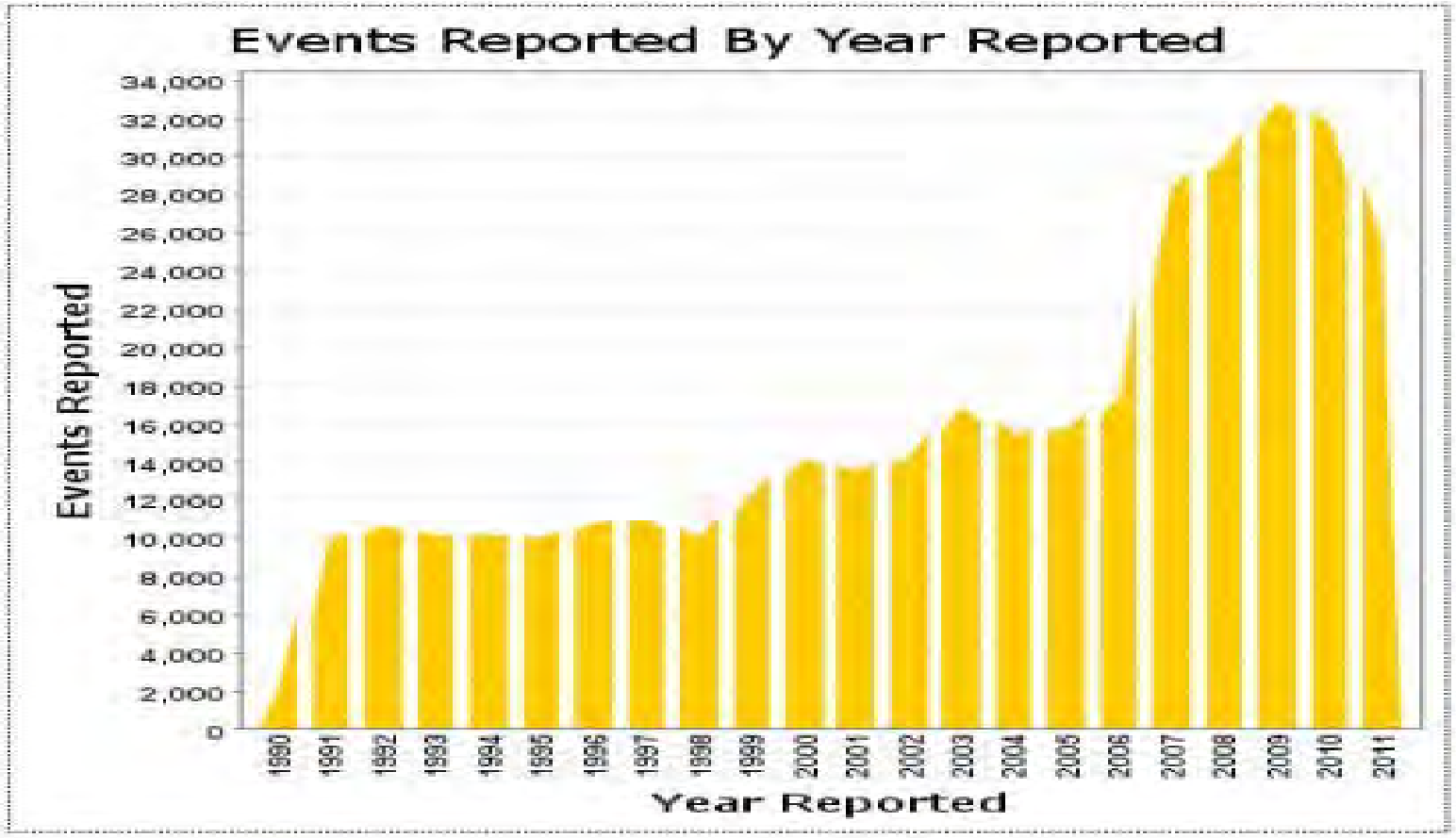


(No. Products > 300)

Some Examples of Therapeutics:

- Immune globulins
- Hematopoietic stem cells
- Fibrin sealants
- Antivenins
- Therapeutic vaccines
- Factor replacement
- Volume expanders
- Alpha 1 anti-trypsin inhibitor
- C1 esterase inhibitor
- Thrombin and anti-thrombin
- Fibrinogen concentrate

