Respondent's Exhibit O

EXPERT REPORT OF STEVEN N. GOODMAN, M.D., M.H.S, Ph.D.

Introduction

In this report, I will provide my evaluation of the current epidemiologic evidence pertaining to thimerosal-containing vaccines and the development of autistic disorders in children. I will also comment on the reasoning and conclusions presented in the report of petitioners' expert witness, Dr. Sander Greenland. My opinions are summarized as follows:

- There is no extant evidence in humans that thimerosal, or mercury exposure in general, can or does cause autistic disorder in children.

- The totality of the current epidemiologic evidence strongly supports the conclusion that thimerosal-containing vaccines are not related to the development of autistic disorder.

- The claim that the epidemiologic evidence does not apply to a rare subtype of autism requires a biologic explanation as to why this particular form of autism might be caused by thimerosal exposure when more common forms of autism are not, i.e. that there are different forms of autism that have different causal determinants. In the absence of such evidence or a scientifically reliable explanation in support, such a claim is mere speculation.

Qualifications

I am experienced in the science, theory, and facts surrounding this particular question, by virtue of my medical training as a pediatrician, subsequent training and experience as an epidemiologist and biostatistician, my widely recognized expertise on inference and evidence synthesis, and as a former member of the Institute of Medicine ("IOM") Committee on

Immunization Safety that, in 2001 and 2004, reviewed, in two separate reports, the evidence relating to thimerosal-containing vaccines and autism. The details of my background are as follows.

1. I am an Associate Professor in the Department of Oncology at the Johns Hopkins School of Medicine, with joint appointments in Epidemiology, Biostatistics, and Pediatrics. I am currently acting director of the Division of Oncology/Biostatistics.

2. I received an AB in Biochemistry from Harvard College (1976), an M.D. from New York University School of Medicine (1981), and completed a three year residency in Pediatrics at St. Louis Children's Hospital, Washington University (1984) and was board-certified in Pediatrics in 1986. I received a M.H.S. in Biostatistics and a Ph.D. in Epidemiology at the Johns Hopkins School of Public Health in 1989. After completing my Ph.D., I joined the faculty of Johns Hopkins School of Medicine, where I remain today. In addition to my joint appointments, I am a faculty member in the Johns Hopkins Berman Bioethics Institute, the Center for Clinical Trials, chair the Epidemiology department's curriculum committee and am co-director of the doctoral program in Epidemiology.

3. I am the author of more than 100 scientific papers, scholarly reviews, and book chapters covering a broad range of topics, including basic scientific research, evidence synthesis, epidemiology, and inferential, methodological, and ethical issues in epidemiology and clinical research.

4. Much of my professional career has been devoted to the evaluation and synthesis of complex bodies of epidemiologic and experimental evidence, and this expertise has been widely recognized by respected national bodies, as evidenced in my activities as:

4.1. Editor of the journal *Clinical Trials: Journal of the Society for Clinical Trials*, since 2004.

4.2. Senior Statistical Editor for *Annals of Internal Medicine,* one of the world's premier medical journals, since 1987.

4.3. First author of the "Causal Criteria" chapter in the US Surgeon General's 2004 report on "Smoking and Health," which set forth the principles of causal reasoning and evidential standards to be used in that assessment.

4.4. I am the Scientific advisor and Medical Advisory Panel member for the national Blue Cross-Blue Shield Technology Assessment Program.

4.5. Member of the Medicare Coverage Advisory Commission (2001-2004)

4.6. Member of numerous committees and panels of the Institute of Medicine, US National Academy of Sciences, including:

- Veterans and Agent Orange (1998)
- Immunization Safety Review (2001-2004)
- Treatment of Post-traumatic Stress Disorder in Veterans (2007)

5. In addition to the above, I write and teach extensively at the Johns Hopkins Bloomberg School of Public Health in meta-analysis and evidence synthesis, clinical and epidemiologic research methods, and inferential principles.

6. I have served as an investigator on many grants and contracts from a wide variety of research agencies and foundations, including the National Cancer Institute, the Agency for Health Research and Quality (AHRQ), Centers for Disease Control and Prevention, the National Library of Medicine, and others.

