

Vaccines and Autism

What do Epidemiological Studies Really Tell Us?



VACCINES AND AUTISM – WHAT DO EPIDEMIOLOGICAL STUDIES REALLY TELL US?

Coalition for SAFE MINDS

“We have 16 studies already that clearly state that vaccines do not cause autism.”

– Amy Pisani, Executive Director, Every Child By Two

“16 studies have shown no causal association between vaccines and autism, and these studies carry weight in the scientific industry.”

– Dr. Nancy Snyderman, NBC Today Show Medical Editor

“The science is largely complete. Ten epidemiological studies have shown MMR vaccine doesn’t cause autism; six have shown thimerosal doesn’t cause autism.”

– Dr. Paul Offit, “Autism’s False Prophets”

“My daughter, who had been completely normal until getting nine vaccines in one day, was suddenly no longer there.”

–Terri Poling, RN, JD, mother of Hannah, who received federal compensation for her vaccine-induced autism.

“So if a child was immunized, got a fever, had other complications from the vaccines. And if you’re predisposed with the mitochondrial disorder, it can certainly set off some damage. Some of the symptoms can be symptoms that have characteristics of autism.”

–Julie Gerberding, MD, Former Director of the CDC

“I think the government, or certain public health officials within the government, have been too quick to dismiss the concerns of these families, without studying the population that got sick.”

– Dr Bernadine Healey, Former Director of the National Institutes of Health

A NOTE FROM SAFE MINDS:

There are 16 epidemiological studies here on MMR vaccines, thimerosal and autism. These studies represent the most often cited papers by scientists, public health officials and members of the media when trying to refute any evidence of an association between vaccinations and autism.

There are serious methodological limitations, design flaws, conflicts of interest or other problems related to each of these 16 studies. These flaws have been pointed out by government officials, other researchers, medical review panels and even the authors of the studies themselves. Taken together, the limitations of these studies make it impossible to conclude that thimerosal and MMR vaccines are not associated with autism.

In addition, Poul Thorsen, a prominent researcher responsible for a series of epidemiological studies which utilized the Danish Psychiatric Central Research Register reviewed in this report was indicted April 13th, 2011 by a federal grand jury on 13 counts of fraud and 9 counts of money laundering based on a scheme to steal grant money the CDC had awarded to governmental agencies in Denmark for autism research. According to United States Attorney Sally Quillian Yates, "Grant money for disease research is a precious commodity. When grant funds are stolen, we lose not only the money, but also the opportunity to better understand and cure debilitating diseases. This defendant is alleged to have orchestrated a scheme to steal over \$1 million in CDC grant money earmarked for autism research. We will now seek the defendant's extradition for him to face federal charges in the United States."

As fraud charges regarding Thorsen surface, along with our findings outlined in this report that the Denmark Register was unreliable, SafeMinds is calling for an independent federal investigation of these studies for data manipulation and scientific misconduct. Further background information on these studies, the charges against Dr. Thorsen, and documents obtained through the Freedom of Information Act that support SafeMinds' concerns are available on our website, www.safeminds.org.

Safe Minds would like to acknowledge the previous work in this regard gathered by the "Fourteen Studies" project at Generation Rescue: <http://www.14studies.org/about.html>

One additional study on autism and thimerosal was published in September 2011 while this paper was in completed draft form. This study's methods produced a result that demonstrated that thimerosal exposure was protective against autism. Further analysis of this study is forthcoming but not included here.

PART 1

MAJOR GAPS IN KNOWLEDGE

Conventional wisdom holds that the autism-vaccine question has been “asked and answered,” and that at least 16 large, epidemiological studies have thoroughly addressed and debunked any hypothesis that childhood vaccination is associated with an increased risk of autism spectrum disorder.

But there are numerous critical flaws in such an oversimplified generalization, and they are rarely given close examination by public health experts or members of the media.

It is particularly discouraging that members of the scientific community are so willing to dismiss a hypothesis that has yet to be fully tested. Overconfident pronouncements such as those found in the quotes above do nothing to advance either the cause of science or our understanding of the complex issues involved. They are, instead, the product of misunderstanding and wishful thinking, brought about by the overzealous drive to ‘disprove’ an unpopular and possibly disquieting theory.

Respected medical opinion-makers such as Dr. Snyderman and Dr. Offit mislead the public when they categorically state that there is “*no link*” between vaccines and autism. Their misguided conclusions are based on incomplete knowledge and misinterpretations, and likely to be influenced by personal and professional conflicts of interest; conflicts illustrated by their intimate and lucrative financial bonds with GlaxoSmithKline (Snyderman) and Merck (Offit), - two of the world’s leading vaccine manufacturers.

There is a host of reasons why the cavalier dismissal, by scientists and physicians, of any possible vaccine-autism association is premature, shortsighted, and wrong.

But first, some clarification about terminology. Frequently, a counter-claim to those made by the likes of Snyderman and Offit is that ‘*epidemiological*’ studies cannot be used to establish or refute, causality.

Epidemiology is the study of the distribution and determinants of disease in the human population; the basic science and fundamental practice of public health (Nordness, 2006).

Epidemiological studies may be descriptive or analytical (see for example Hennekens and Buring, 1987), Descriptive epidemiology aims to describe the general characteristics of disease distribution in relation to person, place and time. Studies of this type provide information to health care providers and those responsible for resource allocation and may also be used to generate hypotheses about disease causality, but their design precludes them from being used to test hypotheses.

The studies cited in support of ‘no vaccine-autism association’ are not flawed because they are *epidemiological*, they are, almost invariably, flawed because their aims, design, analytic procedures or conclusions have been inappropriate, and in some instances, plain wrong.

Analytical epidemiology involves using comparative studies to test hypotheses about associations between an exposure and a disease. Analytical studies can be observational or experimental, but both involve evaluation of associations between exposure and diseases, and both are well placed to do just that.

The studies frequently referred to as indicating ‘*no association between vaccines and autism*’ have, for the most part, been population-based, observational studies. As such it is quite possible for them to have helped confirm or refute the role of vaccines in causality. The reason they have failed is not because epidemiology is a ‘*blunt tool*’, nor is it because ‘*epidemiology could never pick up on such a small effect*’. It is because the studies have either been badly designed, or not designed with the right hypothesis in mind.

In the following analysis, we review and critique the analytical epidemiology studies most commonly cited as evidence against the “autism-vaccine” hypothesis. We must make clear at the outset, however, that this critique addresses only a fraction of the “autism-vaccine” connection. In fact, the studies reviewed here have explored only two discrete (and frequently confused) exposures: one vaccine, the measles-mumps-rubella vaccine (MMR) and one vaccine ingredient, the ethyl mercury based preservative, thimerosal. None of these studies have addressed possible interactions between the two exposures or the effect of these exposures in the larger context of an expanded childhood immunization program. No study has yet been conducted comparing total health outcomes in vaccinated human children with unvaccinated children. As a result, the gap between the study sample reviewed here and a full examination of vaccination exposure and autism risk remains quite large and largely unexamined.

However, with respect to the body of analytical epidemiology on MMR and thimerosal, we draw the following conclusion. The evidence in the studies that are most often claimed to provide conclusive proof dismissing a connection between these exposure and autism do not stand up to close scrutiny. Many of them do not provide evidence one way or another with respect to the hypothesis; some of them provide evidence actually supporting an exposure effect; others are too poorly designed to extract any reasonable conclusions; and in some instance the data have been manipulated in ways that border on misconduct.

In short, although the question of the connection between autism and vaccines has been asked, we have yet to see any reliable and informative answers.

PART 2

FLAWS AND LIMITATIONS OF MMR STUDIES

Major Reviews – There have been at least two major reviews of the main studies claiming to examine a potential association between MMR vaccine and autism spectrum disorders. They are the 2005 Cochrane Review and the 2004 Institute of Medicine Immunization Safety Committee Report.

1) The Cochrane Review: “Vaccines for measles, mumps and rubella in children.” October 2005.¹

According to their sponsors, the Cochrane Reviews report on published (and sometimes unpublished) studies which investigate the effects of interventions for prevention, treatment and rehabilitation in a healthcare setting. Most Cochrane Reviews focus on randomized controlled trials, but other types of evidence may also be taken into account. The reviews are considered by most experts to provide the gold standard of evidence-based medical science.

In 2005, Cochrane published a review of published studies on the safety and efficacy of MMR vaccine. Their search revealed more than 5,000 papers on the subject, though only 139 of them “possibly satisfied” the reviewers’ inclusion criteria. In the end, they reported on and summarized about 31 studies, only a few of which pertained to autism spectrum disorders (ASD).

Main results - MMR was “likely to be associated” with febrile convulsions within two weeks of vaccination, but “unlikely to be associated” with Crohn's disease, ulcerative colitis, mumps or autism.

General Limitations: the authors concluded that:

- There was a moderate-to-high probability of bias in all but one of the cohort studies.
- The internal validity of some studies was problematic, and the presence of selection, performance, attrition, detection and reporting biases influenced the reviewers’ confidence in these findings. The most common type of bias was selection bias.
- There was only limited evidence of MMR’s safety compared to single component vaccines from studies with a low risk of bias. The few studies least likely to be affected by systematic error pointed to a likely association with increased febrile convulsions in the first two weeks post-vaccination.

■ The cohort studies' conclusions "that MMR is 'safe,' 'equally safe,' 'well-tolerated,' or has 'low-reactogenicity,' need to be interpreted with caution given the potential for confounding.

■ In the cohort studies, the validity of the conclusions was affected by selective reporting in the comparative analysis, with just over half the responses from participants in some cases.

■ There was a lack of clarity in reporting and systematic bias which made it "impossible" to compare the various studies through quantitative synthesis of data.

■ There were general difficulties in ascertaining adequate numbers of unexposed children due to the high uptake of vaccines and the extent of vaccination programs. This is a methodological problem likely to be encountered in all comparative studies of established childhood vaccines.

■ There was a "lack of adequate description of exposures (vaccine content and schedules)" in all cohort studies.

■ The failure of any study to provide descriptions of all outcomes was a recurring problem.

■ Some reports offered inadequate explanations for missing data, accepting as 'adequate' explanations such as 'nonresponse to questionnaire' and 'medical records unavailable'.

■ The external validity of the studies was low. Descriptions of the study populations, response rates, vaccine content and exposure - all important indicators of generalizability - "were poorly and inconsistently reported."

■ There were inadequate and inconsistent descriptions of reported outcomes, limited observation periods (maximum 42 days) and selective reporting of results. All of these problems contributed to the reviewers' decision not to attempt pooling data by study design

SUMMARY – Although the reviewers determined that MMR vaccine was "unlikely to be associated" with autism, they concluded that "meaningful inferences from individual studies lacking a non-exposed control group are difficult to make." They added that there were disappointed by their inability to identify effectiveness studies with population or clinical outcomes.

Many critics question how the authors of Cochrane's MMR Review could find an "unlikely" association with autism when - in the very same paper - they also concluded that:

- (a) the design and reporting of safety outcomes in MMR vaccine studies, are largely inadequate and

- (b) that critical design and reporting flaws need to be improved and standardized definitions of adverse events adopted.

Sallie Bernard, of SafeMinds, wrote that the Cochrane Review “gives MMR a free pass.” She said the review “Assumes that this version of vaccine is as safe as can be, and so beneficial there is no need to worry about the fact that the safety studies are inadequate. Would this happen for any other drug? Isn’t it possible, even probable, that the vaccine is effective but still has safety lapses and could be improved?”

In a review presented at the International Meeting for Autism Research (IMFAR) Carol Stott, a UK epidemiologist and Chartered Psychologist, wrote that, given the Cochrane Review’s conclusions, it is important to examine the extent to which the various clinical and population studies have been designed appropriately and with specific reference to the original hypothesis and, thus, to examine the extent to which claims of the hypothesis being refuted or supported are valid.

2) Institute of Medicine, “Immunization Safety Review: Vaccines and Autism.” May, 2004²

In February 2004, the IOM’s Immunization Safety Committee held a hearing on the possible association between MMR, thimerosal and autism. The committee reviewed all published and unpublished epidemiological studies on causality as well as potential biologic mechanisms to explain a possible vaccine-autism causal association. Its findings were released in a May, 2004 report. The committee’s conclusions hold wide sway over many scientists, physicians and much of the media to this day.

Main Results: The committee concluded that the body of epidemiological evidence “favor” rejection of a causal relationship between the MMR vaccine and autism,” further stating that studies examining the association between MMR and autism consistently showed evidence of no association between the MMR vaccine and autism.

Limitations:

- Because the “vast majority” of ASD cases cannot be accurately sub-classified, if there is a subset of individuals with autism syndrome triggered by exposure to vaccines, our ability to find it is very limited in the absence of a biological marker.
- Although there is no convincing evidence to date that a clearly defined subgroup with susceptibility to MMR-induced autism has been identified, genomics and proteomics could reveal in the future whether or not any genetic susceptibility to vaccine-induced autism exists.
- A lack of unexposed children is another limitation. The committee noted that they had previously called for studies to enroll children whose families opted against the MMR vaccine, but so far, this type of study has been difficult to do with sufficiently large numbers.

■ The committee also noted that its 2001 report did not exclude the possibility that MMR “could contribute to autism in a small number of children because the epidemiological studies lacked sufficient precision to assess rare occurrences.”

■ They also noted that it was possible that epidemiological studies would not detect a relationship between autism and MMR vaccination in a subset of the population with a genetic predisposition to autism.

The latter two points are covered in the introduction to this document. While the points are well received, it is important to note that ‘epidemiological’ studies lack neither precision nor accuracy simply by virtue of them being ‘epidemiological’. It is entirely possible to design population based studies to maximize the likelihood of identifying small effect sizes; the fact that this hasn’t yet been achieved in the vaccine-autism debate is the fault of the workmen, not the tools.

SUMMARY: The IOM Committee gave far more emphasis to epidemiological (population based) studies than biological studies, such as clinical studies in children, laboratory studies, and animal model studies. Since the IOM report was released in May, 2004, a large amount of biological data have been generated from several published studies to support an association between vaccines – including MMR - and ASD. A new IOM review that includes these studies is needed.

INDIVIDUAL MMR STUDIES

The Cochrane Review and the 2004 IOM Report both referenced a number of MMR-autism studies when concluding that the evidence favors rejection of a causal association. These papers make up the bulk of the MMR investigations included in the “16 studies” referred to by Doctors Snyderman and Offit. They include nine studies on MMR:

1) A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism.³

Authors: Kreesten Meldgaard Madsen, M.D., Anders Hviid, et. al.

Publication & Date: *New England Journal of Medicine*, November 7, 2002.

Online at: <http://content.nejm.org/cgi/content/full/347/19/1477>

Details: This paper is often referred to as the “Danish MMR Study”. The authors conducted a retrospective cohort study of all children born in Denmark from January 1991 through December 1998. Information on MMR-vaccination status and on autism status was obtained via Danish health records. Out of 537,303 children in the cohort, 440,655 (82.0 percent) had received the MMR vaccine. A total of 316 children with a diagnosis of autistic disorder and 422 with a diagnosis of other autism-spectrum disorders were identified (a proportion of 13.7-per-10,000, or about 1-in-730).

Results: After adjusting for potential confounders, the relative risk of autistic disorder among MMR-vaccinated children vs. the unvaccinated group was 0.92 and the relative risk of another autistic-spectrum disorder was 0.83. In other words, MMR-exposed children were 17-percent LESS likely to have an ASD than unexposed children: The vaccine reportedly had a statistically significant “protective effect.”

Authors’ Conclusions: “This study provides strong evidence against the hypothesis that MMR vaccination causes autism.”

WHAT CRITICS SAID:

Walter Spitzer, Professor Emeritus of Epidemiology, McGill University et al., in a letter published in the March, 2003 issue of the *NEJM*, noted that there were still some methodological problems outstanding with regard to the Danish study.⁴

Spitzer charged that researchers did a clinical record review of just 40 cases (13%), which he claimed was inadequate, especially if the purpose was only to validate an existing diagnosis. Spitzer claimed that ‘...without a multidisciplinary review of original

lifetime records as well as double verification in a large descriptive single cohort, important errors would have been unavoidable, both in classification and numbers for the numerators.” Spitzer et al. also raised the question of whether pediatric clinical psychologists, pediatric neurologists and speech therapists were involved in the review and whether the reviewers were blind as to exposure status.

