Lessons Learned from Adverse Events and Assessment of Causal Relationships

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Introduction of IPV U.S. 1955

- April 14: Francis Field Trial Results Announced by March of Dimes
- April 15, Nationwide Immunization
- April 24, First cases of paralysis

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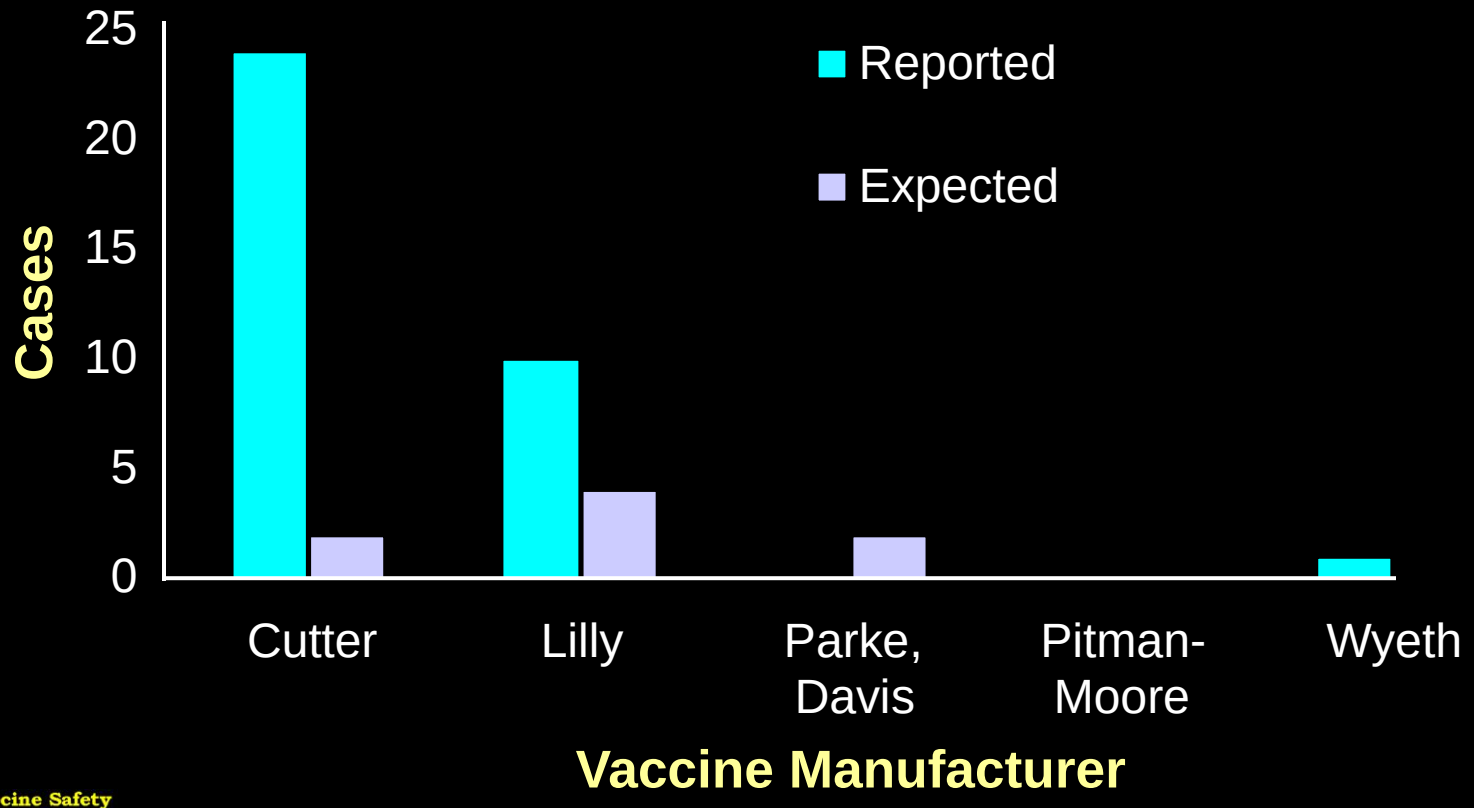
Poliomyelitis Among Children Inoculated in School Clinics

April 17 - May 14, 1955



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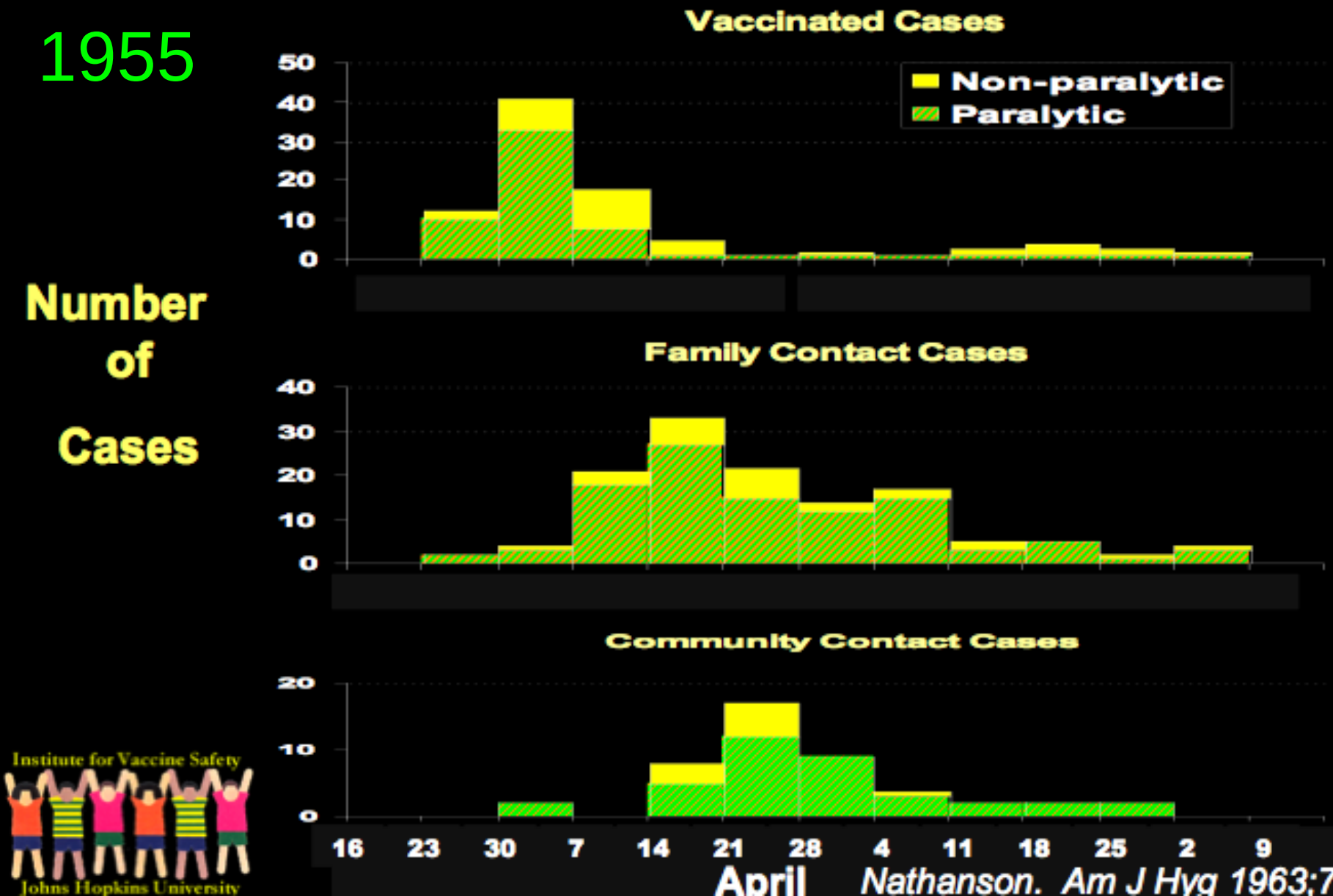
Source: Nathanson. Am J Hyg 1963;78:46.

Cutter-associated Polio Cases (260)

1955



Nathanson. Am J Hyg 1963;78:46

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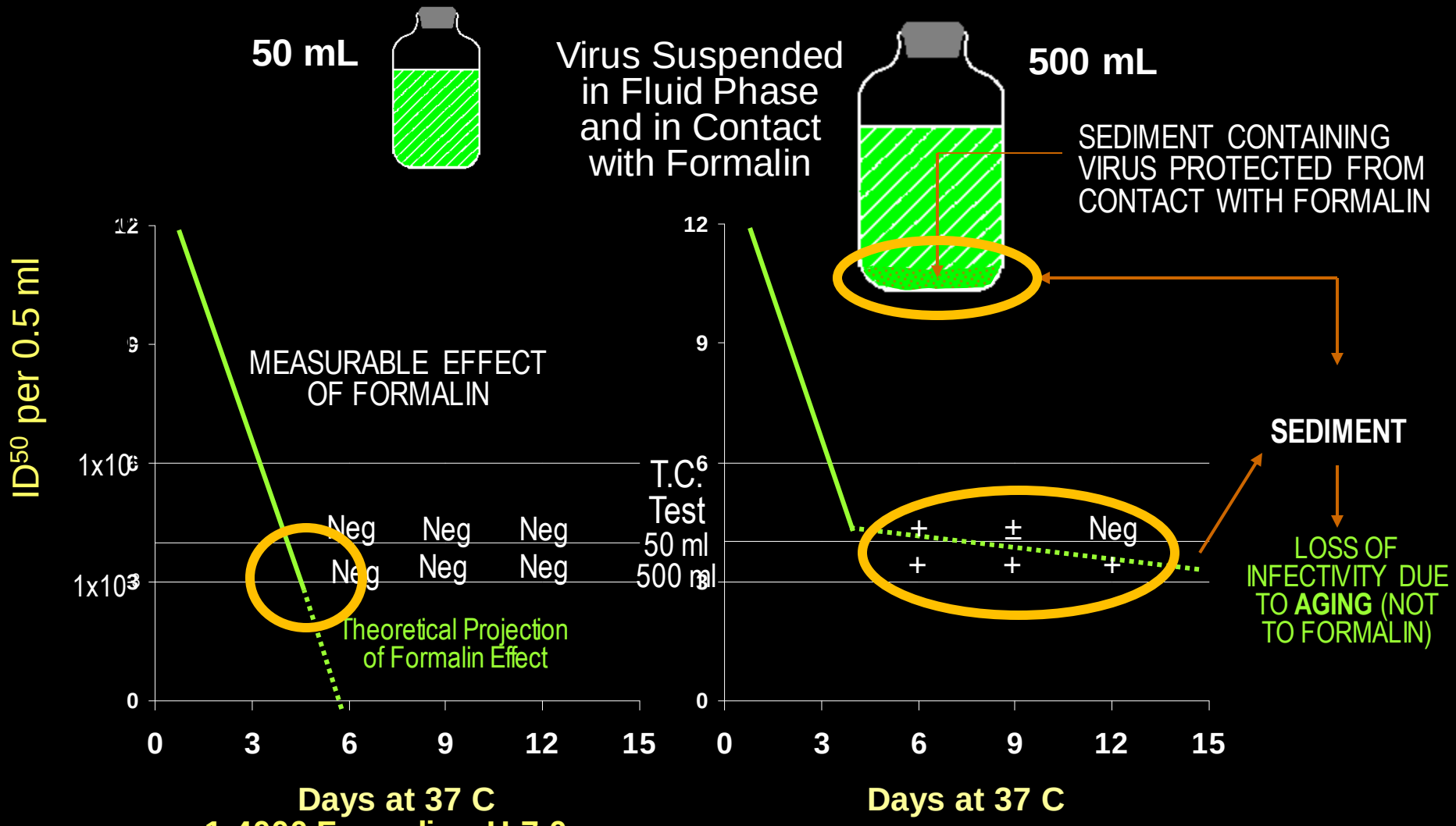
Effects of Virus-Formaldehyde Contact Upon Rate of Destruction of Virus Infectivity