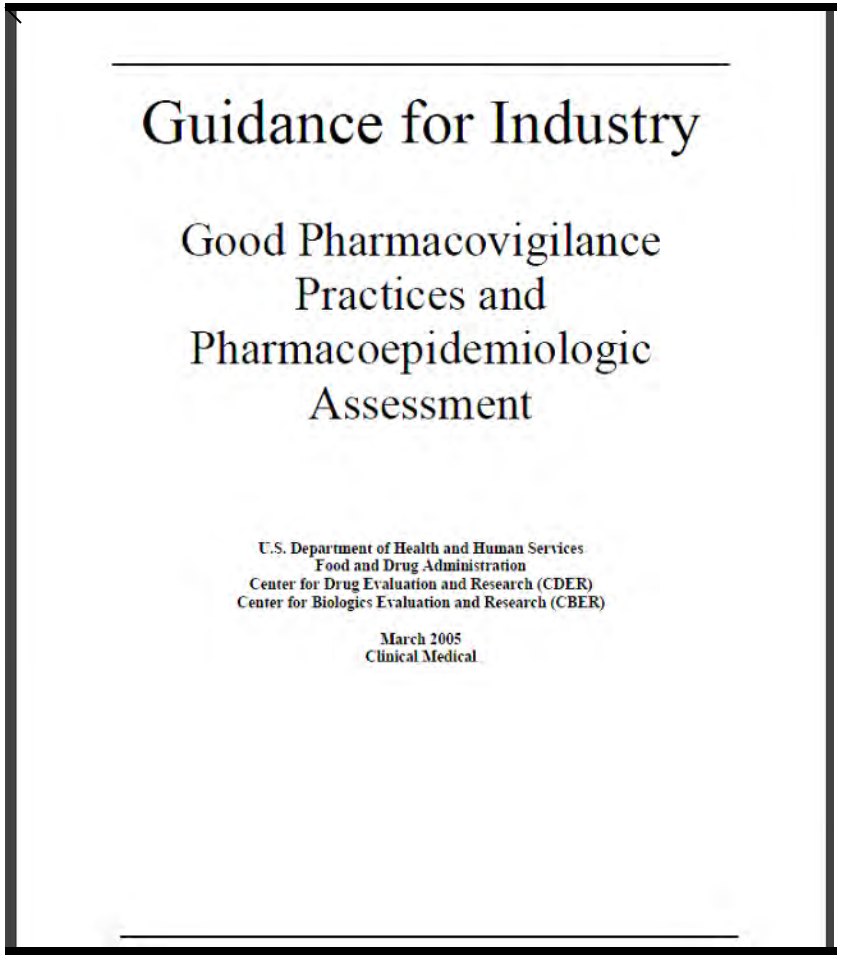
Volume of Reports to VAERS



Source: CDC WONDER

Good Pharmacovigilance Practices

- Identifying and describing safety signals
- Investigating a signal through observational studies
- Interpreting safety signals
- Developing a pharmacovigilance plan



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

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf

Safety Issues that May Warrant Further Investigation

- New, unlabeled events, especially if serious
- An apparent increase in the severity of a labeled event
- Occurrence of serious events thought to extremely rare in the general population
- Identification of a previously unrecognized at-risk population
- Other concerns identified by the sponsor or FDA

Source: Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, p.10

Assessment of a Potential Safety Risk

- Strength of association (relative risk of the adverse event associated with the product)
- Temporal relationship of product use and the event
- Consistency of findings across available data sources
- Biologic plausibility
- Seriousness of the event relative to the disease being treated
- Potential to mitigate the risk in the general population
- Degree of benefit the product provides, including the availability of other therapies

Source: Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, p.18

Product-based Monitoring

- Serious reports to VAERS are reviewed on a routine basis
- Each licensed product is systematically reviewed on a periodic basis
    - Every product is evaluated at least annually
- Frequency of systematic review is based upon number of reports received for each product
    - Products receiving the most reports are reviewed monthly

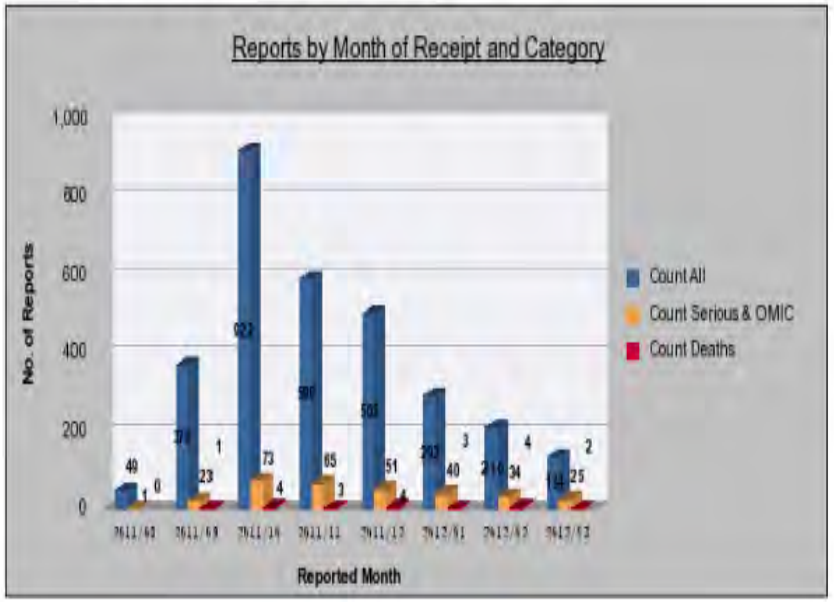
Detecting Safety Signals – Number of Reports

