

SCIENCE COURTS, ABUSES OF BUREAUCRATIC AUTHORITY AND AUTISM

*A Critique of the Institute of Medicine's Findings and
Process in Vaccines and Autism, 2004*

October 20, 2006

SUMMARY OF KEY ARGUMENTS

The CDC directly funded the IOM for the establishment and maintenance of the Immunization Safety Review Committee (The Committee) and played an integral role in planning each meeting subsequent to interim findings of the committee.

The Committee, intended as a competent, disinterested and unbiased panel, was instead skewed, financially conflicted and biased

The Committee officials omitted information showing causation between autism and vaccinations (i.e., case studies, mechanistic studies and presentations) to the full committee.

The Committee used methodology in order to dismiss causation between vaccines and autism, by inappropriately changing “biological plausibility” to “biological mechanisms” standard of proof metrics.

The Committee deliberations focused on policy issues with a strong bias that any causal finding would cause an unwanted decline in vaccination rates. Very little discussion was devoted to the science at hand. Ad hominem attacks served as a major basis for rejection of causation between the MMR vaccination and autism.

The Committee’s project manager openly discussed lies to the public as an acceptable possible strategy

Comments made by Committee officials alluded to CDC exerting strong control over the outcomes of each meeting.

Additional contractual information regarding the CDC’s role in Committee conduct has NOT been released by the CDC.

CONCLUSION: THE COMMITTEE FAILED TO FULFILL ITS DUTIES AS AN IMPARTIAL PANEL

As a panel of judges, The Committee was unsuited for its charge:

- not scientifically competent in the relevant areas,
- financially conflicted in some cases, and
- ideologically biased, as evidenced by prior policy statements and affiliations

Further, over the course of its deliberations, The Committee

- changed the rules of evidence
- failed to consider important evidence, while relying heavily on flawed evidence
- raised its standard of proof to an impossibly high level
- adjusted its agenda to serve the interests of its client, the CDC, an interested party in the controversy

In its private discussions, The Committee displayed an pervasive bias

- summarily dismissing relevant science with ad hominem attacks on individual scientists
- openly discussing the need to lie to the public and to defend the vaccine program regardless of the evidence, or “no matter what”
- openly discussed the reality of inappropriate CDC influence

RECOMMENDATION: CONVENE A NEW IOM PANEL MORE SUITED TO THE ISSUES AT HAND

Shift from the loaded question

- Are vaccines dangerous? (and the presumptive verdict: No!), to the relevant public health issue:
- Why are so many children sick?

Specifically, a new Committee should address the following questions

- How should the scientific community interpret and respond to the reported trend in autism rates in the United States?
- What does the trend data and the existing body of etiological research suggest in terms of the relative contribution of genes and environment in autism?
- Among environmental factors, which of the following deserve consideration as contributors to the interactions that produce autism

The new Committee's composition should redress in a comprehensive way the problems with the old Committee

[NOTE: THE IOM WORKSHOP ON AUTISM AND THE ENVIRONMENTAL COVERED SOME OF THIS AGENDA AND WAS A SUCCESSFUL FIRST STEP]

OVERVIEW OF PRESENTATION

The IOM Immunization Safety Review Committee (The Committee) had a clear charter, but its charter changed over time amidst conscious efforts to influence its findings

The Committee itself was skewed in composition, financially conflicted and biased

The Committee considered evidence of (flawed) epidemiology alone, ignored relevant evidence and precluded consideration of case study evidence entirely in its autism findings

The Committee changed the standard of proof in the vaccine safety review criteria from Biological Plausibility to Biological Mechanisms in order to favor an outcome that would fully reject any causation hypothesis

The Committee adjusted its agenda to serve the interests of its client, the CDC, an interested party in the controversy

The Committee displayed a pervasive bias in its private discussions to suppress relevant science

THE CHARGE TO THE INSTITUTE OF MEDICINE IMMUNIZATION SAFETY REVIEW COMMITTEE

Established in 2000 based on an interagency agreement (IAA) from the CDC through the NIH (obtained by FOIA)

Committee was charged to look at *up to three* vaccine safety hypotheses each year put forward by the DHHS Interagency Vaccine Group over a period of three years:

- CDC (NIP and NCID)
- NIH (NIAID)
- NVICP
- FDA
- Center for Medicare and Medicaid Services

THE CHARGE TO THE COMMITTEE: KEY GOVERNING DOCUMENTS

Interagency Agreement (IAA) between the CDC and the NIH to contract the IOM to create the Vaccine Safety Review Committee

These IAA documents lay out both the charge and the conduct of the IOM ISR Committee

In addition, these documents specify the methods for dissemination of the committee's findings

Documents include

- The IAA Contract to the IOM, signed by officials from the CDC (William Nichols) and the NIH (Anthony Fauci, M.D.)
- The Contract/Work/Statement (CSW) delineating the composition and conduct of the Immunization Safety Review Panel

Many other documents exist in the CDC's possession that haven't been released despite pending FOIA requests.

The Institute of Medicine documents are out of reach as the FOIA does NOT apply to them.

THE CHARGE TO THE COMMITTEE: APPROACH, SCOPE AND DELIVERABLES

Topics for consideration in meetings

- Dictated by the CDC Contracting Officer and Project Officers (presumably K. Stratton, IOM and M. McCormick, HSPH; CSW, pg. 3)
- For each topic, the “contractor is responsible in compiling and summarizing background data,” although others may have input (CSW, pg. 3)

Scope of findings envisioned

- Vaccination policy
- Research agenda
- Refereed technical publications
- Vaccine injury compensation litigation (committee deliberations shared with ACIP and NVICP officials)

Vaccine policy recommendations to range between:

- “Minimal unintended disruption of routine immunization services”
- “Changes in recommendations for vaccine use pending further investigation” (CSW, pg. 2)

Distribution of committee outputs to include

- Presentations at governmental, medical and scientific meetings
- Complete reports available on the IOM website
- Information dissemination to the media/general public and health professionals

THE CHARGE TO THE COMMITTEE: SELECTED EXCERPTS

Vaccine safety review described as, “until more definitive scientific evidence becomes available, an *interim* review by an independent body could help evaluate for providers and the public the *credibility* of a new vaccine safety hypothesis.”

Credibility of a hypothesis based on “biologic plausibility, competing alternative hypotheses, as well as the available scientific evidence to date.”

At the end, “knowledge gaps and research needs would also have been identified.”

Source: CSW, pg. 2 (emphases added)

THE CHARTER AND PROCEDURES OF THE COMMITTEE CHANGED OVER THE COURSE OF ITS DELIBERATIONS IN A CONSCIOUS EFFORT TO INFLUENCE ITS FINDINGS

Starting Point (ISRC Contract)	By Meeting #9
Interim review until more solid research has been completed for a given adverse event	Meeting #9 constituted a final review essentially closing the door on further research into the vaccine/autism hypotheses
Independent, not as an agent of the government	The government (i.e., CDC) predetermined the meeting outcomes
Summarize currently available literature	Specific literature and investigators were omitted from consideration
Biologic plausibility of the hypothesis based on current knowledge of adverse event	Biological mechanisms consistent with disease etiology
Overall causality	Causality at an epidemiological level only
Recommend further research, surveillance and changes in vaccine use	Comments from closed door session #1 preclude recommendations for additional research or vaccine schedule changes
No financial, professional or personal conflict of interest	Committee members have numerous financial, professional and personal conflicts of interest
Standard method to determine appropriate level of scientific concern	Methods for determining scientific concern changed drastically starting in meeting #4
Agree on criteria the panel will use to assess relative value strengths and weaknesses of the assessed materials	Assessment criteria changed drastically starting in meeting #4

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OBSERVATIONS BASED ON COMMITTEE COMPOSITION AND ATTENDANCE

The committee was heavily weighted towards representatives from public health and pediatric disciplines.

No committee members were experts in autism and toxicology, despite 3 meetings involving autism and 2 involving mercury toxicity.

Despite 4 meetings around immunological adverse events, there was only one immunologist on the committee.

The committee findings were strongest against causality when Wilson, the only immunologist on the committee, was absent.

Meeting #8 regarding neurological disorders was held despite the absence of Bennett Shaywitz, the only neurologist on the committee.

The two committee members with the strongest conflicts of interest (McCormick and Parkin) were in attendance at every meeting.

THE COMPOSITION OF THE IMMUNIZATION SAFETY REVIEW COMMITTEE

MARIE C. McCORMICK, M.D., Sc.D. (*Chair*),
Summer and Esther Feldburg Professor of
Maternal and Child Health, Department of
Society, Human Development and Health,
Harvard School of Public Health, Cambridge, MA

RONALD BAYER, Ph.D., Professor, Department of
Sociomedical Sciences, Mailman School of Public
Health, Columbia University, New York, NY

ALFRED BERG, M.D., M.P.H., Professor and Chair,
Department of **Family Medicine**, University of
Washington School of Medicine

ROSEMARY CASEY, M.D., Associate Professor of
Pediatrics, Jefferson Medical College, and
Director, Lankenau Faculty Pediatrics,
Wynnewood, Pennsylvania

JOSHUA COHEN, Ph.D., Senior Research Associate,
Harvard Center for Risk Analysis, Harvard School
of Public Health

BETSY FOXMAN, Ph.D., Professor, Department of
Epidemiology, School of Public Health, University
of Michigan

CONSTANTINE GATSONIS, Ph.D., Professor of
Medical Science and Applied Mathematics, and
Director, Center for **Statistical Sciences**, Brown
University

STEVEN GOODMAN, M.D., M.H.S., Ph.D.,
Associate Professor, Department of Oncology,
Division of **Biostatistics**, Johns Hopkins School of
Medicine, Baltimore, NY

ELLEN HORAK, M.S.N., Education and Nurse
Consultant, Public Management Center, University
of Kansas

MICHAEL KABACK, M.D., Professor, **Pediatrics** and
Reproductive Medicine, University of California,
San Diego

REBECCA PARKIN, Ph.D., M.P.H., Associate Dean
for Research and Public Health Practice, School of
Public Health and Health Services, George
Washington University, Washington, D.C.