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

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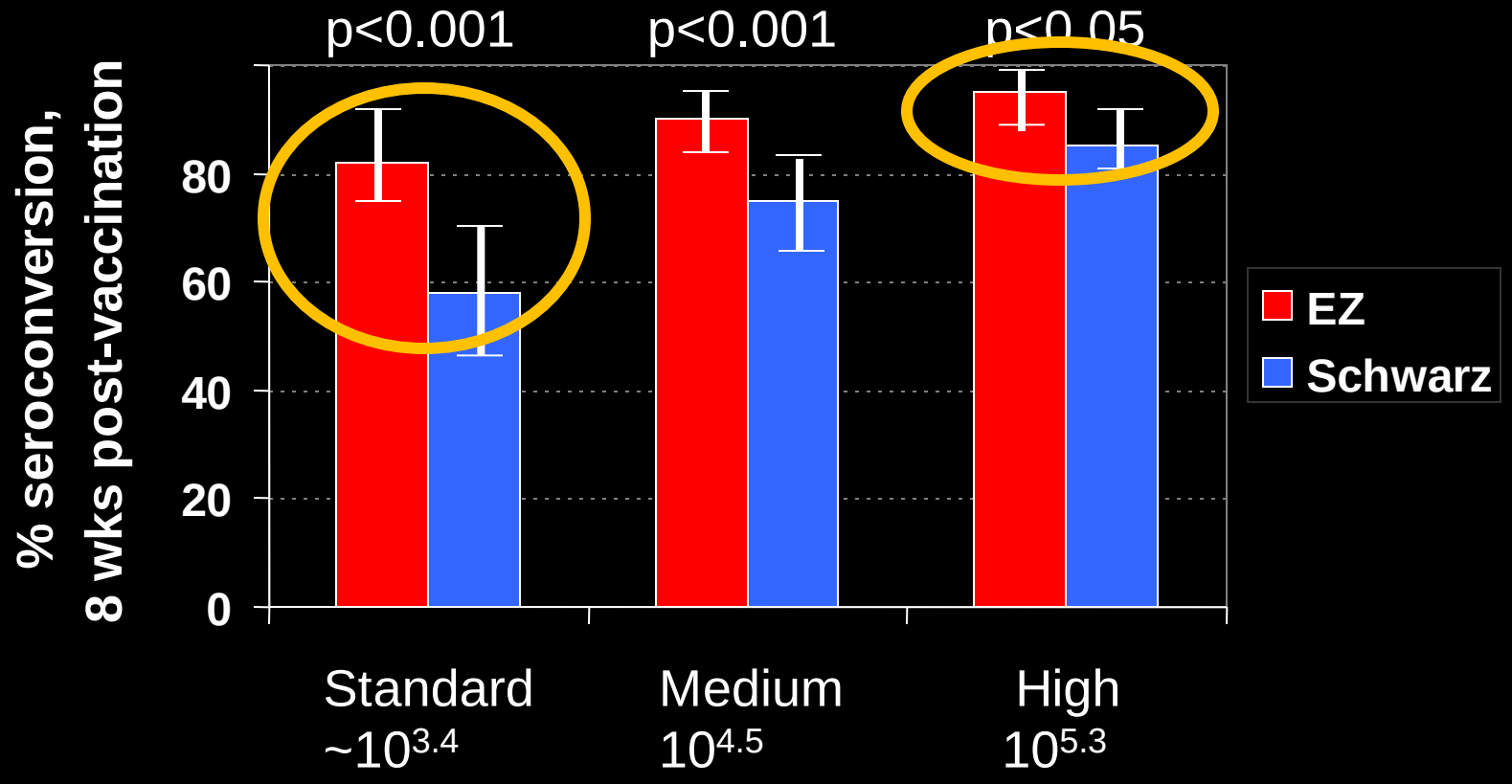
EZ Measles Vaccine Trial, Mexico City Seroconversion Rates, 6 Month-olds



1990: High titer vaccine recommended by WHO

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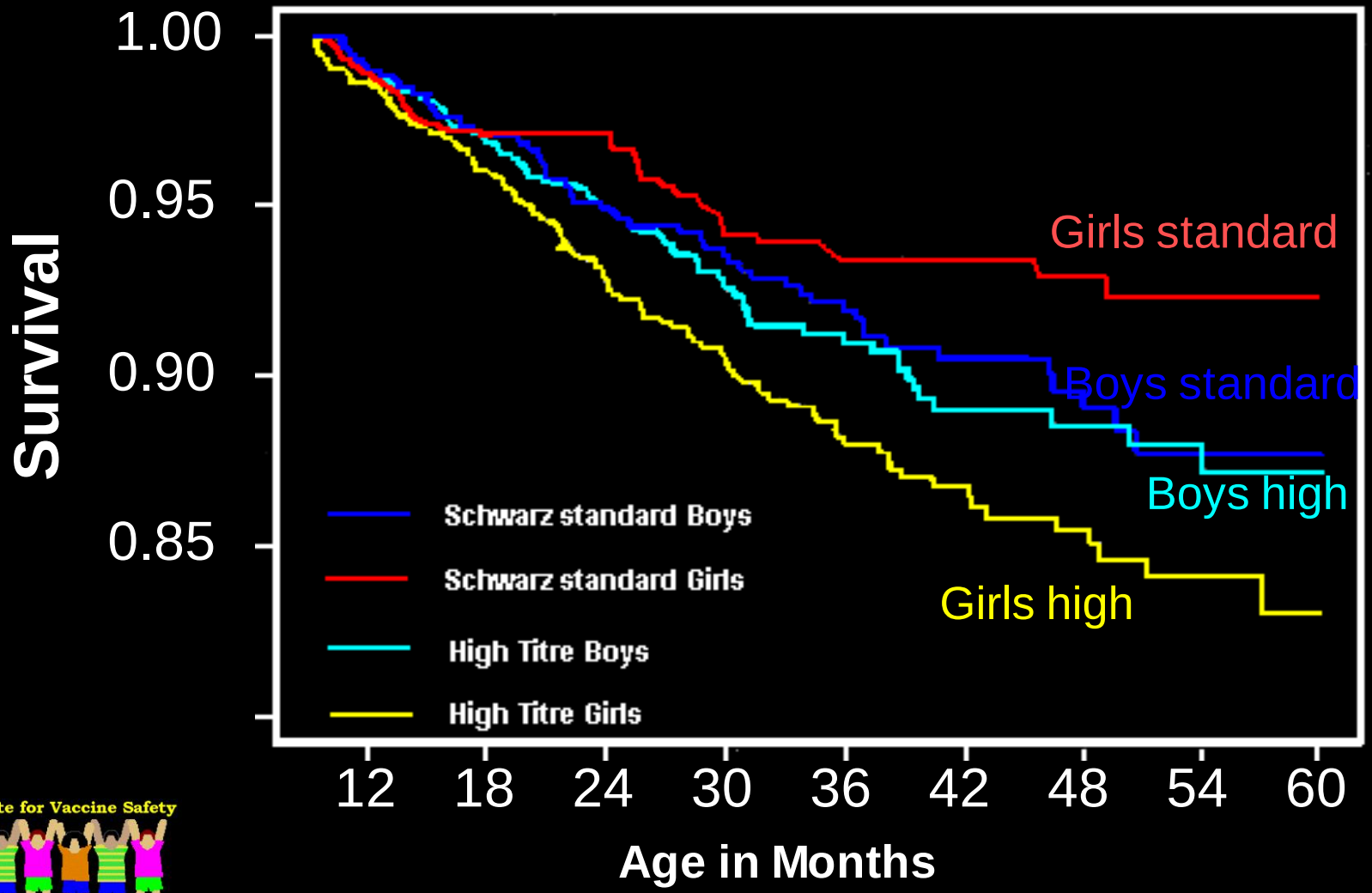
Source: Markowitz. NEJM 1990;322(9):580.

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



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Source: Aaby. Am J Epi 1993;138(9):746.

Mortality Following High Titer* Vaccines by Country and 1990 Infant Mortality Rates

Increased Mortality	IMR
Guinea Bissau	122
Senegal	78
Haiti	110

No Increased Mortality	
Mexico	29
Peru	56
Philippines	52
U.S.	8

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*$\geq 10^{5.0}$ TCID $_{50}$

Halsey PIDJ; 12:462-5, 1993

Libman et al. PIDJ;21:112, 2002


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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"

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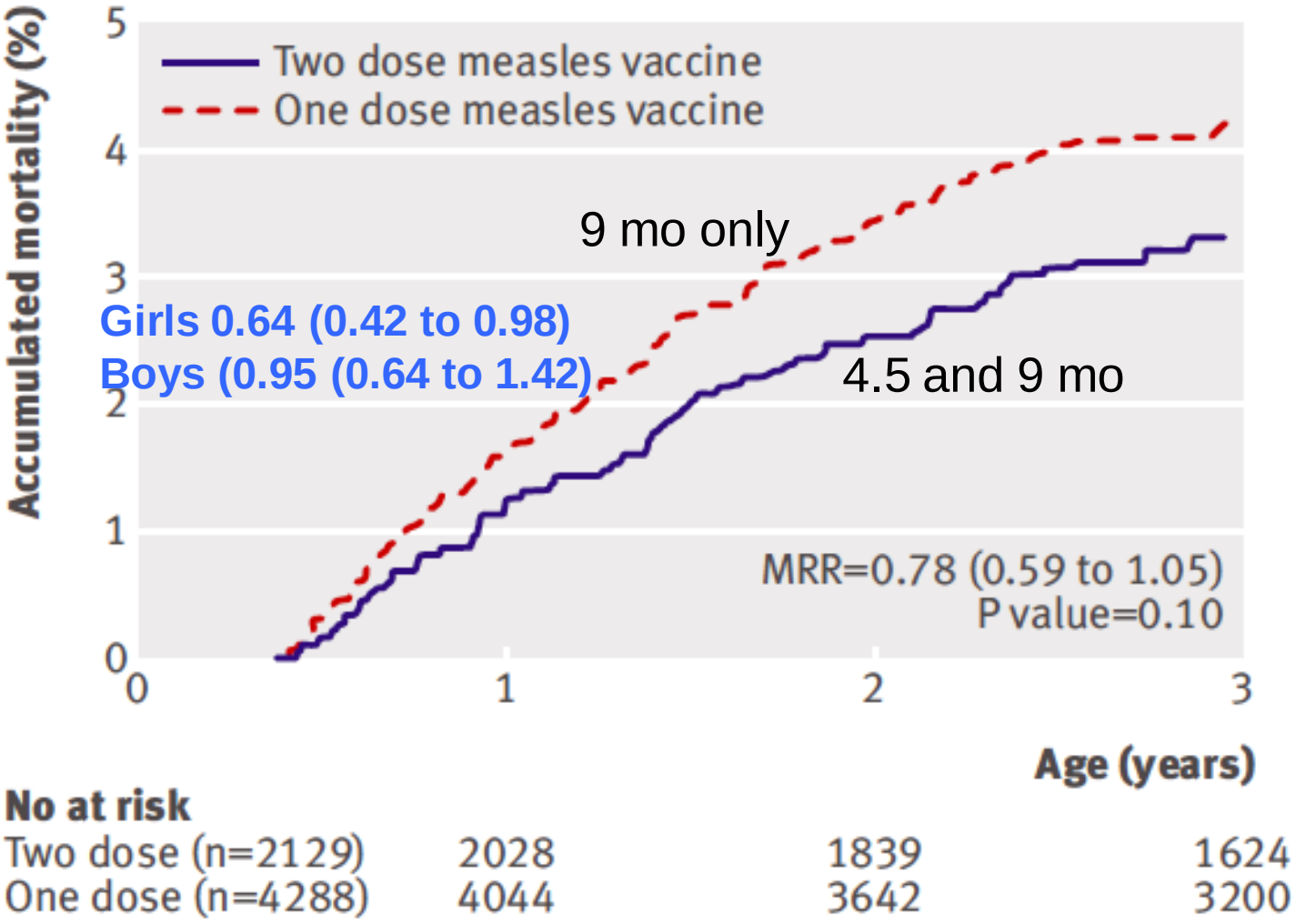
Randomized Trial of Standard Titer Measles Vaccine on Mortality

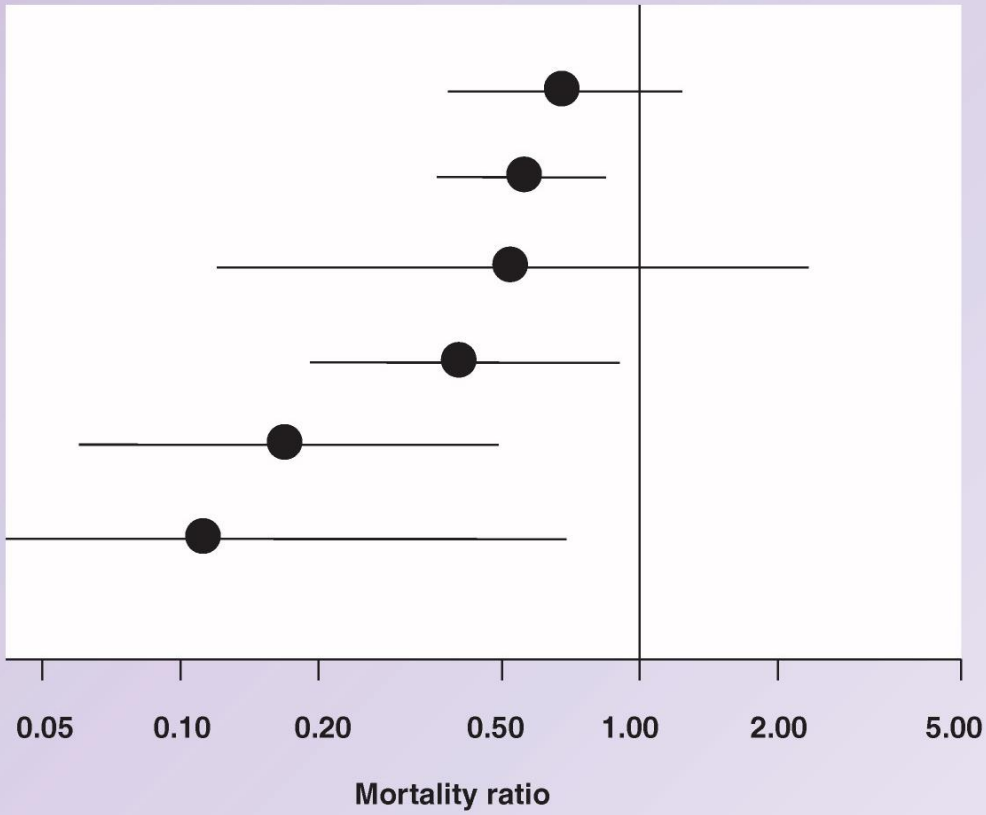


22% reduction (not significant Less than noted in multiple observational studies

Aaby et al.
BMJ 2010;341: c6495

Observational Studies Suggest Reductions in Mortality Associated With BCG Vaccine

