How mercury was absolved: creativity, collusion and censorship

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Abstract

Thimerosal and the Occurrence of Autism, Negative Ecological Evidence from Danish Population-Based Data by Madsen *et al.* was hurriedly published in the September 2003 issue of *Pediatraics* and was considered a "well-designed epidemiological study" by the Institute of Medicine (IOM) Vaccine Safety Review (VSR) Committee at its February 9, 2004 meeting. The study appears to be curiously absent of mechanisms typically associated with good scientific effort. This narrative details concerns regarding Madsen *et al.* such as their changes in participant selection methods, mid-study expansion of cohort populations, and changes in diagnostic grouping. These concerns were formulated in a letter to the Editor-in-Chief of *Pediatrics.* They were not addressed, and the letter was never published. The following is an update of the concerns addressed in the letter to *Pediatrics*.

Keywords: mercury, Thimerosal, autism, vaccination

1. Introduction

The May 18, 2004 published findings from the Institute of Medicine (IOM) Vaccine Safety Review (VSR) Committee report on "Autism and Vaccinations" concludes, in part, with the following:

> "Given the lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thimerosal and autism, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk [1]."

Given the IOM's conclusions, my concerns are two-fold. First, there are at least three points that, if left without clarification, invalidate the Danish, Madsen *et al.* 2003 study, *Thimerosal and the Occurrence of Autism, Negative Ecological Evidence from Danish Population-Based Data* which was published in the September 2003 issue of *Pediatrics* [2]. This is of primary concern because the Madsen *et al.* study is one of the works that the IOM Vaccine Safety Review (VSR) Committee deemed "well-designed." My concern related to the Madsen *et al.* publication is not that the study may be disconfirmatory evidence central to the thimerosal-autism controversy; but rather that Madsen *et al.* contribute more confusion than clarity to the scientific researchers interested in autism and thimerosal. This is demonstrated by at least three epidemiological nonsequitors: changes in participant selection methods, expansion of cohort populations completed mid-study, and changes in diagnostic grouping that markedly skewed findings.

2. Creativity

The collection of inpatient treatment data since 1971 was polluted by adding outpatient data post 1994 (Fig. 1). Madsen *et al.* attempts to reconcile this disparity by writing:

> "In additional analyses we examined data using inpatients only … to elucidate the contribution of the outpatient registration to the change in incidence. The same trend with an increase in the incidence rates from 1990 until the end of the study period was seen (data not shown) [2]."

This is an incredible claim in light of their previous declarations. First, within the same study, Madsen *et al.* claim: "The proportion of outpatient to inpatient activities was about 4 to 6 times as many outpatients as inpatients [2] …" Perhaps more importantly, in an earlier publication, Madsen *et al.* use the same data to purport: "In our cohort, 93.1 percent of the children were treated only as outpatients [3]…" This creates a huge disparity between the study published in *Pediatrics* and the previous one published in *The New England Journal of Medicine,* which purported to use the same data.

The former study claims "4 to 6 times as many outpatients as inpatients", yet the latter study maintains that 93.1% of all cohorts were outpatients and 6.9% were inpatients, yielding a proportion in excess of 13.5:1. Despite the authors' remarks claiming that the outpatient registration did not substantively change the incidence in autism, we may easily see, by making an adjustment for the more valid claim of 13.5:1 (Fig. 2), that the original assertion of a statistically valid upward trend is due only to the difference in accounting of the cohorts before and after 1995.

Two additional corrections need be made in order to accurately reflect the autism incidence rates in Denmark thus contributing to our Figure 3. First, it is necessary to address Madsen's changes in diagnostic grouping. According to the authors:

> "The date of onset was defined as the first day of the first admission leading to a diagnosis of psychosis proto-infantilis (*International Classification of Diseases, Eighth Revision* [*ICD-8*]: 299.00) or psychosis infantilis posterior (*ICD-8*: 299.01) or from 1994 onward, infantile autism (*International Classification of Diseases, 10th Revision* [*ICD-10*]: F84.0) or atypical autism (*ICD-10*: F84.1) [2]."

