Causality Assessment and Vaccine Safety

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Does ___ Vaccine “Cause” ___?

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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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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

“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)
  - Immune competence
  - Secondary bacterial infections
  - Lack of immunization, time since immunization?

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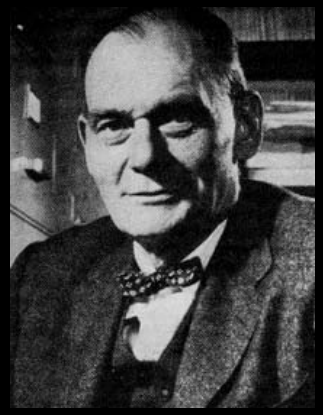
Attenuation of Wild-type Measles Virus to Make a Vaccine



John Enders

Sam Katz

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1954

24 passages human kidney tissue

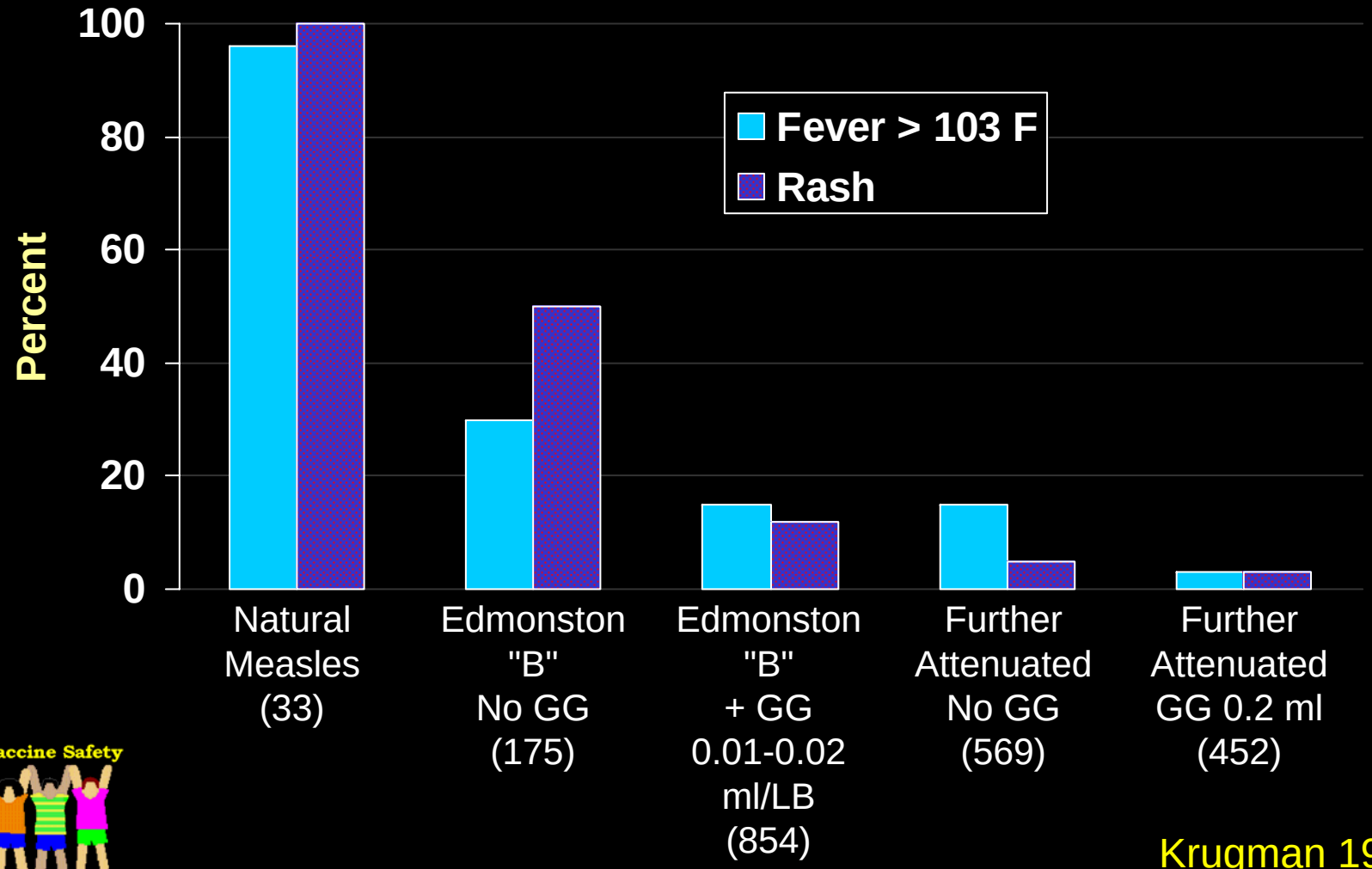
28 passages primary human amnion tissue

6 passages chick embryos

Chick embryo cells

Vaccine 1963

Fever and Rash Following Measles Vaccination With and Without Immune Globulin (GG)