- Compare the number of reports, serious reports, and death reports in the current reporting period to prior reporting periods

1) Report counts for the period 3/1/2012 to 3/31/2012

Report Counts	USA	Foreign	Unknown	Total
All	131	3	0	134
Serious & OMIC	22	3	0	25
Deaths	2	0	0	2

2) Reporting trends for 12 months prior to surveillance period



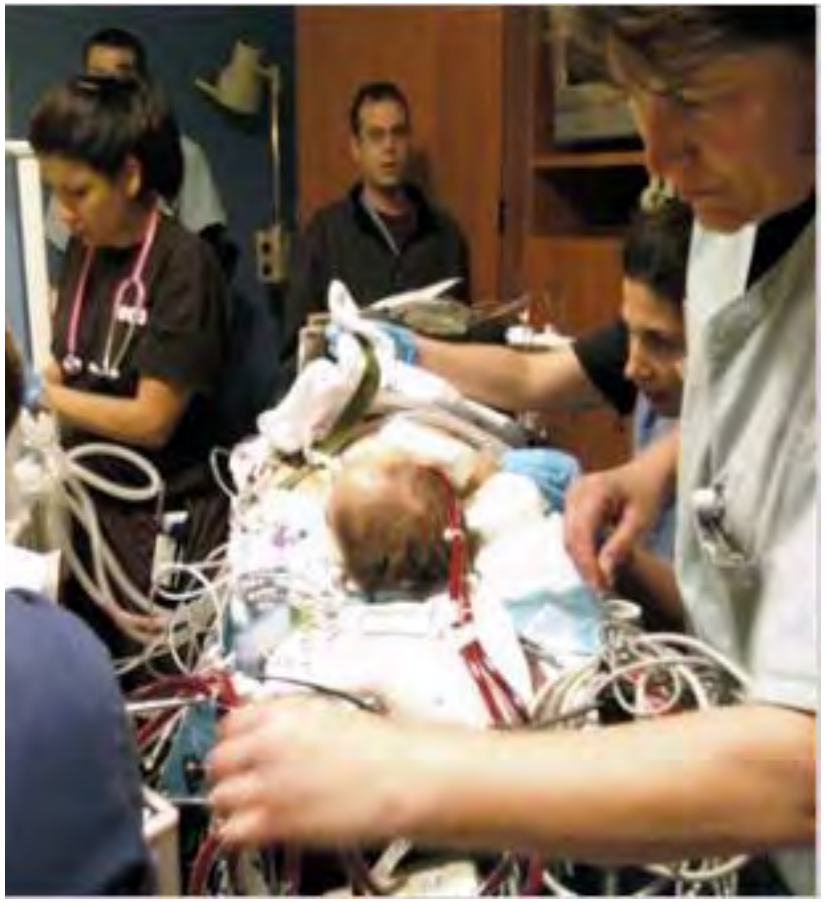
Most Frequently Reported Preferred Terms

Preferred Terms	3/1/12 - 3/31/12 (surveillance period)		Preferred Terms	3/2/11 - 2/29/12 (1 Year prior to surveillance period)	
	Serious and OMIC	Death		Serious and OMIC	Death
Pyrexia	7	1	Pyrexia	108	1
Pallor	4	1	Vomiting	42	2
Crying	3	0	Condition aggravated	35	2
Anaphylactic reaction	2	0	Irritability	32	2
Apnoea	2	1	Convulsion	30	0
Convulsion	2	0	Death	30	30
Diarrhoea	2	0	Crying	29	3
Dyspnoea	2	0	Febrile convulsion	29	1
Lethargy	2	0	Cough	24	0
Peripheral coldness	2	1	Diarrhoea	24	0

- Are any of the PTs from this period unexpected, more severe, or more frequent than in the previous time periods?
- PTs may be common to the same cases (apnea = convulsion)

Serious and Unusual Conditions

- Deaths
- Serious events
- Events with lasting sequelae
- Conditions of special interest
  - GBS following influenza vaccine
  - Neurologic complications
- Cases in these categories are reviewed during each periodic surveillance
- If warranted, a case series may be assembled



Source: www.af.mil

Other Aspects of Periodic Review

- Literature review
  - Observed adverse events may have been observed and published by others
  - Similarities between reported and published cases may help establish patterns
- Data mining
  - Identify events in which the observed number exceeds the expected number
  - Data mining will be covered in detail by Dr. Martin tomorrow

Symptom: PT	HLT	EB05
Accidental overdose	Overdoses	3.84
Agitation	Anxiety symptoms	3.55
Dysgeusia	Sensory abnormalities NEC	3.29
Crying	Neurological signs and symptoms NEC	2.66
Incorrect route of drug administration	Maladministrations	2.62
Screaming	Speech articulation and rhythm disturbances	2.04
Wrong drug administered	Maladministrations	2.02

