Lessons Learned from Adverse Events and Assessment of Causal Relationships

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Johns Hopkins University
Lessons Learned

1000s of lessons learned
Many vaccines not successful
Some caused harm
Introduction of IPV U.S. 1955

- April 14: Francis Field Trial Results Announced by March of Dimes
- April 15, U.S. Nationwide Immunization
- April 24, First cases of paralysis
Cutter-associated Polio Cases (260)

1955

Number of Cases

Vaccinated Cases
- Non-paralytic
- Paralytic

Family Contact Cases

Community Contact Cases

April

Effects of Virus-Formaldehyde Contact Upon Rate of Destruction of Virus Infectivity

Virus Suspended in Fluid Phase and in Contact with Formaldehyde

Theoretical Projection of Formalin Effect

MEASURABLE EFFECT OF FORMALIN

SEDIMENT CONTAINING VIRUS PROTECTED FROM CONTACT WITH FORMALIN

LOSS OF INFECTIVITY DUE TO AGING (NOT TO FORMALIN)

Salk JE. Am J Pub Health 1956;46(1):1
The Cutter Incident

- Lessons:
  - Scaling up creates new problems
  - Quality control every change
  - Need epidemiologic post-licensure safety assessment
EZ Measles Vaccine Trial, Mexico City Seroconversion Rates, 6 Month-olds

% seroconversion, 8 wks post-vaccination

- Standard ~$10^{3.4}$
- Medium $10^{4.5}$
- High $10^{5.3}$

p<0.001 for all comparisons

1990: High titer vaccine recommended by WHO

Source: Markowitz. NEJM 1990;322(9):580.
Survival Curves From 9 Months of Age by Sex for Recipients of the Schwarz Standard and High-titer Measles vaccine.

Children Born Between February 1987 and April 1990 in Niakhar, Senegal

<table>
<thead>
<tr>
<th>Increased Mortality</th>
<th>IMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea Bissau</td>
<td>122</td>
</tr>
<tr>
<td>Senegal</td>
<td>78</td>
</tr>
<tr>
<td>Haiti</td>
<td>110</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Increased Mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>29</td>
</tr>
<tr>
<td>Peru</td>
<td>56</td>
</tr>
<tr>
<td>Philippines</td>
<td>52</td>
</tr>
<tr>
<td>U.S.</td>
<td>8</td>
</tr>
</tbody>
</table>

\[ \geq 10^{5.0} \text{ TCID}_{50} \]

Halsey PIDJ; 12:462-5, 1993
Libman et al. PIDJ;21:112, 2002
High Titer Measles Vaccines

• Lessons:
  – Dose of measles vaccine important—probably specific to measles
  – Safety in one population ≠ safety in all
  – Unfortunate generalization by some to vaccines “overwhelm the immune system”
Randomized Trial of Standard Titer Measles Vaccine on Mortality

Aaby et al. BMJ 2010;341:c6495

22% reduction (not significant)
Less than noted in multiple observational studies

Girls 0.64 (0.42 to 0.98)
Boys (0.95 (0.64 to 1.42)

MRR=0.78 (0.59 to 1.05)
P value=0.10
Causality Assessment
What do we mean when we say a vaccine “causes” an adverse event?

- **Population:** The vaccine increases the risk of the event.
- **Individual:** The vaccine was a factor in the patient developing the adverse event.

*Coggan and Martyn Lancet 2005; 365: 1434–37*
Usual criteria for determining a causal relationship between vaccines and adverse events

Epidemiologic Studies: Evidence of increased risk in vaccine recipients vs controls,

or

Definitive laboratory tests linking disease to vaccine component

A few exceptions
Randomized Placebo Controlled Trials

- **Recruit**
- **Population**
- **Enroll**
  - **Participants**
  - Selected: healthy, age, gender?
- **Randomize**
  - **Vaccine**
  - **Placebo**
- **Outcomes**

Double blind evaluations
## Investigating Causal Relationships
Randomized Placebo-Controlled Double Blind Trials

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Disorder</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>a</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>b</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td>c</td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>d</td>
</tr>
</tbody>
</table>

### Risk

- **Risk**
  \[
  \frac{a}{a+b} \quad \frac{c}{c+d}
  \]

### Relative Risk

- **Relative Risk**
  \[
  \frac{a}{a+b} \quad \frac{c}{c+d}
  \]
Prospective Randomized Trials for Detection of Adverse Events