One might wonder why the authors feel comfortable changing the diagnostic grouping. Although the authors do not fully address the effect of this change, data presented in Figure 1 of the Madsen *et al.* 2003 study show that the autism incidence prior to 1994 is on average approximately 6/10,000 patients (derived by summing the incidence data for each of the three age groups presented and dividing that sum by the inpatient to

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total patient ratio). In contrast, the earlier Madsen *et al.* 2002 publication reports autism incidence from anywhere between 1.2/10,000 (DSM IV criteria) to 30.8/10,000 (ICD-10 criteria). The earliest available study on the incidence of autism in Denmark [4] reports an intermediate value of 4/10,000. Thus, using the pre-1992 ICD-8 psychosis infantilis incidence derived from the 2003 Madsen study (6/10,000), the ICD-10/ICD-8 diagnosis ratio is at least 5:1 (i.e., 30.8 divided by 6) and may be as high as 25:1 (30.8 divided by 1.2). To remain conservative in the analysis, a correction factor of 5:1 is applied to the data in Figure 3.

Second, one last correction needs be made in order to accurately reflect the autism incidence rates in Denmark thus resulting in our Figure 3. In an article published in the American Journal of Preventive Medicine, Stehr-Green *et al.* write: "Prior to 1992, the data in the [Danish] national register did not include cases diagnosed in one large clinic in Copenhagen (which accounts for approximately 20% of cases occurring nationwide) [5]." This presumably means that all data points up to 1992 should be multiplied by 1.2 to correct for this discrepancy.

Figure 3 therefore reflects the aforementioned correction factors, which are applied to the Madsen *et al.* 2003 data (previously revised for a correct inpatient to outpatient ratio, as in Figure 2). In contrast to Madsen's published claim, our correction for the disparity between the two studies (i.e., Madsen *et al.* 2002 versus Madsen *et al.* 2003), which purport to utilize the same data, reveals a dramatic decrease in autism incidence after 1993—particularly among the 2-4 year-old cohort.

Further examining the 2-4 year-old cohort, it is apparent that, when the discrepancy in the diagnosis codes before and after 1993 is not corrected for, the Madsen *et al.* 2003 study is essentially statistically indeterminate. This is demonstrated in Figure 4, which shows P-values and Odds Ratios (OR) for average autism incidence calculated before and after 1993 for the 2-4 year-old cohort when applying corrections for diagnosis code differences before and after 1993 of between 0.5 and 25. At a correction of 1.0 (i.e., no factor applied), autism incidence is nearly identical before and after the removal of thimerosal at an OR of 1.17 (P=0.39). In fact, a statistically significant increase in autism incidence after the removal of thimerosal is seen only if the correction is *lowered* to 0.6 (OR=1.95, P<0.05). Conversely if a modest upward correction of 2.0 is applied, a statistically significant decrease in autism incidence for this cohort is seen (OR=0.59, P<0.05). At a correction of 5.0, used to calculate autism incidence in Figure 3, the odds ratio becomes 0.23 (P<0.0005). Thus, at most (i.e., at a correction of 1.0), the Madsen *et al.* 2003 study is indeterminate. When the data are treated properly, however (at a correction of 2.0 or greater), it is easily shown that autism incidence decreased in the 2-4 year-old cohort as a direct consequence of the removal of thimerosal.

3. Collusion

On December 10, 2002, Assistant Surgeon General and Director of CDC's National Center on Birth Defects and Developmental Disabilities sent a "personal" letter to the Editor-in-Chief of Pediatrics that started:

> "I am writing in support of an expedited review and consideration of the enclosed manuscript that examines the association between thimerosal, an ethyl mercury containing preservative[,] and autism."

The letter ended:

> "I feel this is a very important study that deserves thoughtful consideration by the Journal. Its findings provide one strong piece of evidence that thimerosal is not causally linked to autism. Thank you for your consideration."

By so stating, CDC not only validated the study's methodology and findings but, indeed, also anointed them strong and reliable enough to rule out a causal link between Thimerosal and regressive autism—prior to a proper peer review.

On February 9, 2004 the study was pronounced a "well-designed epidemiological study" by the Vaccine Safety Review Committee of the Institute of Medicine. The committee rejected outright the "hypothesis" that thimerosal could trigger autism because it was theoretical and lacked supporting evidence. The committee also opinioned that further research to find the cause of autism should be directed toward other lines of inquiry "that are supported by current knowledge and evidence and offer more promise for providing an answer."

