



# Charge to the Committee

Review the epidemiologic, clinical, and biological evidence regarding the adverse health events associated with specific vaccines covered by VICP.

HRSA presented a list of specific adverse events for the committee to consider.

We were not asked to assess efficacy or benefits of vaccines to individuals or the population at large.



# Committee Membership

**Ellen Wright Clayton** (Chair), Vanderbilt University

**Inmaculada B. Aban**, University of Alabama,  
Birmingham

**Douglas J. Barrett**, University of Florida College of  
Medicine

**Martina Bebin**, University of Alabama at Birmingham

**Kirsten Bibbins-Domingo**, University of California, San  
Francisco

**Martha Constantine-Paton**, Massachusetts Institute of  
Technology

**Deborah J. del Junco**, University of Texas Health  
Science Center at Houston

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# Committee Membership (cont.)

**Betty A. Diamond**, The Feinstein Institute for Medical Research

**S. Claiborne Johnston**, University of California, San Francisco

**Anthony L. Komaroff**, Brigham and Women's Hospital;  
Harvard Medical School

**B. Paige Lawrence**, University of Rochester School of  
Medicine and Dentistry

**M. Louise Markert**, Duke University Medical Center

**Marc C. Patterson**, Mayo Clinic



# Vaccines

Measles, mumps, and rubella vaccines (MMR)

Varicella zoster vaccine

Influenza vaccines (except 2009 H1N1)

Hepatitis A vaccine

Hepatitis B vaccine

Human papillomavirus vaccine (HPV)

Tetanus-containing vaccines other than those containing the whole cell pertussis component (DT, TT, aP)

Meningococcal vaccine



# Committee Membership and Process

15 members with expertise in pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law. All conclusions represent the consensus of the entire committee.

The committee met 8 times, including 3 open sessions.

The committee added 10 vaccine-adverse events to the list



# Evidence Review

Medical librarian conducted 3 comprehensive searches and spot searches. Search terms are in Appendix C.

Peer-reviewed literature (no abstracts, unpublished data)

Original research only



# General Framework for Causation

Epidemiologic weight of evidence (3 categories; 2 have a “direction” of increased risk, decreased risk, or null)

Mechanistic (biological and clinical) weight of evidence (4 categories; can only be used to “support” causation)

Causality conclusions (4 categories)



# Weighing Epidemiologic Evidence

Methodologic issues:

A priori definition of exposure

Verification of vaccine administration and adverse event

Control of confounding and bias

Adequacy of follow-up

Development and use of eligibility criteria

Precision, validity, and consistency of reported results →

Confidence



# Weight of Epidemiologic Evidence

**High:** *Two or more* studies with *negligible* methodological limitations that are *consistent* in terms of the direction of the effect and taken together provide high confidence.

**Moderate:** *One* study with *negligible* methodological limitations, *or a collection* of studies *generally consistent* in terms of the direction of the effect, provides moderate confidence.

**Limited:** One study or a collection of studies *lacking precision or consistency* provides limited, or low, confidence.

**Insufficient:** *No* epidemiologic studies of *sufficient* quality found.



# Evaluating Biological Mechanisms

- Direct infection; persistent infection; reactivation
- Immune-mediated mechanisms
  - T-cell
  - Antibodies and autoantibodies
  - Complement activation
  - Hypersensitivity reactions
  - Immune complexes
- Tissue responses
  - Fevers and seizures
  - Molecular mimicry
  - Antigen persistence
  - Epitope spreading
  - Bystander activation/Autoreactivity
  - Increased cytokines
  - Superantigens
- Injection related
- Coagulation

# Important Attributes of Case Reports

**Necessary but not sufficient:** vaccine confirmation, physician-diagnosed health outcome, appropriate temporality

**Additional information:** rechallenge, exclusion of other likely causes, clinical information in workup, confirmation of vaccine-strain virus

Animal and *in vitro* studies viewed with some caution.

Similarities to effects of natural infection alone merely gets evidence out of lacking and into weak.



# Weight of Mechanistic Evidence

**Strong:** One or more cases in the literature, for which the committee concludes the vaccine was a contributing cause of the adverse event, based on an *overall assessment of attribution* in the available cases **and** *clinical, diagnostic, or experimental evidence* consistent with relevant biological response to vaccine.