• Designed for detection of reactions:
  – Common
  – Acute

• Not generally designed to detect:
  – Uncommon
  – Vague onset
  – Delayed onset
Post-licensure Safety Studies

1. Passive surveillance
2. Active surveillance
3. Individual case assessment
4. Epidemiologic studies
Retrospective or Non-concurrent Cohort Studies

- Defined population.
- Identify vaccinated and unvaccinated prior to risk period.
- Identify all cases in defined time period.
- Compare rates of disease in vaccinated and unvaccinated.
## Investigating Causal Relationships

### Retrospective or Non-concurrent Cohort Studies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Disorder</th>
<th>Risk</th>
<th>Rel Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>( \frac{a}{a+b} )</td>
<td>( \frac{a}{a+b} )</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td>( \frac{c}{c+d} )</td>
<td>( \frac{c}{c+d} )</td>
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<tr>
<td>no</td>
<td>yes</td>
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<td>no</td>
<td>( \frac{c}{c+d} )</td>
<td>( \frac{c}{c+d} )</td>
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- **Not randomized:** Self selection for vaccine?
Relative Risk of Sudden Infant Death Syndrome by Day after DTP: Tennessee

Healthy Vaccinee Effect: children with illnesses not vaccinated

DTP does not increase the risk of SIDS

Griffin et al. NEJM 1988;319:618-23
Investigating Causal Relationships
Case-Control Studies

- Disorder
  - case
  - control

- Vaccine
  - no
  - yes

Potential Problems:
- Not randomized
- Selection bias?
- Matching?
Bell’s Palsy

Facial nerve

Facial muscles
### Switzerland: Odds Ratios for Receipt of Vaccines <91 Days Prior to Bell’s Palsy

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Case Patients (N=250)</th>
<th>Controls (N=722)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal LT inactivated influenza</td>
<td>63 (25.2%)</td>
<td>7 (1.0%)</td>
<td>84.0 (20.1-351.9)</td>
</tr>
<tr>
<td>Parenteral inactivated influenza</td>
<td>10 (4.0%)</td>
<td>41 (5.7%)</td>
<td>1.1 (0.6-2.0)</td>
</tr>
</tbody>
</table>

LT toxin induced local inflammation  
No consistent association with other vaccines

*Halsey N et al. Vaccine 2015;33:S1-67*
# Vaccine Only Studies

## Disorder

<table>
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<tbody>
<tr>
<td>yes</td>
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<td>no</td>
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**Advantage:**
- Self controlled
- No need for randomization of matching
- Compare risk of disease in time windows
Vaccine Only Studies

Vaccination

Febrile Seizures

0-1
14-15

Days after vaccination

Compare the incidence of disease in risk window vs. control window

Self controlled: avoid potential biases
Risk of febrile seizures on days 0-1 vs 14-15 after TIV alone, PCV13 alone and simultaneous TIV and PCV13
## Case Only Studies

### Disorder

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<td>b</td>
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<tr>
<td>no</td>
<td>yes</td>
<td>c</td>
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</tr>
<tr>
<td>no</td>
<td>no</td>
<td>d</td>
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Compare likelihood of having received vaccine in different time windows

**Potential Problems:**
- Selective reporting of cases after vaccine?
- Need to include all cases
Bradford Hill Causality Criteria

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biologic gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy

You do not need to prove the pathogenic mechanism to establish a causal association

## Ecologic Studies

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Disorder</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>a</td>
<td>a/(a+b)</td>
</tr>
<tr>
<td>no</td>
<td>c</td>
<td>c/(c+d)</td>
</tr>
<tr>
<td>yes</td>
<td>b</td>
<td>a/(a+b)</td>
</tr>
<tr>
<td>no</td>
<td>d</td>
<td>c/(c+d)</td>
</tr>
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</table>

- Very weak evidence.
- Usually uninformative for establishing causality.
Core and Atypical Autism Cases Under 60 Months of Age and Fitted Trends by Year of Birth 1979-92: UK