Periodic Reports from Manufacturers

- FDA requires manufactures to submit Periodic Adverse Experience Reports (PAERs)
- Manufacturers may submit Periodic Safety Update Reports (PSURs) instead of PAERs
- These reports are submitted
  - Quarterly for the first three years
  - Annually after 3 years
- Some manufacturers provide analysis and interpretation in addition to the basic elements

Medical Officer Use of PAERs/PSURs

- Provides distribution information (not always included)
- Provides information on labeling and safety-related changes made by manufacturer
- Provides information on regulatory actions taken by other regulatory agencies
- Provides updates on currently monitored safety issues (not always included)
- Provides information (and MedWatch forms) for non-15 day reports. Line-listing of PTs can be a useful tool to monitor the number of reports for a serious but expected PT of interest (MMR and ITP)

Features Suggesting a Product-Event Association

What data might alert the epidemiologist to a product problem?

Factors Involved in Interpreting Safety Signals

- Biologic plausibility
- Temporal relationship of product use and the event
- Evidence of positive re-challenge
- Absence of an alternative explanation
- An apparent increase in the severity of a labeled event
- Occurrence of serious events thought to be extremely rare in the general population
- Identification of a previously unrecognized at-risk population

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf

Biologically Plausible Event in the Expected Time Frame

Onset of Intussusception after Rotashield

- Licensed by FDA in August, 1998
- VAERS reports between Sept. 1998 and June 1999 revealed temporal clustering within 7 days after 1st dose
- Temporary suspension recommended
- Manufacturer voluntarily withdrew vaccine

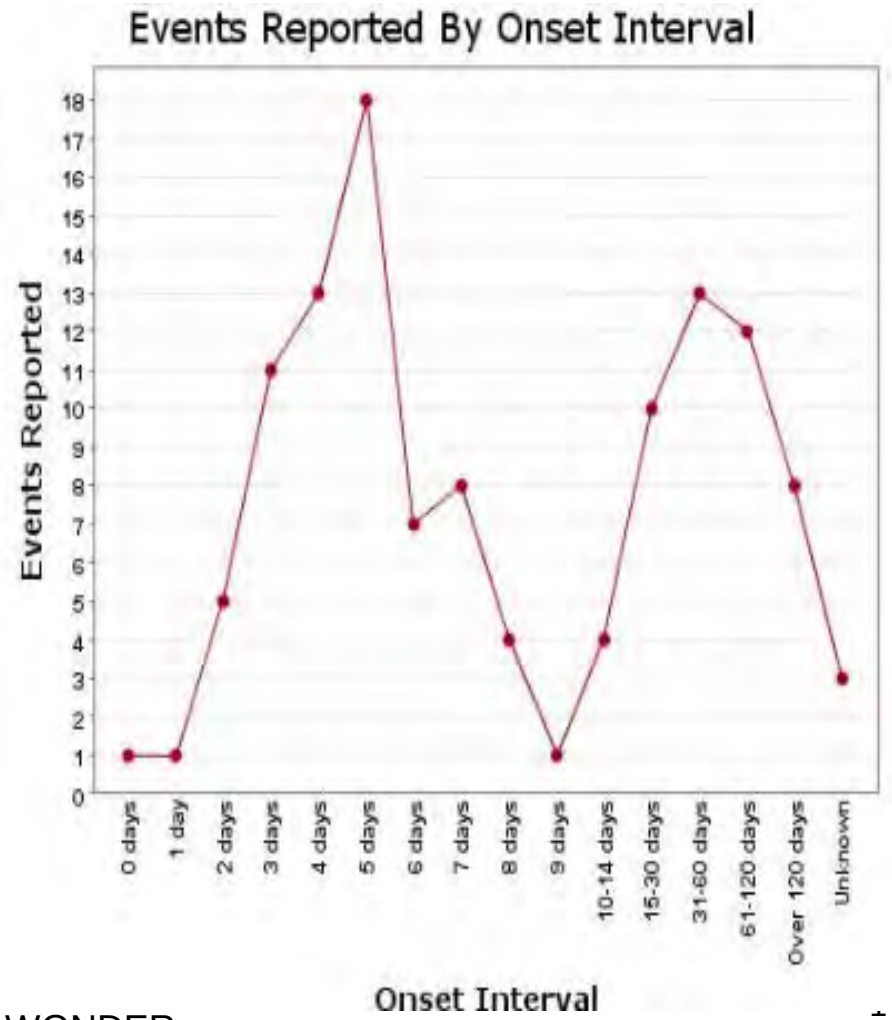


Chart source: CDC WONDER

Evidence of positive re-challenge

- **"Pt stated that subsequent to MMR #1 and #2, she experienced significant swelling from knee down bilaterally. She stated that the swelling started 3 days post each vax and lasted 3 days."**
  - Transient arthritis may occur in up to 10% of postpubertal females following rubella vaccine (Red Book, 2009 ed.)
- **"Wheezing within 24 hours of 1st 2 Hep-B shots."**
  - Anaphylaxis occurs in approx. 1 in 600,000 recipients (Red Book, 2009 ed.)
- **"Within 3 days of receiving the TD vax, the pt again lost all her hair."**
  - 16 cases of hair loss with positive rechallenge reported between 1984-97 (Wise R, Kiminyo K, Salive M. Hair loss after Routine Immunizations. JAMA 1997 Oct 8;278(14):1176-8.)