# Weight of Mechanistic Evidence (cont.)

**Intermediate:** At least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.

On occasion, the committee determined that at least two cases, taken together, while *suggestive*, were nonetheless insufficient for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. This evidence has been identified in the text as “**low-intermediate.**”



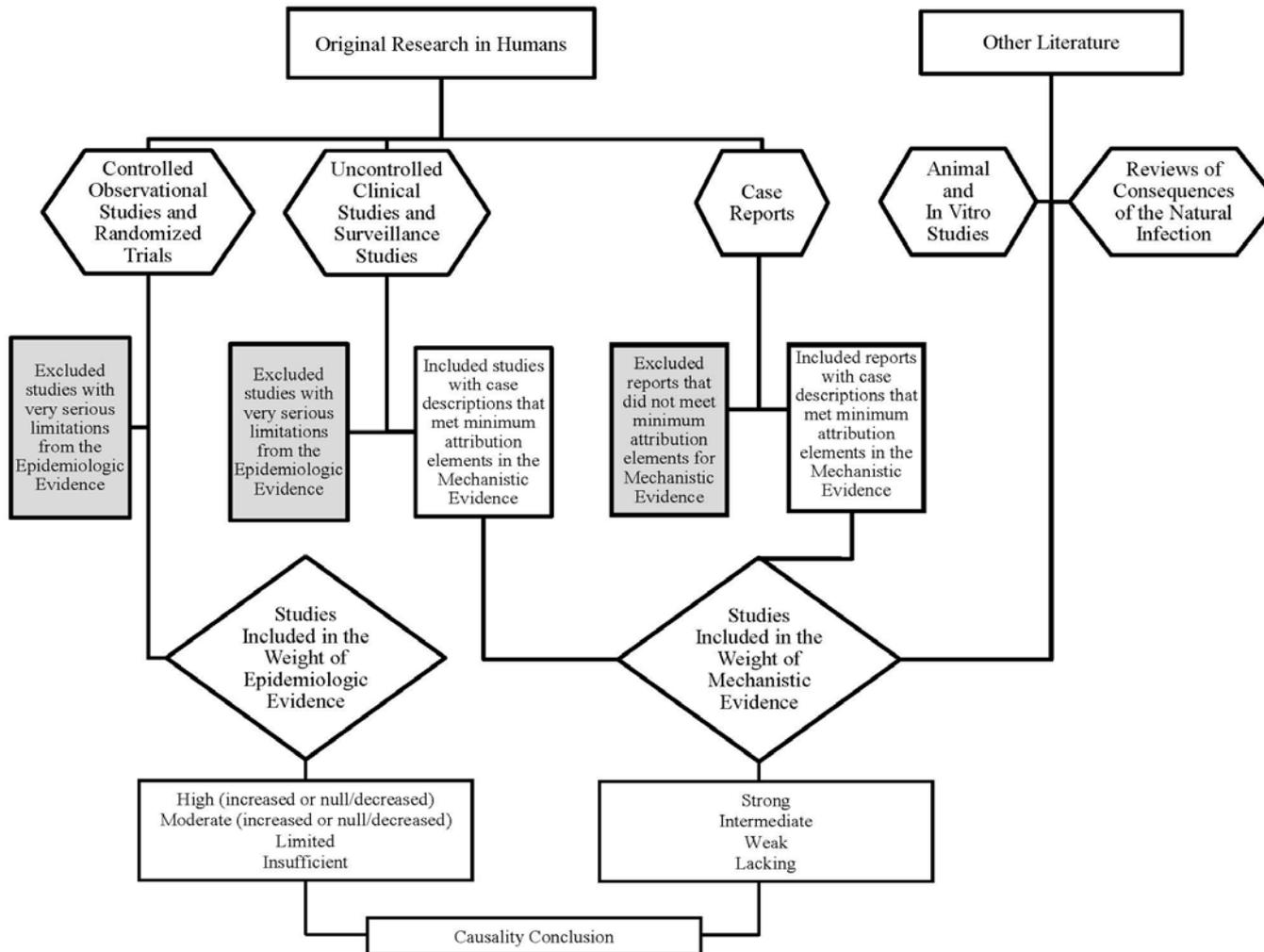
# Weight of Mechanistic Evidence (cont.)

**Weak:** Insufficient evidence from cases in the literature for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.

**Lacking evidence of a biologic mechanism:** No clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine, regardless of the presence of individual cases in the literature.