Though the power of the published study was high, it was “misleading,” Spitzer et al. claimed. In elaborating this point Spitzer et al. explained that if, for example, one assumed a vulnerability to MMR-induced disease in 10% of the regressive ASD cases, with 95% of this group being vaccinated, and if 80% of the non-regressive ASD cases were also assumed to be vaccinated, then “the odds ratio for MMR as a risk factor for regressive autism would be 4.17.”

However, if children with autism, regardless of sub-types, were combined and compared against non-affected controls, the odds ratio would plummet to just 0.97. “Thus a small non-statistically significant reduction in uptake of MMR in the 90% of non-regressive autistic children would mask a strong causal association in a small subgroup,” Spitzer et al. Whilst the sub-group might be small, they claim, ‘...conservatively the 10% would represent 50,000 children in the U.S. alone with a financial burden of disease to parents and government of at least \$1.25 billion per year.”

Goldman and Yazbak, in a letter published in the *Journal of American Physicians and Surgeons*, pointed out the “substantial under-representation of autism diagnoses and vaccination status for children born in the later study years.”⁵ Children with ASD in Denmark are diagnosed at about 5 years old; many were simply too young to receive an ASD diagnosis by the end of the study period. This would apply to all children under the age of 36 months and, in a practical sense, to many of the 3-5 year olds. Among children born in 1997 and 1998, who made up a substantial proportion (39%) of the total years of observation time, many had yet to even receive an MMR vaccine all.

In fact, ASD prevalence among children aged 5-9 years increased from a mean of 8.38/100,000 in the pre-licensure era (1980-1986) to 71.43/100,000 in 2000, making the adjusted prevalence rate-ratio 4.7 for the post-licensure period compared with the pre-licensure period. This suggested a temporal association between the introduction of MMR vaccination in Denmark and an almost five-fold increase in autism cases.

Mark Blaxill, SafeMinds director, in an unpublished critique written for SafeMinds , criticized the use of person years rather than prevalence by birth group as the choice of outcome measure. He pointed out that although person-years is common incidence measure in epidemiological studies, it is an odd choice in the study of a chronic disease like autism. He argued that “there is no really good reason (and the authors offer none) to consider duration of the disorder as opposed to its presence. Autism is generally considered a lifelong disorder, so the effect is the same among two year olds as it is among eight year olds.”

Analyzing the Denmark data using case prevalence measures reveals importance problems with Madsen et al. according to Blaxill. Most notably, he points out that the most straightforward analysis of the data provided by the study authors directly contradicts their conclusion (see table below). The actual prevalence of autism in the 440,655 children who received MMR vaccinations in Denmark was 6.1 per 10,000 as compared to the rate of 4.9 per 10,000 in the 96,648 unvaccinated children. At the population level, the risk of autism was therefore 26% higher in the group vaccinated with MMR, a calculation the authors never reported. Blaxill highlighted two biases:

Unadjusted Relative Risk of Autism in MMR-Vaccinated Danish Children			
	Total	Vaccinated	Not vaccinated
Population	537,303	440,655	96,948
Cases			
Autistic	316	269	47
Other ASD	422	352	70
Total ASD	738	621	117
Rates per 10K			
Autistic disorder	5.88	6.11	4.86
Other ASD	7.85	7.99	7.24
Total ASD	13.74	14.09	12.11
Relative risk			
Autistic disorder			1.26
Other ASD			1.10
Total ASD			1.16

1. Biased exposure adjustment. Madsen et al. introduce an adjustment for the timing of diagnosis relative to the timing of MMR vaccination. The authors determined that six of the children diagnosed with autism and seven of those diagnosed with other autistic spectrum disorders had such an early onset of the symptoms that the disorder was diagnosed before the MMR vaccine was administered. They decided that this reversed sequence of events argued against a causal role for MMR in autism, so they placed these vaccinated children in the group they called "unvaccinated" even though they had clearly received MMR vaccine. In moving autistic children into the unvaccinated group, the authors increased the pool of unvaccinated children by 13% and reduced the pool of vaccinated children by 2%. This adjustment substantially reduced the relative risk of autism among the vaccinated group, from 1.26 in the table above to 1.09 at the population level.

The MMR hypothesis argues more specifically, however, that vaccination of an otherwise normal child will contribute to an *autistic regression*. To test this hypothesis, the most relevant population would exclude all cases with early onset autism, both from the vaccinated group (as the study authors chose to do) and from the unvaccinated group (which they chose not to do). The method chosen by the authors artificially raised the incidence rate in the control group. If, instead of moving early onset (but clearly vaccinated) cases into the "unvaccinated" group, the authors had removed all early onset

cases from both groups, they would have increased the relative risk of autism in the vaccinated group to 1.28, instead of reducing it to 1.09.

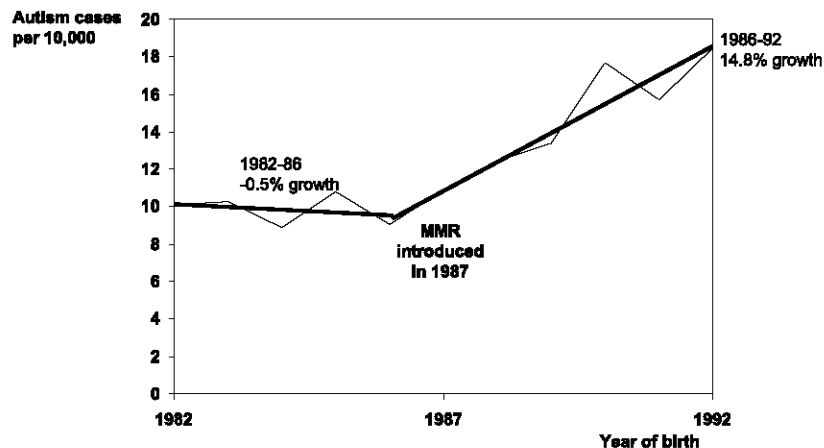
2. Age adjustment bias effect. The use of person-years also had a more direct effect on the published risk of MMR on autism, by introducing a skew in the sample by age group. In reporting a relative risk 0.92 (a level that suggests a protective effect of MMR in autism) rather than the case-based relative risk of 1.09, the authors weighted certain portions of their sample (the older children with more person-years) more heavily than others. Given the wide variation of risk by age, extra weight was actually given to portions of the sample with relative risks well below 0.92. Blaxill made a rough calculation of the relative risks of autism comparing children born in 1997-98 (children were one and two years of age when the data was collected) to those born between 1991-96. This calculation shows an even higher protective effect (relative risks of 0.87 and 0.77 for children with autism and autism spectrum disorders, respectively).

The distribution of relative risks is highly variable across birth years, more than would be expected under the null hypothesis of no vaccination effect. This raises questions about the quality of the vaccination data records among the older children. The apparent high rate of autism among unvaccinated older children could reflect lost vaccination records or other data integrity problems.

Carol Stott, Mark Blaxill, and Dr. Andrew Wakefield, claimed in the *Journal of American Physicians and Surgeons*, that Madsen et al. appeared to have adjusted inappropriately for age.⁶ That being the case, Stott et al. argued, the findings need to be reinterpreted,” Stott et al. went on to state that in the absence of such adjustment, there is a statistically significant 45% excess risk of autism in recipients of the MMR vaccine and therefore, an apparent association between MMR and autism in this Danish population.

In addition, Stott et al. argued that a proper trend analysis would compare autism rates not by age at diagnosis but rather by date of birth. They obtained data from the same registry used by the authors that showed a clear upward trend in autism rates in birth cohorts born after the introduction of MMR in Denmark (see below).

AUTISM PREVALENCE IN DENMARK BY BIRTH YEAR: 1982-92



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The Boston Consulting Group

-3- ASD

Prevalence in Denmark by year of birth, 1982-1992. Annual growth rate before MMR was -0.5%, but rose to 14.8% after MMR introduction in 1986.

Moreover, Stott et al. claimed that the authors of the Danish study had selected a particular adjustment to their population groupings that removed a total of 13 ASD cases from the vaccinated group and placed them in the unvaccinated group. This single adjustment reduced the relative risk of autism associated with MMR vaccination at the population level by 17%, from 1.26 to 1.09. Stott et al. claimed that if the authors had removed all cases diagnosed before two years of age from their risk analysis, the relative risk at the population level would have risen from 1.26 to 1.28.

And Blaxill added another commentary of his own: "I conclude that the authors' conclusion is not warranted. In my opinion, the Madsen article is useful in many ways but it definitely does not rule out MMR as a cause of autism, particularly not in a subgroup of the affected children."

WHAT THE COCHRANE REVIEW SAID:

- Follow up on medical records terminated just one year after the last day of admission to the cohort. "Because of the length of time from birth to diagnosis, the Cochrane reviewers felt it became '... increasingly unlikely that those born later in the cohort could have a diagnosis."

- The study was judged to have a "moderate" probability of bias.

- Interpretation of the study was “made difficult by the unequal length of follow up for younger cohort members” and the “use of date of diagnosis rather than onset of symptoms for autism.”
- The study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.”
- There was inadequate description of exposures, such as vaccine content and schedules.
- The study suffered from “clearly missing unintended-event data” and many participants were missing for adverse event monitoring. Adverse event data were missing in up to 1-in-5 participants (20%).
- The study failed to provide descriptions of all outcomes monitored.

SUMMARY:

Madsen et al. argue no effect of MMR vaccination on autism in Danish children and even suggest there might be a protective effect to MMR exposure. Unfortunately, their study is plagued with questionable methodological choices, unexplained data anomalies and biased adjustments. In any study that asks a fundamental question about relative proportions of exposure in affected vs. unaffected groups, accurate definitions and classifications of (a) exposure and (b) affected status are crucial to the validity of any conclusions drawn from the data. Numerous criticisms of Madsen et al. highlight a source of error in one or another of these classifications. Methodology questions aside, more straightforward approaches to the population data they report suggest an increased risk of autism in Danish children based on MMR exposure, especially when adopting a case-based approach rather than relying on person-years. A simple comparison of autism rates by birth year shows a clear increase in autism rates after the introduction of MMR in Denmark. These analyses demonstrate that frequent references made based on Madsen et al. regarding the safety of MMR are incorrect.

2) Neurologic Disorders After Measles-Mumps-Rubella Vaccination.⁷

Authors: Annamari Mäkelä, MD, J. Pekka Nuorti, MD, and Heikki Peltola, MD,

Publication & Date: *Pediatrics*, November 2002

Online at: www.pediatrics.aappublications.org/cgi/content/full/110/5/957

Details: This paper is often referred to as the “Finnish MMR Study”. The authors conducted a retrospective cohort study linking individual MMR vaccination data with a hospital discharge register among 535,544 children in Finland, aged 1-to-7 years old, who were vaccinated between November 1982 and June 1986 in Finland. The authors looked for changes in the overall number of hospitalizations for autism after vaccination throughout the study period and for hospitalizations due to inflammatory bowel disease for children with autism. For encephalitis and aseptic meningitis, they compared the number of events observed within 3 months after vaccination to the number of events in the subsequent 3-month intervals for 24 months.

Results: Of the 535,544 vaccinated children, 199 were hospitalized for encephalitis, 161 for aseptic meningitis, and 352 for autistic disorders (a rate of 6.7-per-10,000). In 9 children with encephalitis and 10 with meningitis, the disease developed within 3 months of vaccination, revealing no increased occurrence within this designated risk period. Because there is no specific “risk period” for autism following vaccination, the authors looked for changes in the number of hospitalizations for autism after MMR vaccination for the study as a whole. They found no clustering of autism hospitalizations, which ranged from 3 days to twelve and a half years. None of children with ASD had hospital visits for inflammatory bowel diseases.

Authors’ Conclusions: “We did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, or autism.”

WHAT CRITICS SAID:

F. Edward Yazbak, MD: Makela *et al.* were so intent on shooting down Wakefield’s work that even in a paper titled “Neurologic disorders after MMR,” they found a way to mention that no hospitalized children with autism had IBD. But regardless of what Makela says, the fact is that the number of individuals who received assistance for IBD from the Social Security Institution in Finland doubled in nine years (from 9,737 in 1992 to 20,807 in 2001).

The whole study is based on ONE comparison. If the children in the first group developed symptoms of encephalitis and meningitis within two weeks of vaccination, then causation is implied (medically and medico-legally). In this case, a comparison with the control group is meaningless and the author’s conclusion is unwarranted.⁸

WHAT THE COCHRANE REVIEW SAID:

- This study suffered from a “moderate” risk of bias.
- It was “weakened” by the loss of 14% of the original birth cohort and the effects of the rather long time frame of follow up. What the impact of either of these factors was in terms of confounders is open to debate.
- The long follow up for autism was due to the lack of a properly constructed causal hypothesis.
- The study failed to report complete vaccine identification information, including lot numbers, adjuvants, preservatives, strains, product and manufacturer.
- There was a lack of adequate description of exposure (vaccine content and schedules).
- The authors provided “inadequate” explanations for missing information, even though there were clearly missing unintended-event data on as many as 20% of the participants.
- The study had discrepancies in reporting of denominators and was classified to be at moderate risk of bias.

What the IOM said: The study suffered from one primary limitation: its exclusive reliance on hospitalization records. This made it impossible to identify children with ASD who were not hospitalized, but rather seen in an outpatient setting. The IOM went on to say that “While the authors stated that it is common in Finland for children with autism to be admitted to the hospital for observation and testing, a diagnosis of autism does not always involve hospitalization.”⁹

What Science-Based Medicine.com said: “Using ‘hospitalizations’ as criteria for finding children with autism (is) not a good way to find autism cases, I agree.”¹⁰

SUMMARY:

The “Finnish MMR study” fails to make explicit the exact definition of ‘caseness’, particularly with respect to autism. The criticisms leveled at the study are crucially important in this respect. First, there is a failure to differentiate between autism per se, and the sub-group who are proposed to be at increased risk (i.e. those with regressive onset). There is also a degree of circularity in the statement that those whose encephalitis was ‘unrelated to vaccination’ were excluded. To deselect particular cases before analysis, on the basis of a proposed non-relationship between exposure and outcome is poor epidemiological practice. Further, it implies that decisions about causality were made after the event, on the basis of criteria which were not made explicit to the reader. At face value, the exclusion of these cases would appear to work in favor of those proposing a possible association between exposure and hospitalization; but this would only be the case if the lack of association was real. No evidence is presented which

allows formulation of an opinion on this. The most problematic factor, however, is in the assumption that children hospitalized 'for autism' somehow represent the very well defined group of children that are proposed to be at risk of an adverse event following vaccination. This assumption simply has no validity, and neither, therefore, do any conclusions based on data related to this group.

3) No evidence for a new variant of measles-mumps-rubella-induced autism.¹¹

Authors: [Fombonne E](#), [Chakrabarti S](#)

Publication & Date: *Pediatrics* October 2001

Abstract Online at: <http://www.ncbi.nlm.nih.gov/pubmed/11581466>

Details: A link had been hypothesized between MMR vaccine and a type of ASD where developmental regression and gastrointestinal symptoms appear shortly after vaccination. The hypothesis involves 3 claims: 1) this is a new type of ASD, 2) this new type is responsible for the reported ASD rate increase, and 3) this new type is associated with symptoms suggestive of persistence of measles infection. If such a new "autistic enterocolitis" syndrome had some validity, then 1 or more of the following 6 predictions should be supported by empirical data:

- 1) Childhood disintegrative disorder has become more frequent
- 2) The age of first parental concern for ASD children exposed to MMR is closer to the average age of vaccination than in non-exposed children
- 3) ASD regression autism has become more common in MMR-vaccinated children
- 4) The age of onset for regressive ASD clusters around the MMR and is different from that of autistic children without regression.
- 5) Children with regressive autism have distinct symptom and severity profiles
- 6) Regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder.