General population	Age (months)*
Benin[†,§]	4–35
Guinea-Bissau[¶,#]	0–6
Guinea-Bissau[**,††]	0–8
Malawi[**,§§]	7 days–9 months
Guinea-Bissau[**,¶¶]	0–6
Guinea-Bissau[**,##]	1–8

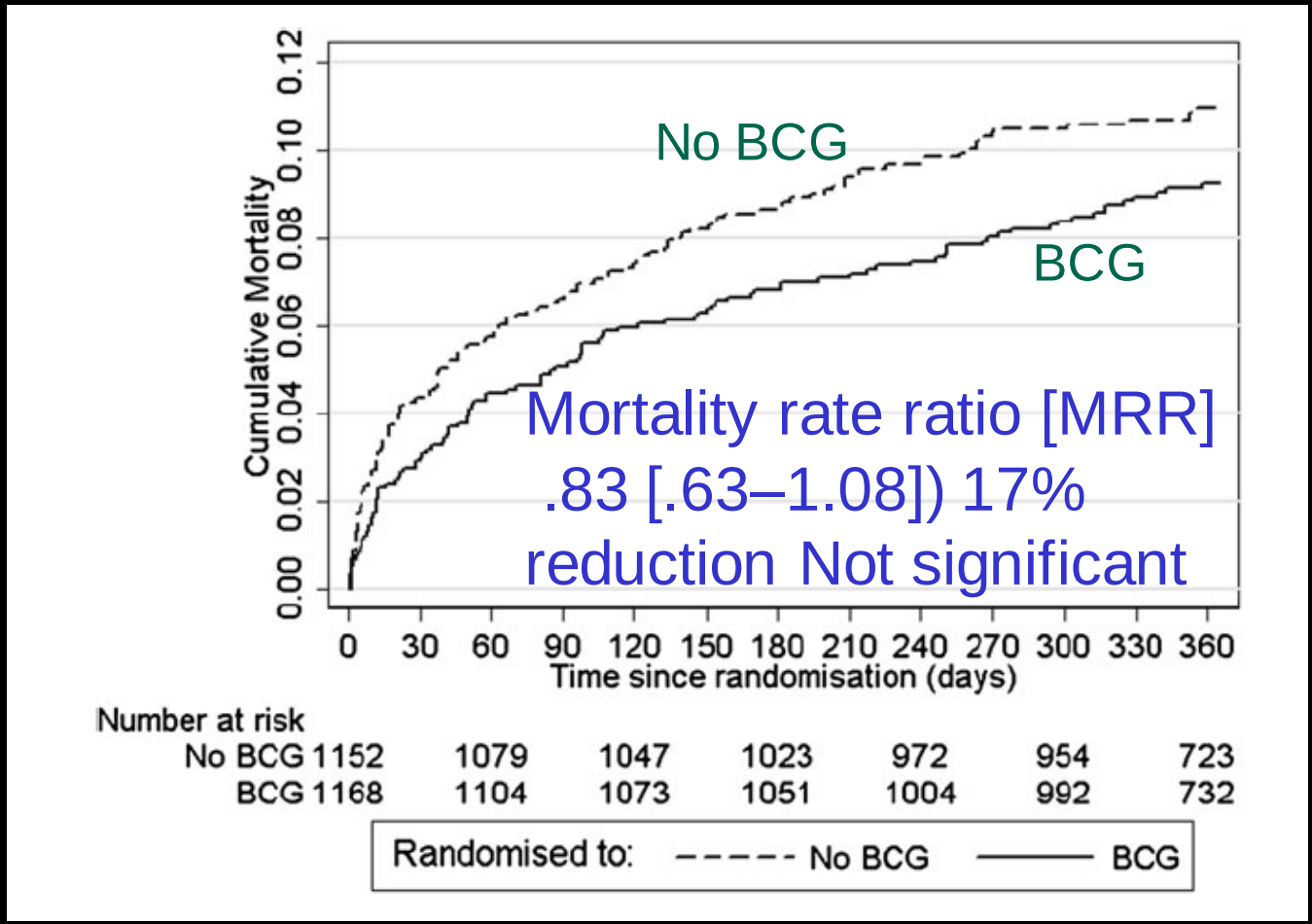


Roth et al Expert Rev Vaccines. 2006 Apr;5(2):277-93.

Randomized Trial of BCG Early in Life on Mortality: Guinea-Bissau

Expected reduction 25%,

WHO review of nonspecific effects pending



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Aaby et al. JID 2011;204:245–52

Causality Assessment

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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.

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Coggan and Martyn Lancet 2005; 365: 1434–37

Types of "Causal Factors"

- "sufficient"
- "necessary"
- "necessary and sufficient"
- "contributing"
- "attributable"

For most adverse events known to be caused by vaccines, the vaccine is a contributing cause.

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Rothman AJPH 2005; 95:s91

Coggan and Martyn Lancet 2005; 365: 1434–37

“sufficient cause”

- “a set of minimal conditions and events that inevitably produce disease”

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Rothman AJPH 2005; 95:s91

Wild-type Measles virus is a sufficient cause of measles

- Almost all susceptible develop the disease
- Host contributing factors affecting severity:
  - Age, gender?
  - Exposure intensity (dose)
  - Nutritional status (vitamin A deficiency)
  - Immunocompromised
  - Secondary bacterial infections

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Bradford Hill Causality Criteria

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

K. Rothman. Causation and Causal Inference. In: Rothman KR and Greenland S, Modern Epidemiology. Lippincott; 1998

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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

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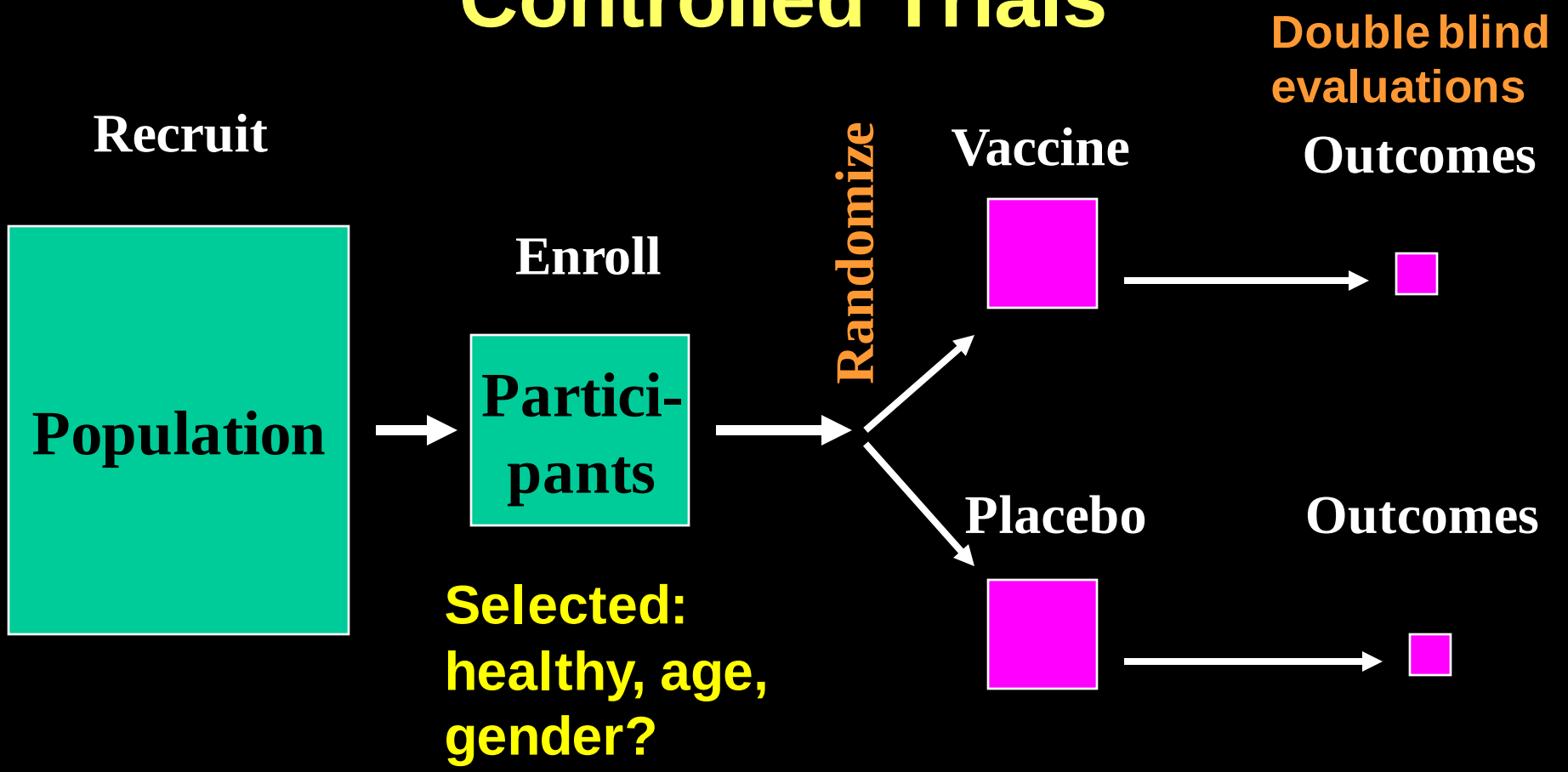
Randomized Placebo Controlled Trials



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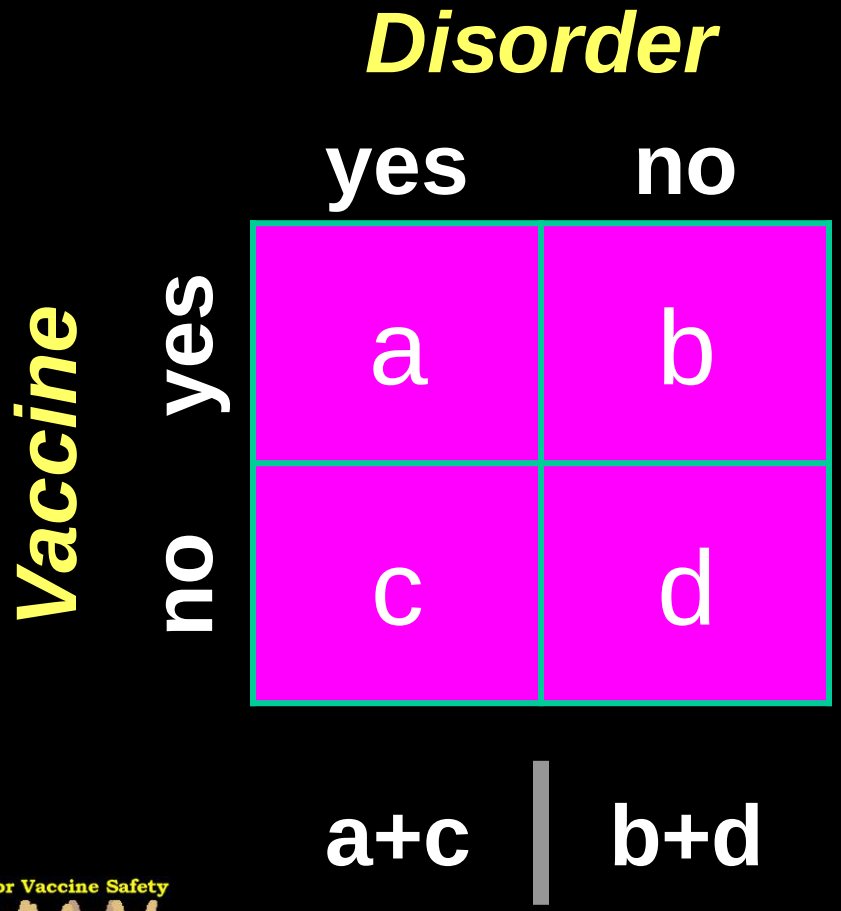
Investigating Causal Relationships

Randomized Placebo-Controlled Double Blind Trials



Risk

$$\frac{a}{a+b} \qquad \frac{c}{c+d}$$

Rel Risk

$$\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

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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

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Post-licensure Safety Studies

1. Passive surveillance
2. Active surveillance
3. Individual case assessment
4. Special studies

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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.