Report source: CDC WONDER, search "vaccine positive rechallenge"

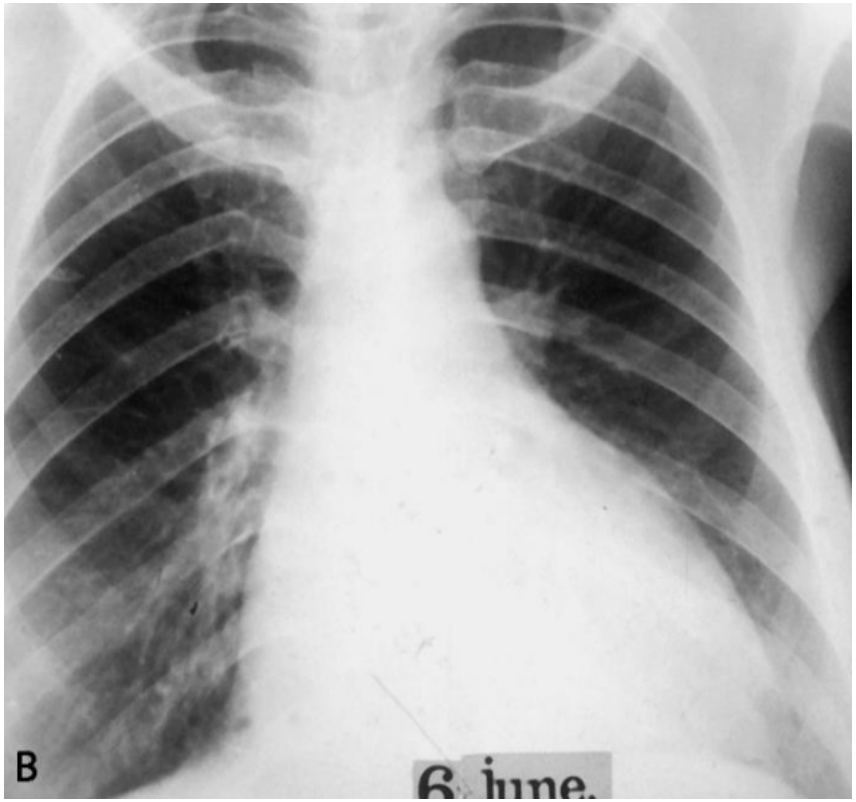
Absence of an Alternative Explanation

- 20y/o M w/ hx small pox vac on 22Sep08, c/o 2d retrosternal chest pain. Pain 5/10 severity. No prior hx of pain.
- Denies SOB, fever, chills, n/v/d.
- No hx HTN, HLD, DM, tob use, or fam hx of cardiac dz..
- EKG with diffuse ST elevation and PR depression. CK-MB, Trop-I, myoglobin, and LDH all elevated. (from CDC WONDER, VAERS ID 327009)

Photo source: www.jtfgtmo.southcom.mil

Smallpox Vaccine and Cardiac Issues

- Young, healthy male with no obvious risk factors for heart disease or MI
- CXR w/o obvious cardiomegaly. Pt presented with chest pain, worsened by deep breathing.
- Dx: myopericarditis
- 1 in 175 first time vaccinees may develop myocarditis (see “ACAM2000 Questions and Answers” at www.fda.gov)



X-ray source: Palmer and Reader, The Imaging of Tropical Diseases, http://tmcr.usuhs.mil/tmcr/toc.htm

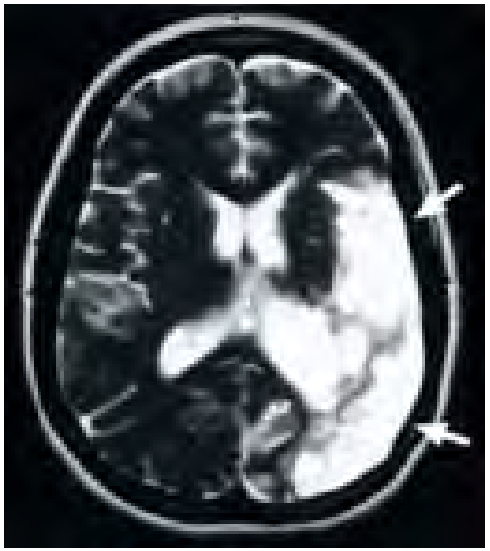
Counterpoint: Alternative Explanation Present