The authors used three samples. Data on 96 children (95 immunized with MMR at a median age of 13.5 months) in the UK who were born between 1992 and 1995 and had a PDD diagnosis were compared with data from two other clinical samples (1 pre-MMR [n = 98] and 1 post-MMR [n = 68]) of patients with autism. Reliability was excellent on Autism Diagnostic Interview-Revised (ADI-R) scores, age of parental concern, and developmental regression. Data on bowel symptoms were also available from pediatric and parental sources, while vaccination dates were obtained from computer records.

Results: The authors state that prevalence of childhood disintegrative disorder was 0.6-per-10 000 – a very low rate, consistent with other estimates, and not suggestive of an increased frequency of this form of pervasive developmental disorder in samples of children who are immunized with MMR. Meanwhile there was no difference in the timing of first parental concern between the two MMR-exposed samples (19.3 and 19.2 months) and the pre-MMR sample (19.5 months). "Thus" the authors claim "MMR immunization was not associated with a shift toward an earlier age for first parental concerns.

Meanwhile, the proportion of children with developmental regression reported in the post-MMR sample (15.6%) was no different from the pre-MMR sample (18.4%); and

there was no suggestion that ASD regression had increased in frequency since MMR was introduced. The authors note that children with regressive ASD had no other developmental or clinical characteristics, a finding which, they claim, would have argued for a specific, etiologically distinct phenotype. Parents of regressive ASD children detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months), and the difference in time between MMR vaccination and parental recognition was not significant (248 vs. 272 days). GI symptoms were reported in 18.8% of cases, with constipation the most common (9.4%).

No inflammatory bowel disorder was reported, nor was there any association between regression and GI symptoms. Only 2.1% of the sample had both GI symptoms and regression, "a rate (sic) that did not exceed chance expectations."

Author's Conclusions: "No evidence was found to support a distinct syndrome of MMR-induced autism or of 'autistic enterocolitis'," and the study adds to "large-scale epidemiologic studies that all failed to support an association between MMR and autism at the population level."

WHAT CRITICS SAID:

Critics question the basic assumptions behind the hypothesis, namely that if 'autistic enterocolitis' is real, then one or more of the authors' six predictions would be borne out by the data.

■ **Prediction (1)** - *"childhood disintegrative disorder has become more frequent"*.

According to the study, the prevalence of childhood disintegrative disorder was very low, 0.6/10,000, and therefore had *not* become more frequent. But that figure is many times lower than estimated prevalence of regressive autism found in other studies, suggesting that the two cannot be equated.

■ **Prediction (2)** - *"the mean age of first parental concern for autistic children who are exposed to MMR is closer to the mean immunization age than in children who are not exposed to MMR."*

The mean age at first parental concern was 19.3 months in the two MMR samples and 19.5 months in the pre-MMR sample. But just because one might expect to find a difference, the similar results do not really prove anything. For example, children in the pre-MMR sample were still exposed to live virus from monovalent measles.

■ **Prediction (3)** - *"regression in the development of children with autism has become more common in MMR-vaccinated children."* The study found that regression in MMR-vaccinated children was no more common than regression in the pre-MMR sample, and had not increased in frequency. Furthermore, the children who did regress were no more likely to have other developmental or clinical characteristics, which would have supported the argument for a distinct regressive ASD phenotype.

The problem here is that the samples were quite small: two MMR-exposed samples of 96 and 68 children and one pre-MMR sample of 98. With numbers this small, only a few cases either way would have impacted the results.

■ **Prediction (4)** - *"the age of onset for autistic children with regression clusters around the MMR immunization date and is different from that of autistic children"*. The study found that parents of autistic children with developmental regression detected the first symptoms at a very similar age (19.8 months) to those of autistic children without regression (19.3 months). The study also found that the mean intervals from MMR to parental recognition of autistic symptoms were comparable in autistic children with or without regression (248 days vs. 272 days, not significant).

Vaccine-induced regression would not necessarily be expected to cluster around the time of MMR vaccination, but could be delayed by weeks, months, or even years in some individuals. There is no reasonable scientific justification to believe the children who regressed following MMR should be recognized at a different time than those who did not regress after the vaccine. And though the difference was deemed to be "not significant" (248 vs. 272 days) it is still an unexplained margin of 10%.

■ **Prediction (5)** - *"children with regressive autism have distinct symptoms and severity profiles."*

Not enough is known about 'autistic enterocolitis' to make such an assumption about external characteristics into a key test.

■ **Prediction (6)** - *"regressive autism is associated with gastrointestinal symptoms and/or inflammatory bowel disorder"*.

It is impossible to say that none of these children had signs of inflammatory bowel disorder because none of them underwent colonoscopy.

WHAT THE COCHRANE REVIEW SAID:

■ This study was assessed as having a "high likelihood" of bias.

■ In fact, the number of biases and their likelihood to negatively impact the study "was so high that interpretation of the results was impossible."

■ The population description in this study raised doubts about the generalizability of the conclusions to other settings.

■ This study failed to report complete vaccine identification information, including lot numbers, adjuvants, preservatives, strains, product and manufacturer.

■ There was a lack of adequate description of exposure (vaccine content and schedules) in the study.

■ This study failed to report any vaccine strains at all and failed to provide descriptions of all outcomes monitored.

SUMMARY:

The Fombonne and Chakrabarti study is flawed in a variety of ways. The biggest weakness is in its misinterpretation of the actual hypothesis of an association between a specifically defined sub-group of children and the exposure (MMR) of interest. It is on this erroneous understanding that the authors' assumptions are based. The assumptions are not valid and any findings based on them are consequently of little interest. The inadequate study design (in terms of poor definitions of cases, controls and exposures) also means that any other uses to which the data might be put are extremely limited.

4) MMR vaccination and pervasive developmental disorders: a case-control study.¹²

Authors: Smeeth L, et al.

Publication & Date: *Lancet*, September 11, 2004;364:963-9

Abstract online at: <http://www.ncbi.nlm.nih.gov/sites/entrez>.

Details: The authors conducted a matched case-control study using the UK General Practice Research Database. They included children born in 1973 or later who were diagnosed with a pervasive developmental disorder at a GP physician setting between 1987 and 2001. Controls were matched on age, sex, and general practice.

Results: 1,294 cases and 4,469 controls were included. Of the PDD cases, 1,010 (78.1%) received the MMR vaccine before their recorded diagnosis, compared with 3671 controls (82.1%) before the age at which their matched case was diagnosed. After adjustment for age at joining the database, the odds ratio for association between MMR and pervasive developmental disorder was 0.78 for the non-practice matched control group and 0.86 for the practice matched control group. Once again, the vaccine apparently had a protective effect: MMR vaccinated children were 22% less likely to have PDD compared with the non-practice matched control group and 14% less likely to have PDD than the practice matched control group. "Findings were similar when restricted to children with a diagnosis of autism, to those vaccinated with MMR before the third birthday, or to the period before media coverage of the hypothesis linking MMR with autism.

Authors' Conclusions: "Our findings suggest that MMR vaccination is not associated with an increased risk of pervasive developmental disorders."

WHAT CRITICS SAID:

- Problems in the study design operate against the probability of detecting an increase in risk.
- There are significant changes from the methodology first proposed and subsequently cited in the present paper. Critics say it was crucial that case groups comprised only regressive, or late-onset, PDD, but Smeeth et al. confess (on p 967) that they were unable to do this.
- The small sample size is an issue – In order to complete such a matched-pair study with an estimated control exposure rate of 80%, the appropriate sample size would be 7,145 cases - almost six times the number of cases used in Smeeth et al.
- Two failings (below) in particular are "of such significance as to invalidate the conclusion that MMR vaccine is not associated with onset of autism in children." (Wakefield)

- The authors state that they were “not able to separately identify the subgroup of cases with regressive symptoms to investigate the hypothesis that only some children are vulnerable to MMR-induced disease and that this is always regressive. In this single statement they make it clear that they have not conducted an investigation of “what has been referred to as ‘the Wakefield hypothesis.’”
- The paper “cannot be said to have concluded anything of relevance to the (Wakefield) hypothesis and has been grossly over-interpreted.
- Despite the authors’ assurance that all diagnoses would be validated by a detailed review of hospital letters and information from parental questionnaires, only 25% of cases had their records examined and no questionnaire was used.
- Other “substantial changes in the methodology” were also not explained in the paper, which therefore “meets neither the criteria for testing the original question nor those laid-down by the authors themselves.”

WHAT THE COCHRANE REPORT SAID:

- Although the study “appeared to be carefully conducted and reported,” the database used “had no unexposed (to MMR) representative controls.” And though the 4% to 13% figure of unexposed controls was regarded by the authors as “representative,” such small numbers “may indicate some bias in the selection of controls.”
- This underrepresented control “problem appeared to provide the rationale for the design of DeStefano 2004” (another study reviewed by Cochrane).
- In this study, it was “impossible” to determine the “precise nature of controlled unexposed to MMR and its generalizability.”
- This study suffered from a “moderate” risk of bias.
- This study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.
- This study failed to report any vaccine strains at all.
- The authors provided “inadequate” explanations for missing information, even though there were “clearly missing unintended-event data” on as many as 20% of the participants.

SUMMARY:

The Smeeth et al. study goes a step further in highlighting the inadequacy of study designs that fail to isolate the correct case-group by specifically stating their intention to

do so, (in a pre-study protocol discussion) and then clearly informing the reader that they failed to deliver on this intention. This represents a fundamental and fatal failure to address the right hypothesis. This means, in turn, that the study fails to add any data of scientific value regarding the vaccine-autism hypothesis whatever its other features might be.

5) “Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta.”¹³

Authors: Frank DeStefano, et al.

Publication & Date: *Pediatrics*, February 2004

Abstract online at:

www.ncbi.nlm.nih.gov/pubmed/14754936?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Details: The authors conducted a case-control study in metropolitan Atlanta, where 624 ASD case children were identified from multiple sources and matched to control 1,824 children on age, gender, and school. This study assessed the association between MMR vaccine and the onset of autism among three age strata: up to 18, 24 and 36 months. Vaccination data were abstracted from immunization forms required for school entry. Records of children who were born in Georgia were linked to Georgia birth certificates for information on maternal and birth factors.

Results: The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children. 70.5% of ASD cases and 67.5% of control children were given the MMR vaccine between 12 and 17 months of age. Similar proportions of case and control children were vaccinated before 18 or before 24 months. “No significant associations for either of these age cutoffs were found for specific case subgroups, including those with evidence of developmental regression.” More case (93.4%) than control children (90.6%) were vaccinated before 36 months, and this association was strongest in the 3- to 5-year age group.

Authors’ Conclusions: “Similar proportions of case and control children were vaccinated by the recommended age or shortly after and before the age by which atypical development is usually recognized in children with autism (i.e. 24 months). Vaccination before 36 months was more common among case children than control children, especially among children 3 to 5 years of age, likely reflecting immunization requirements for enrollment in early intervention programs.”

WHAT CRITICS SAID:

The authors did not discuss the causes of the present epidemic now affecting the United States, but “simply stated that the MMR was unlikely to be the cause of regressive autism because children diagnosed with autistic disorders in Atlanta, Georgia received their first MMR vaccine at about the same age as unaffected children.”¹⁴

DeStefano and colleagues performed a case-control study comparing age at first MMR vaccination in children from the Atlanta metro area (2). By 36 months of age,

significantly more cases with autism (93%) had received MMR than controls (91%)(Odds Ratio 1.49; 95% confidence interval [CI] 1.04-2.14). This association was strongest in the 3 to 5-year age group with an Odds Ratio of 2.34. Due to diagnostic delay, a significant proportion of this group had yet to be diagnosed with autism, potentially underestimating this risk. Moreover, in a subgroup analysis looking at children with different disease characteristics, they found a significant association between MMR vaccination by 36 months and autistic children with no evidence of mental retardation (IQ>70; OR 2.54 [1.20-5.00]). The odds ratios were increased to 3.55 in a subgroup analysis adjusted for birth weight, multiple gestation, maternal age and maternal education, thus strengthening the association between age-of-exposure to MMR and autism.¹⁵

WHAT THE COCHRANE REPORT SAID:

- Even though the authors concluded there was “no significant difference” between cases and controls in the age at first vaccination up to 18 months and 24 months, more cases received MMR before 36 months, making the two groups different in an important sense.
- This conclusion “showed bias in the enrollment of cases which may not be representative of the rest of the autistic population of the city of Atlanta, USA where the study was set.”
- This study offered “inadequate explanations” for missing data.
- This study had the highest rate of excluded cases – more than one-third of the total – among all studies reviewed by Cochrane.
- Reporting on vaccine coverage and the “structure of comparisons” in this study were unclear, “raising the possibility of bias.”
- This study suffered from a “moderate” risk of bias.

SUMMARY:

The DeStefano et al. study contains a number of important methodological flaws. Notably, however, the study group showed significant differences between cases and controls in age at vaccination. To dismiss this as being unimportant simply on the basis of similar overall proportions of case and control children being vaccinated by the recommended age is careless at best; contrived at worst. This is one of the few studies where any attempt has been made to look at a group of children with regressive onset, and it is one of the few to have demonstrated differences in age of exposure between case and control groups. This provides direct support for a role of MMR in increasing autism risk. That this alone didn't raise questions and stimulate genuine discussion in the paper itself is striking.

6) “Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.”¹⁶

Authors: B Taylor, et al.

Publication & Date: [Lancet](#). 1999 Jun 12;353(9169):2026-9

Abstract online at:

http://www.ncbi.nlm.nih.gov/pubmed/10376617?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum

Details: The authors studied children with autism born since 1979 who were identified from special needs/disability registers and special schools in eight North Thames health districts, UK. Clinical records were linked to immunization data from the child health computing system. Investigators looked for trend changes in incidence or age of diagnosis when MMR was introduced to the UK in 1988. Clustering of onsets within defined post-vaccination periods was investigated by the case-series method. The researchers also recorded information on bowel problems (when they exceeded 3 months in duration), onset of parental concern about the child's development, and regression (if there was documented decline in the child's development or parents reported loss of skills).

Results: We identified 498 cases of autism (261 of core autism, 166 of atypical autism, and 71 of Asperger's syndrome). There was a steady increase in cases by year of birth with no sudden "step-up" or change in the trend line after the introduction of MMR vaccination. There was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated. There was no temporal association between onset of autism within 1 or 2 years after vaccination with MMR. Developmental regression was not clustered in the months after vaccination. No significant temporal clustering for age at onset of parental concern was seen for cases of core autism or atypical autism with the exception of a single interval within 6 months of MMR vaccination.

Authors' Conclusions: "The authors reported a significant increase in onset of parental concern at six months post vaccination. They argued that this may have been due to multiple testing, caused by an unclear causal hypothesis, and concluded that the evidence did not support an association with autism. "If such an association occurs, it is so rare that it could not be identified in this large regional sample," they wrote.

WHAT CRITICS SAID:

■ Older children, born in 1984-1986, also received the vaccine as part of the United Kingdom's Catch-up campaign.

- The authors erroneously concluded that the rise in autism started several years before MMR was introduced and therefore had nothing to do with this vaccine. In fact a substantial number (n=36) of their cohort had formed part of the Catch-up campaign, and the step-up in autism occurred at precisely the time the first children received MMR vaccine in North London.
- In their defense, the authors claimed that review of the records in the older recipients of MMR had identified parental concerns before MMR vaccination. They used this argument as justification for interpretation of a graph which simply presented number of children with autism versus year of birth, and owed nothing to apparent expressions of parental concern.
- The authors tested the hypothesis of temporal clustering of age at diagnosis of autism in defined time periods post MMR vaccination, an analysis which, because of the considerable delay in diagnosis, is likely to bias towards a negative finding.
- Despite this, they still found significant clustering of diagnoses by 6 months post MMR.
- The authors tested a hypothesis and found a positive association.