Krugman 1965

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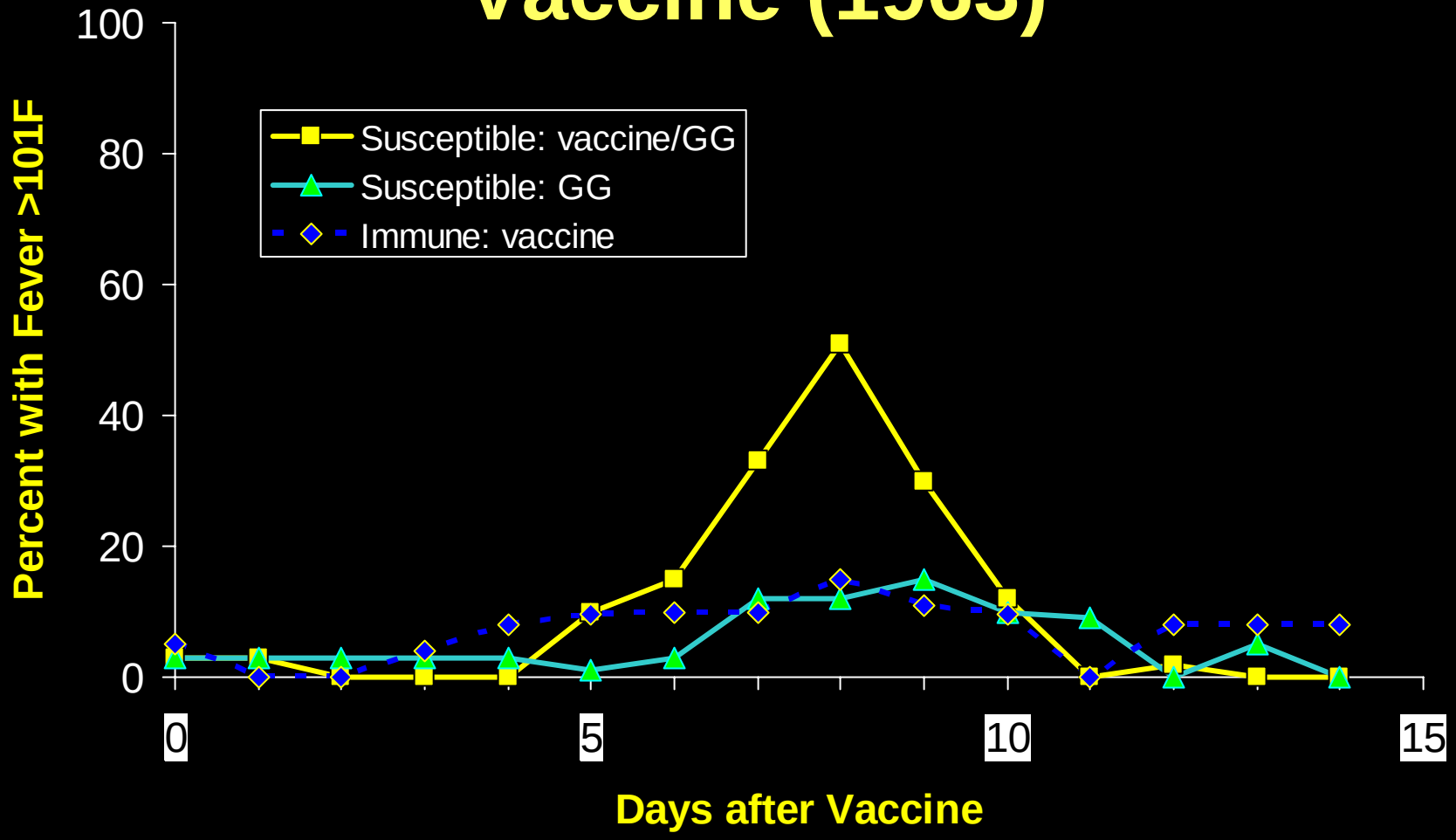
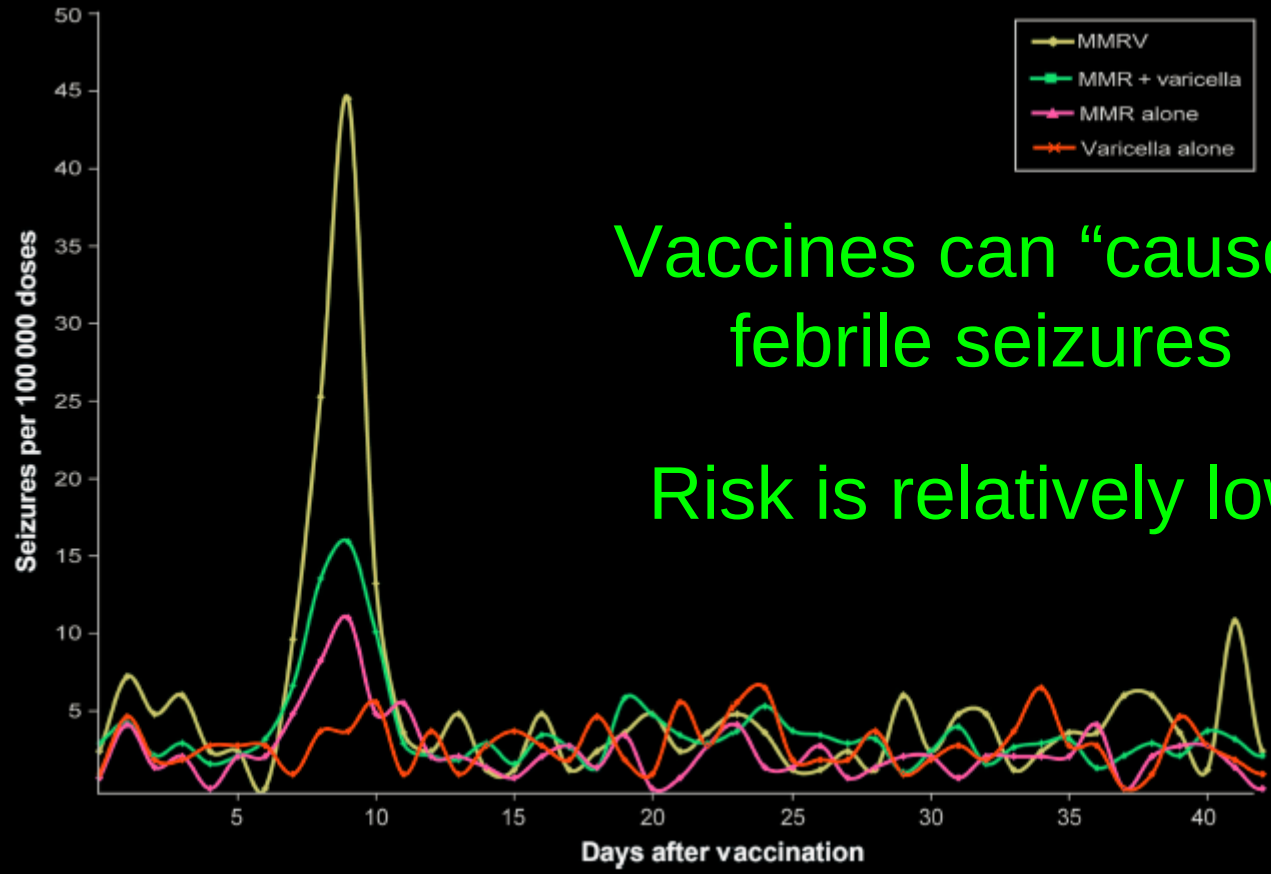
Percent of Children with Fever Following Edmonston B Measles Vaccine (1963)