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Investigating Causal Relationships

Retrospective or Non-concurrent Cohort Studies

Vaccine	Disorder: yes	Disorder: no
yes	a	b
no	c	d
	a+c	b+d

Risk $\frac{a}{a+b}$

Rel Risk $\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$

Potential Problem: Self selection for vaccine?

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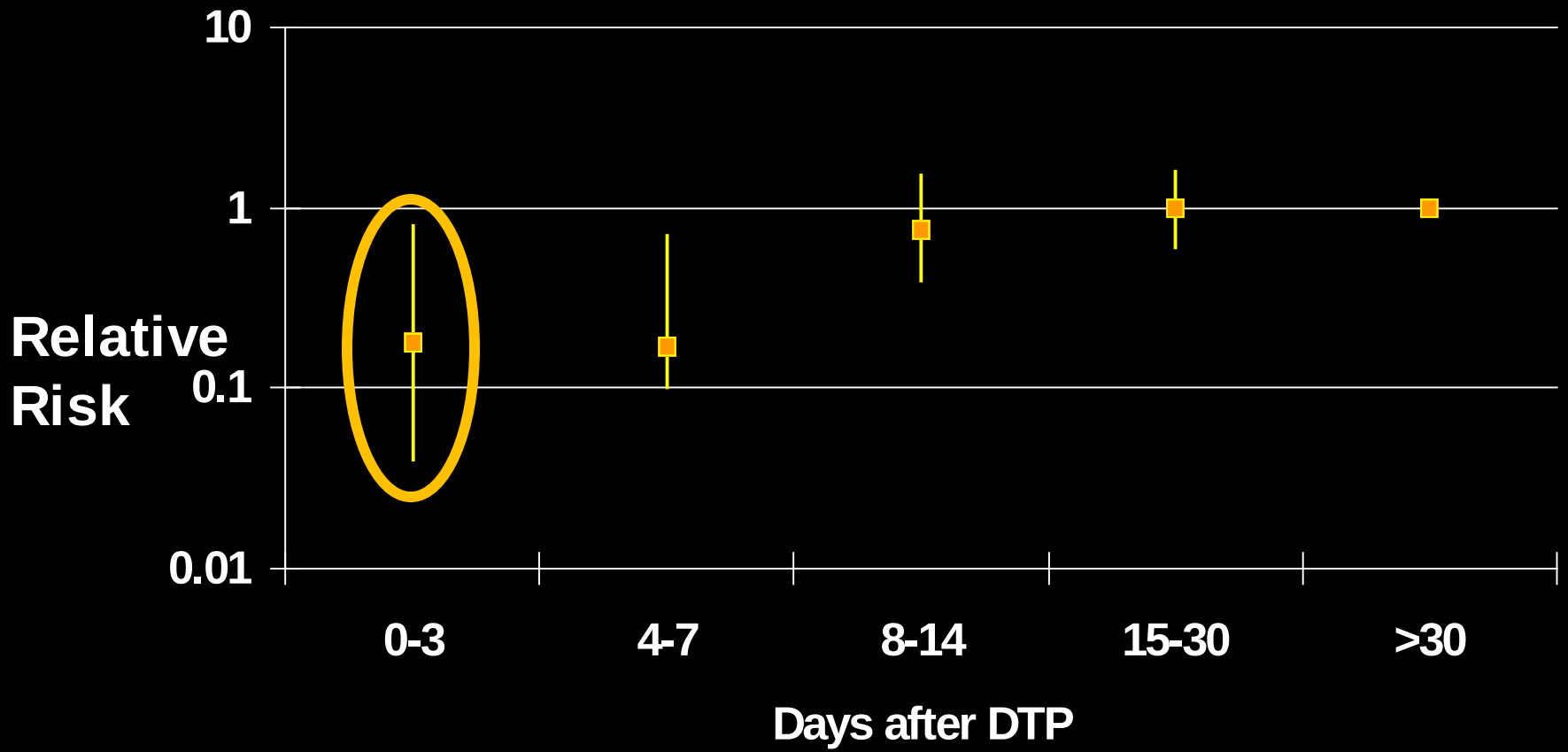
Relative Risk of Sudden Infant Death Syndrome by Day after DTP: Tennessee



Healthy Vaccinee Effect: children with illnesses not vaccinated

DTP does not increase the risk of SIDS

Griffin et al. NEJM 1988;319:618-23

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Investigating Causal Relationships

Case-Control Studies

Disorder

Vaccine	**case**	**control**
yes	a	b
no	c	d

Odds Ratio

$$\frac{a/b}{c/d} \qquad \frac{ad}{bc}$$

Potential Problems:

- Not randomized
- Selection bias?
- Matching?

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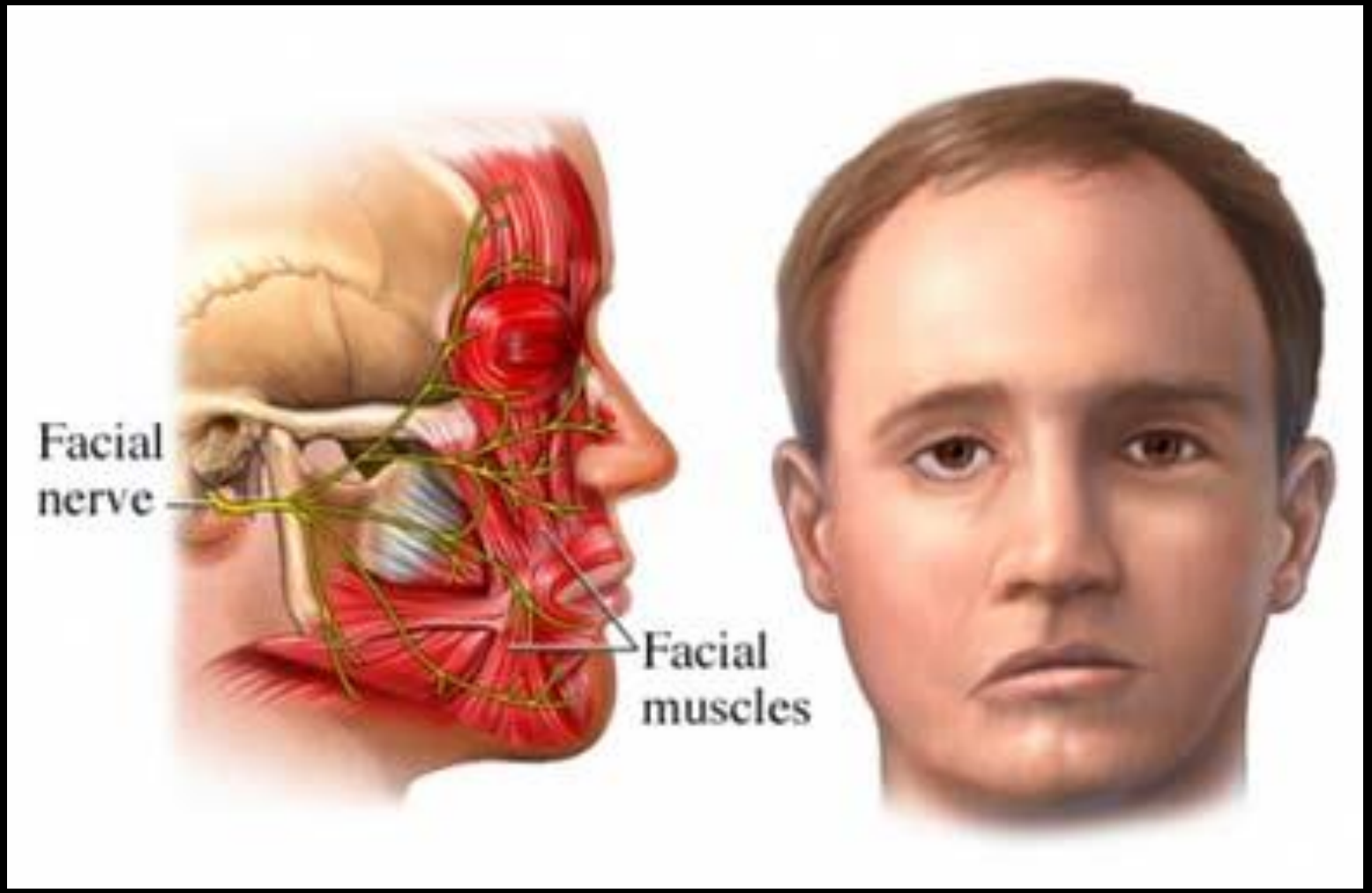
Bell's Palsy



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www.elib.gov.ph/edatabase

Switzerland: Odds Ratios for Receipt of Vaccines <91 Days Prior to Bell's Palsy

Vaccine	Case Patients (N=250)	Controls (N=722)	Adjusted Odds Ratio (95%CI)
Intranasal inactivated influenza	63 (25.2%)	7 (1.0%)	84.0 (20.1-351.9)
Parenteral inactivated influenza	10 (4.0%)	41 (5.7%)	1.1 (0.6-2.0)

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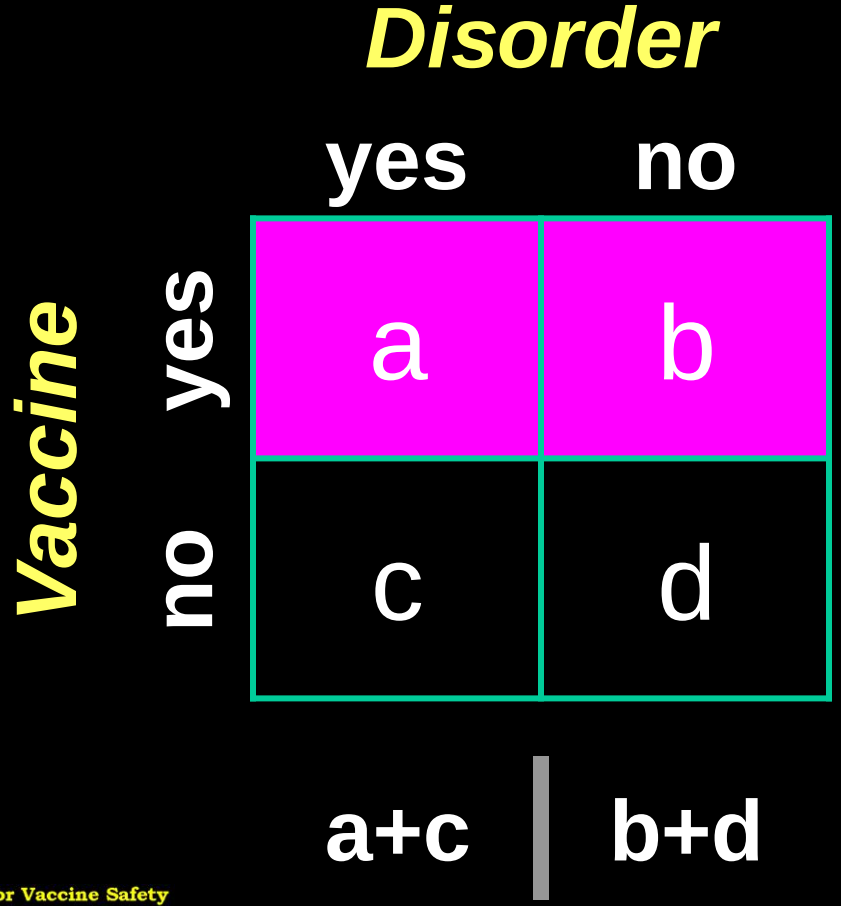
Mutsch M, et al. NEJM 2004;350:896.