BENNETT SHAYWITZ, M.D., Professor of **Pediatrics**
and **Neurology**, Co-Director, Yale Center for the
Study of Learning and Attention, New Haven, CT

GERALD MEDOFF, M.D., Professor, Department of
Internal Medicine, Washington University School
of Medicine, St. Louis

CHRISTOPHER B. WILSON, M.D., Professor and
Chair, Department of **Immunology**, University of
Washington

Health Promotion and Disease Prevention Board Liaison

RICHARD B. JOHNSTON, Jr., M.D., Professor
of **Pediatrics**, Associate Dean for Research
Development, University of Colorado School
of Medicine and National Jewish Medical and
Research Center

COMMITTEE ATTENDANCE BY DISCIPLINE

Meeting	Public Health**	Pediatrics	Statistics	Neurology	Internal Medicine	Immunology	Other
MMR, 4/01	Bayer Foxman Horack Parkin	Berg Casey Kaback Johnston*	Gatsonis Cohen Goodman	Shaywitz	Medoff	--	Davis- Anthony
Thimerosal & NDDs, 10/01	Bayer Parkin	Berg Casey Kaback Johnston*	Gatsonis Cohen	Shaywitz	Medoff	Wilson	--
Multiple antigens, 2/02	Bayer Foxman Horack Parkin	Berg Kaback Johnston*	Gatsonis Cohen Goodman	Shaywitz	Medoff	Wilson	Davis- Anthony
Hep B & DND, 5/02	Bayer Horack Parkin	Berg Casey Kaback Johnston*	Gatsonis Cohen Goodman	Shaywitz	Medoff	---	--
SV40 & cancer, 10/02	Foxman Parkin	Kaback Johnston*	Gatsonis Cohen Goodman	Shaywitz	---	Wilson	--
SIDS, 3/03	Bayer Foxman Horack Parkin	Berg Casey Kaback Johnston*	Gatsonis Cohen	Shaywitz	Medoff	Wilson	---
Flu and CNS, 10/03	Bayer Foxman Horack Parkin	Berg Casey Johnston*	Goodman	---	Medoff	Wilson	---
Vaccines & Autism, 5/04	Bayer Foxman Horack Parkin	Berg Casey Kaback Johnston*	Gatsonis Cohen Goodman	Shaywitz	---	---	---

* Ex officio member

**Marie McCormick attended all meetings

COMMITTEE PARTICIPATION INFLUENCED OUTCOMES, AS VACCINE RISKS WERE ACCEPTED/REJECTED WITH LOW/HIGH PUBLIC HEALTH/PEDIATRIC PARTICIPATION

Meeting	Absent	Public Health and Pediatrics Presence and Outcomes
#2 MMR and Autism	Wilson	69% (9/13) No connection
#3 Thimerosal and Neuro-developmental Disorders	Davis-Anthony, Foxman, Goodman, Horak	60% (6/10) Connection biologically plausible
#4 Multiple Immunizations and Immune Dysfunction	Casey	62% (8/13) Insufficient info on allergies, switch to biological mechanisms, some mechanisms are strong
#5 Hep B vaccine and demyelinating disorders	Foxman, Wilson, Davis-Anthony	64%(7/11) Insufficient evidence, weak biological mechanisms
#6 Polio, SV40 virus and cancer	Bayer, Berg, Casey, Horak, Medoff, Davis-Anthony	50%(4/8) Insufficient evidence, biological mechanisms strong/moderate
#7 Vaccines and SIDS	Bayer, Goodman, Davis-Anthony	64% (7/11)Ranging between reject to favoring acceptance
#8 Influenza vaccines and neurological complications	Cohen, Gatsonis, Kaback, Shaywitz, Davis-Anthony	78% (7/9) Ranging between reject to favoring acceptance
#9 Vaccines and autism	Medoff, Wilson, Davis-Anthony	73% (8/11)Reject all hypotheses

STATEMENT BY DR. HARVEY FINEBERG, IOM PRESIDENT, REGARDING IOM ISR COMMITTEE CONFLICTS AND BIASES

Specifically, members of Immunization Safety Review Committee had no ties to vaccine manufacturers, had not made policy statements regarding vaccines; had not served as expert witnesses--paid or unpaid--in any vaccine-related litigation; and had not worked for nor received recent funding for research on vaccine safety from the agencies that sponsored the study. As is the case with all IOM projects, their service was entirely voluntary; they received no compensation.

-Statement issued June 27, 2005; <http://www.iom.edu/CMS/27733.aspx>

FINANCIAL CONFLICTS OF INTEREST AMONG COMMITTEE MEMBERS

Committee members were not to possess any financial, professional or personal conflicts of interest with the contracting agencies or regarding the topics to be considered. In reality, such conflicts were common...

McCormick

- The CDC hired Dr. Mary Jean Brown, an assistant professor in the Harvard School of Public Health Department of Maternal and Child Health (then chaired by Dr. McCormick) to serve as the Chief of the Lead Poisoning Prevention branch in the National Center for Environmental Health in 2003. Dr. Brown maintained an adjunct appointment at Harvard after beginning her new position at the CDC.
- The department Dr. McCormick chaired at Harvard (Maternal and Child Health) received a grant from the CDC 4 months prior to the issuance of the 5/17/04 report on vaccines and autism.

Parkin

- Former CDC employee
- Received grant money from the CDC during the course of the committee's deliberations.

Davis-Anthony

- Owned stock in vaccine manufacturer Merck

Wilson

- Served in the Public Health Service (which has oversight for the CDC) during the 1970's

DEMONSTRATION OF BIAS : IMMUNIZATION POLICY STATEMENTS BY DR. ALFRED BERG

RECOMMENDATION

All children without established contraindications should receive diphtheria-tetanus-pertussis (DTP), oral poliovirus (OPV), measles-mumps-rubella (MMR), conjugate *Haemophilus influenzae* type b, hepatitis B, and varicella vaccines, in accordance with recommended schedules (see *Clinical Intervention*). Hepatitis A vaccine is recommended for children and adolescents at high risk for hepatitis A virus (HAV) infection. Pneumococcal vaccine and annual influenza vaccine are recommended for children and adolescents at high risk (see *Clinical Intervention* and Chapter 66). See Chapter 67 for recommendations on postexposure prophylaxis against selected infectious diseases, and Chapter 25 for recommendations regarding the Bacille Calmette-Guérin (BCG) vaccine.

Policy statement from, *Guide to Clinical Preventive Services, 2nd Edition*, Chapter 65, "Childhood Immunizations." (Authored by Dr. Alfred Berg) Report of the U.S. Preventative Services Task Force, DHHS, Office of Public Health and Science, Office of Disease Prevention and Health Promotion, 1996, p. 767

THE AMOUNT OF THIMEROSAL INVOLVED IN DR. BERG'S POLICY RECOMMENDATION

“All children without established contraindications should receive diphtheria-tetanus-pertussis (DTP), oral poliovirus (OPV), measles-mumps-rubella (MMR), conjugate Haemophilus influenzae type b, hepatitis B, and varicella vaccines, in accordance with recommended schedules.”

Age	Vaccine	DTP	OPV/IPV	MMR	Hib	Hep B	Varicella	Total Hg Exposure	Cumulative Hg Exposure
2 weeks	Thimerosal Dosage	---	---	---	---	12.5	---	12.5	12.5
2 months		25	0	---	25	12.5	---	62.5	75
4 months		25	0	---	25	---	---	50	125
6 months		25	---	---	25	12.5	---	62.5	187.5
12 months		---	---	0	---	---	0	0	187.5
15 months		25	0	---	25	---	---	50	237.5

Thus, in 1996, Dr. Berg recommended that children receive the full dosage of mercury in thimerosal as shown in the far right column above.

Based on his public policy statements, Dr. Berg had a demonstrable bias toward denying causation between thimerosal and autism.

SUMMARY: THE COMMITTEE WAS SKEWED, FINANCIALLY INTERESTED AND IDEOLOGICALLY BIASED

Committee membership was heavily weighted toward public health and pediatric representatives, had no toxicologists or environmental scientists and only a single immunologist, who failed to attend critical meetings

Committee composition varied by topic based on attendance and was associated with differences in findings

Four committee members had financial conflicts of interest, including ties to the CDC and stock ownership in vaccine manufacturers that should have disqualified them from participation.