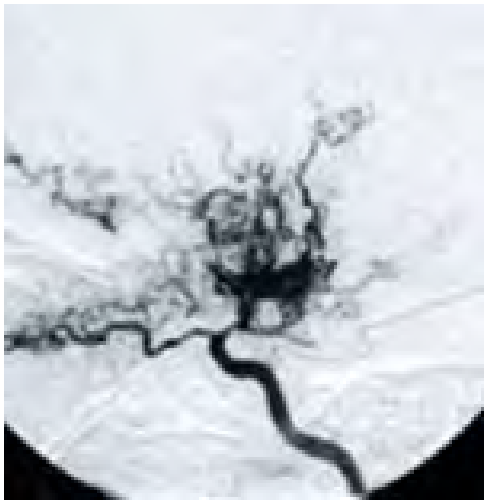
- Healthy 1 year old male with no significant past medical history received varicella vaccination
- 7 days later, parent noted facial asymmetry and arm weakness
- CT reveals a stroke
- Varicella disease increases risk of stroke, so could the vaccine also pose a risk?

Photo source: Public Health Image Library

Alternative Explanation Present

- In this case, further evaluation revealed the patient had moyamoya disease, which dramatically increases risk of stroke
- Retrospective cohort study of 3.2 million children found no increase in stroke among vaccinated children at any time period in the 12 months following vaccination[1]
- Therefore, vaccine is unlikely to be contributory in this case





[1]Donahue J, et al. Varicella vaccination and ischemic stroke in children: Is there an association? Pediatrics. 2009 Feb;123(2):e228-34.

Photos used with permission of Dr. Gary Steinberg and the Stanford Moyamoya Center

Increase in the Severity, Frequency, or Specificity of a Labeled Event.

- Example: Octagam, an intravenous immune globulin licensed in U.S. in 2004
  - Prior to 2010, thromboembolic events (stroke, MI) rare
    - 1 stroke in 6357 patients receiving 92,958 infusions[2]
  - In 2010, 7 thromboembolic events reported, leading to a recall
  - Root cause: residual Factor XIa in the final product[3]
- Adverse event profile of established products can change with time
- Continuous monitoring is needed to ensure safety

[2]Debes A, Bauer M, Kremer S. Tolerabilibity and Safety of IVIg Octagam…Pharmacoepidemiol Drug Saf. 2007 Sep;16(9):1038-47.

[3]www.fda.gov/.../BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM266168.ppt

Extremely Rare Events in the General Population

- Example: Tysabri (natalizumab) and Progressive Multifocal Leukoencephalopathy (PML)
- Tysabri approved in 2004 for treatment of Multiple Sclerosis and Crohn's Disease
- PML is a progressive neurologic disease, often leading to death or severe disability within months. An opportunistic infection with JC virus, seen in immunocompromised patients.
    - Risk in general population is estimated to be 1 in 200,000[4]

[4]Holman R, Torok T, Belay E, *et al*. PML in the United States, 1979-1994…Neuroepidemiology 1998;17(6):303-9.

Tysabri and PML

- 3 cases of PML reported in pre-licensure trials
  - All patients on prior immunosuppressant therapy
- Post-licensure reports of PML in patients who *had not* received prior immunosuppressant therapy
- Risk factors described and risk estimated