Vaccine Only Studies



Potential Problems:

- Selection bias?
- Need to include all cases

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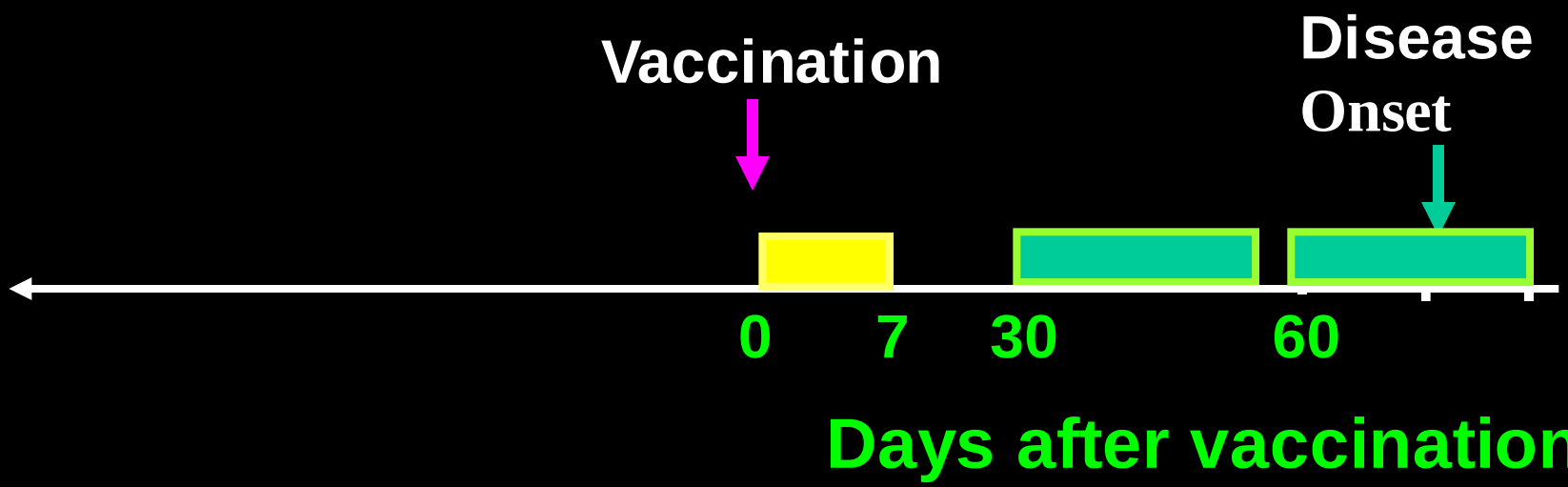
Vaccine Only Studies



Compare the incidence of disease in different time periods after receiving vaccines

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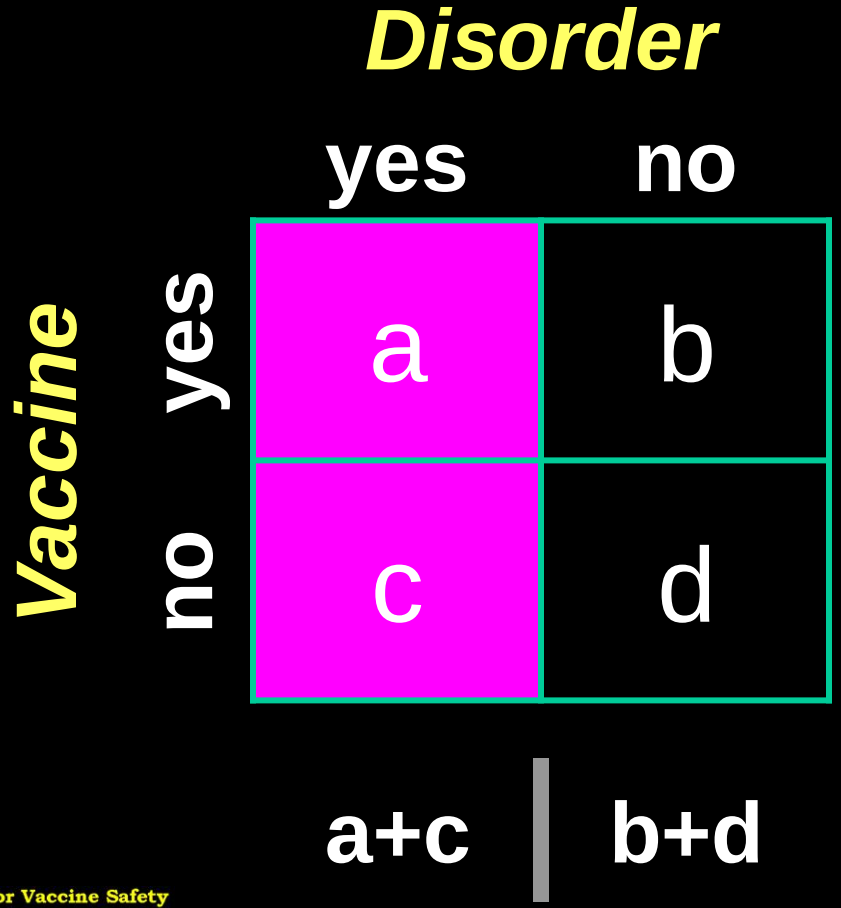
Case Only Studies



Potential Problems:

- Selection bias?
- Need to include all cases

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Ecologic Studies

Vaccine	*Disorder* yes	*Disorder* no
yes	a	b
no	c	d
	a+c	**b+d**

Risk

$$\frac{a}{a+b} \div \frac{c}{c+d}$$

Risk Ratio

$$\frac{a}{a+b} \div \frac{c}{c+d}$$

- Very weak evidence.
- Usually uninformative for establishing causality.

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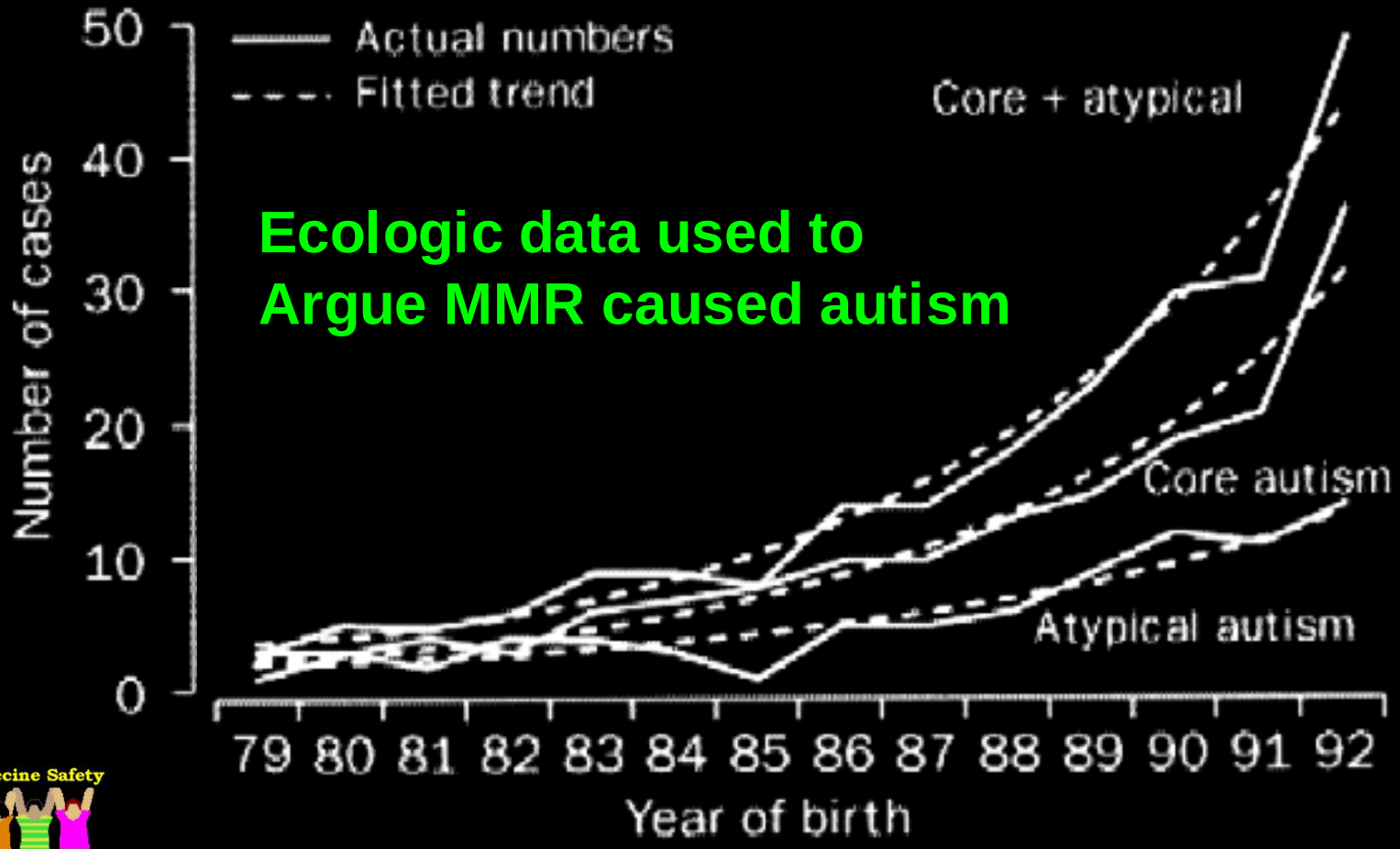
Core and Atypical Autism Cases Under 60 Months of Age and Fitted Trends by Year of Birth 1979-92: UK



Ecologic data used to Argue MMR caused autism

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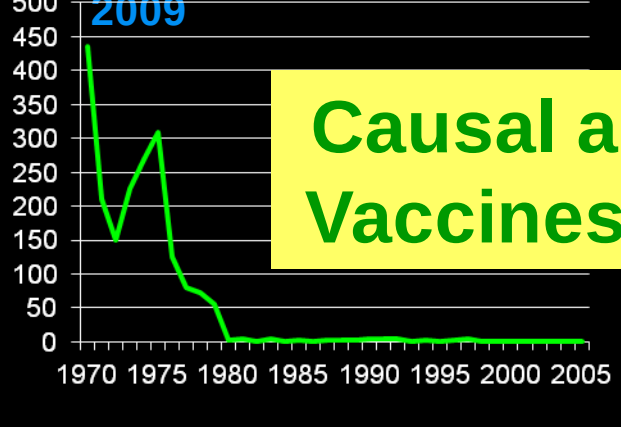
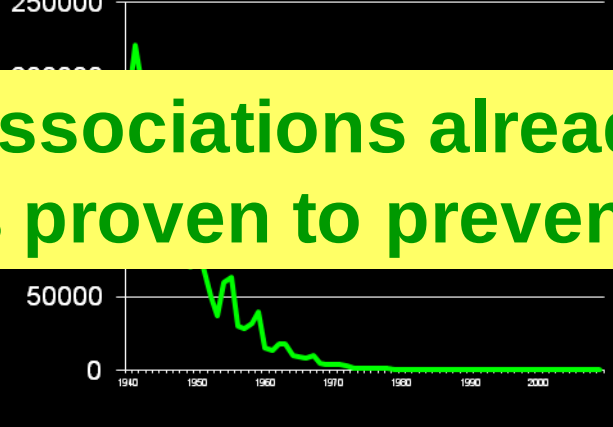
Source: Lancet 1999;353(9169):2026.

Ecologic Data Used to Demonstrate Effectiveness of Licensed Vaccines

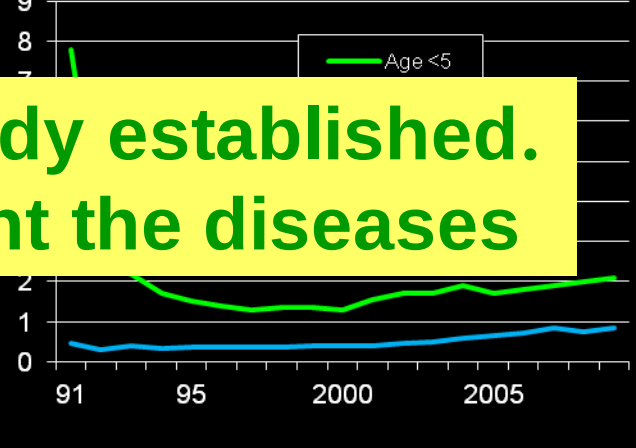
Diphtheria: 1970-2009



Pertussis: 1940-2009

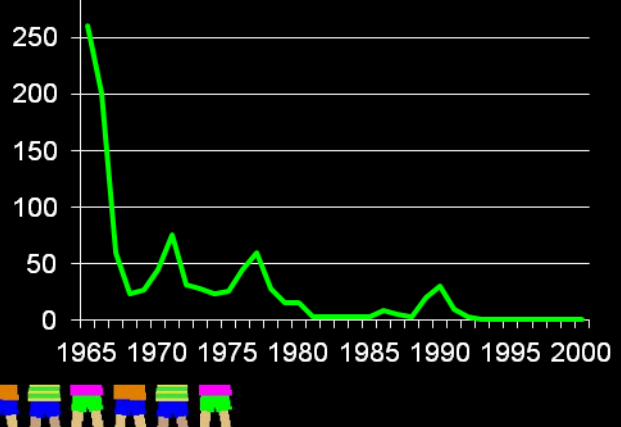


Hib: 1991-2009

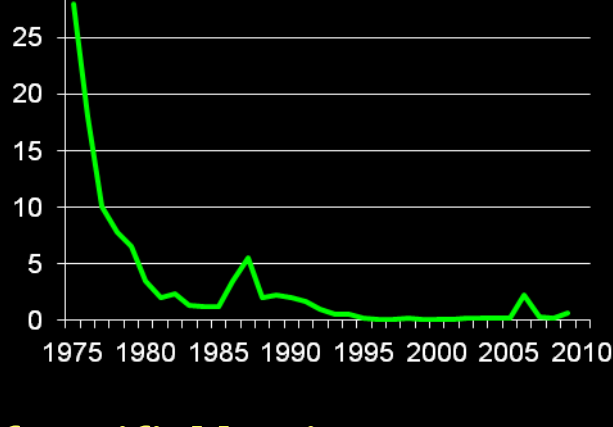


Causal associations already established. Vaccines proven to prevent the diseases

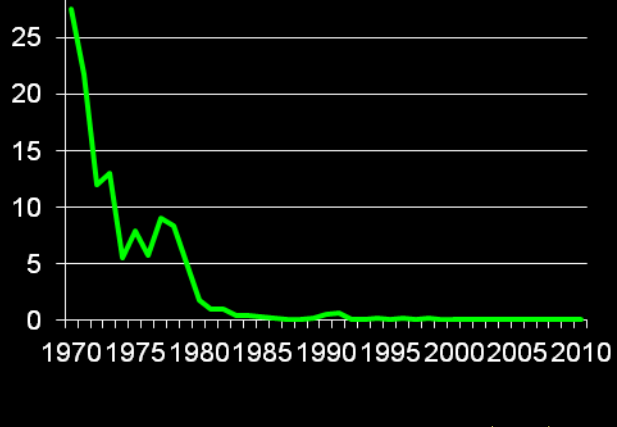
Measles 1974-2009



Mumps: 1975-2009



Rubella: 1970-2009



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Summary of Notifiable Diseases - US 2009. MMWR 2001;58(53):1-1

