Causality Assessments in IOM Vaccine Safety Studies

Richard B. Johnston, Jr., M.D.
University of Colorado
IOM Vaccine Committees

- 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 *favored* absence, needed controlled observational or clinical studies.
- To conclude acceptance of causality, usually relied on case series/reports.
Types of Evidence Reviewed

• Human experiments (RCT)
• Animal experiments
• Observational: Case-control, cohort, other controlled studies
• Case reports, case series
• Biologic plausibility
VAX / AE 1
DPT & Rubella (1991)

• 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)

• 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
• 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)

- 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)

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

• 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

- 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

- 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.