At least one committee member was on record as promoting the vaccine schedule he was now being asked to evaluate, a statement that should have disqualified him from participation

An additional three (Gatsonis, Horak and Medoff) reported making vaccine policy statements to the rest of the committee. Such statements (unknown at this time) could have disqualified them from participation

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CONCLUSIONS ON THE “EVIDENCE” FROM IOM ISR COMMITTEE MEETINGS PERTINENT TO AUTISM

Meeting 2:

“Evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders.” IOM ISR Report 4/23/01, p. 6

Meeting 3:

“Evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay,” IOM ISR Report 10/1/01, p. 5

CHANGES IN THE “RULES OF EVIDENCE “OVER THE COURSE OF COMMITTEE DELIBERATIONS

	1994 Criteria	Meeting 2 - MMR	Meeting 9 - thimerosal
Evidence Basis	In the absence of epidemiology studies favoring a causal relationship, individual case reports and case series were relied upon, along with presence or absence of demonstrated “biologic plausibility.”	The absence of epidemiologic studies favoring a causal relationship was the sole basis for the rejection of a causal relationship between MMR and ASD.	Causality was determined by epidemiologic studies favored by the committee, only one of which was completed using the U.S. vaccine schedule on children in the U.S.
Role of Epidemiology	Case control studies are the only feasible research design for rare events.	Lack of relationship in epidemiologic studies was used to reject a causal relationship.	Epidemiologic studies that were inconclusive or that did not show a relationship were the sole basis to reject causality. The committee rejected several studies providing support for a causal relationship.
Case Studies	Absence of case studies cannot be used to reject causality. Challenge-rechallenge studies have a major effect on the causality assessment.	Case studies “uninformative.” The existence of challenge-rechallenge cases was not pursued further.	Despite the existence of such data, no case studies regarding thimerosal exposure were considered by the committee.
Biologic Assessment	Biological plausibility based on <i>current knowledge of adverse event</i> .	Biologic models linking MMR and ASD are “fragmentary.” No relevant animal model.	The committee switched the biologic assessment criterion from “plausibility” to “biologic mechanism” consistent with the adverse event. Supportive studies classified as “theoretical” due to the paucity of evidence on the mechanisms of autism.

Epidemiology alone

CONCLUSIONS FROM FINAL IOM VSR COMMITTEE MEETING (VACCINES AND AUTISM, 5/16/04 REPORT)

Epidemiology

“Epidemiological studies examining thimerosal-containing vaccines and autism, including three controlled observational studies (Hviid et al., 2003; *Verstraeten et al., 2003*; Miller, 2004) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003), consistently provided evidence of no association between thimerosal-containing vaccines and autism, despite the fact that these studies utilized different methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom).” [IOM ISR Committee 5/14/04 report, Exec. Summary, pg. 5, italics added]

Final judgment

“Thus, based on *this body of evidence*, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.” (ibid., italics added)

The final conclusion was based entirely on epidemiology, with only one disputed study involving children in the U.S. (Verstraeten et al. 2003). Other country studies were carried out by conflicted parties and with populations exposed to lower thimerosal levels than children in the U.S.

SEVERE PROBLEMS WITH EPIDEMIOLOGY EVIDENCE IN 5 CITED STUDIES

Study (population)	Author conflicts: Vaccine makers	Author Conflicts: Policy makers	Data problems (selected)	Model problems (selected)
Verstraeten et al '03 <i>Pediatrics</i> (U.S. VSD)	Verstraeten (GSK, undisclosed)	DeStefano (CDC) Rhodes (CDC) Chen (CDC)	Exclusion of cases with high exposures and outcomes	Systematic reduction of risk findings over report generations
Stehr-Green et al '03 <i>AJPM</i> (Denmark, Sweden)	Stellfeld (SSI)	Simpson (CDC) Stehr-Green (CDC consultant)	Registrations confused with incidence	Observation period overlapped major registration changes
Hviid et al '03 <i>JAMA</i> (Denmark)	Hviid (SSI) Stellfeld (SSI) Melbye (SSI) Wohlfahrt (SSI)		Lost cases unexplained	Years of birth chosen to obscure MMR effect
Madsen et al '03 <i>Pediatrics</i> (Denmark)	Plesner (SSI)	Thorsen (CDC)	Registrations confused with incidence	Observation period overlapped major registration changes
Andrews et al '04 <i>Pediatrics</i> (U.K.) [cited as Miller 2004 by IOM ISR]		Andrews (CDSC) Miller (CDSC) Grant (CDSC)	Positive health effects of mercury exposure	Multicollinearity Regression results hidden

POSITIVE CASE/CONTROL EPIDEMIOLOGY STUDIES DISMISSED OVER DATA AND METHODS CONCERNS

- 1: Geier DA, Geier MR. A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis. *Med Sci Monit.* 2005;11(4):CR160-70.
- 2: Geier D, Geier MR. Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis. *Int J Toxicol.* 2004;23(6):369-76.
- 3: Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Med Sci Monit.* 2004;10(3):PI33-9.
- 4: Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. *Pediatr Rehabil.* 2003;6(2):97-102.
- 5: Geier MR, Geier DA. Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. *Exp Biol Med.* 2003;228(6):660-4.

Consideration of Case Studies

WEIGHT OF CASE STUDIES IN DETERMINING CAUSALITY (STRATTON ET AL. 1994)

Although *Can It?* causality is usually addressed from epidemiologic studies, an affirmative answer can occasionally be obtained from individual case reports. *Thus, if one or more cases have clearly been shown to be caused by a vaccine (i.e., Did It? can be answered strongly in the affirmative), then Can It? is also answered, even in the absence of epidemiologic data*

Susceptibility of the vaccine recipient (i.e., rechallenge): *Has he or she received the vaccine in the past? If so, how has he or she reacted? Does his or her genetic background or previous medical history affect the risk of developing the adverse event as a consequence of vaccination?*

Characteristics of the adverse event: *Are there any available laboratory tests that either support or undermine the hypothesis of vaccine causation? For live attenuated virus vaccines, has the vaccine virus (or a revertant) been isolated from the target organ(s) or otherwise identified? Was there a local reaction at the site at which the vaccine was administered? How long did the adverse event last?*

Rechallenge: *Was the vaccine readministered? If so, did the adverse event recur?*

THE COMMITTEE CHAIR'S GENERAL ATTITUDE OF SKEPTICISM REGARDING "CAN IT?" CASE INFORMATION

Dr. Johnston: Barbara Loe Fisher [NVIC] could give you names. Mrs. Fisher said she had cases. I think she came up to say if you needed any cases to demonstrate the points, you could have them.

Dr. McCormick: *She was demonstrating causality.*** She was taken by your case series that you did—the Guillaume Barre (*sic*) and whatever, the tetanus. She was all ready to get you cases to prove causality.

Dr. Wilson: Well, let's see them.

Dr. McCormick: *Let's not do that.* Do you have a free weekend that you want to plod through them?

-Source: pp 149-150, IOM ISR Meeting 1 closed door meeting transcript, 1/12/01, emphasis added

**i.e., 1994 IOM Report – Stratton et al.1994

MORE REGARDING CONSIDERATION OF CASE STUDIES

Dr. McCormick: And question came up in terms of previous formulation of this, is can it? Do we have any evidence whatsoever that even in a single individual, MMR can cause autism? And we felt both the biologic plausible evidence that we are seeing does not support this. It was a very preliminary and fragmentary body of evidence.

We are not accepting the rechallenge cases, because we really don't have them described. And the animal model is not contributory. So we don't have any biological evidence to offset what is a consistent series of epidemiologic studies. (but she dismissed the Fisher and Wakefield case reports, and she is pushing to reject causality).

Source: 3/10/01 closed door meeting transcripts, p. 30

Dr. Shaywitz: There was no case report. Everybody cites the tetanus -- the man with tetanus who got an injection, and the second time got tetanus again or got Guillain-Barre. But that's not even here. We don't even have single case reports that are convincing.

Source: 3/10/01 closed door meeting transcripts, p. 17

But Mrs. Fisher's case reports were NOT examined (re: 1/12/2001 transcript)

MORE REGARDING CONTRIBUTION OF CASE STUDIES

Dr. Foxman: I'm curious what everybody thinks, but also it seems to me to say I feel comfortable saying favors rejection, and the type of evidence we would like to see. Can we make some statements like that, that because there is no well documented case series showing that it can happen, because there is not a complete biological model by any way, shape, or form. ***And that at this point there is just really no evidence.***

Source: 3/10/01 closed door meeting transcripts,
p.33, emphases added

Dr. McCormick: I think there another level of evidence here. We've got there is a consistent body of controlled epidemiologic studies that show no association. We have case series that are not contributory.

Source: 3/10/01 closed door meeting transcripts,
p. 68 (emphasis added)

MORE REGARDING CONSIDERATION OF CASE STUDIES

Dr. McCormick:...if we are willing to consider that it could occur in some other groups, even though they are not detectable at the epidemiologic level, *then we are basically saying it can cause the adverse reaction...*

...Kathleen [i.e., Dr. Stratton] was indicating that this “can it,” “is it ever possible” argument might reflect much more in the way of better described case histories or individual cases, like the rechallenge cases. Where an individual could say, yes, it can happen.