7. I have not heretofore served as an expert witness in any litigation related to mercury or thimerosal and autism.

Introduction

There are two main categories of evidence underlying the conclusion that thimerosal exposure and autism are unrelated. The first category is empirical evidence based primarily on epidemiologic studies in human subjects that have examined the purported association, as well as related evidence in populations that have been exposed to high levels of mercury. The second category is biological or mechanistic evidence relating to the underlying processes, pathophysiology, neurobiology and genetic concomitants of autism. The latter evidence often comes from the laboratory or from intensive investigations in relatively small numbers of autistic subjects. This report will focus mainly on the epidemiologic evidence, but proper epidemiologic inference typically rests on a foundation of biologic understanding. Although sometimes not readily apparent on the surface, the role of a biologic explanation or mechanistic reasoning in an epidemiologic study appears in how questions are framed, how diseases are defined, what

measurements are taken, how analyses are done, and how observations are grouped and interpreted. It is a mistake to look at any epidemiologic study or finding in purely statistical terms; the evidence is properly viewed as a combination of empirical evidence guided by biologic understanding.

A particularly well known example of the way in which statistical results that are uninformed by biology can be misleading was shown in a paper published in the 1980s in *The Lancet*. Epidemiologist Richard Peto described in this paper the findings of a very large randomized trial of a drug for the treatment of myocardial infarctions. He observed an overall mortality reduction of 30% ($p < 0.004$), but then broke the results down by astrological sign. In that analysis he observed a significant 71% reduction among those patients born under the astrological sign of Leo, and nonsignificant effects within each of the remaining eleven astrological birth signs [ISIS-1 Collaborative Group, 1986]. In a subsequent study, a treatment effect was seen overall ($p<0.0001$), but not in patients born under the signs of Gemini or Libra ($p>0.5$) [ISIS-2 Collaborative Group, 1988].

The point of this analysis was not to demonstrate that astrologic signs affect people's medical fates, but rather the opposite. Peto wanted to show that if one claims that an effect in a particular subgroup is different from that seen in the whole population, then that claim must be based on legitimate biologic distinctions between persons in that subgroup and the rest of the population. The fact that astrologic signs are scientifically invalid risk predictors is not found in the statistics per se, but rather in the lack of any plausible biologic mechanism by which astrologic signs could influence treatment efficacy.

Dr. Greenland's Expert Report

This same principle applies to the reasoning used by Dr. Greenland in his report. He does not contest the evidence of the many epidemiologic studies that show no causal relationship between thimerosal exposure and autism in general. In fact, he states, "The brief overview given above [n.b. of all epidemiologic studies] supports the idea that the association of MCV [mercury containing vaccines] with autism is small or nonexistent." Instead, he contends that this evidence does not apply in the petitioners' case, or more generally, to all subjects who have regressive autism, or who have an even rarer subtype that he terms "clearly regressive autism." While the explanation is fairly extensive, Dr. Greenland's argument can be distilled down to one sentence: the regressive autism phenotype is too rare for an elevated risk to be detected in studies of autism that do not separate out the regressive autism subgroup. It is critical to note that Dr. Greenland never actually claims that thimerosal is related to regressive autism; he is quite careful in every instance to state that "if" they are related, the extant studies cannot disprove that relationship. But he is completely silent on the actual likelihood of that relationship. I will show here why, even granting the narrow technical correctness of his arguments, the hypothesis that thimerosal raises the risk of regressive autism has even less scientific standing than Peto's astrological predictors.

On a purely mathematical basis, it is indeed possible that a certain rare subgroup might be experiencing an elevated risk that is not statistically detectable amidst broader populations. The size of the subgroup puts a mathematical bound on how high that undetectable elevation in risk might be - the larger the subgroup, the smaller the bound. If the subgroup is rare enough, that risk can be high. Proving an absolute negative (i.e. the impossibility of an elevated risk in every

member of a population) is impossible. Any estimate based on a finite sample has some degree of statistical imprecision. This statistical imprecision is reflected in the "confidence intervals" around the summary risk estimates, whose meaning and interpretation Dr. Greenland correctly describes. He notes that the upper limits of most confidence intervals in the cited literature are compatible with sizable relative risks in a rare enough subgroup.

This argument has several critical flaws, and does not diminish the relevance of the large body of negative evidence about thimerosal and autism to the claim that thimerosal causes regressive autism. First, it requires that thimerosal exposure only raises the risk of this one subtype of autism (i.e., regressive), with no effect on any other form of autism. That is the only scenario in which we could see zero effect overall and – exploiting the limits of statistical imprecision – claim there might be a few subjects at elevated risk. But positing such a scenario does not make it true; it requires biological evidence as to why different autism phenotypes would have completely different causes. Dr. Greenland presents no such biological evidence or an explanation for how it might be so. His cancer analogy is inappropriate, since different types of cancer affect recognizably different organs, tissues, and cells that, in consequence, have well characterized and dramatically different phenotypes, biology, prognoses, and treatments. These types of biological distinctions in cancer are not known to apply to autism phenotypes, and no scientific evidence is offered for the speculation that they might.