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

Post Vaccination Seizures Among 12-23-Month-Olds by Vaccine

VSD Study Population – 2000-2008



Vaccines can "cause" febrile seizures

Risk is relatively low

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Klein NP, et al. Pediatrics 2010;126:e1-8.

Factors Associated with Febrile Seizures

- Vaccine:
  - Type
  - Strain (live)
  - Other components
  - Other vaccines simultaneously
- Host:
  - Age
  - Genetics?
  - Other?

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Vaccine Factors Affecting the Risk of Adverse Events

1. Type: live, killed, subcomponent
2. Strain
3. Attenuation
4. Dose
5. Adjuvants
6. Preservatives
7. Stabilizers
8. Purity
9. Route administered
10. Other vaccines simultaneously

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Host Related Factors Affecting the Risk of Adverse Events

1. Age
2. Gender
3. Prior doses of vaccine
4. Prior infection with agent
5. Skin color
6. Preexisting hypersensitivity
7. Immune competence
8. Genetics

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How Vaccines "Cause" Adverse Events

1. Injection process
2. Contamination
3. Replication of live agent
4. Direct effect of vaccine component
5. Host immune response to component
6. Unknown

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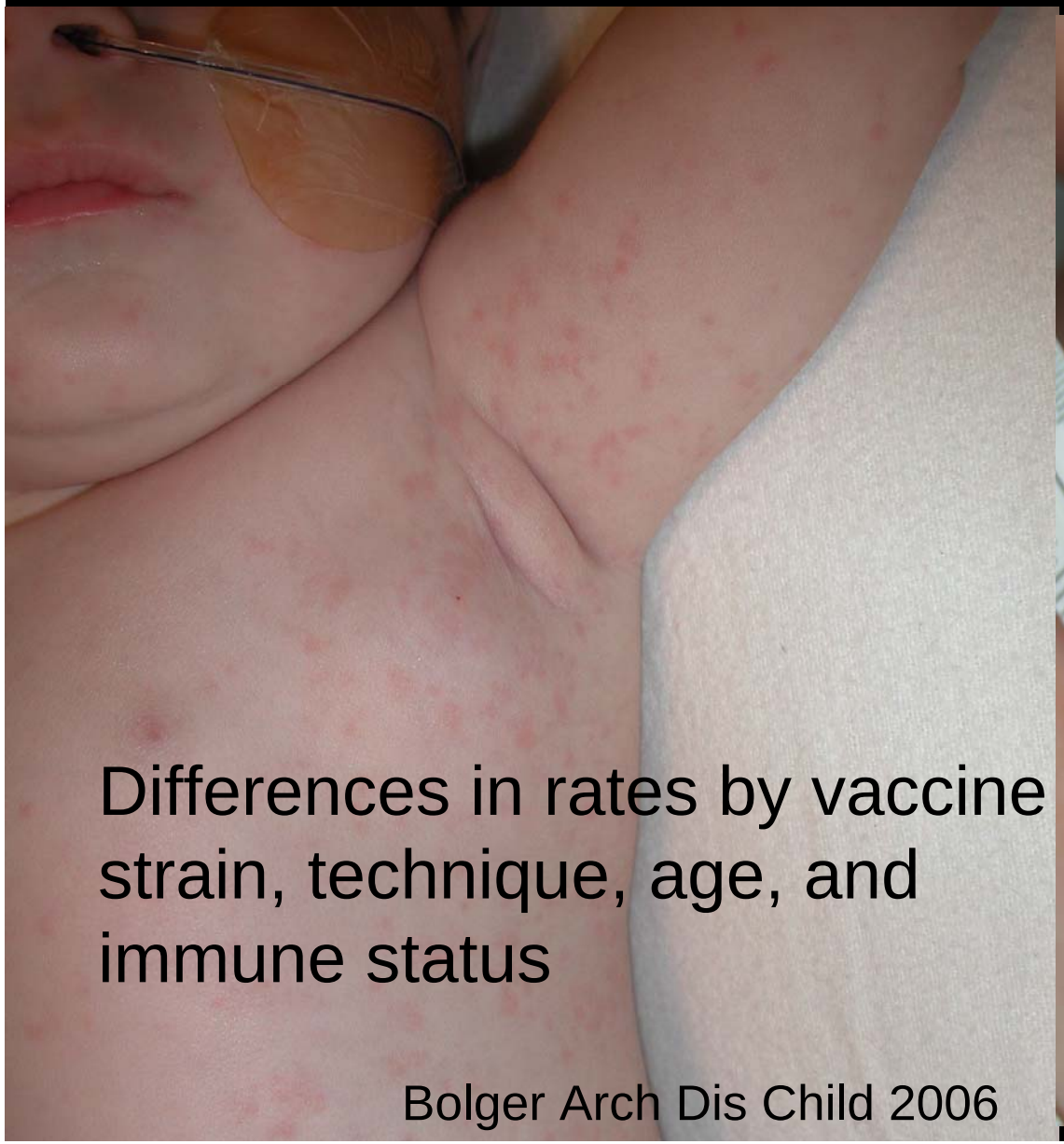
Many Adverse Events Have Vaccine and Host "Causal" Factors