Ecologic data used to Argue MMR caused autism

Ecologic Data Used to Demonstrate Effectiveness of Licensed Vaccines

Causal associations already established. Vaccines proven to prevent the diseases

<table>
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<tbody>
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<td>yes</td>
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<tr>
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<td>no</td>
<td></td>
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<tr>
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<td>yes</td>
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<td>d</td>
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<tr>
<td>no</td>
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<td></td>
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</tr>
</tbody>
</table>

\[
\text{Risk Ratio} = \frac{a}{a+b} \quad \text{and} \quad \frac{c}{c+d}
\]
1998: Case reports of Children with Autism after MMR

www.autismpedia.org
Bad Science in Case Reports Continues

4 cases onset 4, 5, 5 and unk. mos after vaccine

Neuromyelitis optica following human papillomavirus vaccination

Til Menge, MD, Bruce Cree, MD, PhD, Andreas Saleh, MD, MPH, Tim Waterboer, PhD, Achim Berthele, MD, Sudhakar Reddy Kalluri, MSc, Bernhard Hemmer, MD, Orhan Aktas, MD, Hans-Peter Hartung, MD, Axel Methner, MD and Bernd C. Kieseier, MD

* SHOW AFFILIATIONS | + SHOW FULL DISCLOSURES
Correspondence & reprint requests to Dr. Menge: menge@uni-duesseldorf.de

Published online before print June 20, 2012, doi: 10.1212/WNL.0b013e31825fdead
Neurology July 17, 2012 vol. 79 no. 3 285-287
Decrease in HPV Acceptance in Denmark Following Promotion of Rumors by Journalists

5. HPV VACCINE UPTAKE OF FIRST DOSE BY BIRTH COHORT IN THE NORDIC COUNTRIES

Palle Valentiner-Branth, MD, PhD
Department of Infectious Disease Epidemiology
Statens Serum Institut, Denmark 2016
False Assumptions of Causal Associations

Post hoc, ergo propter hoc

After this, therefore because of this
Case Reports
Integral to Medical Education

Case 6-2015: A 16-Year-Old Boy with Coughing Spells

Michael R. Wessels, M.D., Kathryn S. Brigham, M.D.,
and Alfred DeMaria, Jr., M.D.

PRESENTATION OF CASE

Dr. Mark A. Goldstein (Pediatrics): A 16-year-old boy was seen in the adolescent medicine outpatient clinic of this hospital in late spring because of coughing spells.

The patient had been well until approximately 3 weeks before the current presentation, when cough and nasal congestion developed and persisted, without fever or chills. He took fexofenadine hydrochloride, without improvement. Three days before the current presentation, he awoke at night with a severe coughing spell, with associated post-tussive emesis and trouble breathing. His parents took him to the emergency department of another hospital. On examination, he appeared to be in no distress; the temperature was 37.0°C, the blood pressure 152/87 mm Hg, the pulse 107 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while he was breathing ambient air. The mucosa of the posterior oropharynx had a cobblestone appearance and the uvula was midline; there was no tonsillar edema or exudate. Nasal congestion, boggy nasal mucosa, and serous effusions behind both tympanic membranes were evident. The lungs were clear on auscultation, and the remainder of the examination was normal. A diagnosis of allergic rhinitis with the upper-airway cough syndrome (postnasal drip)
Case Reports are Storytelling

https://lukezahrahnd.wordpress.com

Nat Farbman 1947

http://english.cntv.cn/program

www.bundleontheweb.com
25+ Journals of Case Reports
Consort Guidelines for Clinical Trials

Schulz et al PLoS Med. 2010

Need Similar Standard Guidelines for Case Reports
Limitations in the Use of Passive Reports for Causality Assessment

1. Incomplete data
2. Diagnoses not verified
3. Usually temporal association only
4. Faulty numerators and denominators
   - Reporting bias
5. Cannot be used for calculating true risks
6. Primarily hypothesis generating

MMWR. 2003 Feb 14;52(06):113
Causality Assessment from Individual Case Reports

• Causality established (usually):
  – Isolation of live vaccine agent in normally sterile body fluid.
    • Yellow fever vaccine virus in liver.
    • Polio vaccine (OPV) virus in CSF.
    • Measles vaccine virus in lung of child with leukemia.