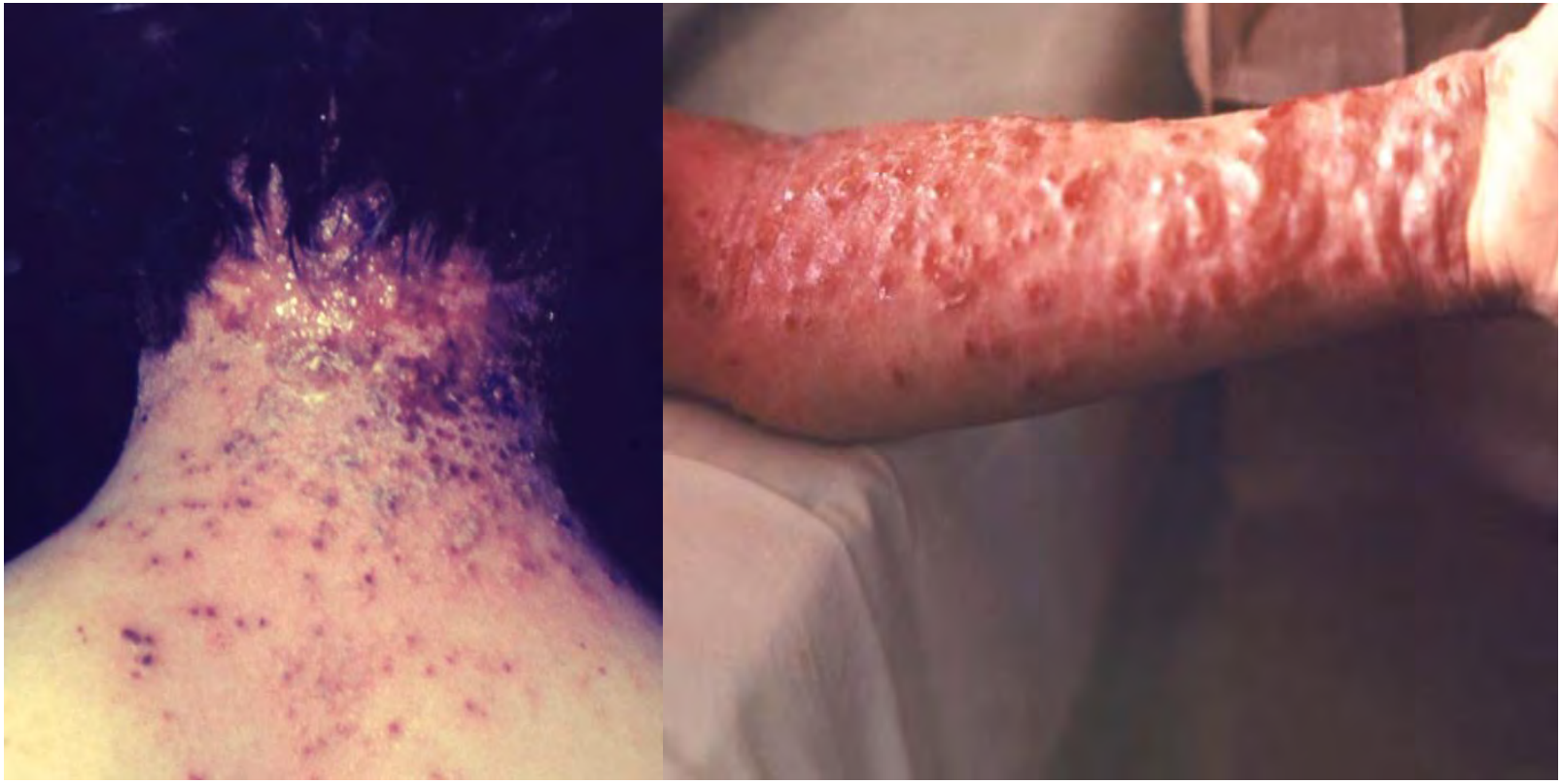
	Anti-JCV Antibody Positive*	Anti-JCV Antibody Positive*
Tysabri Exposure†	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1-24 months	<1/1,000	2/1,000
25-48 months	4/1,000	11/1,000

http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm?utm_source=fdaSearch&utm_medium=website&utm_term=tysabri%20PML%20risks&utm_content=1

Previously Unrecognized At-Risk Population

Source: Public Health Image Library and S. Winiecki

Eczema and Smallpox Vaccine



- Patients with a history of eczema are known to be at risk for eczema vaccinatum

Photo source: Public Health Image Library

A Genetically At-Risk Population: An Example from Europe

- In 2010, several regulatory authorities in Europe noted an increase in narcolepsy-cataplexy cases following the H1N1 vaccine Pandemrix
- Pandemrix is not a U.S. licensed vaccine
- Following these findings, CBER investigated H1N1 vaccines licensed in the U.S. and found no safety signals

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/08/news_detail_001105.jsp&mid=WC0b01ac058004d5c1

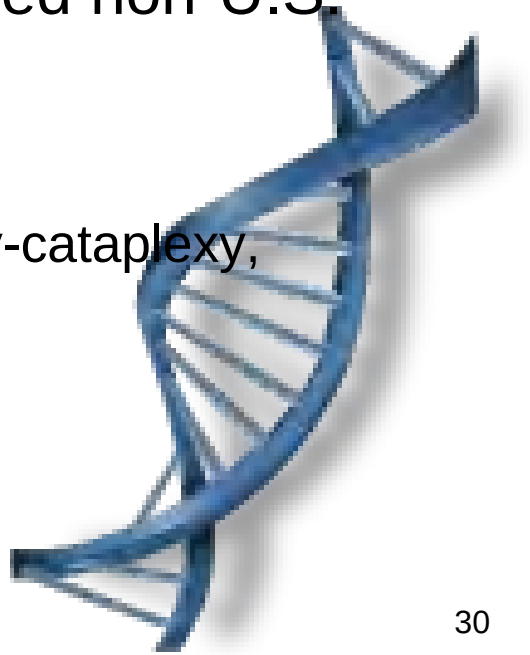
Narcolepsy-Cataplexy: Background

- Narcolepsy: rapid and frequent episodes of falling asleep
- Cataplexy: sudden attacks of loss of voluntary muscle control. Patient remains conscious but is unable to move or respond
- Can result in falls, injuries, drowning, suffocation
- Very strongly linked to HLA DQB1*0602

Photo source: Public Health Image Library

Narcolepsy-Cataplexy Following H1N1 Influenza Vaccine in Europe

- In early 2010, 3 sleep centers noted an increase in abrupt onset narcolepsy-cataplexy cases
- Of 31 cases identified, 14 were post-H1N1 vaccination and 2 were post-influenza[5]
- Of the 14 post-vaccination cases, 11 received non-U.S. licensed, adjuvanted vaccines
- All 16 were positive for DQB1*0602
  - While these individuals are at risk for narcolepsy-cataplexy, H1N1 vaccination may have triggered the onset
  - Could HLA typing be the first “vaccinogenomic intervention?”