Case Reports

Vaccine	Disorder: yes	Disorder: no
yes	a	b
no	c	d
	a+c	b+d

~~*Risk*~~ ~~$\frac{a}{a+b}$~~ ~~$\frac{c}{c+d}$~~

~~*Risk Ratio*~~ ~~$\frac{a}{a+b} \div \frac{c}{c+d}$~~

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Case Reports of Individuals With AEFI Based on Temporal Relationships Only

AJRI American Journal of Reproductive Immunology

Original Article

Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

Serena Colafrancesco[1,2], Carlo Perricone[1,2], Lucija Tomljenovic[1,3] and Yehuda Shoenfeld[1,4,*]

Article first published online: 31 JUL 2013

DOI: 10.1111/aji.12151

Issue

American Journal of Reproductive Immunology

Volume 70, Issue 4, pages 309–316, October 2013

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

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MMWR. 2003 Feb 14;52(06):113

Pediatr Infect Dis J. 2004 Apr;23(4):287-94.

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.
  -

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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)

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Sem in Ped Infect Dis 2002 July;13(3):205-14

Causality Assessment from Individual Case Reports

- Causality not established:
  - Antigen detection or PCR without sequencing.
    - False positives
    - Contamination
    - Coincidental infection

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Measles Virus does not Persist in Children with Autism Spectrum Disorder

	ASD	Controls
Uhlmann (intestine) 2002	75/91	5/70
Martin (intestine) 2002	62/68	4/39
Kawashima (PBMC) 2000	3/9	0/8
No sequencing of amplification products		
D'Souza (PBMC) 2006		
• Uhlmann assay*	0/38	0/15-18
• Kawashima assay*	0/23	0/16
• Probe-based Fusion Assay	0/54	0/34

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*** PCR products not measles - host origin**

D'Souza Y. Pediatrics 2006;118(4):1665.

Causal Associations Usually Cannot by 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

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Immediate Hypersensitivity Reactions

- Pathogenesis known
- Short interval from vaccine to reaction
- Unlikely for other exposures
- Skin testing with vaccine components

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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

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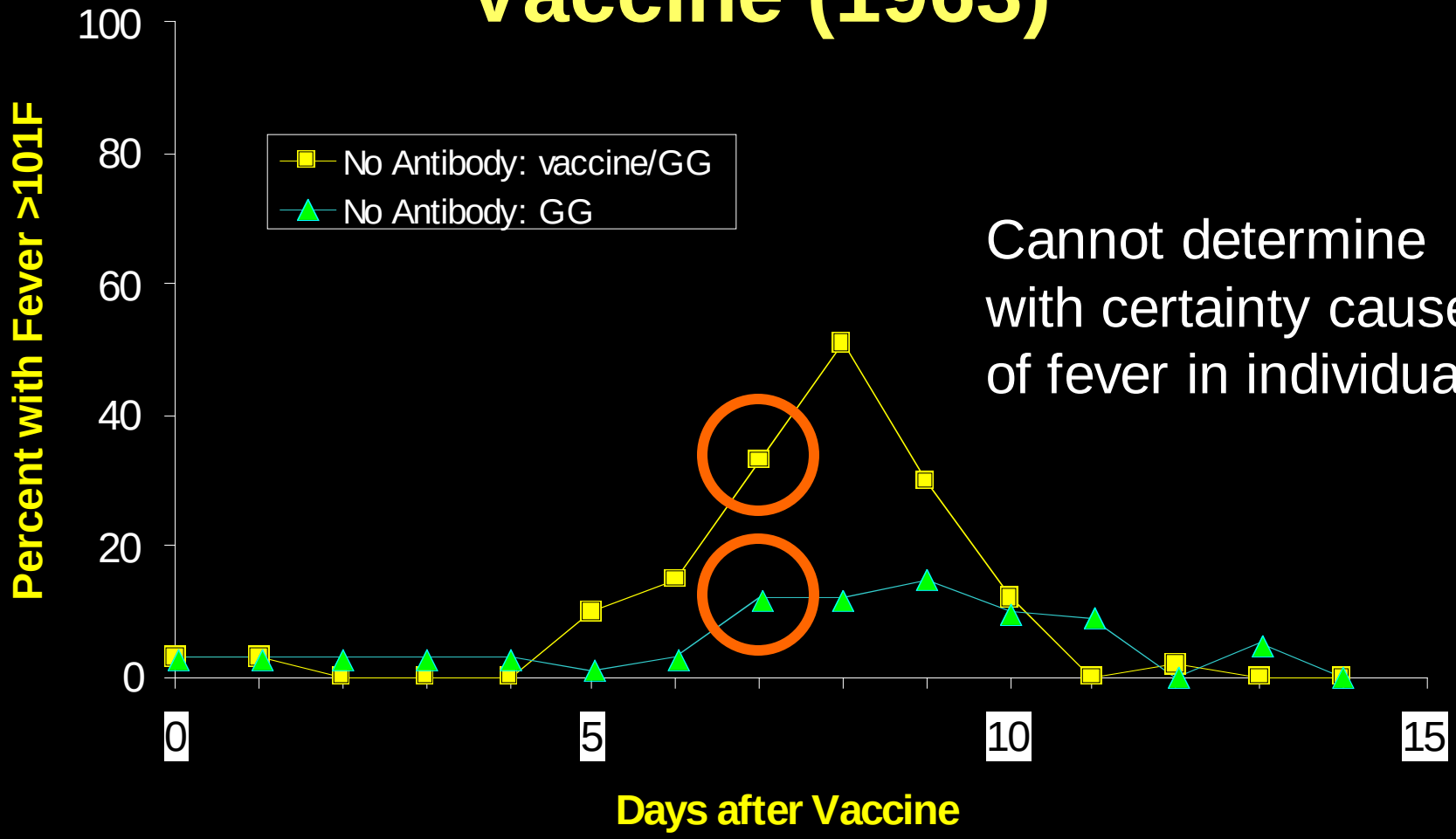
Percent of Children with Fever Following Edmonston B Measles Vaccine (1963)



Cannot determine with certainty cause of fever in individuals

Adapted from Martin CM. Am J of Dis of Children 1963;106:270.

Investigating Individual Case Reports

- No Known Causal Association
- No Specific Laboratory Test

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Case Reports and Temporal Associations for Diseases of Unknown Etiology

- The number of cases does not matter
  - 1, 10, 100, or 1,000

- Need rates: vaccinated vs unvaccinated to establish causal association

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Post-licensure Investigation of Individual Case Reports of AEFI

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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

Vaccine 2012;30(39):5791-8.

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

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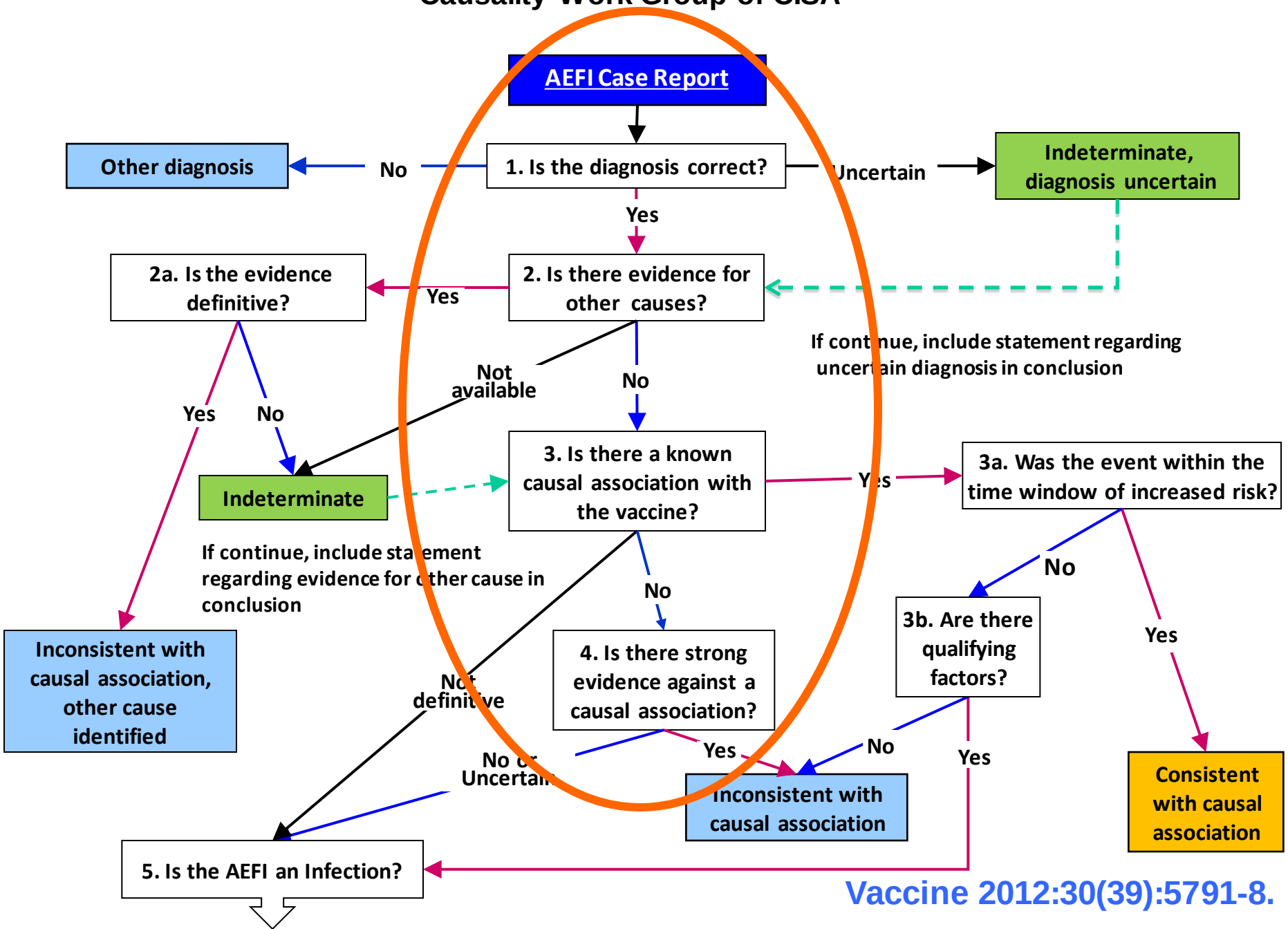
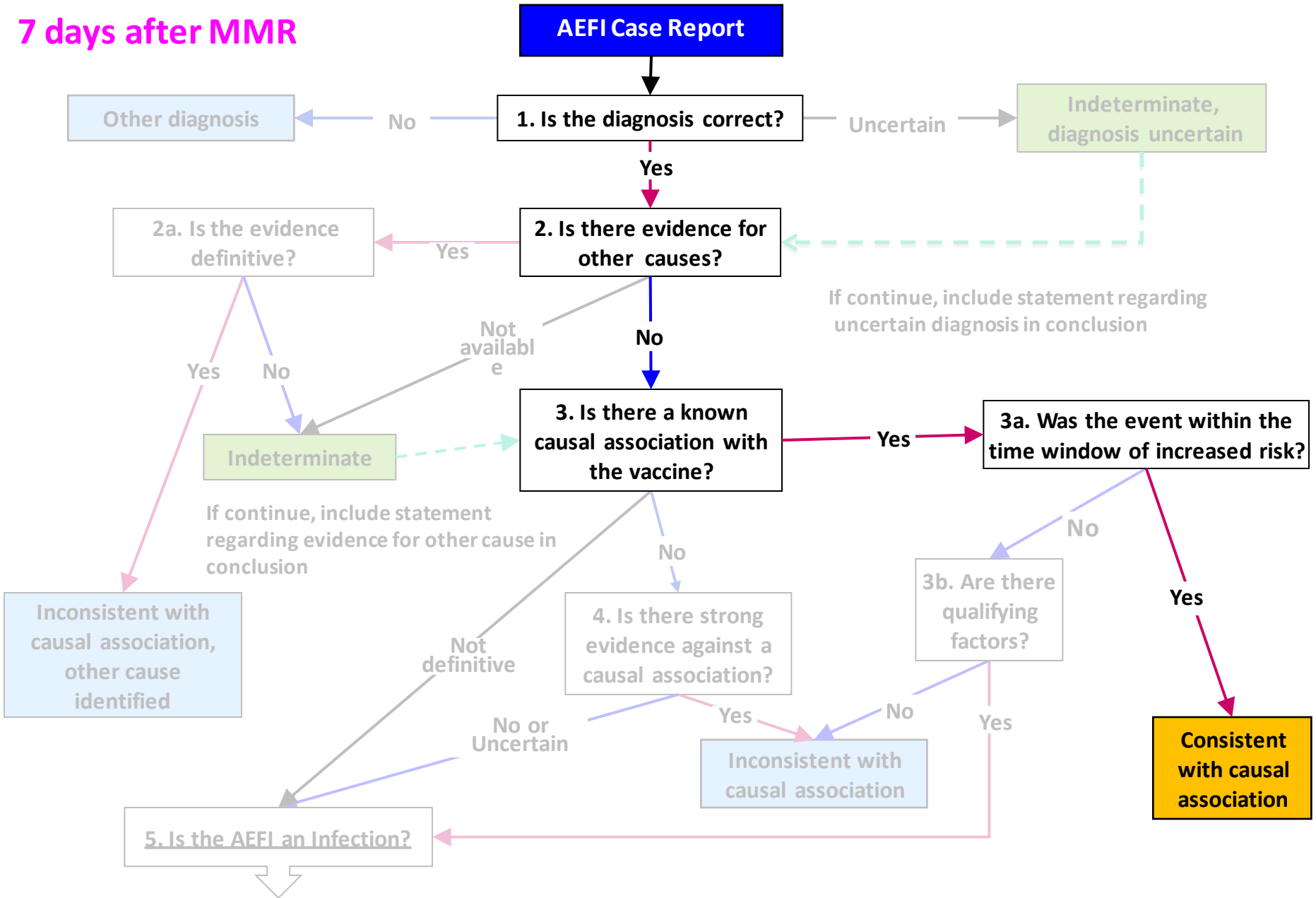
CISA Review of Case Reports of Adverse Events Following Immunizations
Causality Work Group of CISA