Differences in rates by vaccine strain, technique, age, and immune status

Bolger Arch Dis Child 2006

Most Adverse Events Associated with Vaccines have Multiple Causes

Our tasks:

- Identify other causes
- Separate coincidental events from events “caused” by vaccines

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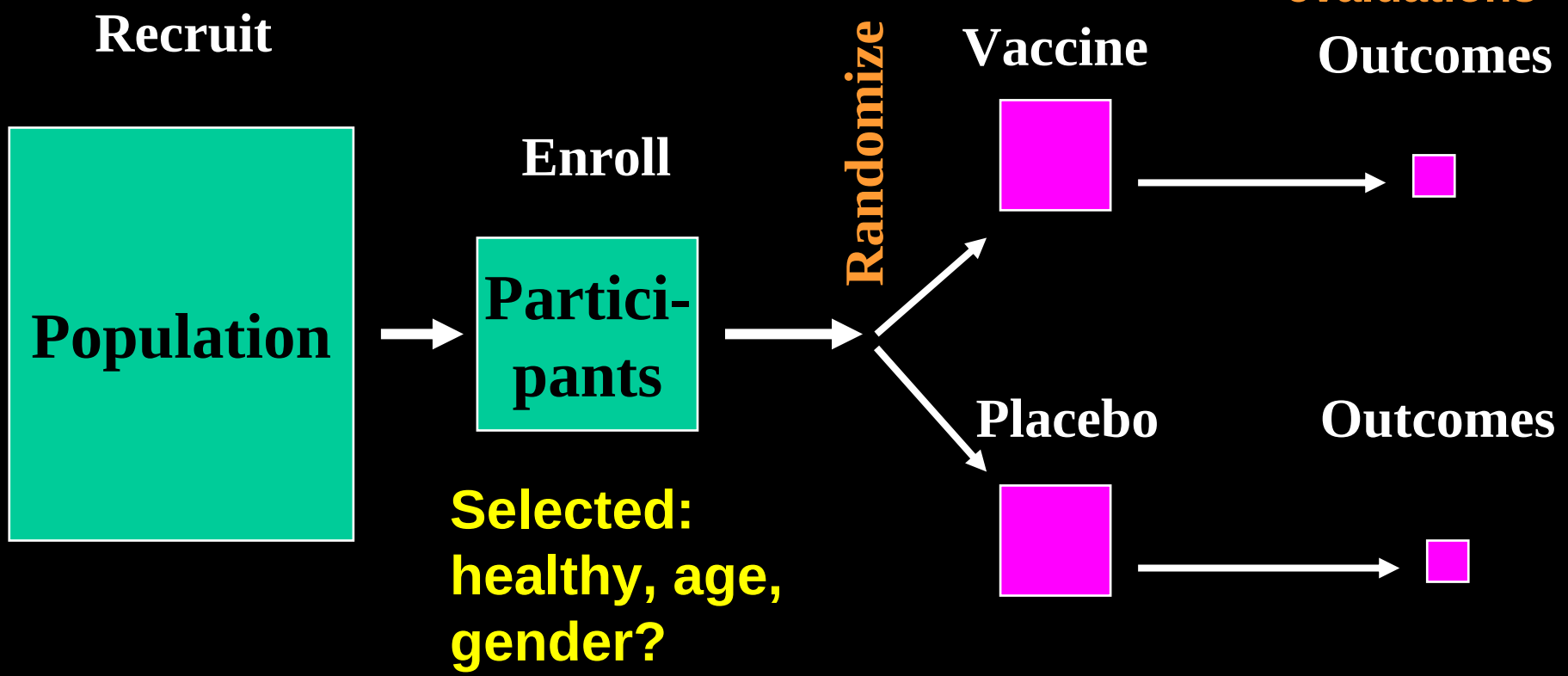
Randomized Placebo Controlled Trials



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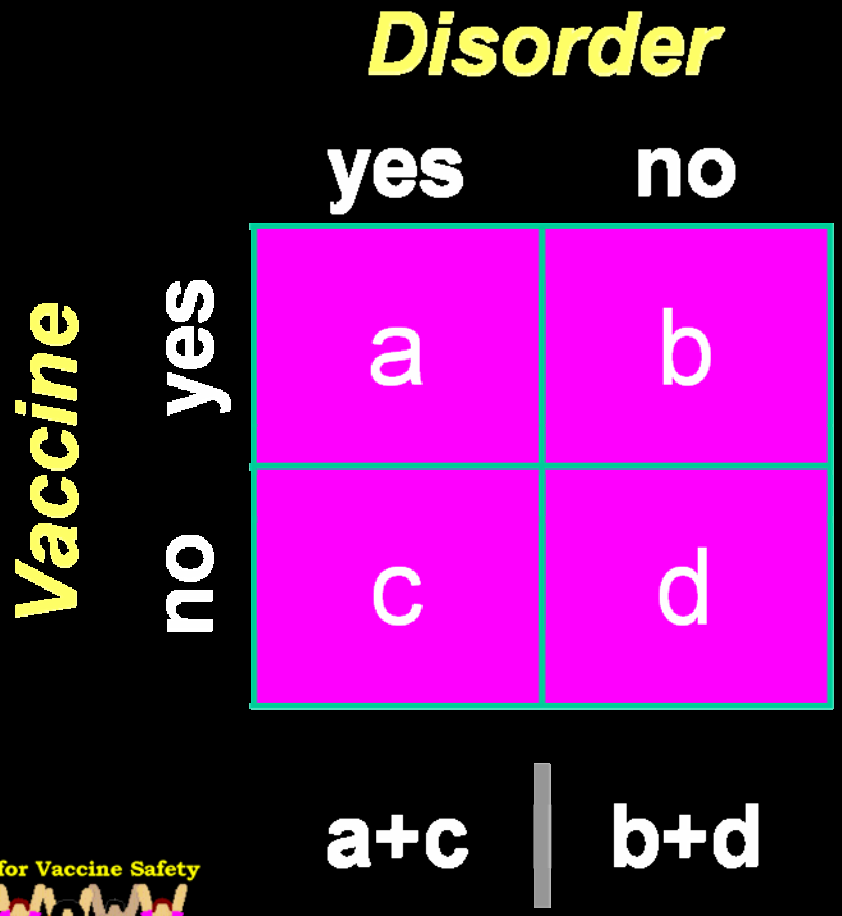
Investigating Causal Relationships