-Source: 3/10/01 closed door meeting transcript

Dr. McCormick exerted her influence as committee chairperson numerous times to reject looking at contributory case studies.

WAKEFIELD'S 11 CASE STUDIES

(1998, Lancet 1998 Feb 28;351(9103):637-41

After his original presentation to the IOM ISR on 3/8/01, Wakefield was asked to provide his slides to the committee on 3/9/01 (2002 Latitudes, 5[3] p. 6).

Closed door deliberations on 3/10/01 make it clear that the committee wanted additional information but committee leadership chose not to request such data from Wakefield.

Despite the comprehensive data provided and the deliberations by the committee, Wakefield's case study information was mentioned only in passing in the 4/23/01 report on MMR and autism,

"The committee is aware that there might be some cases of rechallenge that could be assessed (Wakefield, 2001). If well-documented and reviewed by appropriate clinicians, these reports and similar data could provide evidence in favor, but not necessarily prove causality, of the hypothesized relationship in a small number of children."

-Source: 4/23/01 Report on MMR and Autism, p. 57.

ON THE SPECIFIC CONTRIBUTION OF WAKEFIELD'S CASE STUDIES

Dr. Wakefield presented the only case study information considered by the IOM ISR Committee for meeting #2 regarding the MMR vaccine and autism. Thus the consideration of such information was essential for the committee's deliberation. In this regard, individual case data were available for consideration.

Dr. Stratton: The part where it says at least in some individuals in some situations. That was allowing for that *truly wonderful idiosyncratic, well documented case report*. I think "can it" is still for the most part, answered by epidemiologic studies, or by a positive answer to the question "did it"? And "did it" is answered if you have a case report where it's just *very, very clear that the person got it*. So we clearly don't have any case report.

Dr. Shaywitz: The only thing you have is Wakefield's little slide with the red dots

Source: 3/10/01 closed door meeting transcripts
p.3, emphases added

ON THE SPECIFIC CONTRIBUTION OF WAKEFIELD'S CASE STUDIES

However, the exchange below makes it clear that the committee members requested more data on these studies.

Dr. Goodman: I actually have a problem with verified. I think that is a very loaded term. It's a coded word of saying everything else, Wakefield, anything we don't like is unverified.

Dr. Gatsonis: *Well, we need to say something. For instance, what are we going to do about the 11 challenge/rechallenge cases? Do we believe in it? It was evidence. It was published in some sense. Do we say published evidence?*

Dr. Goodman: Yes, I think published evidence.

Dr. Gatsonis: We also had unpublished things in our evidence.

Dr. Goodman: Yes, the Fombonne.

Dr. Foxman: He did have published reviews though.

Dr. Gatsonis: We need some words.

Dr. Medoff: Based on the available data. **Did Wakefield give us data?***

Source: 3/10/01 Closed Door transcript, p. 34, emphases added

This question was NOT answered by the committee officials (McCormick and Stratton), who had the authority and responsibility to request additional information.

THE COMMITTEE DEFAULTED ON ITS CONTRACTUAL ABILITY TO REVIEW ADDITIONAL INFORMATION

In an atypical review as specified by the contract:

- **The closed-door sessions were not required to be contiguous with public sessions**
- **Additional data regarding rechallenge cases could be requested prior to closed-door sessions**
- **Background papers could be commissioned on additional data**

Thus, the committee had the power and finances to review the Wakefield hypothesis in further detail but either

- **Chose not to, or**
- **Were led to believe by the leadership that they couldn't complete such a detailed review.**

SUMMARY: THE COMMITTEE CHANGED AND VIOLATED THE RULES OF EVIDENCE AND IGNORED RELEVANT EVIDENCE DURING ITS PROCEEDINGS

Changes in the rules of evidence, as set forth in their 1994 guidelines, were permitted

All committee findings were based on large scale epidemiology studies

The thimerosal controversy was addressed through consideration of only five flawed epidemiology papers, only one of which was conducted in the US and three of which were duplicative

Epidemiology studies supporting an association with thimerosal and autism were summarily rejected

Case study evidence was not considered

Committee leadership discouraged committee members from considering case study evidence and failed to pursue opportunities to make such evidence available to the committee

OVERVIEW OF PRESENTATION

The IOM Immunization Safety Review Committee (The Committee) had a clear charter, but its charter changed over time amidst conscious efforts to influence its findings

The Committee itself was skewed in composition, financially conflicted and biased

The Committee considered evidence of (flawed) epidemiology alone, ignored relevant evidence and precluded consideration of case study evidence entirely in its autism findings

The Committee changed the standard of proof in the vaccine safety review criteria from Biological Plausibility to Biological Mechanisms in order to favor an outcome that would fully reject any causation hypothesis

The Committee adjusted its agenda to serve the interests of its client, the CDC, an interested party in the controversy

The Committee displayed a pervasiveness in its private discussions to suppress relevant science

What about the biological assessment?*

*As per the original contract establishing the IOM ISR Committee

ACCEPTED METHODS FOR EVALUATING VACCINE SAFETY DATA

Biological Plausibility

Case Reports, Case Series and Uncontrolled Observational Studies

Controlled Observational Studies (Large clinical studies, epidemiological studies, etc.)

Source: IOM Report, “Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality,” Stratton et al. 1994

SUMMARY OF FINDINGS FROM 1994 IOM REPORT

TABLE 1-1 Summary of the Evidence For or Against a Determination of a Causal Relationa

Vaccine and Adverse Event	Biologic Plausibility ^b	Case Reports, Case Series, and Uncontrolled Observational Studies	Controlled Observational Studies and Controlled Clinical Trials
<i>Diphtheria and Tetanus Toxoids^c</i>			
Encephalopathy	Demonstrated	Indeterminate	Against (DT) No data (Td, T)
Infantile spasms ^d (DT only)	Theoretical only	No data	Against
Residual seizure disorders other than infantile spasms	Theoretical only	Indeterminate (DT, T) No data (Td)	No data
Demyelinating diseases of the central nervous system	Demonstrated	For	No data
Guillain-Barré syndrome	Demonstrated	For (T) Indeterminate (DT, Td)	No data
Mononeuropathy	Theoretical only	Indeterminate (T, Td)No data (DT)	No data
Brachial neuritis	Theoretical only	For (T) Indeterminate (Td) No data (DT)	No data

Source: Stratton et al. 1994, p. 6

This committee found that there was a causal relationship between the tetanus toxoid vaccination and Guillain-Barre syndrome, despite the lack of any controlled observational studies.

Thus, epidemiology is *not necessary* to prove a causal relationship.

THE ACCEPTED DEFINITION OF BIOLOGICAL PLAUSIBILITY, AT THE COMMITTEE'S START

“Biologic plausibility and coherence: The vaccine-adverse event association should be plausible and coherent with ***current knowledge*** about the biology of the vaccine and the adverse event. Such information includes experience with the naturally occurring infection against which the vaccine is given, particularly if the vaccine is a live attenuated virus. Animal experiments and in vitro studies can also provide biologic plausibility, either by demonstrating adverse events in other animals that are similar to the ones in humans or by indicating pathophysiologic mechanisms by which the adverse event might be caused by receipt of the Vaccine”

Source: Stratton et al., 1994 p. 22

YET THE COMMITTEE SWITCHED TO *BIOLOGICAL MECHANISMS* IN THE COMMITTEE REPORT, MEETING #3 2/2002 (FIRST MEETING POST-THIMEROSAL)

“The examination of experimental evidence for biological mechanisms has been referred to in previous reports of this committee (IOM, 2001a, 2001b) and others (IOM, 1991, 1994) as an assessment of ‘biological plausibility.’ The committee has noted, however, that the term is a source of confusion on at least two fronts. First, it is associated with a particular set of guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence; and second, readers sometimes regard the term with a degree of certainty or precision the committee never intended. For example, a relationship between immunization and a particular adverse event may be found to be biologically plausible at the same time that the epidemiological evidence is found to be inadequate to accept or reject a causal relationship.”

Given the resulting lack of clarity, the committee believes that the adoption of new terminology and a new approach to its discussions of experimental biological data are warranted. The committee will thus review evidence regarding ‘biological mechanisms’ that might be consistent with the proposed relationship between immunization and a given adverse event. This biological assessment section of the report is written distinct from any argument regarding the causality of such relationships. Beginning with this report, the committee will summarize the biological mechanisms as theoretical only, or as having derived from either experimental evidence in animals or *in vitro* systems or from mechanism-related, biological evidence in humans of response to vaccine or infectious disease antigen. If there is either experimental evidence (e.g., from animals) or evidence in humans for a mechanism, the committee will designate it as weak, moderate, or strong. Though the committee tends to judge biological evidence in humans to be ‘stronger’ than experimental evidence, the strength of the evidence also depends on other factors, such as experimental design and sample size. The conclusions drawn from this review will depend both on evidence and scientific judgment.”

Source: pp. 2-3, report executive summary, emphases added

WHY SWITCH FROM BIOLOGICAL PLAUSIBILITY TO BIOLOGICAL MECHANISMS?

Previous conclusions regarding thimerosal and neurodevelopmental disorders (NDDs),

- “The committee concludes that although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, *the hypothesis is biologically plausible.*” (Committee Report 10/1/01 regarding thimerosal and NDDs).