FIGURE S-1 Epidemiologic and Mechanistic Evidence



# Causality Conclusions

*Evidence convincingly supports a causal relationship.*

*Evidence favors acceptance of a causal relationship.*

*Evidence is inadequate to accept or reject a causal relationship.*

*Evidence favors rejection of a causal relationship.*



## Evidence that Determined the Causality Conclusions

EPIDEMIOLOGIC ASSESSMENT						MECHANISTIC ASSESSMENT					CAUSALITY CONCLUSION			
High increased	High null/decreased	Moderate increased	Moderate null/decreased	Limited	Insufficient	Strong	Intermediate	Low-Intermediate	Weak	Lacking	Inadequate to Accept or Reject	Favors Rejection	Favors Acceptance	Convincingly Supports
High increased														Convincingly Supports
						Strong								Convincingly Supports
		Moderate increased												Favors Acceptance
	High null/decreased*												Favors Rejection	
			Moderate null/decreased, Limited, or Insufficient**											Inadequate to Accept or Reject
								Low-Intermediate, Weak, or Lacking***						Inadequate to Accept or Reject

\* Causality conclusion is favors rejection only if mechanistic assessment is **not** strong or intermediate.

\*\* Causality conclusion is inadequate to accept or reject only if mechanistic assessment is **not** strong or intermediate.

\*\*\* Causality conclusion is inadequate to accept or reject only if epidemiologic assessment is **not** high increased, high null/decreased, or moderate increased.

# Inadequate to Accept or Reject Causation? What Does That Mean?

Some might interpret that to mean either of the following statements:

- Because the committee did not find convincing evidence that the vaccine *does* cause the adverse event, the vaccine is safe.

OR

- Because the committee did not find convincing evidence that the vaccine does *not* cause the adverse event, the vaccine is unsafe.

*Neither of these interpretations is correct.* “Inadequate to accept or reject” means just that—inadequate.



# Inadequate to Accept or Reject Causation? A Caveat

If there is evidence in either direction that is *suggestive but not sufficiently strong* about the causal relationship, it will be reflected in the *weight-of-evidence assessments* of the epidemiologic or the mechanistic data.

However *suggestive* those assessments might be, in the end the committee concluded that the evidence was inadequate to accept or reject a causal association.



# Convincingly Supports (14 Vx-AE)

**Varicella:** Disseminated Oka VZV without other organ involvement; Disseminated with pneumonia, meningitis, or hepatitis; Reactivation; Reactivation with meningitis or encephalitis

**MMR:** Febrile Seizures; Measles Inclusion Body Encephalitis (immunoincompetent only)

**Anaphylaxis:** MMR; Varicella; Influenza; Hepatitis B; TT; Meningococcal

**Injection-related:** Deltoid bursitis; Syncope



# Favors Acceptance (4 Vx-AE)

**HPV:** Anaphylaxis

**MMR:** Transient arthralgia in women and in children

**Influenza:** OculoRespiratory Syndrome



# Favors Rejection (5 Vx-AE)

**MMR:** Autism; Type 1 diabetes

**DT,TT, aP:** Type 1 diabetes

**Influenza:** Bell's palsy; Asthma exacerbation or reactive airway disease episodes in children and adults (TIV only)



# Inadequate, but the Epidemiologic Evidence Is “Moderate” (9 Vx-AE)

**Influenza:** Seizures; GBS; LAIV-asthma/RAD (moderate null); Stroke, MI, all cause mortality (moderate decreased risk; only 1 study each)

**MMR:** Meningitis (moderate null)

**Hepatitis B:** First demyelinating event (moderate null);  
Type 1 diabetes (moderate null)



# Inadequate, but the Mechanistic Evidence Is “Low-Intermediate” (7 Vx-AE)

**MMR:** Chronic arthralgia and Chronic arthritis in women;  
Hearing loss

**Hepatitis B:** Acute Disseminated EncephaloMyelitis,  
First demyelinating event, vasculitis

**Injection-related:** Chronic Regional Pain Syndrome



# We Anticipate and Hope That Future Studies Will Permit More Causal Conclusions to Be Reached

One of our goals was to be as transparent as possible about our process to provide a framework for future analysis



# Find Out More!

[www.iom.edu/vaccineadverseeffects](http://www.iom.edu/vaccineadverseeffects)

PDF version of report and dissemination material  
available for free

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# A Note in Closing

This report would not have been possible without:

- The collaborative work of the committee members who brought their diverse perspectives and expertise to bear on this enormous task
- The extraordinary efforts of the staff
- The wise leadership of Kathleen Stratton who brought years of experience to this project