4. Coverup

Another disturbing remnant related to the Madsen study is the absence of concern for nullifying arguments in frontline publications. That is, when confronted with evidence that invalidates an already published study, the medical community has ignored substantive criticism by appealing to the IOM's findings. On 4/13/04, my concerns regarding the Madsen *et al.* 2003 publication, previously detailed herein, were submitted as a letter to the Editor-in-Chief of the journal, *Pediatrics*. This letter was, in fact, solicited by one editor who noted that the rebuttal would be most appropriately submitted as a letter to the editor rather than as a Post-publication Peer Review (P3R) submission. Soon after the submittal of this letter, the authors of the Madsen *et al.* 2003 publication, "Thimerosal and the Occurrence of Autism, Negative Ecological Evidence from Danish Population-Based Data," were notified of the letter and given a chance to reply to the issues elucidated therein. These researchers chose NOT to reply, and on June 9, 2004, the Editor-in-Chief of *Pediatrics* rejected the submitted letter without addressing the substance of my concerns.

> "A major review carried out by the U.S. Institute of Medicine published last month (May 2004) found no evidence that thimerosal was linked to autism. Similarly, investigations by the UK Committee on Safety of Medicine, Europe's Agency for the Evaluation of Medicinal Products and the World Health Organization concluded the preservative was safe. I consider this issue closed.
>
> Sincerely,
> <s>
> Editor-in-Chief, Pediatrics
> University of Vermont College of Medicine
> Pediatrics Editorial Office
> 89 Beaumont Ave, Given D201
> Burlington, VT 05405-0068"

The journal *Pediatrics*, like the members of the Institute of Medicine Vaccine Safety Review Committee, chose politics over science, thus squelching true debate over the issues surrounding vaccine safety. It is all too often misunderstood that conventional publications do not customarily circulate studies

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and censure subsequent, substantive materials that challenge the validity of such works. The previous example demonstrates a perhaps desired effect of the IOM VSR's May 18th conclusions. Additionally, it is completely clear that these findings were based upon profoundly flawed science, in contrast to what most professionals expect: solid, "well-designed" epidemiological studies and valid findings.

My first concern detailing three criticisms of the Madsen *et al.* findings invalidates the Danish study. The three criticisms together support intentional misconduct more than mere carelessness. The Madsen *et al.* publication takes on the form of a study, but leaves the aftertaste of propaganda through the apparent use of incongruent language, suspicious data collection, and data omission all of which are mechanisms used to confuse rather than clarify. Indeed, such mechanisms suggest that this team of researchers was trying to fabricate "truth" in contrast to true science, which seeks to discover it. In light of their declared outcome, one might be left wondering why they did not recommend a continued use of thimerosal as an autism preventative. Given the authors' trivializations, omissions, inconsistent data interpretations between studies, and complete lack of self-criticism, it seems prudent to treat Madsen's conclusions with extreme skepticism.

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The original draft of this manuscript first appeared on the Vaccine Autoimmune Project for Research and Education (VAP) at http://www.vaproject.org/.

I wish to thank the friends who have helped with the preparation of this manuscript and its mathematical calculations.

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[2] Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, *et al.* Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics 2003 Sep.;112(3 Pt 1):604–6

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Figure 1. Uncorrected data from Madsen *et al.* 2003 [3]