WHAT THE COCHRANE REPORT SAID:

- The absence of unvaccinated controls limits the inductive statements that can be made from this study.
- The authors were “uncertain as to the power and generalisability of the findings from the single case-only design study.”
- “This study demonstrates the difficulties of drawing inferences in the absence of a non-exposed population or a clearly defined causal hypothesis.”
- This study failed to report complete vaccine identification information, “including lot numbers, adjuvants, preservatives, strains, product and manufacturer.”
- This study failed to report any vaccine strains at all.

WHAT THE IOM SAID

There was an association between bowel problems and developmental regression – with almost twice the rate of bowel symptoms found in the regressive population. Thirty-one of the 118 children [26 percent] with regression and 49 of the 351 children [14 percent] without regressive autism reported bowel symptoms. “Single and multivariable logistic regression models, however, showed no association with these factors and MMR vaccine.”

SUMMARY:

Taylor et al. is another study that set out to address the issue of vaccine exposure in the correct set of (regressive onset) children and found an association between exposure and age of onset (within 6 months of exposure) and between regressive onset autism and bowel disease – both factors of crucial importance to the Wakefield hypothesis. The fact that the authors report the findings, but fail to discuss their potential importance, devalues the paper substantially. In addition, the design was not one from which observations on causality could be made and should be considered a descriptive study. Nonetheless the study provides clear evidence to support further evaluation of the precise factors outlined by the Wakefield hypothesis as being key to the potential MMR-autism association

7) “No effect of MMR withdrawal on the incidence of autism: a total population study”¹⁷

Authors: Hideo Honda, Yasuo Shimizu, and Michael Rutter,

Publication & Date: *Journal of Child Psychology and Psychiatry*. June, 2005.

Abstract online at: <http://www.ncbi.nlm.nih.gov/pubmed/15877763>

Details: The authors studied cumulative incidence of ASD up to age seven for children born from 1988 to 1996 in Kohoku Ward, Yokohama, Japan. Japan is unique, because MMR was introduced in 1989 and discontinued in April 1993. ASD cases included all cases of pervasive developmental disorders according to ICD-10 guidelines.

Results: MMR coverage dropped considerably in Yokohama in the birth cohorts of 1988 through 1992, (because of safety concerns over the strain of live mumps virus being used), and not a single MMR vaccine was administered in 1993 or thereafter. “In contrast, cumulative incidence of ASD up to age seven increased significantly in the birth cohorts of years 1988 through 1996 and most notably rose dramatically beginning with the birth cohort of 1993.”

Authors’ Conclusions: “The significance of this finding is that MMR vaccination is most unlikely to be a main cause of ASD, that it cannot explain the rise over time in the incidence of ASD, and that withdrawal of MMR in countries where it is still being used cannot be expected to lead to a reduction in the incidence of ASD.”

CRITIQUES OF THE STUDY¹⁸

- The study tells us little about ASD incidence of ASD prior to 1988, when MMR was introduced. But we do know that the published *prevalence* of ASD did not exceed 25-per-10,000 at any time in Japan prior to 1988.
- Annual incidence of ASDs for children born in 1987 was 20-per-10,000, but after MMR was introduced, in 1988, annual incidence *more than quadrupled*, to 85.9-per-10,000 for children born in 1990.
- But then, MMR coverage began to decline dramatically, as concerns over the mumps viral component grew. ASD incidence likewise declined during this period, to 55.8 for children born in 1991 – representing a drop of 35%.

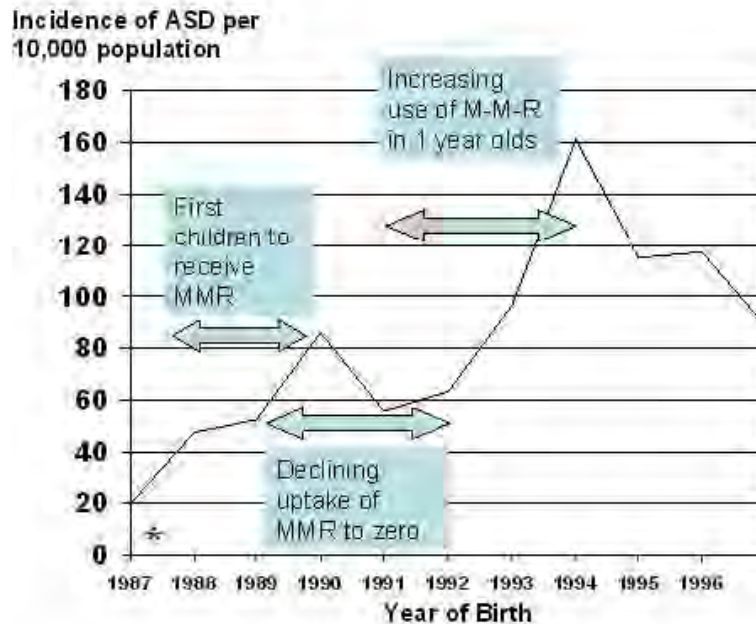


Figure 1. Annual trends in cumulative incidences up to seven years of childhood autism and other ASD.

■ Following complete discontinuation of MMR in 1993, ASD incidence rose again, this time quite dramatically, to 161-per-10,000 for children born in 1994. However, during this time the recommended schedule was changed to include three single vaccines (M-M-R, given four weeks apart), which gained widespread acceptance, causing coverage to increase significantly.

■ For all practical purposes, children vaccinated according to the new schedule were still receiving 'M-M-R' at around age one. Giving the three separate vaccines in such close proximity amounts to overlapping exposure, in biological terms.

■ Early MMR trials showed clear evidence of 'interference' between the viruses in the combined vaccine, mediated through an altered immune response. The safety consequences of this 'interference' are completely unknown.

■ Children who have natural measles (or single measles vaccine) and natural mumps infections within the same year are at significantly greater risk of later inflammatory bowel disease,¹⁹ which is consistent with an 'interference' phenomenon that could increase the risk of long-term measles virus infection and delayed disease.

■ The authors are wrong to examine MMR as the single exposure of interest, when in biological terms, exposure to M-M-R through three consecutive monovalent vaccines actually increased after 1993 when MMR was discontinued.

■ The data, therefore, could be interpreted as indicating a major influence of the pattern of exposure to these vaccine viruses on ASD incidence in this Japanese population.

■ More importantly, the data suggest a possible re-challenge effect of close temporal exposure to these three vaccine viruses on ASD incidence at the population level, whereby the exposure (MMR) has been introduced, removed (voluntarily through lack of public confidence), and then re-introduced (as M, M, and R close together).

■ ASD numbers increased and decreased in direct proportion to the total number of children vaccinated with the three live viruses. There is evidence of an effect not only from de-challenges and re-challenges, but there is also a “dose-response” relationship on a population level.

■ Such a dose-response relationship on a population level is rare; and is evidence of a possible causal association.

■ The interpretation by Public Health officials that this is the “last word on the subject” and that these data prove that MMR is safe is misleading and suggests a very limited perspective of the issues and a misunderstanding of published concerns on viral interference in a trivalent live-virus vaccine.

Undisclosed Conflict of Interest: Co-author Michael Rutter has close associations with the drug industry, including GlaxoSmithKline. He was a paid expert witness on their behalf in the UK MMR vaccine damage litigation. That was not declared in the Honda/Rutter paper.

SUMMARY:

Despite the methodological problems in Honda et al., and quite apart from the fact that an ecological study of this kind cannot be used to make attributions about causality, the unrecognized challenge-rechallenge effect of vaccination on autism rates in Japan provide yet another piece of support for the MMR-autism link. Because this study failed to clearly interpret the true population risk in the exposure of interest—assuming the removal of an exposure that in reality had remained— the conclusions drawn by the authors are based on erroneous reasoning. Although drawing overly strong conclusions about an association between MMR-type exposures and autism would be premature in light of the study’s ecological design constraints, the data clearly indicate that further scrutiny of the data is required.

8) “Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations.”²⁰

Authors: Eric Fombonne, MD, et al.

Publication & Date: *Pediatrics*, July 2006

Online at: <http://pediatrics.aappublications.org/cgi/content/full/118/1/e139>

Details: This cohort study surveyed 27,749 children born from 1987 to 1998 who went to 55 schools in the largest English-speaking school district in Montreal, Quebec. Children with PDDs (the Canadian term for ASD) were identified by a special needs team. The investigators looked at exposure to thimerosal by age 2 years and MMR coverage - which was estimated using vaccination rate surveys. The Canadian schedule called for an MMR injection at 12 months of age, up to 1995, when a second dose at 18 months was added.

Results: The authors found 180 children (82.8% of them males) with a PDD diagnosis at the surveyed schools, for a prevalence rate of 64.9 per 10,000. For autistic disorder, the rate was 21.6-per-10,000; for PDD-NOS it was 32.8-per-10,000; and for Asperger’s syndrome, 10.1-per-10,000. “A statistically significant linear increase in pervasive developmental disorder prevalence was noted during the study period,” the authors wrote. The PDD prevalence in thimerosal-free birth cohorts was significantly higher than among children who received thimerosal (59.5-per-10,000 vs. 82.7-per-10,000 – in other words, thimerosal-exposed children were 16% less likely to have an ASD).

Meanwhile, MMR coverage averaged 93% during the study period, though rates declined from 96.1% in the older birth cohorts (1988–89) to ~92.4% in younger birth cohorts (1996–1998). Thus, PDD rates “significantly increased” during the same period when MMR uptake rates “significantly decreased.” Moreover, PDD prevalence went up at the same rate before and after the second MMR dose was introduced in 1996, “suggesting no increased risk of pervasive developmental disorder associated with a 2-measles-mumps-rubella dosing schedule before age 2 years. Additional analyses to test for the potential effects of exposure or diagnosis misclassification yielded the same results.”

Authors’ Conclusions: PDD prevalence in Montreal was high, and increased in recent birth cohorts, as it had in most other countries. This rise was due to “a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification, (and) improved access to services.” There was no evidence that PDD had become more frequent, regression with autism had not become more common, and children with regressive autism did not have different profiles to those in the control group. These results “ruled out” an association between PDD and 1- or 2-dose MMR vaccinations.

WHAT CRITICS SAID

■ Fombonne et al. evaluated children enrolled in only one of Montreal’s five school boards, Lester B. Pearson School Board (LBPSB), but they cautioned that PDD rates in

LBPSB may not have been representative of rates elsewhere and suggested that data from other school boards should be assessed but claimed, “this information was not available in the survey data that we could obtain.”

■ Data from all five Montreal school boards was easily obtainable from the Ministry of Education of Quebec, and they showed that enrollment at LBPSB in 2003-04 represented only 14% of all total school board enrollments in Montreal, but the PDD rates were significantly higher than all four other school boards *combined*. In some cohorts, prevalence was three times higher in LBPSB than in other districts.²¹

■ Fombonne et al. could not possibly have accurately estimated the citywide rates of PDD merely by assessing just this one school board; any conclusions about a relationship between vaccines and PDD rates in Montreal may be seriously flawed.

■ By choosing to study only a small subset of the children in Montreal’s schools, the authors committed a serious selection bias.

■ LBPSB includes a Center of Excellence in Autism, so its high rates of PDD are likely influenced by the fact that it is the only totally inclusive school board of the Province of Quebec and has a very high ratio of integration of students with PDD into regular classes. Many families of children with PDD often seek to enroll them in LBPSB resulting in an overestimate of true PDD rates in Montreal as a whole.

■ Fombonne et al. chose to study MMR coverage rates, rather than the number of MMR vaccines received. He ignored the fact that autism rates increased following a doubling of the MMR exposure after 1996 when a second MMR shot was added to the schedule and chose to emphasize that a rise in PDD rates coincided with a decline in MMR coverage.

■ Fombonne also ignored the possible effect of mass measles immunization campaigns in Quebec that delivered a second dose of measles to a large number of infants and children throughout 1996.²² The subsequent rise in PDD shortly after that campaign is clearly depicted in their figures.

■ MMR coverage data was taken from the city of Quebec, rather than from Montreal, where the PDD data was gathered. MMR data “were available through N. Bouliane, of the Direction de Santé Publique de la Capitale Nationale,” the authors wrote. But the “Capitale Nationale” refers to Quebec City, not Montreal, some 265 kilometers away. Ms. Bouliane confirmed that the MMR vaccination rates were from the Quebec City.

■ Published MMR vaccine surveys from Montreal show that rates among children 24 to 30 months old did not fall during the period in question, but actually increased from 85.1% in 1983 (Baumgarten)²³ to 88.8% in 1996-97 (Valiquette)²⁴ to 96% in 2003-04 (Health Department Survey).²⁵

■ This suggests that in Montreal, PDD prevalence and MMR vaccination rates were in fact increasing in tandem during the study period.

■ F. Edward Yazbak, MD, FAAP, wrote to *Pediatrics* to protest,²⁶ and said that “Readers deserve to know why the authors compared developmental data from a specific group of children in Montreal with MMR vaccination data from the city of Quebec, some distance away.”

■ In response, Dr. Fombonne failed to address the criticisms when he wrote to the editor of *Pediatrics* that, “This person (Yazbak) is known to pursue the MMR-autism agenda at all costs in order to 'demonstrate' a link he strongly believes in. All controlled epidemiological research thus far has concluded to the absence of such a link.”²⁷

■ The Editor of *Pediatrics*, Jerold F. Lucey, also wrote to Dr. Yazbak, and stated that “I believe the evidence of no link between MMR and Autism is sufficient. It's not worth publishing more on this subject.”

■ Dr. Yazbak subsequently stated: “I found and reported a glaring error in the paper. The rates of autism in Montreal have as much to do with MMR vaccination rates in Quebec City as pollution in Los Angeles with Diesel buses in Chicago. The lead author refused to respond to my criticism concerning that simple geographic fact and the editor was unable to force him to do so.”²⁸

SUMMARY:

The criticisms of Fombonne are numerous and cover the most basic questions of study design, data quality, data interpretation and consistency. Furthermore, Fombonne's ad hominem attacks on his critics undermine his personal credibility. The single most ‘glaring error’ reported by Dr Yazbak, i.e. that “The rates of autism in Montreal have as much to do with MMR vaccination rates in Quebec City as pollution in Los Angeles with Diesel buses in Chicago”, undermines any of the conclusions drawn by the authors. That simple failure to match exposures and outcome is sufficient by itself to render its conclusions worthless.

9) “MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis.”²⁹

Authors: M. Vestergaard et al.

Publication & Date: *Journal of the American Medical Association*, July 21, 2004

Abstract online at: <http://www.ncbi.nlm.nih.gov/pubmed/15265850>

Details: MMR vaccination increases the rate of febrile seizures, though it is not known if the rate varies according to personal or family history of seizures, perinatal factors, or socioeconomic status, and little is known about the long-term outcome of febrile seizures following vaccination. The authors conducted a population-based cohort study of all children born in Denmark between January 1, 1991, and December 31, 1998, who were alive at 3 months. 537,171 children were followed up until December 31, 1999. While this study did not measure autism, its main outcomes studied were incidence of first febrile seizure, recurrent febrile seizures, and subsequent epilepsy.

Results: A total of 439,251 children (82%) received MMR vaccination and 17,986 of them developed febrile seizures at least once; 973 of these febrile seizures occurred within 2 weeks of MMR vaccination. The rate ratio (RR) of febrile seizures increased during the 2 weeks following MMR vaccination - (RR 2.75, or 175% more likely) and, after that period, were close to the observed RR for non-vaccinated children. The RR did not vary significantly in subgroups of children that had been defined by their family history of seizures, perinatal factors, or socioeconomic status. At 15 to 17 months, the risk difference of febrile seizures within 2 weeks following MMR vaccination was 1.56 per 1000 children overall, 3.97 per 1000 for siblings of children with a history of febrile seizures, and 19.47 per 1000 for children with a personal history of febrile seizures. Children with febrile seizures following MMR vaccinations had a slightly increased rate (19%) of recurrent febrile seizures (RR, 1.19) but no increased rate of epilepsy compared with children who were non-vaccinated at the time of their first febrile seizure.