This kind of argument constitutes a form of patient-specific exceptionalism that is sometimes mistakenly invoked by physicians to explain why the results of clinical trials or prognostic predictions do not apply to a particular patient. Such arguments are scientific only if that patient is distinguishable from the larger group on the basis of a recognized causal or

mechanistic factor. Distinctions based on disease phenotype (e.g. regressive autism) are only meaningful if that phenotype is shown to be associated with a different causal pathway, or has a fundamentally different biology than other phenotypes. We would generally reject such distinctions made on the basis of hair color, or astrologic signs, because these are causally and mechanistically irrelevant factors. This can be true even when we see empirical evidence of such differences, as Peto did. In the case of the thimerosal-regressive autism hypothesis, we do not even have empirical evidence of a difference, which is why this hypothesis rests on an even more speculative foundation than that of astrologic signs affecting one's health.

Dr. Greenland's argument suffers from another serious flaw. He discusses the statistical imprecision of each study, and points out that each study individually does not rule out a sizable elevated risk in a small enough subgroup. This is true only if each study is taken in isolation. But the collective precision of all the studies taken together is greater than any of the studies taken alone. This is a basic principle of meta-analysis, the science of quantitatively combining results from separate studies. Thus, while there is indeed some small residual imprecision even if all of the studies are combined, this imprecision is smaller than in any one study alone, some of whose confidence intervals were already quite narrow (see Table, pg. 14). If the studies' findings were mathematically combined, the much narrower combined confidence limits would put a correspondingly much lower bound on the theoretically possible increased risk of the regressive subtype than that suggested by the divide-and-conquer approach.

Finally, these confidence intervals are two-sided, meaning that they extend into a region indicative of a beneficial effect of thimerosal, as well as a harmful effect. Thus, if a claim is to be made that the confidence intervals do not rule out some degree of a harmful effect of

thimerosal, it must also be admitted that the confidence intervals do not rule out a protective effect of thimerosal as well that lowers the risk of autism. In fact, on the basis of the numbers alone, which almost all fall on the protective side (see Table), a decreased risk of autism following thimerosal exposure is more likely than an increased risk. One must bring in the biologic implausibility of such a protective effect to argue that an effect in that direction is unlikely, again showing the problem of looking at the studies from a purely mathematical standpoint.

Causal inference is based on more than just numbers. What is also taken into account is the possibility for bias, or systematic error, in the underlying studies, as well as the weight and coherency of the evidence supporting a biologic mechanism [Hill, 1965]. All epidemiologic studies are afflicted by the possibility that there is something different about exposed and unexposed populations, other than the exposure itself, that accounts for a difference (or lack thereof) in outcomes -- a phenomenon known as "confounding." The possibility of confounding, however, is markedly reduced under two conditions:

a.) The exposure is unlikely to be related to the true risk; and

b.) Many studies, designed in different ways, in different populations, and using different approaches have similar findings.

Both conditions apply in this case. Whether or not an infant received a thimerosal-containing vaccine is primarily determined by what geographic region and in what calendar period that infant is immunized. It is not related to an infant's risk for developing autism, except through those factors. Most of the epidemiologic studies exploit this "natural experiment" by

comparing cohorts immunized in different years in the same countries, comparing autism rates in two different regions with different thimerosal exposure during the same calendar period, or comparing those with high and low thimerosal exposures in the same vaccination setting. This variety of comparisons and settings increases the confidence that the failure to observe a risk difference is not due to common methodological flaws that bias all the studies in the same direction. As is seen in the Table, none of the studies found a statistically elevated risk of autism from thimerosal, with most studies having point estimates that were in the protective direction. For those studies that looked at population-based incidence trends, these rates either rose more quickly, or the rise was unabated, upon the removal of thimerosal (see Figure, pg. 15). These studies included of hundreds of thousands of children, as well as data from entire countries with linked population registries, yet they offer no hint that thimerosal exposure raises the risk of autism.

The studies of Geier and Geier are not considered here (nor were they by Dr. Greenland) because of well-documented flaws in their methodology [Parker et al., 2004]. As the IOM concluded, the serious methodological flaws in the Geier and Geier studies render them "uninterpretable." [Immunization Safety Review Committee, 2004].