Vaccine 2012:30(39):5791-8.

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

Febrile seizure
12 month old
7 days after MMR

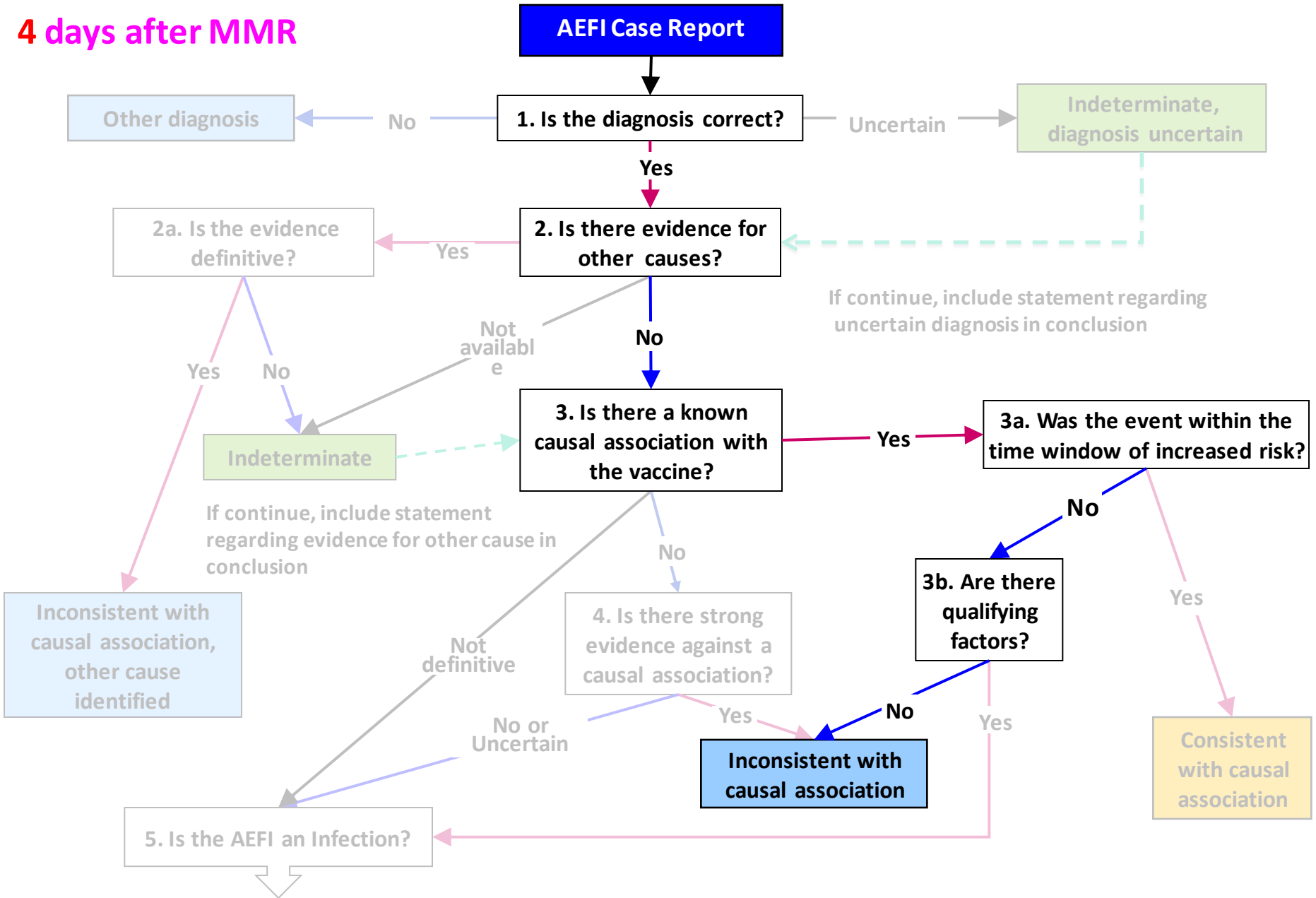


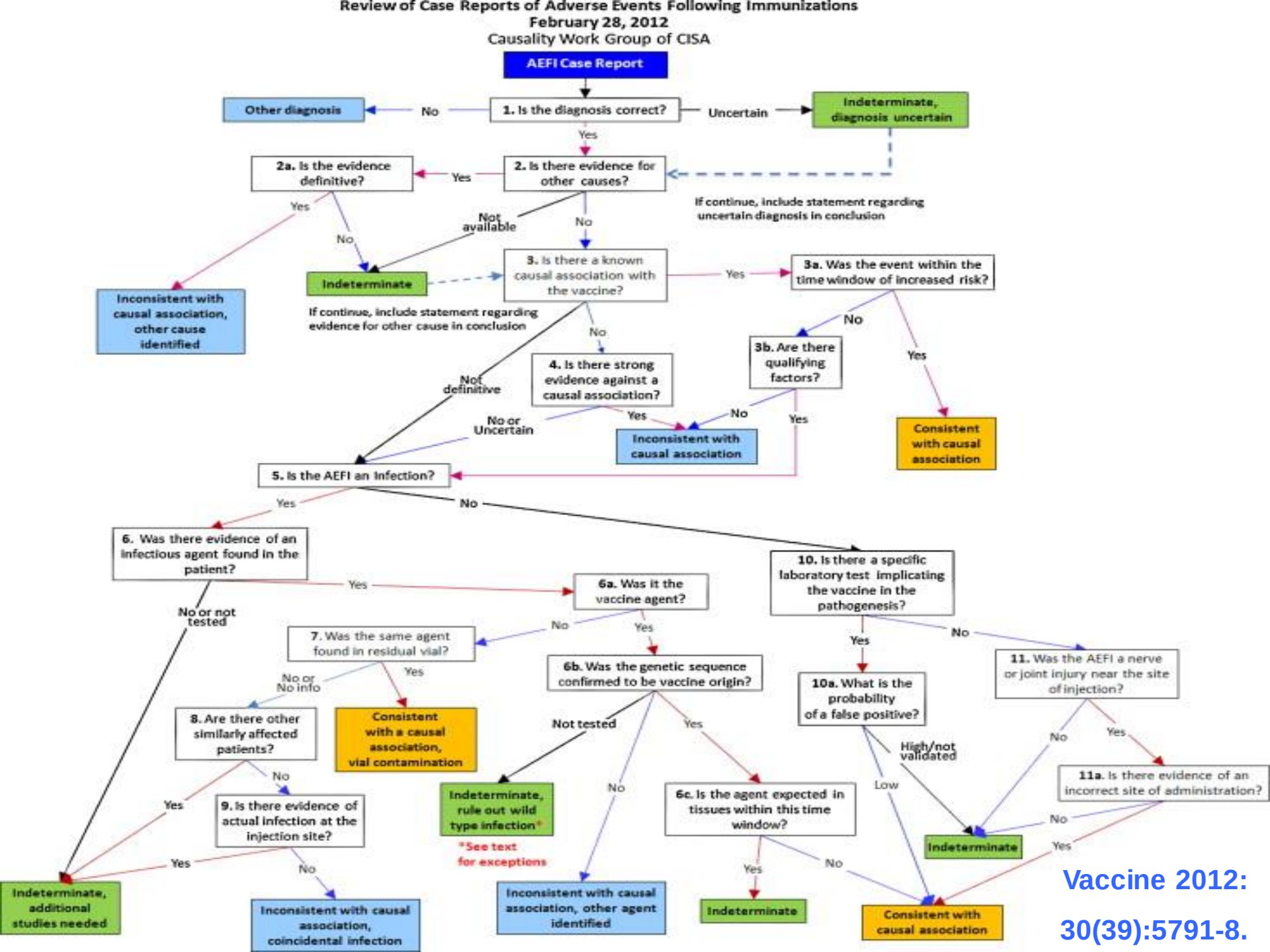
Review of Case Reports of Adverse Events Following Immunizations
Causality Work Group of CISA

Febrile seizure

12 month old

4 days after MMR





Vaccine 2012: 30(39):5791-8.

Algorithm Advantages

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

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WHO Causality Assessment Tool

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

CAUSALITY ASSESSMENT OF AN ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI)