Possible concerns raised by the CDC contract representative after the 10/1/01 report was issued

Also, unlike those of autism, the biological mechanisms for the adverse events considered in the 2/2002 report (i.e. diseases involving immune dysfunction) were well known.

PARENT GROUPS PRAISED THE OCTOBER 2001 REPORT ON THIMEROSAL AND NDDS

“Safe Minds Applauds IOM Recommendations -- Asks for Recall of All Childhood Vaccines Containing Mercury”

“Safe Minds is pleased that the IOM report acknowledges the *biological plausibility* that mercury in vaccines is linked to neurological problems and that children should not be exposed to it in vaccines or any other product, but its recommendations do not go far enough,” said Sallie Bernard, executive director of Safe Minds. “We believe that no child should get any mercury-containing vaccines. We are renewing our call for the immediate removal of remaining stocks of childhood thimerosal-containing vaccines still on pharmaceutical and pharmacists shelves. In addition, we are asking that research be conducted into how to identify and repair mercury damage in children.”

“Safe Minds is pleased that the IOM Committee has recommended a comprehensive and ambitious research program to determine the role of thimerosal in neuro-developmental disorders,” said Mrs. Bernard. “This is what we have been asking for for over a year. Some of these studies are already happening as a result of Safe Minds' and other parent advocate's initiatives. But much more is needed, including a strong commitment from the NIH to fund extensive studies on this issue. We are calling for studies that include treatment for affected children as part of the comprehensive research agenda.”

-Source: SafeMinds press release, 10/01/01 (emphasis added)

THE SWITCH TO BIOLOGICAL MECHANISMS WAS LESS NOTABLE IN IMMUNE DYSFUNCTION COMMITTEE REPORT, 2/2002

Table 5 based on non-vaccine antigens known to produce same or similar autoimmune response considered as adverse events each with *defined mechanisms* (p. 83)

Thus, biological mechanisms for disorders considered in this meeting had been well established scientifically.

TABLE 5 Putative Examples of Molecular Mimicry in Human Autoimmune Disorders with Proposed Cross-Reactive Autoantigens and Infection-Derived Antigens

Disease	Organ/ Autoantigen	Infection/ Antigen	Cross reaction on:
Lyme arthritis	Joints/LFA-1	<i>Borrelia burgdorferi</i> / Osp A	T cells
Rheumatoid arthritis	Joints/Hsp60	Mycobacteria/ Hsp65	T cells
Multiple sclerosis	Brain/Myelin basic protein	Papillomavirus/ L2	T cells
Type I diabetes	Pancreatic β -cells/GAD	Coxsackie B/ P2-C	T cells
Stiff man syndrome	GABA-ergic neurons/GAD	hCMV/DNA binding protein	T cells
Primary biliary cirrhosis	Bile duct/pyrdeH complex	<i>E. coli</i> /PDC-E2	T cells
Rheumatoid arthritis	Joints/DRB1*0401	<i>E. coli</i> /DNAJ/ EBV/gp110	T cells/Antibody
Multiple sclerosis	Brain/Myelin basic protein	EBV/capsid	T cells/Antibody
Myocarditis	Heart/myosin	Chlamydia/60kD protein	T cells/Antibody
Rheumatic fever	Heart/cardiac myosin/heart valves/kidney/ CNS	Streptococci/ M protein b	Antibody
Chagas disease	Heart/B-1 adrenergic receptor	<i>Trypanosoma cruzi</i> /ribosomal protein	Antibody
Myasthenia gravis	Muscle/ acetylcholine receptor	Herpes simplex/gpD	Antibody
Guillain-Barré syndrome	Peripheral nerve gangliosides	<i>Campylobacter jejuni</i> LPS	Antibody

Source: Adapted from Marrack et al., 2001; Wucherpfennig, 2001

THE SWITCH FROM BIOLOGICAL PLAUSIBILITY TO BIOLOGICAL MECHANISMS WAS MORE CONSEQUENTIAL IN THE FINAL COMMITTEE REPORT, 5/16/04

Basis Change:

“Given the resulting lack of clarity, the committee adopted a new terminology and a new approach to its discussions of experimental biological data in its third report (IOM, 2002). The committee now reviews evidence regarding “*biological mechanisms*” that might be consistent with the proposed relationship between immunization and a given adverse event. The biological mechanism evidence reviewed in this report comes from human, animal, and *in vitro* studies of biological or pathophysiological processes” (

Source: Committee Report #9, 5/16/04, Executive summary, p. 2

Rather than evaluating that a hypothesis is plausible (*which was the charter mandated by initial contract*), the exposure must now be found to be mechanistically consistent with the adverse event (i.e., autism)

This is an impossibly high standard of proof to meet if the mechanisms of the adverse event are unclear (e.g., autism, ADHD, etc.)

FURTHER NOTES ON THE SHIFT FROM BIOLOGICAL PLAUSIBILITY TO BIOLOGICAL MECHANISMS IN THE FINAL COMMITTEE REPORT, 5/16/04

The Committee acted without precedent

- **No peer reviewed publications or policy literature provides any standard for defining vaccine adverse events in terms of their invention: “biological mechanisms.”**

In the absence of established biological mechanisms for autism, the committee consciously restricted its potential findings for proposed mechanisms linking vaccine exposures and an adverse event leading to autism

- **any positive finding would necessarily be “theoretical only”**

Nowhere is the reasoning for this change made transparent or its implications for the legitimacy of the review process considered

- **the best available explanation for the change was that The Committee leadership had a deliberate intent to produce findings favorable to its client, the CDC**

THE INFORMATION PROVIDED TO THE COMMITTEE BY THE PROJECT OFFICERS WAS NOT REPRESENTATIVE OF THE RELEVANT LITERATURE ON THIMEROSAL TOXICITY

Biological mechanisms for thimerosal toxicity were inferred based on analogies with methylmercury due to *incomplete science* on thimerosal containing vaccines and neurodevelopmental disorders (Committee Report, “Autism and Vaccines,” 5/16/04, p. 8)

What was the body of science examined? 34 publications related to thimerosal cited in the 5/16/04 IOM ISR Committee report

What is the body of science available? Over 7000 publications based on the 1/19/99 email exchange between Fredrick Varricchio and Leslie Ball of the FDA

From: Varricchio, Frederick
Sent: Tuesday, January 19, 1999 5:31 PM
To: Ball, Leslie
Subject: RE:

Our plan is to get whatever is on the summary for every 100th report. We should have that in a couple of days. I'll let you know when it is here and we can see what to do next.

-----Original Message-----
From: Ball, Leslie
Sent: Thursday, January 07, 1999 11:10 AM
To: Varricchio, Frederick
Cc: Pratt, Douglas R.; Ball, Robert
Subject: RE:

Fred:

Are there 7000 reports just for immune globulins and other biologics? Drugs have been excluded? If there are really 7000 reports for biologics, perhaps you can get records on a subset of 50 or so we can look at them and get a general feel for what's been reported before we go any further. I'll be out of the office for Dr. Hardegrees party until 1:30 or 2 today, or I can discuss it with you tomorrow after 1 pm.

Leslie

-----Original Message-----
From: Varricchio, Frederick
Sent: Thursday, January 07, 1999 10:17 AM
To: Ball, Leslie
Subject:

I HAVE SOME RESULTS FOR YOU. pROBLEM IS THAT THERE ARE 7000 REPORTS THAT MENTION THIMERASOL. WHAT TO DO NOW. OBVIOUSLY LOOKING AT ALL 7000 IS A BRUTE FORCE APPROACH

frederick varricchio

Thus, the Committee (with no toxicologist members) reviewed less than 0.5% of the relevant literature on thimerosal.

THE CHANGE TO BIOLOGICAL MECHANISMS HAD THE EXPECTED EFFECT ON CONCLUSIONS IN THE FINAL COMMITTEE REPORT ON VACCINES AND AUTISM

Biological *Mechanisms* recommendation...

“In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.” Source: Committee 5/16/04 Report, p. 8).

And, since Biological *Mechanisms* are not yet understood...

“Research should be directed towards better understanding the etiology or etiologies of autism [i.e., cause of the disease, added] and on treatments for autism.”

Source: *ibid.*, p. 9

Thus, any experimental evidence supporting the vaccination/autism hypotheses were considered theoretical only and rejected as material evidence.