2004 IOM report

It was these kinds of considerations that led the IOM Immunization Safety Review Committee, of which I was a member, to conclude in 2004 that the totality of the evidence pertaining to an alleged thimerosal-autism association "favors rejection of a causal relationship." This panel was composed of a wide range of individuals with no stake in the controversy, and comprised experts in the domains of toxicology, pediatric neurology, biostatistics, epidemiology,

neonatal medicine, vaccine biology, risk communication, and immunology. While the Committee's conclusory language "favoring" rejection may not seem definitive in its rejection of the thimerosal-autism hypothesis, it represented the strongest null conclusion available to the Committee. The hierarchy of IOM causal conclusions was restricted to the following four categories:

1.) Evidence sufficient to conclude a causal association.

2.) Evidence suggestive but not sufficient to conclude a causal association.

3.) Evidence inadequate to conclude the presence or absence of a causal association, because of conflicting, sparse or poor quality studies.

4.) Evidence favoring rejection of a causal association.

The wording of the final category, and the absence of a category stating that a null association was "proven," is an implicit acknowledgement that empirical studies cannot prove an absolute negative. The final category is meant to encompass those situations in which a sizable number of reliable, large studies, performed in different ways, point to no causal relationship. Further, the absence of evidence of a biologic mechanism, and associated observations (e.g. the absence of autistic symptoms or excess autism incidence in populations with known high mercury exposure) further controvert the biological plausibility of a claimed association [Nelson and Bauman, 2003; Immunization Safety Review Committee, 2004]. These were the exact conditions that convinced the IOM Committee to conclude that the totality of the reliable evidence was suggestive of no causal association between thimerosal-containing vaccines and autism.

Of note, most IOM panels, including the Immunization Safety Review Committee (which issued 9 reports), rarely venture beyond the third category of "inadequate" evidence when the evidence falls short of proof. Scientists often find it difficult to move from the concept of "absence of evidence" to "evidence of absence." With respect to the alleged association between thimerosal-containing vaccines and autism, however, the negative evidence was so consistent, the study populations so large, the study designs and populations so different, and the biological mechanism supporting the association so speculative that the panel felt they had no choice but to express their view that the link was not just "unproven," but rather that the weight of evidence pointed in the direction of no effect [Immunization Safety Review Committee, 2004]. There was no disagreement among panel members with the reports' final conclusions or recommendations, and evidence published subsequent to the Committee's 2004 report has added further support to its conclusion [Andrews et al., 2004; Fombonne et al., 2006; Schechter and Grether, 2008]. As noted, Dr. Greenland did not take issue in his report with the Committee's overall assessment.

Conclusion

In summary, I conclude that the extant human evidence supports the conclusion that thimerosal does not cause autism. Any assertion that this evidence does not apply to a particular case or subset because of the particular autistic phenotype at issue must be supported by biological evidence showing why that phenotype is biologically or causally different from other phenotypes, and why such exposure would raise the risk of only that phenotype and no other. Dr. Greenland offers no such biological mechanism or evidence. I therefore conclude that the petitioners' claim of causal exceptionalism has no scientific foundation, and their claim that

thimerosal-containing vaccines raise the risk of either autism in general, or regressive autism in particular, has no scientific support.

Steven Goodman, MD, MHS, PhD

Table: Summary of epidemiologic evidence relating thimerosal exposure and autism.

Author, country, year	Design	N	Results
Hviid et al Denmark 2003	Retrospective cohort, 1990–1996 Danish National Registries Compared TCV to non TCV cohorts. Individual records	467,450 Children, 440 autistic	Autism RR 0.85 (CI, 0.6 to 1.2) ASD RR 1.12 (CI: 0.88-1.43) Dose response per 25 μg for autism: 0.98 (0.90-1.06)
Stehr-Green et al. Sweden, Denmark 2003	Ecological. Examined inpatient trends in Sweden and Denmark across time period with thimerosal removal in 1992 in Denmark, 1993 in Sweden and 1999 in the US.	N's not provided. All children hospitalized with autism dx.	All incidence trends increased, or accelerated, with the removal of thimerosal from vaccines.
Verstraeten et al USA 2003	Retrospective cohort, 1991–2000 Three HMOs	HMO B: 110,833 children, 202 autistic	Trend analysis for cumulative exposure by 7 mos: RR=1.0 (CI 0.9 to 1.09)
Madsen et al Denmark 2003	Ecological, 1971–2000 Danish National Registry, examined inpatient autism before and after Thimerosal is removed from vaccines in 1992	956 autism cases. Denominator; All persons in Denmark between 1970-2000.	National rates are stable until 1990, steady increase after removal of Thimerosal.
Jick and Kay UK 2004	Case control GPRD records of children born 1990 - 1998.	Autistic: 122 Control: 587	OR = 1.6 (CI: 0.7-3.3)
Heron et al UK 2004	Prospective cohort, 1991–1992 ALSPAC; Child Health Surveillance "Special needs"outcome	N=12,810 Autism not defined.	RR for "special needs" as a function of Hg dose, adjusted: 0.87 (CI 0.78–0.96) Risks of almost all neurodevelopmental outcomes were inversely related to Hg dose.
Andrews et al UK 2004	Retrospective cohort, 1988–1997 Office of National Statistics GPRD	103,043 children 106 autistic	HR autism: 0.89 (CI: 0.65-1.21) No dose response
Fombonne et al. Canada, 2006	Ecological Quebec, Prevalence survey based on school records.	N=27,749 PDD = 180 Autism = 60 ASD = 88	Rates of PDD were lower in thimerosal exposed cohorts, RR= 0.72 (CI 0.52 to 0.99) No effect of thimerosal elimination on PDD or autism rates, except perhaps to increase them.
Schechter and Grether USA, 2008	Ecological, 1995-2006 Autistic children utilizing California Dept. of Developmental Services programs	N's not reported. All children enrolled in program were counted.	Steady rise in population-based prevalence of autistic cases 1995-2006 with zero effect of thimerosal removal in 1999. Numbers in DDS still have not reached population prevalence estimates.