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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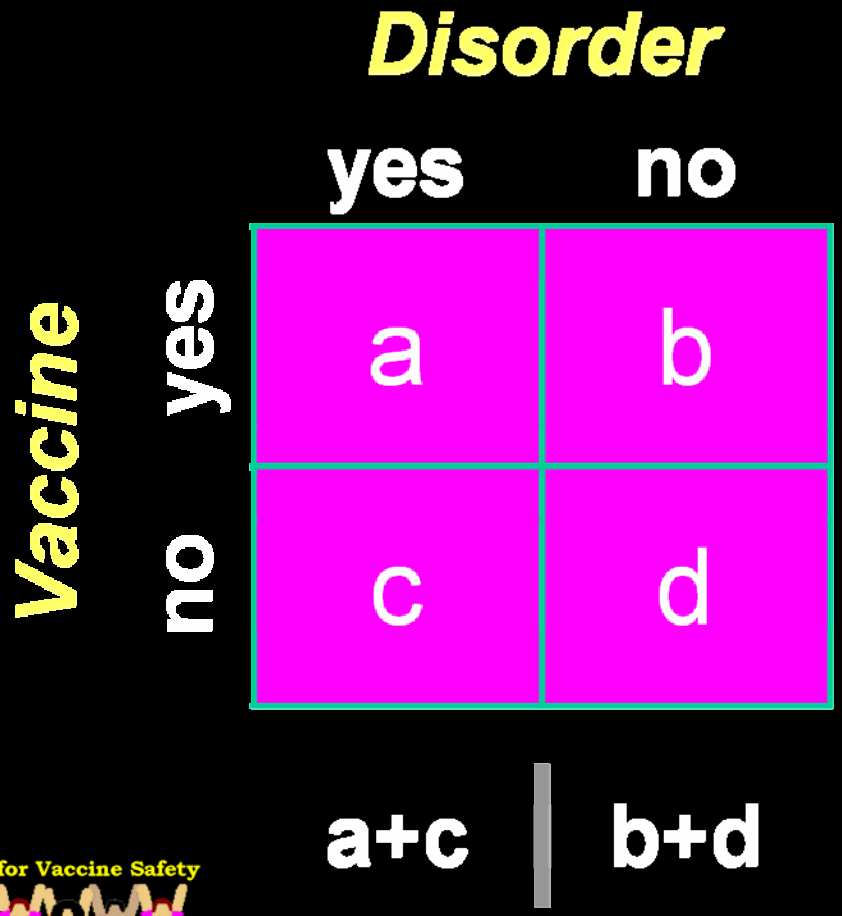
Investigating Causal Relationships

Retrospective or Non-concurrent Cohort Studies



Risk

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

Rel Risk

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

Not randomized: Self selection for vaccine?

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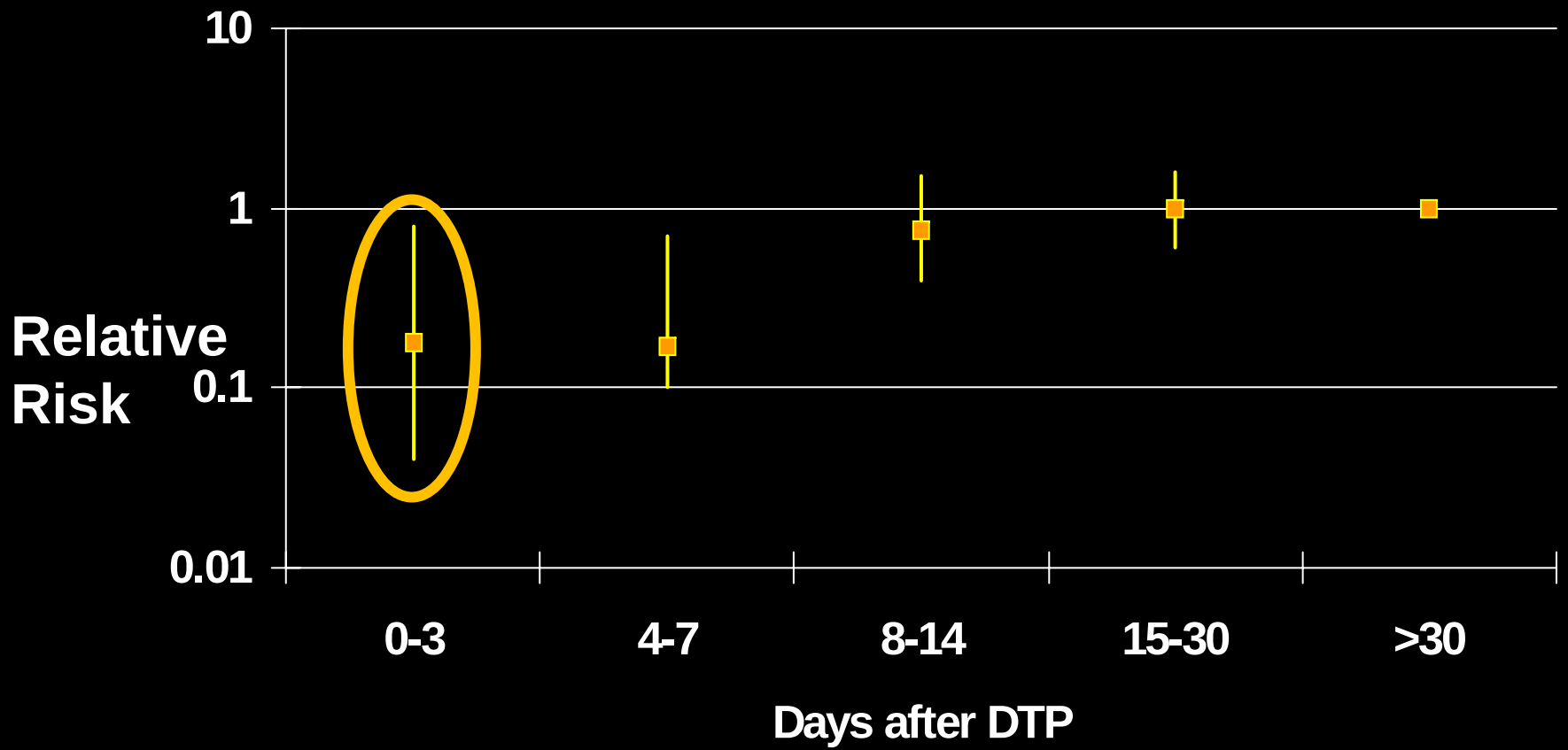
Relative Risk of Sudden Infant Death Syndrome by Day after DTP: Tennessee