SUMMARY: THE COMMITTEE RAISED THE STANDARD OF PROOF FROM BIOLOGICAL PLAUSIBILITY TO BIOLOGICAL MECHANISMS

Biological plausibility has long been the standard for assessing hypothesized vaccine adverse events

The Committee began its deliberations using this clear standard of proof

The Committee chose to change its standards immediately subsequent to issuance of its report on thimerosal and NDDs

There was no public discussion, recognition or authorization of this unilateral change

The change in standards had material consequences on subsequent findings

Raising its standard of proof strongly suggests that Committee leadership sought to influence the likely outcome of future reports rather than comply with its original charter as an unbiased review body

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AGENDA MANAGEMENT: THE CONTRASTS BETWEEN AN IMPARTIAL JUDICIAL BODY AND THE COMMITTEE'S PRACTICES

Docket management in a court of law	Management of The Committee's agenda
Funding for court is independent of parties to a dispute	The CDC funded The Committee as a client of the IOM
Standing body	Three year term, but with a specific extension for Vaccines and Autism topic
Clear criteria for convening hearings and trials	Committee agenda set at the discretion of a single interested party
Opportunity for appeal based on judicial misconduct	No recourse for aggrieved parties
Timing of hearings independent of evidence	Final meeting timed to coincide with publication of a handful of epidemiology studies on thimerosal

THE CHARGE TO THE INSTITUTE OF MEDICINE IMMUNIZATION SAFETY REVIEW COMMITTEE

Established in 2000 based on an interagency agreement (IAA) from the CDC through the NIH (obtained by FOIA)

Committee was charged to look at *up to three* vaccine safety hypotheses each year put forward by the DHHS Interagency Vaccine Group over a period of three years:

- CDC (NIP and NCID)
- NIH (NIAID)
- NVICP
- FDA
- Center for Medicare and Medicaid Services

THE CDC FUNDED THE PROJECT AND PAID \$2 MILLION TO SUPPORT THE COMMITTEE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control and Prevention
INTER/INTRA-AGENCY AGREEMENT (IAA)
Payable Agreements (CDC is Procuring Agency)

1. CDC IAA #: (10 to 13 digits) 00FED17358	2. PARTICIPATING AGENCY IAA #: Y3-AI-0488-01	3. TYPE OF AGREEMENT <input checked="" type="radio"/> New <input type="radio"/> Modification <input type="radio"/> Administrative Modification Number:
4. TITLE OF PROJECT: Vaccine Safety Review Panel		
5. DESCRIPTION OF WORK: (Please attach) see attached	6. AMOUNT: (Not to exceed without written modification) \$2,043,000.00	
7. NAME AND ADDRESS OF PARTICIPATING FEDERAL AGENCY: National Institute of Health 6700-B Rockledge Drive MSC-7600, Room 1131 Bethesda, MD. 20892-7600	LIAISON NAME: Keith Lamirande EMAIL ADDRESS: KLAMIRANDE@nih.gov	PHONE #: (301) 496-7151 FAX #: (301) 402-0520
8. NAME AND ADDRESS OF CDC, CENTER, INSTITUTE OR OFFICE: Centers for Disease Control and Prevention National Immunization Program 1600 Clifton Road, MS E-61 Atlanta, Ga. 30333	LIAISON NAME: Shelia Jones EMAIL ADDRESS: clj1@cdc.gov	PHONE #: (404) 639-8766 FAX #: (404) 639-8616

CDC'S ROLE IN CONTROLLING MEETING TOPICS AND TIMING

Dr. Berg: ...I am interested in the general methodology that this panel is going to use. This may be our only chance, I understand, to talk about methodology. What general methods are we going to prune the tree. How are we going to decide that issue X is more worthy of our time than issue Y.

Dr. Stratton: Actually, you don't have to make that decision. We don't have to make that decision. CDC will tell us which topic we will address when.

Dr. Johnston: That is news to me.

Source: 1/12/01 closed door meeting transcript, p. 50

CDC'S ROLE IN CONTROLLING MEETING TOPICS AND TIMING

Dr. Stratton: All of the sudden, Jeff Copeland and Walt Orenstein and the Surgeon General and everybody is (sic) being beat (sic) over the heads and they need to try to resolve something.

We don't have to make that decision. *Whether we like it or not* - - and there are pros and cons of letting them determine the topic – to be expedient, it is better that they determine it.

Dr. Medoff: *They* are paying for it.

Dr. Stratton: A lot of times we don't actually care about that, within reason. This is a case where it was decided that their need for what to be addressed next was primary. We probably could object if we thought something was totally ridiculous, and we can shape it a little. We have -- you know, what are the boundaries. Does that make you feel any better?

Dr. Berg: Now I am curious what other parts of the methods the CDC has figured out for us.

Dr. Stratton: None.

Dr. Berg: Thank you

Source: 1/12/01 Transcript, pp. 51-52 (emphases added)

MEETING #9: THE CDC AND COMMITTEE PROJECT OFFICERS' PLAN TO REJECT CAUSAL LINKS BETWEEN AUTISM AND VACCINES

By contract, the IOM ISR Committee project officers and the CDC met within 30 days of Meeting #8 (i.e. by April 12, 2004 as per the Contract Statement of Work, p. 3) in order to determine the topic of the next meeting (i.e., meeting #9).

For strategic reasons, the topic for meeting #9 topic was limited to autism only

- *Inclusion of other neurodevelopmental disabilities would negate the committee's ability to summarily reject causation based on epidemiology:*
 - The Verstraeten et al. 2003 publication (then manuscript submitted on 1/24/03) constituting the final version of the CDC's epidemiological study of neurodevelopmental disorders showed a statistically significant relationships between thimerosal exposure and both tics and language delays, *but not autism*.
 - Results of the Miller study (initiated in 2001) like the Verstraeten et al. 2003 publication showed increased risk of tics with increasing thimerosal exposure, *but not of autism*, within the UK cohort.
 - All other epidemiological studies showing negative associations with thimerosal in vaccines (Madsen et al. 2003, Hviid et al. 2003 and Stehr-Green et al. 2003) *were limited to autism*.

MEETING #9: THE CDC AND COMMITTEE PROJECT OFFICERS' PLAN TO REJECT CAUSAL LINKS BETWEEN AUTISM AND VACCINES (2)

- *Any biological mechanisms related to vaccine adverse events hypotheses would be rejected as theoretical only.*
 - The committee changed the basis from biological plausibility (meetings 2 and 3) to biological mechanisms (meetings 4 through 9).
 - Also, unlike those of autism, the biological mechanisms for the adverse events considered in meeting 4 (i.e. diseases involving immune dysfunction) were well known.
 - The biological mechanisms of autism were the most poorly understood of the vaccine adverse conditions examined over the course of the committee.
 - Thus, any proposed hypothesis regardless of the quality and consistency of the elucidated science would be by definition, theoretical.
- *All case information regarding autism-vaccine adverse events had been severely edited by The Committee's project officers:*
 - Dr. Marie McCormick's dismissal of case studies from Barbara Loe Fisher (1/12/01 closed door meeting transcripts, p. 149-150)
 - The lack of further pursuit of case data from Dr. Andrew Wakefield by the project officers despite the requests of ISR Committee members as evidenced in the discussion on p. 34 of the 3/10/01 closed door meeting transcripts.
 - The omission of Dr. Andrew Wakefield (among other scientists) from the agenda of meeting #9. Several scientists notably absent from this meeting (Wakefield, James, Deth, Neubrandner, etc.) possessed relevant case study data.

SUMMARY: THE COMMITTEE ADJUSTED ITS AGENDA TO SERVE THE INTERESTS OF THE CDC, AN INTERESTED PARTY IN THE CONTROVERSY

The CDC was the funding agency for The Committee

Committee leadership discussed the CDC more as a client than as an interested party to a dispute

Committee members expressed concern over CDC's influence over their deliberations

The CDC requested an extension of The Committee's tenure and charter to deal specifically with the topic Vaccine and Autism

The timing of this request coincided with the simultaneous publication of several epidemiology studies on thimerosal and autism

The management of The Committee's agenda was clearly manipulated by the CDC to achieve policy goals rather than an objective and thorough review of a scientific controversy

The role of the IOM as an impartial panel of scientific experts was clearly compromised and designed to serve a specific agency of the government rather than the public interest

OVERVIEW OF PRESENTATION

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EVIDENCE OF PERVASIVE BIAS

Ad hominem attacks on Dr. Wakefield and others

Consistent advocacy by Committee leadership to reject causal arguments

Further committee bias toward unscientific positions: deliberate vagueness and concern over public debate

Inappropriate CDC influence on deliberations

Pervasive CDC advocacy against autism-vaccine hypotheses accepted without criticism

Ad hominem attacks on Dr. Wakefield and others

AD HOMINEM ATTACKS ON WAKEFIELD

Referrals to Dr. Wakefield setting a “trap” and forging a “strategy,” rather than a discussion of the findings of Wakefield, showing clearly an adversarial stance by the ISR Committee

Ms. Davis-Anthony: I'm really concerned about leaving that door open with a second question of biological plausibility. Because when I was listening to Wakefield, he went out of his way to say that he did not have any population-based hypothesis. He only had an individual hypothesis. That was his way of trying to get out of even considering the epidemiological data, which we have no choice in that, because that's why we are here.

On the other hand, if we then fall into *his trap* of confirming or not confirming, or *allowing his biologic plausibility, only based on what he said, not on data that he presented*, our report will focus on that piece, which will force a generalized response to the report on that little door that is opened that will impact what we care most about, is a misinterpretation of what we said by believing that there is this set of people that this really does damage. And we can't say that, because the evidence was not presented.

And that seems to me *that's his strategy, just to leave this little door open, then everybody is going to rush to that little door, and decide that our major decision is really not valid*, because there are these people — we don't know how many of these people there really are out there. So then we have been falling into *the trap that he has set for us* by saying, well, I can't look to the epidemiological data, because there are these individual cases.