Authors’ Conclusions: MMR was associated with a transient increased rate of febrile seizures but the risk difference was small even in high-risk children. The long-term rate of epilepsy was not increased in children who had febrile seizures following vaccination compared with children who had febrile seizures of a different etiology.

WHAT THE COCHRANE REVIEW SAID

- The rate of febrile seizures was significantly higher during the first week after vaccination (RR 2.46) and second week (RR 3.17) but not thereafter. Overall, MMR was associated with a higher risk of febrile seizures (RR 1.1).
- These are plausible conclusions given that MMR is a viral live attenuated vaccine. There appeared to be no association with a family history of febrile seizures but there was

a four-fold increase in risk of seizures within the first two weeks after MMR in siblings of children with epilepsy and a 19% increase in the risk of a second febrile seizure.

■ Overall, this was a well-reported, powerful study with credible conclusions as all possible efforts to account for confounders were made. This was the only cohort study judged to have a low probability of bias.

■ This study failed to provide descriptions of all outcomes monitored.

WHAT CRITICS SAID

■ This was one of the best constructed studies reviewed by Cochrane and carried the lowest risk of bias of all 14 cohort studies. And though the paper did not look at autism, it did find that the risk of febrile seizures more than tripled (RR 3.17) in the second week after MMR vaccination.

■ This study's findings were consistent with other studies showing that MMR vaccination increases the risk of febrile seizures, causing them in 10-to-20-per-10,000 injections, and in 220-per-10,000 children with a previous history of febrile seizures.³⁰

■ In 1994, a panel of the Institute of Medicine, writing about measles vaccine and brain injury or inflammation, concluded: "The National Childhood Encephalopathy Study, a case-control study described in detail in Chapter 5, reported a significant association between measles vaccination and onset of either convulsions or encephalopathy within 7 to 14 days of receiving the vaccine."³¹

■ MMR vaccine, when combined with varicella (chicken pox) live-virus vaccine into the 4-in-1 combination *ProQuad* shot, doubles the risk of seizures in children, compared with two separate MMR and chicken pox vaccines, a CDC study found. The CDC's Advisory Committee on Immunization Practices had recommended the vaccines be administered as separate shots, but subsequently voted to not recommend a preference between ProQuad and giving separate MMR and varicella vaccines. ³²

■ The MMR vaccine, (as well as DTP), is recognized by the US Department of Health and Human Services as a known cause of "encephalopathy" (brain disease) in a small subset of children. Acute encephalopathy induced by MMR exposure in children 18 months and older is associated not only with seizures, but can also cause a "decreased level of consciousness."³³

■ "A significantly decreased level of consciousness" induced by MMR exposure is indicated by the presence of at least one of the following clinical signs for at least 24 hours or greater:

1) Decreased or absent response to environment (responds, if at all, *only to loud voice or painful stimuli*).

Meanwhile “Many children with autism have a reduced sensitivity to pain, but are *abnormally sensitive to sound, touch, or other sensory stimulation,*” according to the National Institute of Neurological Disorders and Stroke (NINDS).³⁴

(2) *Decreased or absent eye contact (does not fix gaze upon family members or other individuals).*

“Children with autism often *avoid eye contact* with other people.”

3) *Inconsistent or absent responses to external stimuli (does not recognize familiar people or things).*

“A baby with autism may be *unresponsive to people* or become indifferent to social engagement.”

■ In **Bailey Banks v HHS**, the Federal Vaccine Court ruled that Bailey’s case of Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS) was a direct result of his development of acute disseminated encephalomyelitis (ADEM), a neurological disorder characterized by inflammation of the brain and spinal cord and damage to the myelin sheath, a fatty coating that insulates nerve fibers in the brain. Symptoms of ADEM include seizures. The judge ruled that Bailey’s ADEM was caused by his MMR immunization, “leading inexorably from vaccination to Pervasive Developmental Delay.”³⁵

SUMMARY:

Verstergaard et al. was more effectively designed than most other MMR safety studies. This analysis, however, did not explicitly include autism as an outcome. Nevertheless, did find an increased risk of febrile seizure following MMR, a finding that is consistent with other studies of MMR. The similarities between the Bailey Banks case—one in which the U.S. government conceded that a febrile seizure after MMR resulted in brain inflammation and an autism spectrum disorder—and the findings reported in this paper are striking. The dismissal of concerns over an adverse event like a febrile seizure highlights the casual and careless manner in which potentially crucial evidence is interpreted.

SOME FINAL REMARKS FROM CRITICS OF EPIDEMIOLOGICAL STUDIES ON MMR AND AUTISM

(The following quotes were part of official presentations made on February 9, 2004 to the Vaccine Safety Committee of the Institute of Medicine.)³⁶

“The current genetic research estimates that no more than 10% of all autistic cases are genetic in origin. Simply put, the remainder 90% of autistic cases is sporadic with a non-genetic etiology. I tend to think that the sporadic form is by and large an “acquired” subset involving autoimmunity. This subset is likely triggered by a virus, possibly measles virus or MMR vaccine. Based upon our experimental research, it is plausible to postulate that an atypical measles infection that does not produce a typical measles rash but manifests neurological symptoms might be etiologically linked to autoimmunity in autism. The source of measles virus could potentially be MMR vaccine or a mutant measles strain, but more research is necessary to establish either of these two possibilities.” -- **Vijendra K. Singh, Ph.D., Research Associate Professor of Neuroimmunology, Utah State University, an international expert in the autoimmune causes of autism.**

“Half of Dr. Wakefield’s theory has been proven correct and accepted in the medical community. Hundreds of children with regressive autism and GI dysfunction have been scoped and clinicians are seeing the inflammatory bowel disease he first described.” -- **(Fmr) U.S. Representative Dave Weldon, MD (R-FL).**

“In light of encephalopathy, presenting in children as autistic regression closely following MMR vaccination. The findings confirm a highly significant statistical association between the presence of measles virus RNA in cerebral-spinal fluid and autistic regression following MMR vaccination.” -- **Jeff Bradstreet, MD, Director, International Child Development Resource Center.**

PART 3

FLAWS AND LIMITATIONS OF THIMEROSAL-AUTISM EPIDEMIOLOGY STUDIES

There has only been one major scientific review of the main epidemiological studies to examine a potential association between thimerosal containing vaccines (TCVs) and autism spectrum disorders: The Institute of Medicine Immunization Safety Committee Report, issued in May, 2004.³⁷

The IOM report focused almost exclusively on large, population-based epidemiological studies based on health records. The committee chose to minimize the importance of several biomedical thimerosal studies conducted in laboratories and animal models. Today, a much larger body of medical literature has been amassed which clearly demonstrates the powerful neurotoxic effects of thimerosal. These are joined by other studies demonstrating the increased risks of simultaneous administration of certain vaccines on the current childhood schedule.

WHAT THE IOM CONSIDERED:

The IOM committee reviewed epidemiological studies examining TCVs and autism, including three controlled observational studies (Hviid et al., 2003; Miller, 2004; Verstraeten et al., 2003) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003). The published papers “consistently provided evidence of no association between TCVs 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),” the committee wrote.

IOM MAIN CONCLUSIONS:

- “Based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.”
- “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.”

LIMITATIONS OF THE IOM REVIEW:

- Because the “vast majority” of ASD cases cannot be accurately sub-classified, “if there is a subset of individuals with autism syndrome triggered by exposure to vaccines, our ability to find it is very limited in the absence of a biological marker.”

■ In fact, the committee admitted, trying to find a cause of autism using population-based epidemiological analyses “requires either a well-defined at-risk population or a large effect in the general population.”

■ But without any known biomarkers, well-defined risk factors, or large effect sizes, “the committee cannot rule out, based on the epidemiological evidence, the possibility that vaccines contribute to autism in some small subset or very unusual circumstances.”

NOTE: Knowledge of biomarkers and risk factors in ASD has increased considerably since the release of the 2004 IOM report.

CRITIQUES OF THE IOM REVIEW

Mark D. Noble, PhD - Professor of Genetics and of Neurobiology and Anatomy, University of Rochester Medical Center³⁸

It is easy to understand why people are not believing the scientific community. It reduces confidence in the scientific enterprise when it turns out that the CDC had information on early versions of the studies of Verstraeten et al. that demonstrated a linkage between thimerosal exposure and autism, that these studies were never published, and that no one has ever explained satisfactorily why different analyses were conducted and why they were changed. But all of these studies have equally debilitating flaws that invalidate any conclusions drawn from them on thimerosal safety. And if it turns out that there is a subset of children for whom additives in vaccines are a problem, then this is important to know. For then we can focus on how to identify these children in advance. The conclusions I have drawn are that we are not going to solve this problem by ignoring it. So let's embrace it. Let's get the data.

Irva Hertz-Picciotto, PhD, MPH, Chief of the Division of Environmental and Occupational Health, University of California, Davis School of Medicine –³⁹

Several large studies finding no association are far from robust, as they suffer from numerous biases that seriously limit their definitiveness. These include: noncomparable sources for ascertainment of cases, uncontrolled confounding, unrepresentative sample due to selective exclusions, and an as-yet unexplained pattern whereby children with earliest vaccines are the least likely to have developmental deficits. Thus, the body of evidence at this point is inadequate to draw conclusions... Several investigations have been ecologic studies, widely known to be the weakest possible epidemiologic design. Even restricting discussion to the individual-level designs, published studies conducted in Denmark, the UK, and the US are characterized by serious, even fatal, flaws. To regain the confidence that we in the medical/public health/scientific community need in order to fulfill our mandate to protect health, we cannot avoid facing these tough scientific questions head-on. This means funding solid scientific

research into vaccines, thimerosal, and the related issues of susceptibility at the population level.

Richard Deth, PhD, Professor of Pharmacology, Northeastern University –⁴⁰

The report aims to close the door on concerns that mercury-containing vaccines might have contributed to the increased frequency of autism. Unfortunately it is obvious that the need to close the door was given a higher priority than reaching reliable scientifically-based conclusions. This is particularly evident when the report shockingly takes a hard-line against further research into this important question ... From the very outset, (IOM committee chairwoman) Dr. Marie McCormick displayed a pugnacious and adversarial attitude toward the presentation of information suggesting a thimerosal/autism link, as opposed to that of a neutral investigator... The report reflects a similar adversarial tone, with a welcoming, uncritical presentation of those epidemiological studies which failed to find a link contrasted to a hypercritical, dismissive approach toward data supportive of a link. The IOM clearly valued the epidemiologic approach and de-valued results derived from autistic individuals. The report was a biased effort at damage control.

Dr. Joachim Mutter, FA, Institute for Environmental Medicine and Hospital Epidemiology, University Hospital Freiburg, Germany and US and UK colleagues –⁴¹

Epidemiological studies which do not consider genetic susceptibility factors, autoimmunity reactions and mercury exposure during pregnancy (amalgam, thimerosal), are not able to detect a statistically significant effect, even if there is one. (NOTE: *None* of the epidemiological studies reviewed by the IOM committee considered any of those factors.)

Rep. Dave Weldon, MD (Congressman from FL at the time) –⁴²

Today's report is premature, perhaps perilously reliant on epidemiology, based on preliminary incomplete information, and may ultimately be repudiated...Unfortunately, the epidemiology studies that the IOM bases its findings on are not immune from conflicts or controversy. Many of the authors have conflicts of interest including funding from vaccine manufacturers, employment by manufacturers, or conflicts in that they implemented vaccine policies that are now being investigated. Furthermore, the studies were designed to examine entire populations and would miss subgroups of genetically susceptible populations.

Boyd Haley, PhD, Professor of Chemistry and Bioorganic Chemistry, University of Kentucky –⁴³

It appears very solid that autistic children do not biochemically handle mercury as do normal children. This is not theoretical, this is biochemical fact -- the IOM members just chose to ignore it as it does not fit into what they wanted to report. (Some) data clearly show that a small subset of the population is being affected by mercury that would be somewhat difficult to detect with a less than elegantly designed epidemiological study, and easy to miss or cover up. This biochemical data does not totally prove thimerosal is causal for autism, but it certainly should have prevented the IOM from saying they 'conclusively' proved thimerosal was not involved. If you do not believe in a hypothesis you replace it with another. That is how science is done.

Coalition for SafeMinds – ⁴⁴

This committee clearly chose to ignore groundbreaking scientific research on the mercury-autism link, and instead the IOM has issued a flawed, incomplete report that continues to put America's children at risk. The problem with this report begins with its violation of nearly every tenet of medical science. Respected researchers everywhere do not support the IOM belief that proof can be solely found in epidemiology... Disclosure of potential conflicts of interest is an essential tenet to good science, but here we have a situation where authors of 'studies' are probably quite literally writing to preserve their jobs. The IOM gave unusual weight to several authors from the Statens Serum Institut (SSI) in Denmark. What the American public needs to know is that the SSI is not only the Danish version – and frequent collaborative partner – of the CDC, but also that country's largest vaccine manufacturer.

WHAT IOM COMMITTEE MEETING MINUTES SUGGEST:

On January 12, 2001, the IOM's Immunization Safety Review Committee held a closed-door meeting convened by Committee Chairwoman Dr. Marie McCormick and Study Director Kathleen Stratton. During the meeting, members discussed their charge from the CDC, which commissioned the review. The minutes were leaked to attorneys for families of children with autism.⁴⁵

At one point, Dr. McCormick seems to imply that CDC officials expect certain pre-ordained results from the study they are sponsoring and paying for:

Dr. McCormick: "CDC wants us to declare, well, these things (vaccines) are pretty safe on a population basis."

And Dr. Stratton announces to the committee what they WON'T be finding or recommending, before a single page of evidence has been presented:

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.”

Later, Dr. McCormick also announces a predetermined finding:

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

SUMMARY: The IOM Committee gave far more emphasis to epidemiological (population based) studies than biological studies, such as clinical studies in children, laboratory studies, and animal model studies. Since the IOM report was released in May, 2004, a large amount of biological data have been generated from several published studies to support an association between thimerosal and ASD. A new IOM review that includes these studies is needed.

INDIVIDUAL THIMEROSAL STUDIES

1) "Autism and thimerosal-containing vaccines: lack of consistent evidence for an association."⁴⁶

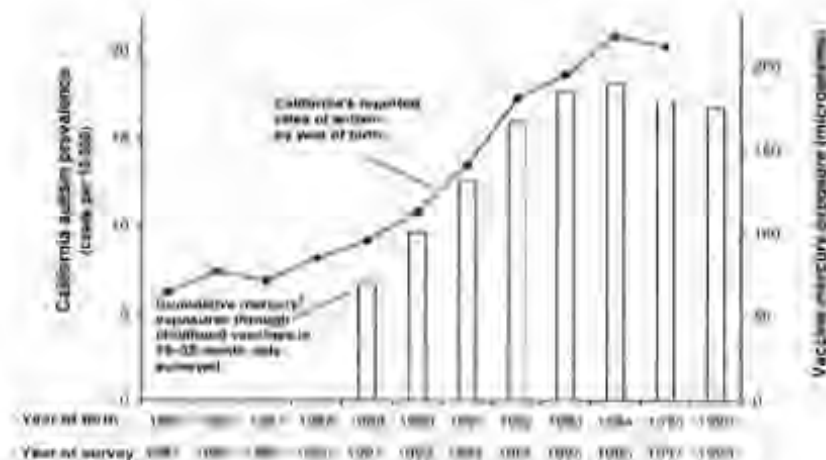
Authors: Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D.

Publication & Date: *American Journal of Preventive Medicine*, August, 2003

Abstract online at: <http://www.ncbi.nlm.nih.gov/pubmed/12880876?dopt=Abstract>

Details The authors compared thimerosal exposures and autism rates among children in Denmark, Sweden, and California. In California thimerosal use in childhood vaccines had continued until 2003, while Sweden and Denmark eliminated it in 1992-1993.