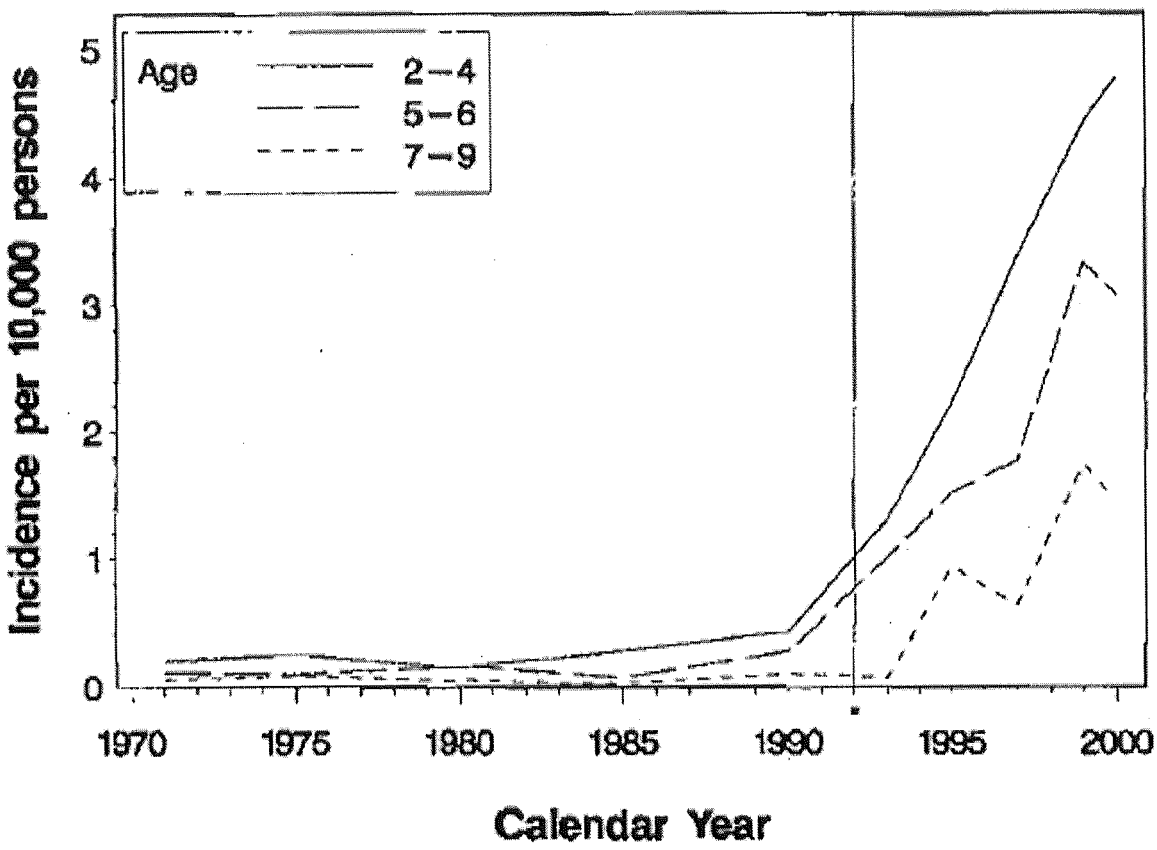

Fig 1. Incidence of autism by age and calendar year. The asterisk (*) indicates removal of thimerosal-containing vaccines in 1992.

Figure: Reprinted From Hviid (2003)

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