

# Causality Assessments in IOM Vaccine Safety Studies

Richard B. Johnston, Jr., M.D.

University of Colorado

# IOM Vaccine Committees

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- Principal purpose: describe relationship, vax/AE
- Asked: Can the vax cause the AE?
- Persistent neutral stance until decision made
- Decisions made by consensus
- Could not conclude absence of causation
- To conclude that evidence *avored* absence, needed controlled observational or clinical studies.
- To conclude acceptance of causality, usually relied on case series/reports.

# Types of Evidence Reviewed

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- Human experiments (RCT)
- Animal experiments
- Observational: Case-control, cohort, other controlled studies
- Case reports, case series
- Biologic plausibility

# VAX / AE 1

## DPT & Rubella (1991)

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- No evidence bearing on a causal relation
- Evidence insufficient to indicate a causal relation
- Evidence does not indicate a causal relation
- Evidence is consistent with a causal relation
- Evidence indicates a causal relation

# VAX / AE 2

## Childhood Vaccines (1994)

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- No evidence bearing on a causal relation
- The evidence is inadequate to accept or reject a causal relation
- The evidence favors rejection of a causal relation
- The evidence favors acceptance of a causal relation
- The evidence establishes a causal relation

# Asthma and Indoor Air (2000)

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- Sufficient evidence of a causal relationship
- Sufficient evidence of an association
- Limited or suggestive evidence of an association
- Inadequate or insufficient evidence to determine whether or not an association exists
- Limited or suggestive evidence of no association

# Categorization of Levels of Evidence (for discussion)

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- Evidence establishes a causal relationship
- Evidence establishes an association and favors a causal relationship
- Evidence suggests an association
- Evidence is inadequate to accept or reject an association/causal relationship
- Evidence favors rejection of an association/causal relationship

[No evidence bearing on a causal relationship]

# Considerations in Inferring Causality (from Bradford Hill)

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- Strength of association (OR, RR; not p value)
- Dose-response relationship
- Temporally correct association
- Consistency of association
- Specificity of association
- Biologic plausibility

# Biologic Plausibility

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- Is the possible causal relationship plausible (reasonable, credible) based on current biologic or medical knowledge of the vaccine and the AE?
- Only *demonstrated* (not just postulated) BP was considered.
- Demonstrated by: established association with natural disease; animal studies; in vitro studies (pathophysiologic mechanisms)

# Consideration of Alternative Explanations

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- Alternative explanation for observed association should be excluded:
  - error* (in design, conduct, or analysis)
  - bias* (systematic tendency to distort)
  - confounding* (failure to recognize another influential factor(s) )
  - chance*
- Alternative hypotheses should be evaluated and compared.

# IOM Vax Safety Forum, 1995-98

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- Mission: Improve vaccine safety
- Representatives from: CDC, FDA, NIH, NVIC/parents, plaintiffs, Merck, Connaught, Wyeth-Lederle, Vax Injury Compensation, neurology, immunology, pediatrics, county health, epidemiology.
- Strategy: Examine issues, propose methods for improvement, educate all involved.