California - The authors examined data that SafeMinds member Mark Blaxill had presented to the IOM Immunization Safety Committee in June, 2001, which showed a time correlation between rising exposure levels and rising case numbers. But "as with most ecologic analyses," they wrote, "the data that Blaxill had compiled had several limitations." For example, the autism definition used by the California Department of Developmental Services (DDS) was somewhat "vague" and difficult to verify, the authors said. Any reported increase might have been caused by greater awareness and changes in diagnostic criteria, including the addition of autistic related illnesses, such as Pervasive Developmental Disorder (PDD), the study asserted, adding that, "These subcategories of PDD accounted for the largest increases in the reported California cases reflected in the data used."



Sweden – The authors reported that autism rates continued to climb after thimerosal was removed from Swedish pediatric vaccines in 1993. Looking only at autism patients in Sweden who were diagnosed in an inpatient (hospital) setting, they found that autism numbers rose and fell in an erratic pattern during 1980-1997, but still had an upward trend over the period. Case rates went from 5 or 6 cases “per 100,000 person-years” before 1985, to a peak of 9.2 per 100,000 person years in 1993. “This was generally similar to the trend in California during the same time period,” the authors said:

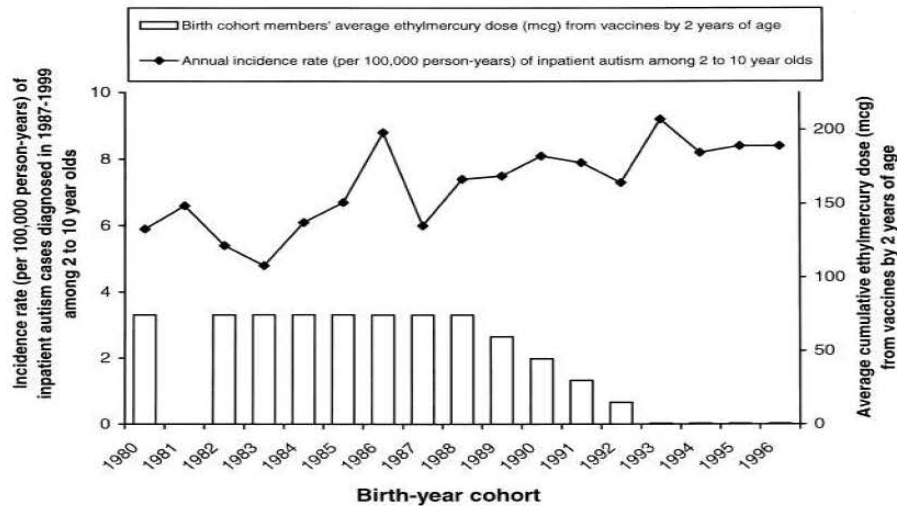


Figure 2. Graphical ecologic analysis comparing average cumulative ethylmercury dose received from vaccines and the incidence rate (per 100,000 person-years) of autism cases in children aged 2 to 10 years diagnosed during 1987-1999 in inpatient settings in Sweden, by birth-year cohort from 1980 to 1996. (Data not available for year 1981.)

Denmark - Case rates in Denmark also went up after thimerosal was removed, in 1992. But this increase was linear, and much more pronounced. Prior to 1992, Danish children were exposed to up to 125 micrograms mercury by age ten months, but reported autism rates during this period remained level, at about 10 new cases a year. By 1999, however, after thimerosal was removed, the reported number of new autism cases had climbed to about 200 – an astonishing 20-fold increase.

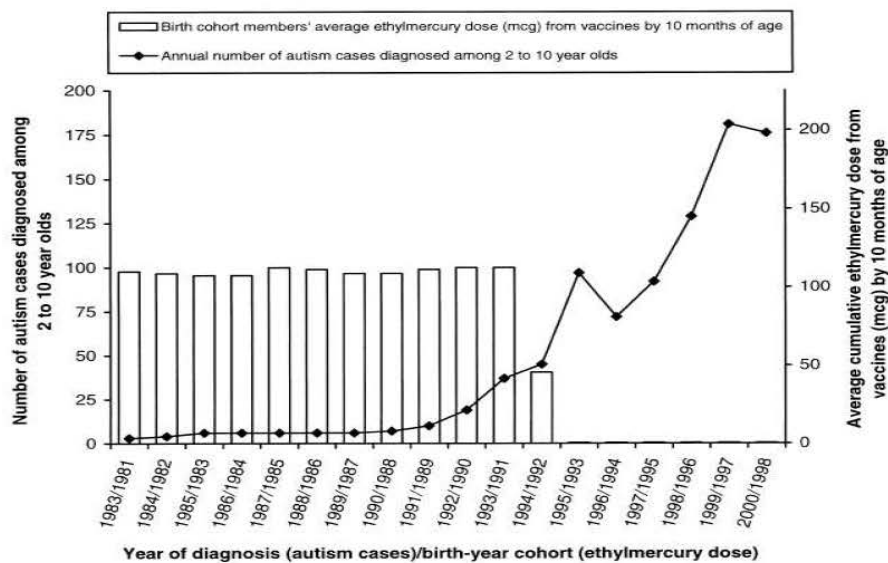


Figure 3. Graphical ecologic analysis comparing the average cumulative ethylmercury dose received from vaccines by birth-year cohort from 1981 to 1998, and the annual number of incident cases of autism in children aged 2 to 10 years diagnosed in Denmark from 1983 to 2000.

Results: “In all three countries, the incidence and prevalence of autism-like disorders began to rise in the 1985-1989 period, and the rate of increase accelerated in the early 1990s,” the authors wrote. But ethylmercury exposure levels were significantly different. The average dose from TCVS increased throughout the 1990s in the United States, but in Scandinavia, thimerosal was removed in the early 1990s.

Authors’ Conclusions: Results from Scandinavia provided “compelling evidence in sharp contrast to the alleged association observed in California” against a thimerosal-autism association, the study said. “The body of existing data, including the ecologic data presented herein, is not consistent with the hypothesis that increased exposure to Thimerosal-containing vaccines is responsible for the apparent increase in the rates of autism in young children being observed worldwide.” More plausible explanations for the increase included: “increased recognition of the disorder, and/or other as-yet-unidentified environmental or genetic factors.”

CRITIQUES OF THE STUDY

Critics point to this study’s most glaring flaw, which appears in the Denmark section. The authors relied on autism prevalence data as reported in the Danish Psychiatric Central Register. But the way in which Denmark diagnosed and tracked autism patients had changed radically over the course of their investigation. This created an important alteration in the study’s entry criteria midway through the study period.

■ **Changing Danish Population** - From 1983-1992, the Danish register only listed autism cases that were diagnosed in an inpatient (hospital) setting. But in 1992 data from a large, state-of-the-art autism clinic in Copenhagen, which was diagnosing about 20% of all cases in the country was added to the national register. That year, the same year that

thimerosal was removed from childhood vaccines, the number of reported autism cases, not surprisingly, saw a significant spike.

■ **Adding Outpatient Cases** - In 1995, for reasons that went unexplained, the national register began including *all* autism cases diagnosed in Denmark, including those diagnosed in outpatient settings. Most people with autism are diagnosed in clinics and private offices, not in hospitals. SafeMinds and other organizations point to a large 2002 study in Denmark - on autism and the MMR vaccine by Madsen et al. (see MMR section) - showing that outpatient-diagnosed cases outnumbered inpatient cases by a 13.5-to-1 ratio in Denmark, accounting for 93% of all autism cases.⁴⁷

■ **New Diagnostic Criteria** - A third change in methodology occurred during the study period as well. In 1993, Denmark updated its psychiatric diagnostic codes and adopted new diagnoses for autistic-related disorders. Government workers conducted training seminars with clinicians in order to promote the new coding system, and an increase in autism and other reported diagnosis was to be fully expected.

■ **Denmark: An Artificial Increase?** This study “manipulates the incidence of autism in an attempt to clear thimerosal-containing vaccines of any role in the etiology of the disease,” a SafeMinds said in a statement. The increase reported in Denmark was “falsely created by the authors’ use of techniques which artificially boosted the number of cases identified.”

■ **Sweden: Inpatient Cases Only** - By counting only inpatient cases in Sweden, the reliability of that country’s data is also called into question. This limitation (counting a minority of the total number of cases) likely accounted for the erratic swings in the annual numbers of autism cases reported in that country.

■ **California: Increase is Real** - Sterh-Green et al. erred by writing that California’s Department of Developmental Services used a “vague” and difficult to verify autism definition. Their speculation that “changes in diagnostic criteria,” including PDD, “accounted for the largest increases” is not supported by the evidence. California’s data included only full-blown cases of autism, and not PDD. If anything, diagnostic criteria for “classic” autism became *narrower* over the years. And the suggestion that changes in criteria or “diagnostic substitution” (from mental retardation to autism) could explain the reported 800% increase in California has been disproven in several published papers. No retraction or correction of the authors’ erroneous claims was made.

WHAT THE STUDY SAID

■ **Inpatient v Outpatient Cases** - The authors noted that the switch from counting inpatient cases only, to counting all cases “Changes over time in the rates of diagnosis of autism-like disorders in inpatient versus outpatient settings may have affected the ascertainment of cases,” the authors said, adding that these very significant changes “may have spuriously increased the apparent number of autism cases.”

■ **Weakness of Ecological Studies** - The authors also noted the inherent weaknesses of relying on large epidemiology investigations called “ecological” studies, in which the unit of analysis is a population group and not individuals. They conceded that these studies are inherently limited in their ability to prove or disprove causation. “Such studies can be useful in exploring possible associations, (and) searching for areas of possible further study,” they wrote. “However, the greatest difficulty in interpreting ecologic studies is that of adequately controlling confounding factors due to unavailability of data and/or methodological limitations.”

WHAT THE CDC SAID ABOUT ECOLOGICAL STUDIES

An unpublished 2008 report from the CDC to the US House of Representatives Appropriations Committee concurs that ecological studies are far from ideal when using computerized population data - in this case the federal Vaccine Safety Datalink (VSD) - to determine an association between vaccines and autism.⁴⁸

“CDC concurs that conducting an ecologic analysis using VSD administrative data to address potential associations between thimerosal exposure and risk of AD/ASD is not useful,” said the CDC paper, which was signed by then Director Julie Gerberging, MD, now President of the Vaccine Division at Merck & Co., Inc. Such an evaluation, she added, “would be uninformative and potentially misleading.”

WHAT THE IOM COMMITTEE SAID:

■ **Shifting Study Population** – In its 2004 report, the Immunization Safety Review Committee agreed that “possible reasons” for the autism increase in Denmark “may be due to the changes in the inclusion criteria in the national register, diagnostic changes (from ICD-8 diagnostic coding to ICD-10), and the fact that, prior to 1992, cases diagnosed in one large clinic (about 20 percent of all cases) were not included.”

■ **Weakness of Ecological Studies** - The committee likewise conceded that “The ecological nature of the study limits the study’s contribution to causality.”

■ **Swedish Contribution is Limited** - As for the Swedish data, “which only reflected cases diagnosed in inpatient settings” the IOM committee admitted that the reported increase might have been caused by “changes in diagnostic criteria and increasing awareness of autism and related disorders.” The Sweden section, likewise, was an ecological analysis, which again “limits the study’s contribution to causality.”

CRITIQUE BY MARK D. NOBLE - PROFESSOR OF GENETICS AND OF NEUROBIOLOGY AND ANATOMY, UNIVERSITY OF ROCHESTER MEDICAL CENTER⁴⁹

One hypothesis to explain the sudden increase in prevalence is that changes in diagnosis and increased interest in autism caused an enhanced recognition of children with these syndromes. Thus, we know that the reported prevalence

from 1971 to 1990 is artificially low, because it doesn't include children who were given a different diagnosis. That means that in its current form, the comparison between the 1971-1990 cohort and later cohorts is fundamentally flawed, because they represent different kinds of information. There is quite an explosive change that is going on between 1995 and 2000. What could explain this? When you read the actual details of this manuscript (Madsen et al., 2003) you find out that, in 1995, a change was made in the information contained in the Danish registry. Prior to 1995 this registry only contained inpatient data, but after 1995 it also included data from outpatients.

In fact, the paper states that this change introduced 4-6 times as many total individuals into the registry. But it did not increase for a biological reason – it increased because they simply were obtaining cases from 4-6 times as many total people. At least in the years 1991-1998, 93.1% of the autism cases were treated only as outpatients. Thus, the addition of outpatients to the analysis in 1995 may have added 13.5 times as many cases of autism to the number of cases reported. If we apply even the most conservative correction factor for non-biological contributions, then a reasonable interpretation ... is that the biological prevalence of PDD fell by 30-40% after the removal of thimerosal from vaccines. Even the application of the lower end of the possible correction factors leads to the conclusion that there was a fall in autism prevalence after thimerosal was removed from vaccines.

SUMMARY: This weak review analyzed data from three different countries where mercury exposures were vastly different, and where autism cases were counted in very different ways. In addition, over the study period, the Danish autism registry switched from counting only inpatient-diagnosed cases (about 13% of the total) to counting both inpatient and outpatient cases (100% of the total). This accounted for most if not all of the “increase” in cases observed after the removal of thimerosal from Danish vaccines.

2)“Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data.”⁵⁰

Authors: Madsen KM, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB.

Publication & Date: *Pediatrics*, September, 2003

Online at: <http://pediatrics.aappublications.org/cgi/content/full/112/3/604>

Details: As in Stehr-Green, the authors looked into “whether discontinuing the use of thimerosal-containing vaccines in Denmark led to a decrease in the incidence of autism. This studied also relied on data from the Danish Psychiatric Central Research Register on all psychiatric inpatient admissions since 1971, and all outpatient contacts in psychiatric departments in Denmark since 1995. The patient population included all children between 2 and 10 years old diagnosed with autism from 1971-2000.

Results: A total of 956 children were diagnosed with autism during the period. “There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990,” the authors wrote. But from 1991 until 2000, the incidence increased and continued to rise after the removal of thimerosal from vaccines, including increases among children born after the discontinuation of thimerosal”

Authors’ Conclusions: Because the reported rate of autism continued to rise after the removal of thimerosal from vaccines in Denmark, the authors said, “Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism.”

CRITIQUES OF THE STUDY

■ **The Same Danish Database** - Critics stated the obvious: This study was little more than a second version of the Danish section included in the Stehr-Green paper, which was published one week earlier. The main flaw in that study, of course, was the major change in the Danish registry – from including inpatient only cases, to including both inpatient *and* outpatient cases.

■ **Repeating the Swedish Mistake in Denmark** - In order to address the issue of adding outpatient cases in 1995, Madsen et al. went back and looked at inpatient cases *only*. Among this small minority of cases, they reported “the same trend with an increase in the incidence rates from 1990 until the end of the study period.” The authors failed to provide these data in their study. And the sampling was essentially identical to the Swedish analysis, in which the IOM committee (in addition to the authors) conceded that the apparent increase in autism incidence could be due to “changes in diagnostic criteria and increasing awareness of autism and related disorders.”

■ **Weakness of Ecological Studies** – This was another ecological analysis which, as the Director of the CDC, Dr. Julie Gerberding, wrote to Congress: the contributions of such studies toward establishing causality are “limited.”

■ **A Very Low Autism Rate** - Even if autism rates were shown to actually be increasing in Denmark, they were remarkably low both before *and* after thimerosal was removed. According to the Madsen study, Denmark’s prevalence rate was a tiny 1-per-10,000 - one of the lowest rates ever reported - before thimerosal’s removal. By 1999 (with the addition of outpatient cases) the rate “rose” to 4-6 per 10,000 - still very low - comparable to US rates *before* thimerosal exposures in that country tripled, around 1990. The rate was also at least *ten times lower* than the estimated 2000 US rate, 60-per-10,000.

■ **Undisclosed Conflicts of Interest** - SafeMinds and others criticized the inherent conflicts of interest among some of the study authors. Two of them worked for the Statens Serum Institut, a Danish manufacturer of thimerosal containing vaccines. According to its mission statement, “Statens Serum Institut is a public enterprise operating as a market-oriented production and service enterprise. In 2002, more than 80% of SSI profits came from vaccines.” Still, this conflict was not disclosed by *Pediatrics*.