So that's my concern. I would want to have it a three, because I really don't think that he presented enough data. Plus, if we are going to talk about those kinds of issues with autism, that's not certain to me, with most us. That goes to the Academy of Pediatrics or somebody who is really looking at everything that impacts autism. How can we just look at the enteric relationship of autism and the brain, when I know there is a lot more to autism than that, to raise that to the top of somebody's research agenda for autism

Source: 3/10/01 closed door meeting transcripts, pp. 37-38, emphases added.

AD HOMINEM ATTACKS ON WAKEFIELD

Inference regarding assumed bias of Wakefield to not “want to understand it,” i.e., any relationship between MMR and autism.

Dr. Goodman: Actually, I wouldn't even say that they have latched onto one. I think some of them were acknowledging that it's been mentioned that they wanted to get away from Wakefield. They want to really understand it.

Source: 3/10/01 closed door meeting transcripts p. 65.

From the committee chair, reduction of the concern around MMR and autism to “vocal parental groups, a fairly mediagenic scientific advocate (Wakefield), and a congressional concern (presumably Rep. Dan Burton)”, which she would conceal in the final report.

Dr. McCormick: Get conclusions out of there. We recommend that they give continued attention to this linkage, because one, it's the seriousness of the natural disease, measles, mumps, and rubella, and the seriousness of the putative adverse outcomes. The salience of the issue and significance of public concern. We had sort of in shorthand said the significance of public concern reflected vocal parental groups, *a fairly mediagenic scientific advocate*, and congressional concern, although we're not going to put that in any text

Source *ibid.*, p. 100, emphases added.

DR. MCCORMICK'S DISMISSAL OF CONCERN BASED ON AN UNPROFESSIONAL ATTITUDE TOWARDS WAKEFIELD, REP. DAN BURTON AND "VOCAL" PARENT GROUPS

Dr. McCormick: It's how far up on its radar screen should this be? Is this a significant problem that they should pay some attention to? And how do we decide that? *Might your criteria involve media savvy advocate like Andrew Wakefield, and have congressional pressure, which is Dave Burton?*

Source: 3/9/2001 closed-door meeting transcripts, p. 78, italics added

Dr. McCormick: *We know there is a very mediagenic advocate who is out there, Andrew Wakefield. We know there is congressional concern, whatever the logic of its basis.*

Source: *ibid.*, p. 131, italics added

Dr. McCormick: *We've got a number of pressures from vocal groups and the mediagenic Wakefield and congressional pressure.*

Source: *ibid.*, p. 133, italics added

THE ONLY IMMUNOLOGIST ON THE COMMITTEE WEIGHS IN, IN ABSENTIA: CHRIS WILSON'S REVIEW OF WAKEFIELD'S WORK

CHRISTOPHER B. WILSON, M.D., Professor and Chair, Department of Immunology, University of Washington. Dr. Wilson conducted an independent review of Wakefield's hypotheses and research to date for the rest of the committee. Here are quotations from that review:

"In summary, I find the epidemiology data argue against an association between the rise in the prevalence of autism and MMR vaccine. However, the evidence is not sufficient to refute such an association."

"Since the argument that MMR is linked to autism is substantially founded on these (i.e., Wakefield's) findings, I believe the committee should recommend that studies seeking to replicate these findings should be commissioned. It is my view that until this evidence is obtained in a convincing manner from two or more groups of unbiased, careful and qualified investigators, we will have to conclude that evidence sufficient to reject this hypothesis is lacking."

Source: Wilson review, p. 1 emphasis added

Dr. Wilson was absent at the closed door meetings 3/9/01 and 3/10/01 to discuss the findings of Wakefield; in addition, Dr. Wilson's review was not provided for consideration by The Committee prior to its deliberations.

DR. COHEN AND DR. MEDOFF DISCUSS WAKEFIELD'S HYPOTHESIS

Dr. Medoff: If he does find antigen, and his PCRs are positive, then that makes it biologically plausible.

Source: closed-door meeting transcripts, 3/9/01, p. 93

Dr. Cohen: I just think it's real important that we make it very clear that in fact we haven't really been asked one question in this case. We are not dealing with monolithic autism. *I mean suppose that Andrew Wakefield next month comes back with great PCR data, and then fills in a bunch of other blanks in everything, and it's like wow, this looks really biologically plausible.*

Source: *ibid.*, p. 89

After this meeting, Dr. Wakefield was able to isolate antigen as well as confirm via PCR that the measles strains in the intestinal nodules of patients were of the same vaccine strain given in the MMR (Uhlmann et al. 2002, Mol Pathol. 2002 55:84). The statements of Dr. Medoff and Dr. Cohen above would suggest that such information should have been obtained by the project officers.

NOTABLE ABSENCES REINFORCED THE COMMITTEE'S BIASES TOWARDS PERSONAL OVER SCIENTIFIC JUDGMENTS

Despite a growing body of information regarding the clinical relationship between MMR exposure and autism, Dr. Wakefield was not invited to the final Committee Meeting on Autism and Vaccinations (2/9/04), nor is there evidence that The Committee attempted to obtain his relevant case information.

Regarding the final study on Autism and Vaccines, Chris Wilson and Gerald Medoff were “unable to attend the meeting on the topic of this report.” (p. v, IOM Report, “Vaccines and Autism,” 5/16/04)

The absence of Wilson and Medoff excluded the only immunologist and internist on The Committee thereby skewing The Committee's composition towards its public health membership (5 out of 11).

In light of the centrality of immunological hypotheses between vaccine adverse events and autism presented at the Committee Open Meeting (2/9/04), these were material absences

Dr. Stratton's consistent advocacy for rejection of causality claims "no matter what"

ATTEMPTS BY DR. STRATTON TO SWAY THE COMMITTEE REGARDING BIOLOGIC PLAUSIBILITY

Dr. Kaback: There is the issue about the trigger. There is this issue about MMR being the trigger.

Dr. Stratton: No, I know, but there are many cases that clearly start before.

Dr. Kaback: Before MMR.

Dr. Stratton: *And so of course it can't cause 95 percent of those.* But there are some cases still unexplained that potentially could be affected in some way by MMR.

Dr. Kaback: But if we looked at some of the data - now again, I agree with you based on the blood spots, based on the videos, which I think very much speaks to that. But the peak age for childhood autism is around 18 months of age. And that is also around the time that MMR, at least in the US, is given.

Source: 3/9/01 closed-door meeting transcripts, pp. 104-5, (emphasis added).

ATTEMPTS BY DR. STRATTON TO SWAY THE COMMITTEE REGARDING BIOLOGIC PLAUSIBILITY (2)

Dr. Stratton: My only point in talking about that was just to make sure that Gerry knew that *I wasn't absolutely putting any credence to a Wakefield syndrome. But 95 or 98 percent of autism, at least that we know, MMR has nothing to do with. And of the residual cases of autism that's all we are dealing with.*

Source: 3/10/01 Closed-door meeting transcripts p. 105, (emphases added)

Dr. Stratton uses hyperbole (i.e., up to 98% of autism cases are not regressive) in order to minimize the impact of a putative MMR-based adverse event. The existence of a significant proportion of regressive autism cases has now been confirmed (Dawson et al. 2005 Arch Gen Psychiatry 562:889).

ATTEMPTS BY DR. STRATTON TO SWAY THE COMMITTEE: *HER JUSTIFICATION FOR LYING TO THE PUBLIC*

Dr. Stratton: I think that as Alicia just point (sic) out is I think when CDC was thinking about significance and we were thinking about, it's more is this such a concern, and the risk of putting it rest (sic), or not putting it to rest does not relate to a recommendation to change the schedule, *but parent decisions and actions to vaccinate or not vaccinate.*

So I think it is not would there be a policy recommendation about it, but do we have reason to believe, or is even a theoretical concern that this is not put to rest. And more and more parents are going to follow this, and get involved, and stop getting immunized, therefore the risk of disease will go up. So it's not a policy recommendation that would lead to measles going up, but the true on the street worry about this. *And is there a benefit to putting to rest no matter what?*

Source: 3/9/2001 Closed-Door Meeting Transcripts,
pp. 120-1 (emphases added).

Stratton suggests that the committee might put to rest the MMR-autism vaccine hypothesis based solely on (unsubstantiated) fears over drops in vaccination coverage, regardless of any plausibility finding.

PARENT GROUPS PRIVATELY PROTESTED DR. MCCORMICK'S BIAS IN PUBLIC DISCUSSIONS OF COMMITTEE REPORTS

“Dear Dr. Shine

“We at SafeMinds would like to express our support for the detailed and thoughtful report prepared by the IOM Immunization Safety Review Committee entitled "Thimerosal-Containing Vaccines and Neurodevelopmental Disorders" (NDDs). At the same time, we are writing to you specifically to express our concern over a pervasive pattern of misrepresentation displayed by the committee chairperson, Dr. Marie McCormick, in the press conference announcing the report. Taken individually, these misrepresentations speak poorly of Dr. McCormick's ability to represent the committee's findings. Taken together, they call into question Dr. McCormick's fitness to serve in the position of Chair of the Immunization Safety Review Committee.

“We have a transcript of the press conference announcing the report's findings on October 1. In the space of a half hour, we noted at least eleven separate misrepresentations...”