Sem in Ped Infect Dis 2002 July;13(3):205-14
Causality Assessment from Individual Case Reports

• Causality established (usually):
  – Isolation of live vaccine agent in normally sterile body fluid.
    • Yellow fever vaccine virus in liver.
    • Polio vaccine (OPV) virus in CSF.
    • Measles vaccine virus in lung of child with leukemia.
  – Rule out wild type virus (genetic sequencing)
Causality Assessment from Individual Case Reports

• Causality **not** established:
  – Antigen detection or PCR without sequencing.
    • False positives
    • Contamination
    • Coincidental infection
Causal Associations Usually Cannot be Determined from Passive Reports of Individual Cases Without Isolation of Vaccine Agent

Possible exceptions:
1. Injection site reactions
2. Immediate hypersensitivity reactions
3. Repeat challenge (no clear criteria)
4. Disorders where general causality has already been established and alternative causes ruled out
Immediate Hypersensitivity Reactions

- Pathogenesis known
- Short interval from vaccine to reaction
- Unlikely for other exposures
- Skin testing with vaccine components
Disorders Known to Have a Causal Association with Vaccines

- Febrile seizure 7 or 10 days after measles vaccine:
  - In the time window of increased rate of fever
  - No specific test to determine cause
Percent of Children with Fever Following Edmonston B Measles Vaccine (1963)

Cannot determine with certainty cause of fever in individuals

Adapted from Martin CM. Am J of Dis of Children 1963;106:270.
CISA Causality Assessment
Objectives

1. To educate providers on the steps involved in assessing causality
2. To standardize the approach for assessing causality in individual patients
3. To improve the understanding of terms used to describe causal relationships

Confusion from Use of Same Terms for Diagnostic Certainty and Causality

**Certainty of Diagnosis**
- Definite
- Probable
- Possible
- Unlikely
- Unknown

**Causal Relationship**
- Definite/certain
- Probable
- Possible
- Unlikely
- Other cause
- Unclassifiable
CISA Review of Case Reports of Adverse Events Following Immunizations
Causality Work Group of CISA

1. Is the diagnosis correct?
   - Yes
   - No

2. Is there evidence for other causes?
   - Yes
   - No

3. Is there a known causal association with the vaccine?
   - Yes
   - No

4. Is there strong evidence against a causal association?
   - Inconsistent with causal association
   - Consistent with causal association

5. Is the AEFI an Infection?
   - Yes
   - No

Other diagnosis

2a. Is the evidence definitive?
   - Yes
   - No

Indeterminate

3a. Was the event within the time window of increased risk?
   - Yes
   - No

3b. Are there qualifying factors?
   - Yes
   - No

Consistent with causal association

Inconsistent with causal association, other cause identified

If continue, include statement regarding uncertain diagnosis in conclusion

Review of Case Reports of Adverse Events Following Immunizations
Causality Work Group of CISA

Febrile seizure
12 month old
7 days after MMR

1. Is the diagnosis correct?

2. Is there evidence for other causes?

3. Is there a known causal association with the vaccine?

4. Is there strong evidence against a causal association?

5. Is the AEFI an infection?

Other diagnosis

2a. Is the evidence definitive?

Indeterminate

Inconsistent with causal association, other cause identified

Not available

Inconsistent with causal association

Yes

No

No or Uncertain

Yes

No

Consistent with causal association

Yes

No

Yes

No

Yes

No

Yes

No

Consistent with causal association

Indeterminate, diagnosis uncertain

If continue, include statement regarding uncertain diagnosis in conclusion

If continue, include statement regarding evidence for other cause in conclusion
Review of Case Reports of Adverse Events Following Immunizations
Causality Work Group of CISA

1. Is the diagnosis correct?
   - Yes
   - No

2. Is there evidence for other causes?
   - Yes
   - No

3. Is there a known causal association with the vaccine?
   - Yes
   - No

3a. Was the event within the time window of increased risk?
   - Yes
   - No

3b. Are there qualifying factors?
   - Yes
   - No

4. Is there strong evidence against a causal association?
   - Yes
   - No

5. Is the AEFI an Infection?
   - Yes
   - No

Other diagnosis

Indeterminate, diagnosis uncertain

Inconsistent with causal association, other cause identified

Other diagnosis

Consistent with causal association

Febrile seizure
12 month old
4 days after MMR

2a. Is the evidence definitive?
   - Yes
   - No

Inconsistent with causal association, other cause identified

Not available

If continue, include statement regarding evidence for other cause in conclusion

Not definitive

If continue, include statement regarding uncertain diagnosis in conclusion

No or Uncertain

Inconsistent with causal association

Consistent with causal association

If continue, include statement regarding evidence for other cause in conclusion

Yes

No

Not definitive

Inconsistent with causal association

Inconsistent with causal association, other cause identified

Yes

No

Not available

If continue, include statement regarding evidence for other cause in conclusion

No or Uncertain

Inconsistent with causal association

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Yes

No

Not definitive

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Inconsistent with causal association, other cause identified