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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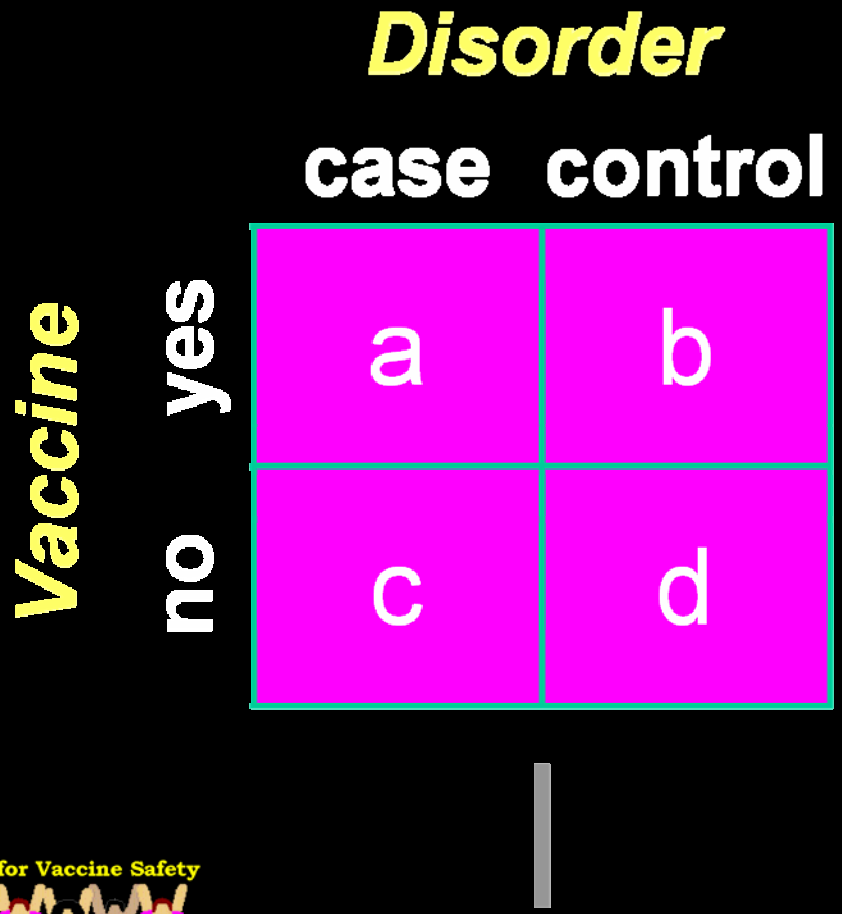
Investigating Causal Relationships

Case-Control Studies



Odds Ratio

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

Potential Problems:

- Not randomized
- Selection bias?
- Matching?

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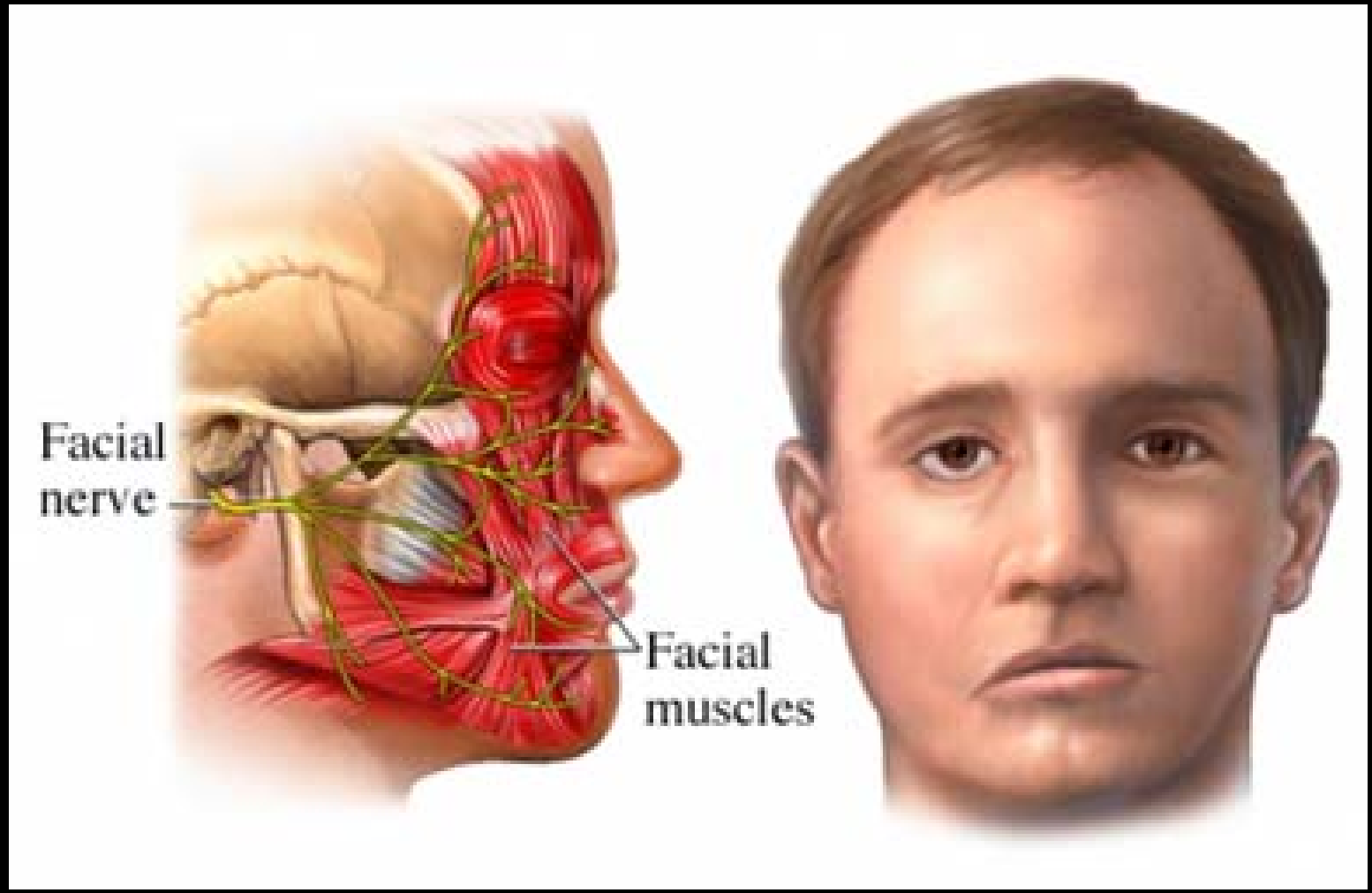
Bell's Palsy