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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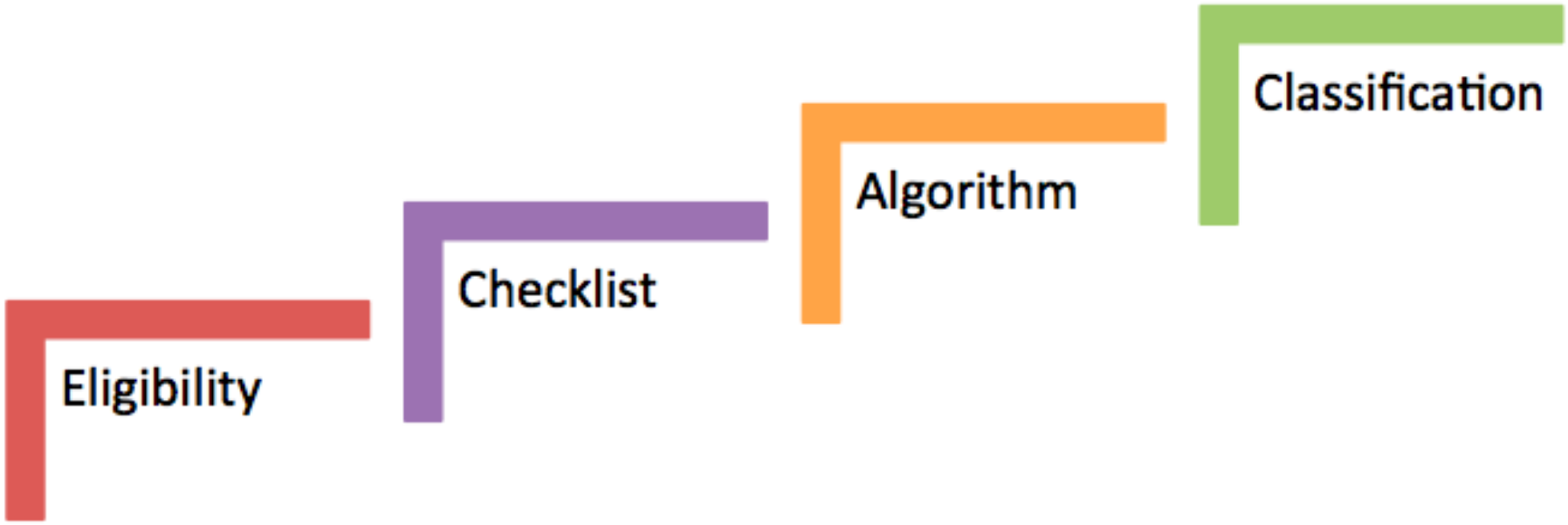
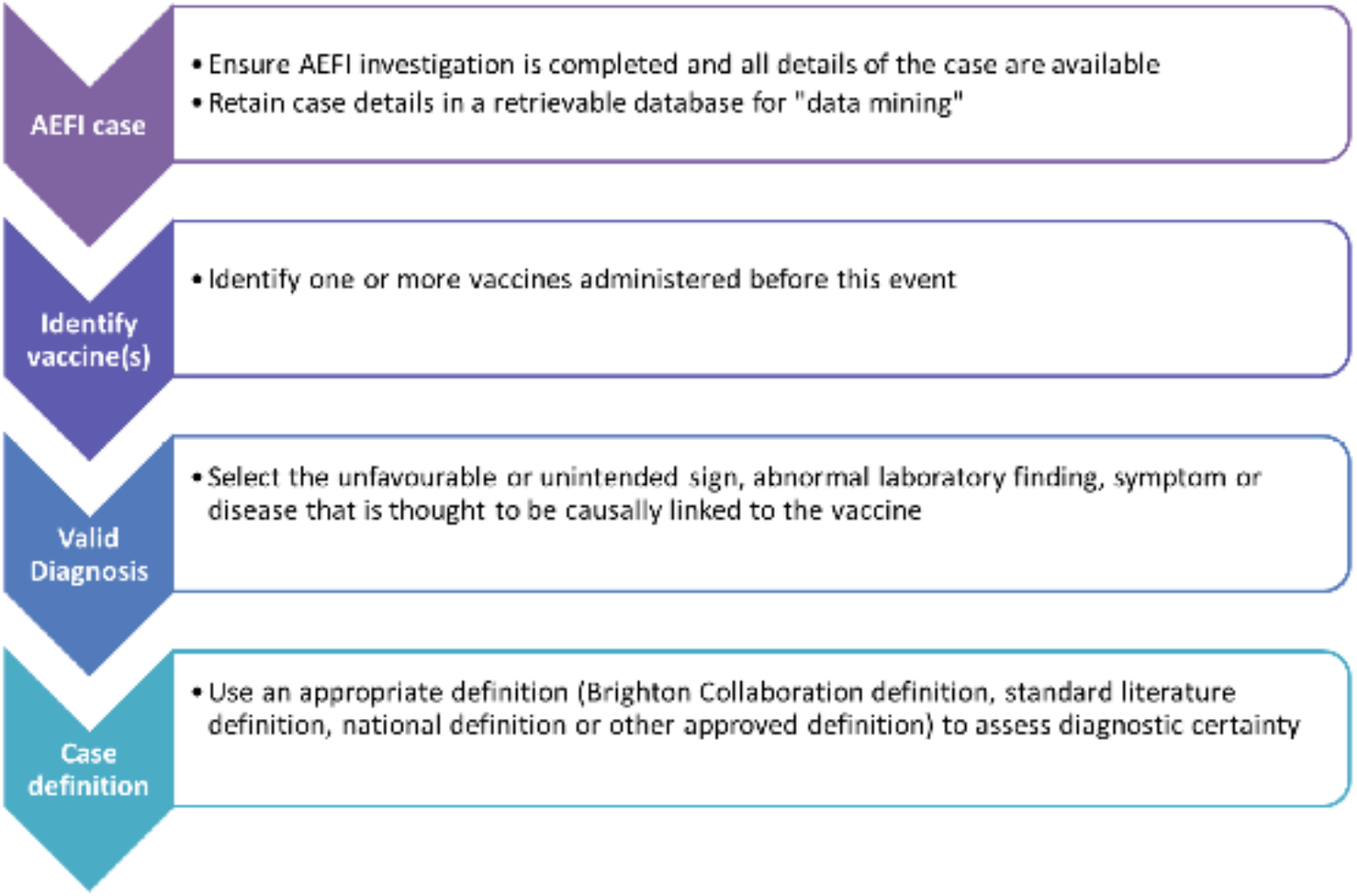
Causality Assessment Steps



Eligibility

Fig. 1. Causality assessment – Eligibility



Step 2: Checklist

I. Is there strong evidence for other causes?

II. Is there a known causal association with the Vaccine / Vaccination

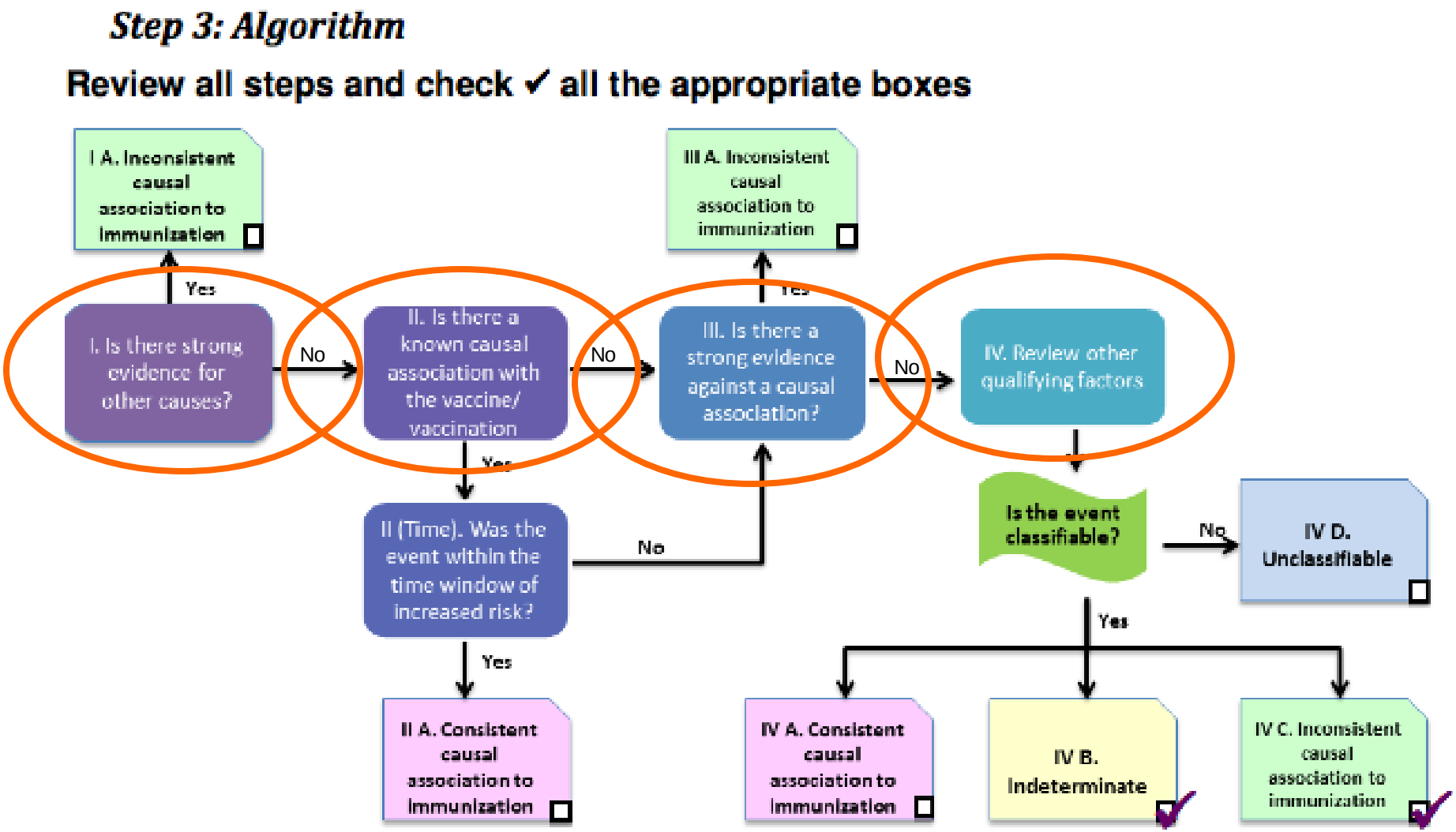
- Relationship with vaccine ingredients
- Immunization error
- Relationship with vaccine administration

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

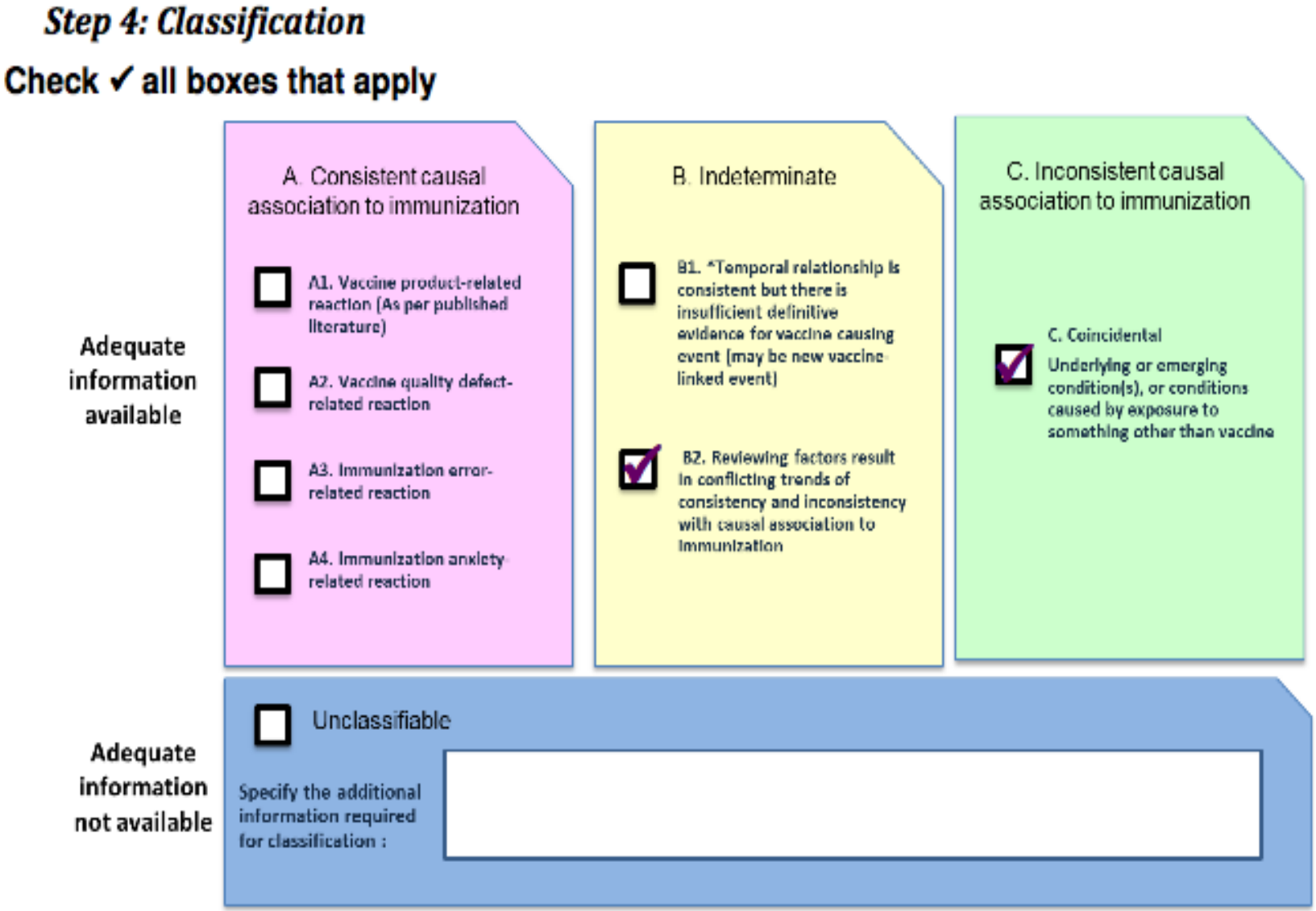
III. Is there a strong evidence against a causal association?

IV. Other Qualifying Factors

3. Algorithm


Step 3: Algorithm
Review all steps and check ✓ all the appropriate boxes
I A. Inconsistent causal association to immunization
Yes
I. Is there strong evidence for other causes?
No
II. Is there a known causal association with the vaccine/ vaccination
No
III A. Inconsistent causal association to immunization
Yes
III. Is there a strong evidence against a causal association?
No
IV. Review other qualifying factors
Yes
II (Time). Was the event within the time window of increased risk?
No
Yes
II A. Consistent causal association to Immunization
Is the event classifiable?
No
IV D. Unclassifiable
Yes
IV A. Consistent causal association to Immunization
IV B. Indeterminate
IV C. Inconsistent causal association to immunization

4. Classification



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

Conclusions

1. Causality assessment is complex
2. Poor understanding among health care providers and the general public
3. Need for standardization and improved education
   - algorithm approach will help
4. Demand good science

Institute for Vaccine Safety

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