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If continue, include statement regarding evidence for other cause in conclusion
Algorithm Advantages

1. Visual
2. Standardized
3. Transparent
4. Tracking assessments
5. Revise assessments as new data become available
WHO AEFI investigation

Purpose: This aide-mémoire proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI by:
- confirming a diagnosis and timing
- identifying details of vaccine(s) administered
- documenting the outcome of the reported adverse event
- determining whether the reported event is solitary or part of a cluster
- reviewing the operational aspects of the programme

When to investigate AEFI
If a detailed investigation is warranted, it should be initiated as soon as possible, ideally within 24 to 48 hours of the case being first reported.

Checklist for AEFI investigation

1. Preliminary steps
   - Develop national guidelines with case definitions for reportable AEFIs, reporting forms, investigation procedures, roles and responsibilities
   - Develop resource documents and training material on reporting, management and investigation of AEFIs
   - Designate and train staff to conduct an AEFI investigation using the investigation form and guidelines
   - Train staff on how to collect and store specimens
   - Have a functioning National AEFI Review Committee with suitable representation
   - Establish procedure, criteria and designate focal persons for notifying and communicating with WHO and UNICEF (if UN-supplied vaccine) or other relevant party depending on procurement mechanism
   - Identify a spokesperson for public communications

2. Receiving a report
   - Provide rapid attention to all reports received and imme-

http://www.who.int/vaccine_safety/initiative/investigation/New_aide-memoire_AEFI.pdf?ua=1
CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI)

Assessment of causality of individual adverse events following immunization (AEFI): A WHO tool for global use

Alberto E. Tozzi, Edwin J. Asturias, Madhava Ram Balakrishnan, Neal A. Halsey, Barbara Law, Patrick L.F. Zuber

WHO/HIS/EMP/QSS. MARCH 2013

Tozzi et al. Vaccine 2013;31(44):5041-6

http://www.who.int/iris/bitstream/10665/80670/1/9789241505338_eng.pdf
Causality Assessment Steps

- Eligibility
- Checklist
- Algorithm
- Classification
Eligibility

Fig. 1: Causality assessment – Eligibility

- **AEFI case**
  - Ensure AEFI investigation is completed and all details of the case are available
  - Retain case details in a retrievable database for "data mining"

- **Identify vaccine(s)**
  - Identify one or more vaccines administered before this event

- **Valid Diagnosis**
  - Select the unfavourable or unintended sign, abnormal laboratory finding, symptom or disease that is thought to be causally linked to the vaccine

- **Case definition**
  - Use an appropriate definition (Brighton Collaboration definition, standard literature definition, national definition or other approved definition) to assess diagnostic certainty
Step 2: Checklist

I. Is there strong evidence for other causes?

II. Is there a known causal association with the Vaccine / Vaccination
   - Relationship with vaccine ingredients
   - Immunization error
   - Relationship with vaccine administration

II (Time). Was the event within the time window of increased risk?

III. Is there a strong evidence against a causal association?

IV. Other Qualifying Factors
3. Algorithm

**Step 3: Algorithm**

Review all steps and check ✓ all the appropriate boxes

1. Is there strong evidence for other causes?
   - Yes
   - No

2. Is there a known causal association with the vaccine/vaccination?
   - Yes
   - No

3. Is there a strong evidence against a causal association?
   - Yes
   - No

4. Review other qualifying factors
   - Is the event classifiable?
     - Yes
     - No

   - IV A. Consistent causal association to immunization
   - IV B. Indeterminate
   - IV C. Inconsistent causal association to immunization
   - IV D. Unclassifiable
4. Classification

**Step 4: Classification**

Check ✓ all boxes that apply

**A. Consistent causal association to immunization**
- A1. Vaccine product-related reaction (As per published literature)
- A2. Vaccine quality defect-related reaction
- A3. Immunization error-related reaction
- A4. Immunization anxiety related reaction

**B. Indeterminate**
- B1. *Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event [may be new vaccine-linked event]*
- B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

**C. Inconsistent causal association to immunization**
- C. Coincidental
  - Underlying or emerging condition(s), or conditions caused by exposure to something other than vaccine

**Unclassifiable**

Specify the additional information required for classification:

*B1: This is a potential signal and maybe considered for investigation*
Conclusions

1. Poor understanding of causality assessment
2. Need for standardization of reporting assumptions of causal associations
3. Demand good science