WHAT AN INTERNATIONAL TEAM OF SCIENTISTS SAID

In 2005, Joachim Mutter of the Institute for Environmental Medicine and Hospital Epidemiology, in Freiburg, Germany and colleagues in the UK and US published a paper in *Neuroendocrinology Letters* that included a serious indictment of the study. It echoed many of the same points made by SafeMinds and others, namely:⁵¹

- Autism counts were based on hospitalized, inpatient records in the first cohort and then changed in the middle of the study period (1995) to include outpatient records. Therefore, the purported increases after 1994 may be explained by the additional recruitment of an existing autism population that did not require hospitalization.

- After 1992, the register added in patients from a large Copenhagen clinic, which accounted for 20% of the caseload in Denmark. The patients from this clinic were excluded prior to 1992.

- The diagnostic category changed after 1993 from “psychosis proto-infantis” of ICD-8 (code 299) to “childhood autism” of ICD-10. Another paper using the same inpatient register reports that the psychosis proto-infantis category includes inpatient cases that do not fulfill the criteria for autism.

- Many of the children were between 7–9 years old, and most were over 4 years old, when recorded. But the onset of autism must occur, by definition in the diagnostic criteria, before three years of age. The most widely used approach to assessing autism trends is to use year of birth as the “incidence time” and to assess trends in autism rates

based on birth year of the study population rather than time at diagnosis or some other measure of incidence.

- Another recent study performed by Madsen et al. reported Danish autism rates of 6 per 10,000 for children born in the 1990s.⁵² These Danish rates are very low in the 1990s compared to the United States. Madsen et al. also report inpatient rates for the pre-1993 “psychosis proto-infantilis” at well below 1 per 10,000. This low rate would contradict the single published survey of autism rates from Denmark, which indicated an autism rate of over 4 per 10,000 as far back as the 1950s.

- Additional confounders were present in the U.S. with high prevalence of autism that were not present in Denmark: Between 1970–92, the only childhood vaccine given in Denmark until 5 months of age was the monovalent pertussis vaccine. In the United States, children were exposed to multiple doses of diphtheria, pertussis, tetanus, polio, hepatitis B and haemophilus influenza B (Hib) vaccines before five months of age in the 1990s.

WHAT THE MEDIA SAID:

The mainstream media portrayed the Madsen study as definitive. *The New York Times* declared: “Study Casts Doubt on Theory of Vaccines’ Link to Autism” and quoted the CDC’s Dr. Robert Davis as saying the evidence was “clear-cut: If you remove cars from highways, you’ll see a marked decrease in auto-related deaths. If thimerosal was a strong driver of autism rates, and you remove it from vaccines, you should have seen some sort of decline — and they didn’t.”⁵³

The Times also quoted Dr. William Schaffner, Chairman of Preventive Medicine at Vanderbilt University in Nashville, as claiming that the study added to “the whole mosaic of studies that have addressed this. Each is imperfect, but they all add up to this theme: thimerosal is not the culprit.”

The paper included a SafeMinds statement asserting that the researchers “artificially boosted the number of cases by adding outpatients and those at a large Copenhagen clinic to earlier inpatient figures.” It also reported that two authors worked for a Danish vaccine maker, “suggesting a conflict of interest.”

WHAT THE AUTHORS SAID:

- **Outpatients “May Exaggerate Incidence”** - The authors conceded that, “because many patients with autism in former years have been treated as outpatients this may exaggerate the incidence rates simply because a number of patients attending the child psychiatric treatment system before 1995 were recorded for the first time, and thereby counted as new cases in the incidence rates.”

- **Greater Awareness, New Diagnostics Can Boost Numbers** - The reported increase in autism in Denmark “may be attributable to more attention being drawn to the

syndrome of autism and to a change in the diagnostic criteria from the ICD-8 to the ICD-10 in 1994.”

■ **Exposure Levels Were Lower Than US** - Echoing criticism that the Danish data are not comparable to other countries, such as the US where mercury exposures were greater, the authors wrote: “Our data cannot, of course, exclude the possibility that thimerosal at doses larger than used in Denmark may lead to neurodevelopmental damage.”

WHAT THE IOM REVIEW SAID:

■ **Limited Contribution** - Adding additional outpatient cases into the Danish register was noted as a potential problem. “A reanalysis was conducted, limiting itself to inpatient data only, and the authors found similar trends in autism rates, although the data were not shown,” the IOM wrote. “However, despite the reanalysis the authors stated that autism incidence after 1995 may have been exaggerated due to the change in including outpatient cases into the Danish Psychiatric Central Register. This limits the study’s contribution to causality.”

SUMMARY: This study is perhaps the least informative of all the thimerosal studies. The shifting definition of cases and limitation, at any point, of only autism cases that were admitted to hospitals make this analysis thoroughly unreliable from the outset.

3)“Association between thimerosal-containing vaccine and autism”⁵⁴

Authors: Hviid A, Stellfeld M, Wohlfahrt J, Melbye M.

Publication & Date: *Journal of the American Medical Association*, October 1, 2003

Online at: <http://jama.ama-assn.org/cgi/content/full/290/13/1763>

Details: The authors conducted a population-based cohort study of all 467,450 children born in Denmark from January 1, 1990, until December 31, 1996. They compared those children who received a thimerosal- containing vaccine with children who were given a thimerosal-free version of the same vaccine.

Results: During “2,986,654 person-years,” the investigators identified 440 cases of autism and 787 cases of other autistic-spectrum disorders. “The risk of autism and other autistic-spectrum disorders did not differ significantly between children vaccinated with thimerosal-containing vaccine and children vaccinated with thimerosal-free vaccine,” they wrote. “Furthermore, we found no evidence of a dose-response association,” an increase in the relative risk for every 25 micrograms of mercury exposure.

Authors’ Conclusions: “The results do not support a causal relationship between childhood vaccination with thimerosal-containing vaccines and development of autistic-spectrum disorders.”

CRITIQUES OF THE STUDY

■ **Mercury Cannot Be “Protective”** - The data in this study show that mercury is *beneficial* to infant children. Those in the thimerosal group had a relative risk of 0.85 for autism, compared with the mercury free group, suggesting a substantial (though not significant) protective effect for thimerosal. This finding is suspicious, and runs counter to all knowledge, science and common sense. More to the point, the outcome suggests the presence of unexamined or unreported bias in the study design and data management that suggest the researchers were prejudiced in a way that makes them unreliable investigators.

■ **Older Children’s Records Missing** - SafeMinds identified a flaw that could well have produced a significant loss of autism case records from the Danish register, rendering the Hviid et al. findings invalid. “The registry allows 10-25% of diagnosed autism cases to be lost from its records each year,” the group wrote in a letter to JAMA.⁵⁵ “The effect of this loss is such that the records will disappear from older age groups to a much greater degree than from younger age groups in any given registry year.” Older children were underrepresented in the cohort, even though they were the ones who received thimerosal-containing vaccines before 1992.

■ **Reanalysis Finds More Autism in Exposed Children** – In the same letter to JAMA, SafeMinds reanalyzed the Denmark data using an alternative method to avoid the “record

removal bias.” Instead, they looked at same-age children – 5-to-9 year olds - but from two different registry years: 1992, when all of the children received thimerosal-containing pertussis vaccines; and 2002, when none of the children received thimerosal. “After adjusting for the lack of outpatient records in the 1992 registry, the analysis found a 2.3 times higher number of autism cases among the 1992 thimerosal-exposed group relative to the 2002 non-exposed group,” SafeMinds said.

■ **No Tracking of Birth Cohorts** - The researchers failed to classify autism cases by birth year. There is often a gap between the number of children diagnosed with autism from any given birth cohort and the number of autism cases reported in any given calendar year. Analyzing the data according to birth cohort would have painted a far more accurate picture, because it would have reduced or eliminated the gap between diagnoses of ASD and reporting of cases.

■ **Undisclosed Conflict of Interest** - “In the Hviid study in JAMA we can clearly see how the data was misinterpreted so a conclusion could be drawn to clear thimerosal from any role in autism,” a SafeMinds statement said. “This misinterpretation is not surprising, given the authors’ employment at *Statens Serum Institut*, a conflict of interest that should have been disclosed.”

WHAT THE AUTHORS SAID

The authors wrote that a “possible weakness” of their paper was that “the date of diagnosis used as the incidence date may differ significantly from the ‘onset of symptoms’ date.” Diagnosis autism is often “a lengthy process,” they wrote, and this is “reflected in the mean ages of diagnoses in this study (4.7 years for autism and 6.0 years for other autistic-spectrum disorders).” Such a limitation, however, “is more likely to be a problem in an incidence study than in a risk factor study.”

WHAT THE IOM SAID

Although the committee considered the study as having “strong internal validity” it also identified various limitations, “including its time-series design,” (as pointed out by SafeMinds), and the “generalizability of the study’s findings to the U.S. situation, especially with regard to the different dosing schedule used in Denmark and the relative genetic homogeneity of the Danish population.”

SUMMARY: This study was marked by missing records, a failure to track birth cohorts, and undisclosed conflicts of interest. Reanalysis of the data actually showed an increased risk of ASD following thimerosal exposure. It also concluded that mercury had a protective effect on the neurodevelopment of children, which flies in the face of all logic and all previous studies of mercury and children.

4) “Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases.”⁵⁶

Authors: [Verstraeten T](#), [Davis RL](#), [DeStefano F](#), [Lieu TA](#), Rhodes PH, [Black SB](#), [Shinefield H](#), [Chen RT](#); [Vaccine Safety Datalink Team](#).

Publication & Date: *Pediatrics*, November, 2003

Online at: <http://www.ncbi.nlm.nih.gov/pubmed/12880876>

Details – This study, conducted by investigators at the CDC using the Vaccine Safety Datalink (VSD) of computerized HMO databases was a two-part “retrospective cohort study.” The first phase looked at potential associations between neurodevelopmental disorders (NDDs) - including autism, ADD, speech and language delay and tics - and thimerosal among 124,170 US children born from 1992 to 1999 at one of two HMOs (A and B).

Because Phase I failed to find a consistent, statistically significant “signal” for autism or ADD, these disorders were excluded as study endpoints in Phase II. In that phase, the most common disorders associated with exposure in phase I (tics, speech delay and ADHD) were assessed among 16,717 children born from 1991 to 1997 in a third HMO (C). Relative risks for neurodevelopmental disorders were calculated for each 12.5 microgram increase of estimated thimerosal exposure in the first, third, and seventh months of life.

Results: In phase I at HMO A, exposure at 3 months of age was associated with an increased risk of tics.” The relative risk for tics was 1.89, meaning exposed children were nearly *twice* as likely to develop the disorder. At HMO B, there was an increased risk of language delay for exposure at 3 months (RR: 1.13) and 7 months (RR: 1.07). However, in Phase II at HMO C, “no significant associations were found,” and “In no analyses were significant increased risks found for autism or attention-deficit disorder.”

Authors Conclusions: “No consistent significant associations were found between TCVs and neurodevelopmental outcomes. Conflicting results were found at different HMOs for certain outcomes. For resolving the conflicting findings, studies with uniform neurodevelopmental assessments of children with a range of cumulative thimerosal exposures are needed.”

A “SIGNAL” DISAPPEARS ACROSS FIVE GENERATIONS OF STUDY

Critics of the Verstraeten paper question the process under which the data were managed across at least five different generations of analysis that lasted more than four years before the official version was published in *Pediatrics*. They charge that the data were put through a rather torturous process of statistical manipulation designed to get the results so badly desired by CDC: Namely, no association between thimerosal and negative outcomes.

Whether done intentionally or not, the various generations of analysis clearly show how an extremely strong “signal” between thimerosal and autism, ADD and other NDDs in the first generation was reduced to almost nothing in the fifth and final published version.

It is important to note that the first four analyses would *never* have come to light without documents obtained by SafeMinds through the FOIA. The group’s FOIA efforts likewise yielded unpublished minutes from a secret, two-day conference held in June 2000 near CDC headquarters outside Atlanta, known as the Simpsonwood Meeting. It is clear from the transcript that many industry and public health experts at Simpsonwood were alarmed by the possible harm being caused by thimerosal – but even more worried about the possible damage that any bad publicity would have on the national and global vaccine programs. Participants voted to keep the meeting secret, and it remained so for two years, when the minutes were delivered to SafeMinds. (See Below).

It is also important to note that Verstraeten himself presented results from some of the earlier VSD analyses – in which the thimerosal signal was still quite significant - to the CDC’s Advisory Committee on Immunization Practices Institute (ACIP) in 2000 and to the Institute of Medicine in 2001 without dismissing the data as being “preliminary” and therefore unreliable (also discussed below)

FIRST ANALYSIS – December, 1999 – Autism Relative Risk = 7.62

In the very first run of the VSD data on thimerosal, lead author Thomas Verstraeten divided all of the children in HMO A and B into four groups: Those who had received zero micrograms of mercury in vaccines by one month of age, those who had received 12.5mcg, those who received 25mcg, and those exposed to more than 25mcg by one month of age.

The results were astonishing. The children exposed to more than 25mcg had extremely elevated relative risks for:

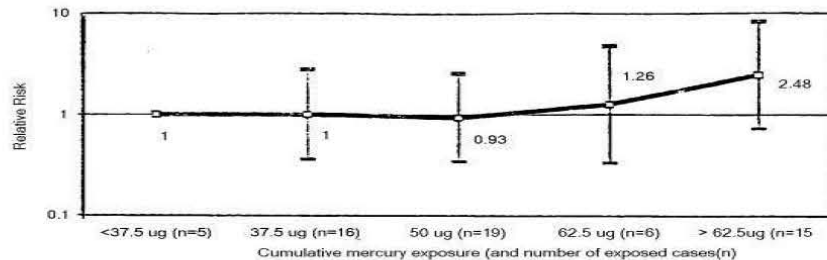
- ADHD: 11.35 times more likely
- Autism: 7.62 times more likely
- ADD: 6.38
- Tics: 5.65
- Speech and Language Delay: 2.08

SECOND ANALYSIS – February, 2000 – Autism Relative Risk = 2.48

Within two months, Verstraeten had reanalyzed the data, incorporating methodological changes suggested by colleagues at the CDC. In the second version, completed in February 2000, the estimated relative risk for autism had fallen considerably – though it was still worryingly high. Children in the two HMOs exposed to the most mercury (62.5mcg) at three months of age were almost two and half times more likely to develop autism (RR=2.48). This calculation was just short of statistical significance because the

low end of the margin of error fell slightly below the risk of 1.0. It's worth noting that Verstraeten excluded children who had been treated with hepatitis B immune globulins "as these were more likely to have high exposures and high outcomes." Most formulations of immune globulins were preserved with thimerosal at that time. These infants were among the most heavily exposed patients and also had dramatically higher rates of autism and other disorders, and yet they were excluded from the analysis at this stage.

Relative risk of Autism from thimerosal exposure at 3 months of age:



SOURCE: Internal CDC report, February 2000 – Obtained through the Freedom of Information Act (FOIA).

Verstraeten was nonetheless alarmed. On December 17, 1999 he sent an email to colleagues Robert Davis and Frank DeStefano under the subject line "It just won't go away," by which one presumes he meant the association between thimerosal and NDDs. "Some of the relative risks increase over the categories, and I haven't yet found an alternative explanation," he said. "Please let me know if you can think of one."

In this second analysis, Verstraeten, Davis and DeStefano candidly wrote that they had associated "increasing risks of neurological developmental disorders with increasing cumulative exposure to thimerosal." They also found "similar increases" for the risk of developmental speech disorder, autism, stuttering and attention deficit disorder, though these increases were not statistically significant. "We can state that this analysis does not rule out that receipt of thimerosal containing vaccine in children under three months of age may be related to an increased risk of neurological developmental disorders."