-Source: SafeMinds private letter to Kenneth
Shine MD, President of the IOM
October 23, 2001

Further evidence of Committee bias

EVIDENCE OF COMMITTEE BIAS: *JUSTIFICATION FOR VAGUENESS*

Dr. Medoff: If I put myself back then in that situation, without knowing what the cause is, it gives some credibility to some of the correlations and associations. You are on less firm ground in dealing with associations that the parents are making. *You can't exclude it.* When you have a definite disease with a definite etiology, we can say with all the confidence in the world, Mrs. Smith, that has nothing to do with what happened to your child, absolutely zero.

Dr. Kaback: That's right, but before that disease is identified and known and characterized and you can give that information. When it's still an unknown situation

Dr. Medoff: When I am dealing with something I know very little about, and somebody raises a question to me about is it possible that the apple that I ate three weeks ago caused - and if I don't know what's going on, I usually don't say to the person, absolutely not. That's a silly notion. *You sort of talk around it.*

Source: 3/9/2001 Closed-door meeting transcripts,
pp.110-1.

EVIDENCE OF COMMITTEE BIAS: *CONCERN OVER OPEN WINDOWS AND LOOP HOLES*

Dr. McCormick: No, because I want to push us on this. Because if we are going to call the biological plausibility two minus, *then we have left this window open*. And so I think we've got to carefully examine the issue of how firm we think this biologic plausibility is. We have heard one biologic model presented, which is fragmentary, preliminary, however you want to describe it. But it certainly isn't a well developed biologic model by any stream.

-Source: closed door transcripts, 3/10/01, p.11(emphasis added)

Dr. Shaywitz: Well, I think that that is really dangerous. I'm sorry to say that, Dick. I like Gerry's statement initially that just leave it, just lump it together. I think the easiest thing for us to do is say it's two minus. Our children and grandchildren are going to get immunized even if there is only monovalent, that was the only thing available.

But it's irrelevant to us personally, but I think that responsibility to the 4 million children born each year, we are really be (*sic*) irresponsible to leave the loop hole of there is that possibility. Well, there is always a possibility

-Source *ibid.* p. 39 (emphasis added).

Inappropriate CDC influence

FOREGONE CONCLUSIONS: DID THE CDC PREDETERMINE OUTCOMES OF COMMITTEE MEETINGS?

Dr. McCormick: ...[CDC] wants us to declare, well, these things are pretty safe on a population basis

Source: 1/12/01 closed door meeting transcript, p. 33

Dr. Stratton: ...The point of no return, the line we will not cross in public policy is pull the vaccine, change the schedule.

We could say it is time to revisit this, but we would never recommend that level. Even recommending research is recommendations for policy.

We wouldn't say compensate, we wouldn't say pull the vaccine, we wouldn't say stop the program.

Source: *ibid.*, p. 74

Dr. McCormick: ...we are not ever going to come down that [autism] is a true side effect...

Source: *ibid.*, p. 97

EXCHANGE IN THE 3/10/01 MEETING REGARDING THE CDC'S MANDATE

Dr. Parkin: Is [CDC] asking us to look at it on a population scale?

Dr. McCormick: No, [CDC]'s asking the question of causality.

Dr. Parkin: Yes, but I'm still asking the question of what is [CDC's] perspective of the level of causality? An agency deals with it on a population scale, individuals deal with it on a biological level.

Dr. Shaywitz: I would argue for just saying the evidence, and just saying the basis of the decision is. I mean you can qualify everything you want, but I think we have to have a strong topic sentence. And I think that you run the risk of not everybody understanding what we mean by epidemiologic, population-based.

Dr. Goodman: We also run the risk of not everybody understanding what the word "unqualified" evidence means either.

Dr. Medoff: I just want to understand what the argument that I'm hearing is. Do you want to take out "epidemiologic" in the top statement?

Dr. Shaywitz: Yes, I want to take out epidemiologic in the top statement.

Source: 3/10/01 closed door meeting transcript, p. 80

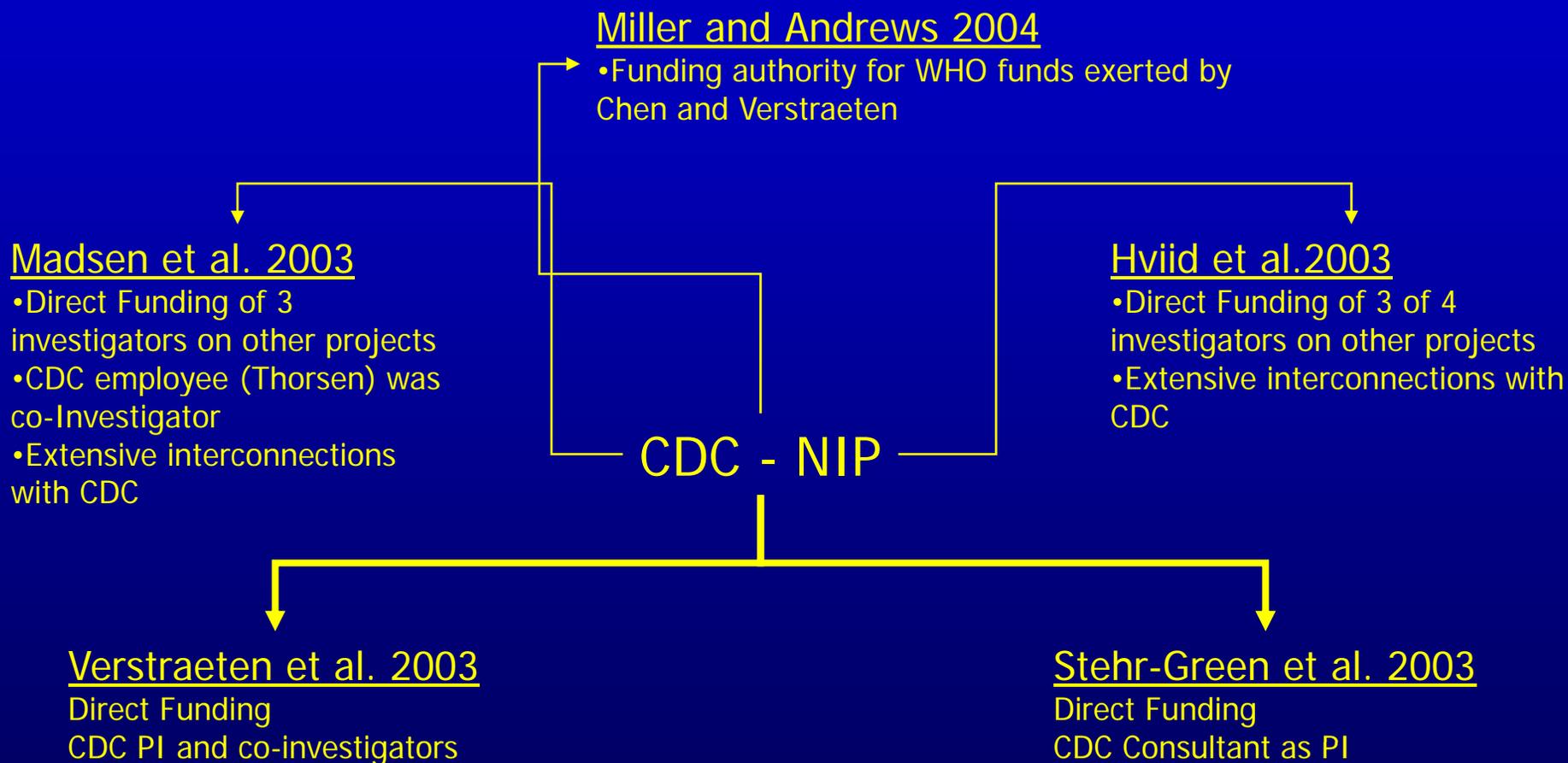
CONTINUED EXCHANGE IN THE SECOND MEETING REGARDING THE CDC'S MANDATE

Dr. Medoff: You just want us to say the evidence favors rejection of the hypothesis?

Dr. McCormick: Yes, that's what *they* want to say. (italics added)

Source: 3/10/01 closed door meeting transcript, p. 81

THE CDC HAD MONETARY CONNECTIONS TO 5 EPIDEMIOLOGICAL STUDIES AROUND THIMEROSAL



CONCLUSIONS

Epidemiological studies are not necessary to determine a causal relationship between an adverse event and particular vaccination (Stratton et al. 1994)

Epidemiology, when considered alone, is insufficient to determine causality (ibid.)

Change of basis from “biological plausibility” to “biological mechanisms” was inappropriate for autism as an adverse effect since biological mechanisms (i.e., etiology) of this disorder are poorly understood (IOM VSR Committee 5/18/04 report).

Relevant case studies of autism as related to vaccines were not provided and in most cases inappropriately dismissed (e.g., 1/12/01 and 3/10/2001 closed door meeting transcripts and omission of Wakefield from the final open meeting).

A pervasive bias was apparent in The Committee to reject causal relationships between vaccines and autism (rather than rule that the evidence was insufficient) based on policy issues rather than the available science (e.g., 1/12/01 and 3/10/01 closed door meeting transcripts, among numerous other citations).

The CDC and the IOM ISR Project Officers exerted inappropriate influence on the IOM ISR Committee in order to assure that a causal relationship between vaccines and autism would be rejected.