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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)

For establishing causality: Prefer multiple studies by different investigators in different populations: "Consistency"

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

Ecologic Studies are Usually not Informative for Establishing Causality

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

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

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

- Very weak evidence

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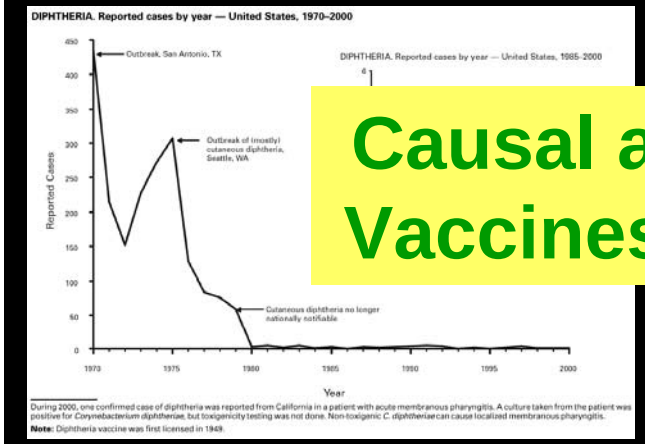
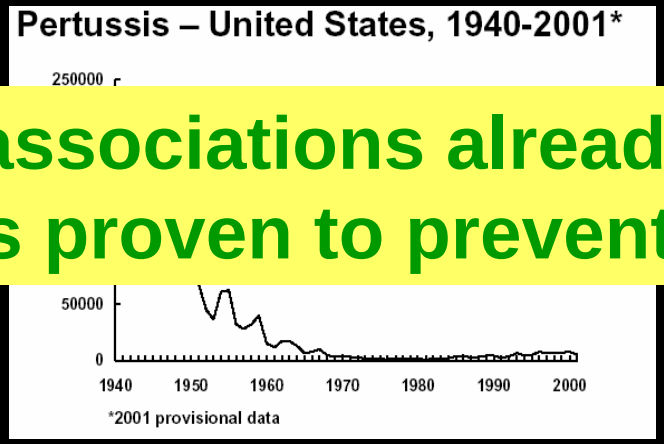
Ecologic Data Used to Demonstrate Effectiveness of Licensed Vaccines