[5]Dauvillers Y, Montplaisir J, Cochen V, et al. Post-H1N1 Narcolepsy-Cataplexy. Sleep 2010Nov 1; 33(11):1428-30.

Narcolepsy-Cataplexy: Evidence for Product-Event Association

- Expected time: 9 of 14 cases had onset 2 – 8 weeks after vaccination. This would seem plausible for an autoimmune mediated effect
- Biologically plausible: Genetically predisposed individuals, a postulated autoimmune mechanism
- Alternative explanations:
  - Role of H1N1 disease
  - Role of recent strep infection (many patients had an elevated ASO titer)
  - General stimulation of the immune system vs. specific autoantibody
  - Role of vaccine adjuvant

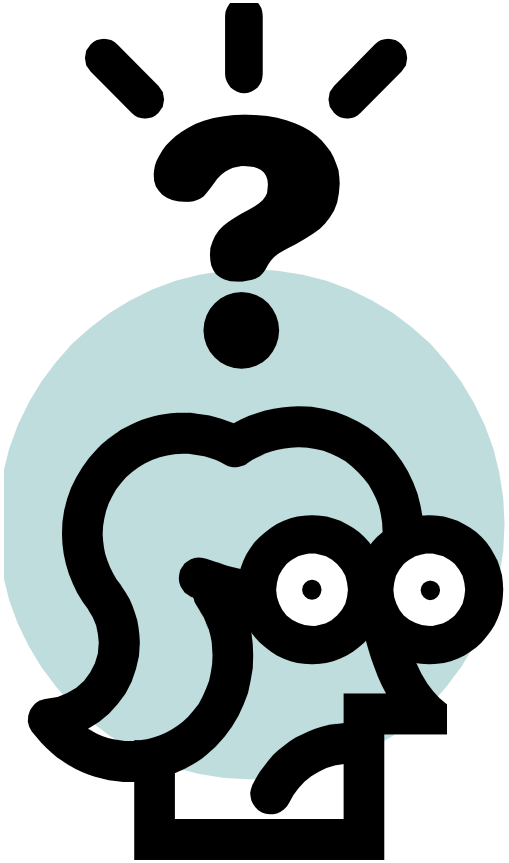
Narcolepsy-Cataplexy: Evidence for Product-Event Association

- An increase in the severity, frequency, or specificity…
  - While not a labeled event, cases had a common and atypical presentation
    - Abrupt onset
    - Unusually severe
    - Atypical age at onset (5 cases >38 years, 2 cases <5 years)

Developing a Case Series

- A mechanism to gather information and examine data for commonalities and patterns
- Most important aspect – the case definition
  - Need to define the process (adverse effect, disease) that you are investigating
    - Brighton Collaboration
    - Regulatory agencies
    - Published articles
    - Professional or patient organizations
- Can serve as the foundation for further investigation but **cannot establish causality**

Questions?



Review Questions

Aspects of periodic product-based review include:

A) Comparing the number of reports in the current period to prior periods

B) Comparing Preferred Terms (PTs) for reports during the current period to PTs from prior reporting periods

C) Conducting a literature search

D) Data mining

E) All of the above

Answer: E) All of the above. Periodic review is a comprehensive, multi-step process.

Review Question 2

A product-event association might be suggested by:

A) An event with an alternative explanation

B) An event within a biologically plausibly time frame

C) A negative re-challenge

D) Multiple reports of a common event

Answer: B) Within a biologically plausible time frame.

Review Question 3

Passive surveillance methods can be used to generate a hypothesis about a product-event association:

A) True
B) False

Answer: A) True. These methods are useful tools to begin to examine a product-event combination for patterns.

Review Question 4

Passive surveillance methods can determine causality:

A) True
B) False

Answer: B) False. Passive surveillance can suggest an association but **cannot** establish causality. Additional studies must be conducted to establish a direct relationship.

Review Question 5

The most important aspect of constructing a case series is:

A) Establishing the time period to study

B) Evaluating the cases

C) Establishing a case definition

D) Making slide presentations

Answer: C) The case definition. Without a quality case definition, you can't be sure what you are measuring and what it means.

Conclusions

- Periodic adverse event review forms the basis for identifying new potential safety concerns
- Product based monitoring includes
  - Reviewing the number of reports and the most frequently reported PTs
  - Reviewing medically important cases (deaths, sequelae)
  - Literature review
  - Data mining
- Specific features of spontaneous reports may suggest a product-event association and lead to hypotheses which are evaluated through additional methods.