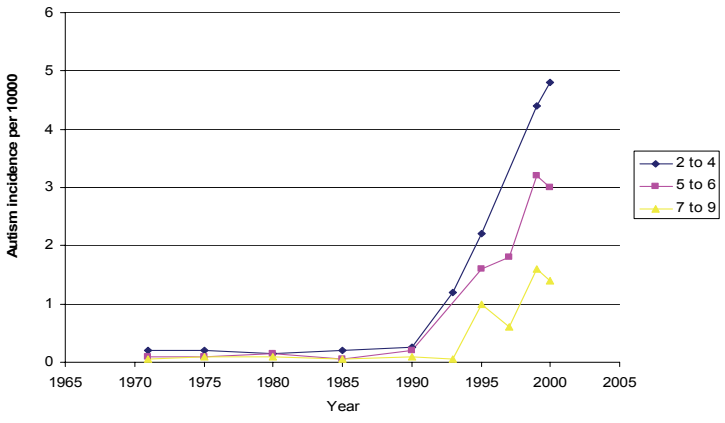


Figure 2. Madsen *et al.* 2003 data corrected for inpatient to outpatient ratios

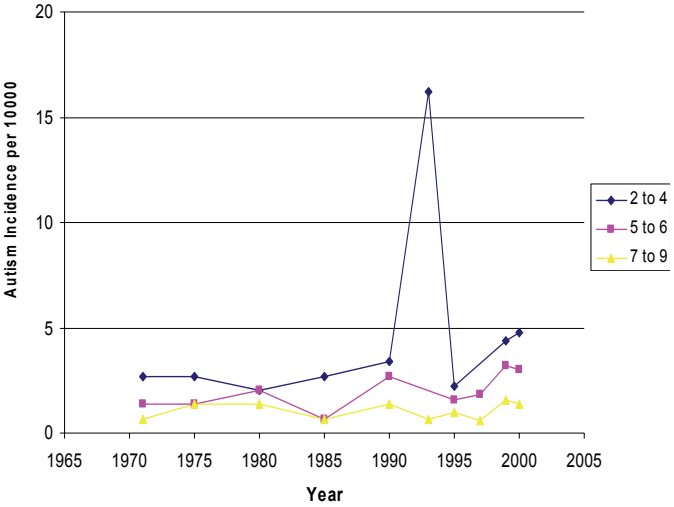


Figure 3. Madsen *et al.* 2003 data corrected for the difference between outpatient to inpatient ratio (13.5:1), diagnoses codes (conservatively at 5:1 based on Madsen *et al.* 2002) and missing data prior to 1992 from the Copenhagen clinic

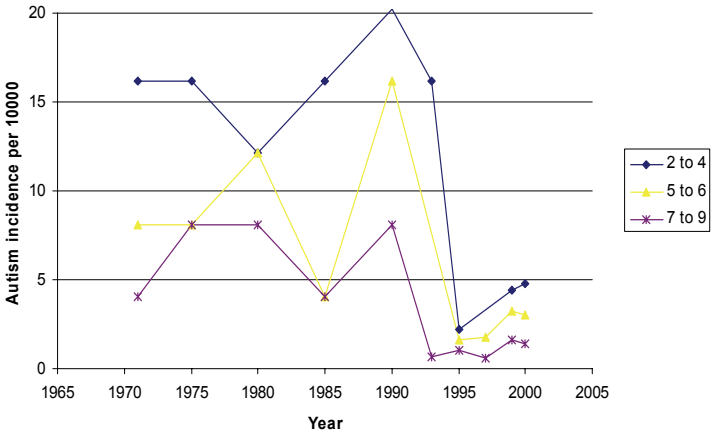
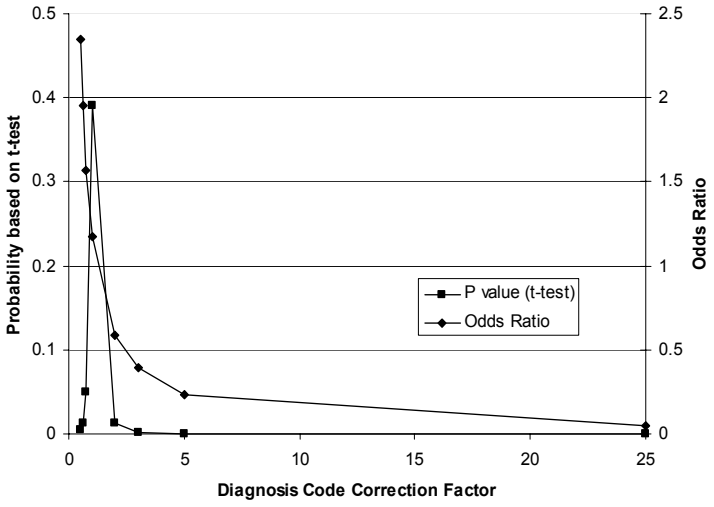


Figure 4. Calculated odds ratios (OR) and P-values for autism incidence before and after removal of thimerosal from vaccines for different diagnosis code correction factors



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