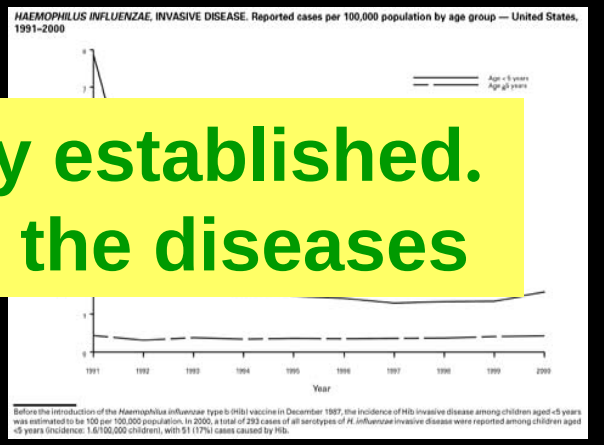
Diphtheria



Pertussis

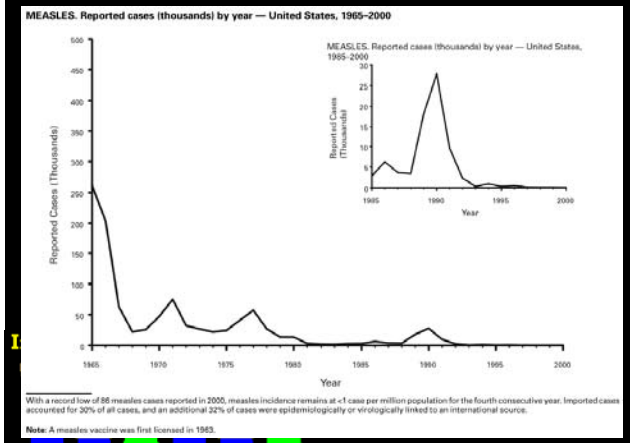


Hib

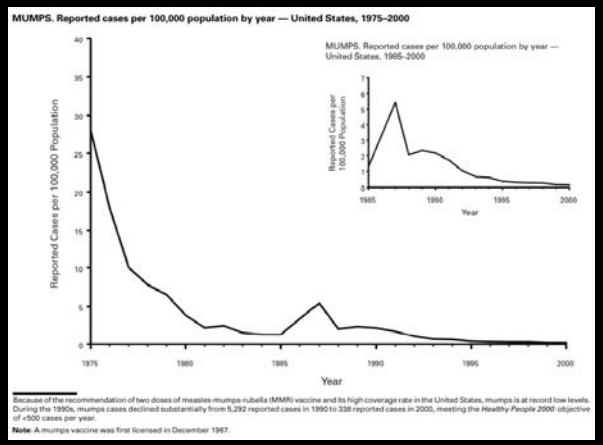


Causal associations already established. Vaccines proven to prevent the diseases

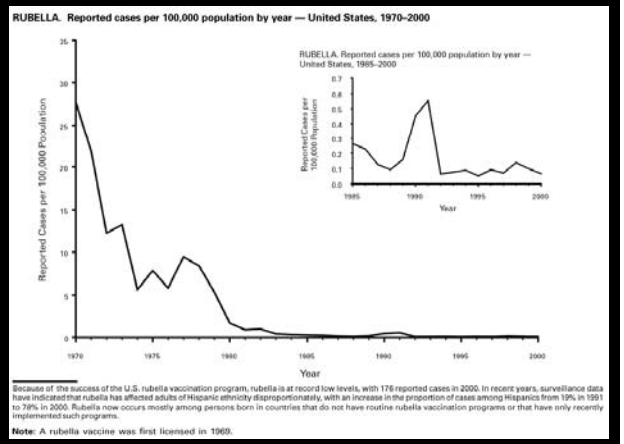
Measles



Mumps



Rubella



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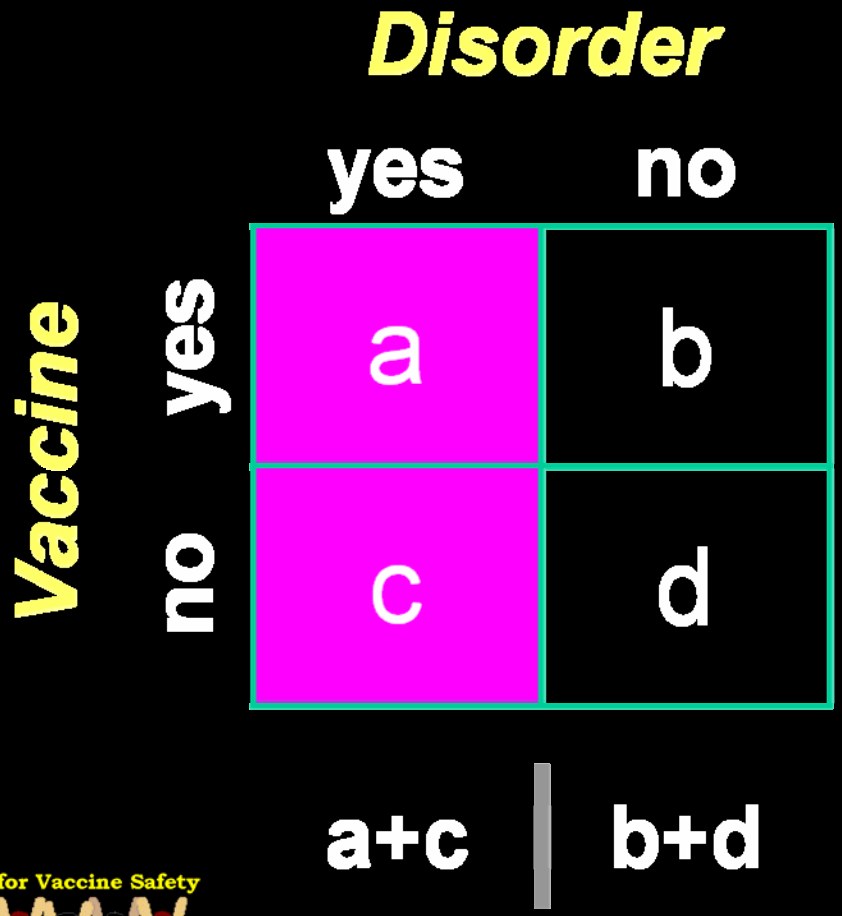
Summary of Notifiable Diseases *--- United States, 2000*

Case Only Assessments



Potential Problems:

- Selection bias?
- Need to include all cases in a defined population

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Usual criteria for establishing a causal relationship between vaccines and adverse events

Evidence of increased risk in vaccine recipients vs controls,

or

Definitive laboratory tests linking disease to vaccine component

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Causality Assessment from Individual Case Reports

- Causality established (usually):
  - Isolation of live vaccine agent in normally sterile body fluid (repeated observations).
    - Polio vaccine (OPV) virus in CSF.
    - Measles vaccine virus in lung of child with leukemia.

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Halsey NA. The Science of Evaluation of Adverse Effects Associated with Vaccination. 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 (repeated observations).
    - 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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Halsey NA. The Science of Evaluation of Adverse Effects Associated with Vaccination. Sem in Ped Infect Dis 2002 July;13(3):205-14

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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Large Local Reaction Following Influenza Vaccine: Delayed Hypersensitivity?

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Pathogenesis Unknown
Probable Host and Vaccine Factors

Questions we often do not ask:

If a vaccine is known to increase the risk of an adverse event:

- Would the event have occurred in the absence of the vaccine?
  - At the same time?
  - At a later time? Did the vaccine accelerate?
- If there are mutiple causal factors, what proportion is attributable to the vaccine?

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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

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

Conclusions

- Causality assessment is complex
- Poor understanding among health care providers and the general public
- Need for education to improve public trust in immunizations

Tomorrow: Individual case assessments.
Tool to possibly help with education

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