THIRD ANALYSIS – June, 2000 -- Autism Relative Risk = 1.69

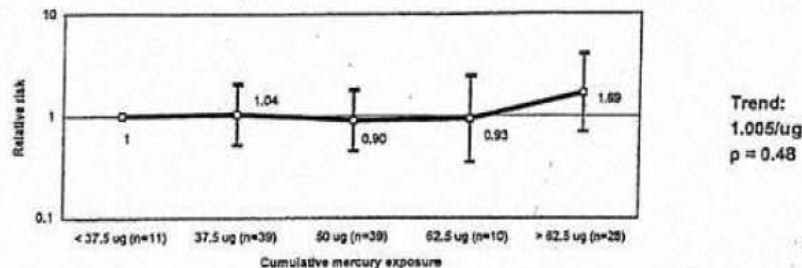
On March 9, 2000, Verstraeten sent another email, obtained through FOIA, about his work on the third generation of analyses. He wrote that the risk of developmental delay began to drop among children who missed their first thimerosal-containing HiB and DTP shots before three months of age. This confirmed his "hypothesis" that "What matters is not getting it before the third month, after which the implications gradually diminish."

Verstraeten also looked at exposure rates and outcomes among 10 premature infants and found that those exposed to 200mcg mercury were five times more likely to have an NDD than preemies exposed to 100mcg. "These findings are very extreme and warrant closer examination," he wrote.

By this time, Verstraeten et al. were preparing a third analysis of the VSD data, incorporating even more changes (i.e. entry criteria, stratification of population groups, etc) to their methodology. Critics say these changes were made deliberately to eliminate the “signal” that would “not go away” (discussed below) while CDC officials have insisted they were just trying to get the “cleanest” and most reliable data possible.

In June, 2000, Verstraeten presented the third analyses at a meeting of the CDC’s Advisory Counsel on Immunization Practices (ACIP) and at the Simpsonwood conference. This time, the relative risk for autism among children given more than 62.5 mcg by three months of age had fallen - from 2.48 to 1.69:

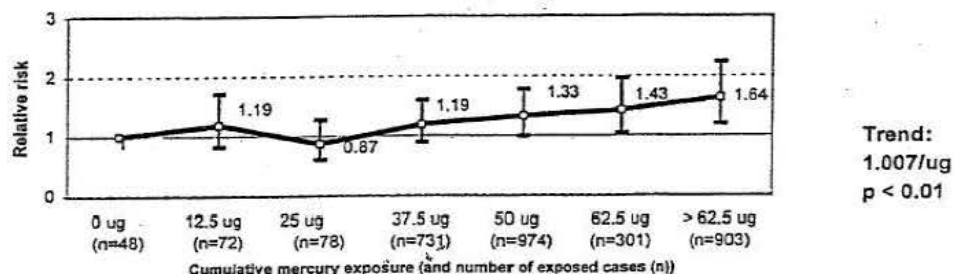
Graph 4: Relative risk + 95 % CI of Autism after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



This still-elevated autism finding was not considered statistically significant because the margin of error dipped below a relative risk of 1.0. But the team did find “statistically significant associations between thimerosal and neurodevelopmental disorders” other than autism. These included:

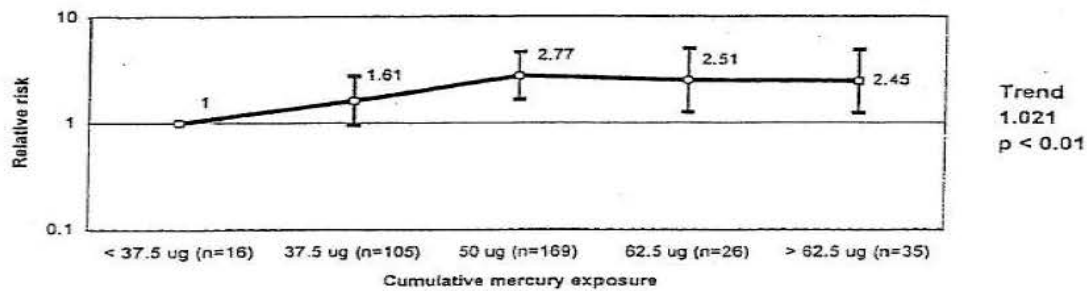
Relative Risk for All NDDs Combined: The RR for this umbrella category of outcomes among children exposed to 62.5mcg at three months was 1.64, meaning these children were 64% more likely to have *any* NDD than children exposed to 0mcg. The risk was considered statistically significant because the margin of error remained above 1.0. And increased risk was completely linear and dose-dependent: It increased by 0.7% for every microgram of mercury exposure:

Graph 2: Relative risk + 95 % CI of Developmental neurologic disorders after different exposure levels of thimerosal at 3 months of age, NCK &GHC, Cycle 7



Relative Risk for Developmental Language Disorder: Statistically significant increased risks for language disorder were found at 3 months (2.1% per mcg). The RR for children receiving 50mcg mercury or more by 3 months of age was especially high. Children who received 62.5mcg had a relative risk of 2.10 compared with children who received 12.5 mcg.

Graph 12: Relative risk + 95 % CI of Developmental language disorder after different exposure levels of thimerosal at 3 months of age, NCK &GHC, cycle 7



Relative Risk for Attention Deficit Disorder: There was a statistically significant, dose-dependent response at six months of age of 0.6% for each microgram of exposure. At 62.5mcg, the RR was 1:30, or 30% more likely to develop ADD.

Other Elevated risks: Increased risks per mcg of exposure were found for:

Speech delay: 1 month (RR: 1.011), 3 months (RR:1.008), 6 months (RR:1.002)

Unspecified Delays: 2 months (RR: 1.005), and 3 months (RR:1.007)

Tics: 3 months: (RR: 1.021)

“Some of these are borderline statistically significant,” Verstraeten told the ACIP meeting. “Some of them are highly statistically significant. What these estimates suggest is that there seems to be an increasing trend, an increasing risk for any of these neurological developmental outcomes, with increasing thimerosal exposure.”

THE SIMPSONWOOD CONFERENCE – June 2000

The same month as the ACIP meeting – June, 2000 - the CDC convened an invitation-only conference at a retreat outside Atlanta called Simpsonwood, where dozens of public health officials, physicians, scientists, and industry executives gathered for a two-day, supposedly off-the-record discussion of the Verstraeten findings. The meeting was not announced to the public, and the transcript was not meant for public consumption. It was, however, included in a FOIA request packet that was delivered to SafeMinds. Members of the public were patently excluded at Simpsonwood, and industry representatives outnumbered panel members.

The task at hand was to review the VSD analysis and determine if a “signal” between TCVs and developmental disorders was there. Participants were also asked for ideas on how to proceed in the ongoing investigation, which was in its first year of what would become four years of analysis and reanalysis. Among the revelations:⁵⁷

- **Troubling data** - Many attendees knew they had a problem. “What if the lawyers get hold of this?” asked one. “There’s not a scientist in the world who can refute these findings.”

- **Deference to industry** - It is clear that the CDC would not recall any mercury containing vaccines, regardless of the risks, out of concern for the financial interests of the vaccine industry. “CDC is not in favor of expressing a preference for a particular vaccine (i.e. thimerosal-free) for fear of alienating the other manufacturers and disrupting a free market economy,” one participant wrote to colleagues after the meeting.

- **Dr. Paul Stehr-Green**, an associate professor of epidemiology at the University of Washington and lead author of the Danish-Swedish thimerosal study, summarized the meeting in a memo obtained through FOIA. He wrote that, despite a prolonged “re-analyses,” the data still showed a “slight tendency for groups with higher exposure to thimerosal-containing vaccines to have higher rates of the same neurobehavioral outcomes.” But, he insisted, the level and consistency of statistical significance of these findings was “unimpressive.” The results did not “offer adequate evidence to support or refute the existence of causal relationship.”

- **Dr. Philip Rhodes** (a CDC statistician) spoke of a certain way that researchers could suppress the signal through changing the exclusion criteria: Restore thousands of children with congenital disorders who were excluded from the study, “which would serve to add ‘noise’ that could obscure the signal. All those kids that Tom (Verstraeten) has excluded, I have thrown them in. I think there is a clear argument that is going too far, but that further brings things down,” Rhodes said. “So you can push, I can pull. But there has been substantial movement from this very highly significant result, down to a fairly marginal result.”

Eventually, those previously excluded children with congenital disorders would indeed be added back into the patient population under study.

- **Dr. Thomas Verstraeten** discussed many of the study’s flaws, including the large number of young children. “One thing that is for sure, there is certainly an under-ascertainment of all of these cases,” he said. “Some children are just not old enough to be diagnosed. So the crude incidence rates are probably much lower than what you would expect, because the cohort is still very young.” As for the most common disorder found, speech delay, Verstraeten said the trend had been “highly statistically significant.” He added that the hypothesis was “biologically plausible.”

Verstraeten was very clear on one central point, however. Despite the changes in methodology and stratification of the data, the signal between thimerosal and NDDs

simply would not vanish. “You can look at this data and turn it around,” he said, “and look at this, and add this stratum, and I can come up with very high risks. And I can come up with very low risks, depending on how you turn everything around. You can make it go away for some and then it comes back for others,” he concluded. “So the bottom line is, okay, our signal will simply not just go away.”

- **Dr. William Weil**, who represented the American Academy of Pediatrics, lectured his colleagues for believing that the signal was weak and not significant:

The number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant. The increased incidence of neurobehavioral problems in children in the past few decades is probably real. Like many repeated acute exposures, if you consider a dose of 25 mcg on one day, then you are above threshold. And then you do that over and over to the same neurons. It is conceivable that the more mercury you get, the more effect you are going to get. The brain and central nervous system are not fully developed at birth. The earlier you work with the central nervous system, the more likely you are to run into a sensitive period for one of these effects. It changes enormously the potential for toxicity. There's a host of neurodevelopmental data that would suggest that we've got a serious problem. To think there isn't some possible problem here is unreal. The number of kids getting help in special education is growing nationally and state by state at a rate we have not seen before. The rise in the frequency of neurobehavioral disorders is much too graphic. We don't see that kind of genetic change in 30 years.

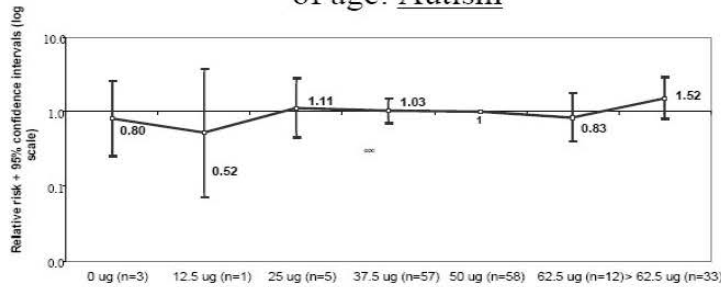
- After the meeting, Verstraeten sent an email to colleagues complaining of the indifferent stance that most of the participants took toward the thimerosal signal that “won't go away.” Their attitude seemed to be that, “if nothing is happening in these studies, then nothing should be feared of thimerosal,” he wrote. “I do not wish to be the advocate of the anti-vaccine lobby and sound like being convinced that thimerosal is or was harmful, but at least I feel we should use sound scientific argumentation and not let our standards be dictated by our desire to disprove and unpleasant theory.”

FOURTH ANALYSIS – July, 2001 – Autism Relative Risk = 1.58

In this fourth analysis, presented at the July 2001 meeting of the IOM's Immunization Safety Review Committee, the VSD team had decided to divide HMO A and B and examine their data separately.

But HMO B, with some 15,000 patients studied, was considerably smaller than HMO A, which had 115,000 patients. After breaking them into two subpopulations, they found that data from the smaller HMO were no longer statistically significant. The smaller HMO simply lacked the “statistical power” of the larger HMO and therefore, results from the two HMOs were no longer “consistent.” The same was true for speech and language delays.

Relative risk associated with exposure at 3 months
of age: Autism



Note: provisional results - may be subject to change



Even so, for some of the estimates, “we found high statistical significance,” Verstraeten told the IOM. “Some of these associations are biologically plausible, and for some, we saw a dose response.”

By now, the team had also completed Phase II of the study, which was to compare results from HMOs A and B with a third, independent HMO, in this case, Harvard Pilgrim of Massachusetts. And though Phase I had found “several significant associations between thimerosal and neurodevelopmental disorders,” Verstraeten said, “in an analysis in a smaller and independent data set, we could not confirm those associations for speech or language delay and ADHD.” And given the lack of statistically significant risk for autism, the team had stopped looking at that outcome altogether in the Harvard Pilgrim data.

The reliance on HMO C to discount the entire study was criticized by Neal Halsey (title here) “Some people who have seen the third HMO, which is Harvard Pilgrim, have said there is no effect there, therefore that disproves the hypothesis,” he testified at IOM. “Well, that is really not true. I don’t know what the real power is of that study to say that there really isn’t an effect there. Power is a very important factor in studies that don’t show an effect.”

The data were inconclusive, but “still suggestive of an effect from thimerosal,” he said.

FINAL ANALYSIS – November, 2003 – Autism Relative Risk = N/A

By the time the study was published in 2003, the authors found just one increased risk for tics in phase I: At HMO A, exposure at 3 months the relative risk was 1.89. At HMO B, B, there was an increased risk of language delay for exposure at 3 months (RR: 1.13) and 7 months (RR: 1.07). But in Phase II at HMO C, “no significant associations were found.” And “in no analyses were significant increased risks found for autism or attention-deficit disorder.”

This was untrue. In the first analysis, there were significant increased risks for autism and ADD, and in the second analysis, there was a significant increased risk for ADD.

CRITIQUES OF THE STUDY

How did the relative risk for autism tumble from 11.35 to null? The four-year, five-generation analysis has been examined closely by many critics, both inside the autism community and among respected scientists, physicians and members of Congress. The many methodological flaws they have identified include:

■ **Inclusion of Young Children** - Researchers included young children, from 0-3 years old, even though the average age of an autism diagnosis was 4.4 years. A diagnosis in the first years of life was rare, so including these children would tend to drive down the overall relative risk. Because they were not yet diagnosed, all of them would have been misclassified under the normal group. But the CDC assumed that autism is diagnosed as frequently in 1-year-olds as five-year-olds.

■ **No Autism Diagnoses Among Youngest Children** - Among the youngest children, who made up 40% percent of all kids in the study, not a single case of autism was reported, which means that 40% of the sample was misclassified.

■ **Underreporting of Autism Cases** - The researchers identified relatively few kids with autism compared to what one would expect to find in the general population. In California at the time, the autism rate (excluding PDD and Aspergers) was around 50-100 per 10,000 children. But the average rate at the two California HMOs was just 11.5 per 10,000. Had they missed, or somehow eliminated four out of five cases? What else could explain this dramatic under-ascertainment? This undercount clearly also means that these cases were misclassified.

■ **Exclusion of ASD cases other than “autism”** - The researchers did not look for outcomes like PDD-NOS and Asperger’s Syndromes, even though they are autism spectrum disorders. This meant that higher-functioning children were not included in the risk ratios. ■ **Stratification of Data** – The authors not only separated HMO A and B to find that data from the smaller HMO alone lost statistical power, they even broke up the larger HMO into subgroups comprised of individual clinics in the network. This “stratification” helped eliminate any consistent statistically significant risk of ADHD or speech disorders that were found within the larger HMO as a whole. Smaller population subgroups have less “statistical power,” and increase the possibility that statistical significance will not be attained.

■ **Elimination of the combined “NDD” Outcome** - By breaking this generalized umbrella outcome into individual categories like ADHD, speech delay and tics, the relative risks and statistical significance of most outcomes were reduced or eliminated. Again, the smaller the stratified subgroup, the greater the chance of reducing statistical power and thus statistical significance.

■ **Elimination of cases diagnosed outside the HMOs** – The authors chose to include only those cases confirmed by a behavioral specialist. But if that specialist was outside the HMO, the diagnosis was not counted. This provided the opportunity to “cherry pick” cases out of the original data set. Among the ADD/ADHD cases, 60% were eliminated because they were not made by an in-network specialist. For speech and language delay, 50% were excluded and for autism, 20% were eliminated.

■ **Higher risk with increased vaccination** - Generally speaking, among the three HMOs studied, the higher the vaccination rate, the greater the risk of adverse outcomes. During the third generation of analysis, for example, HMO C had the highest full vaccination rate, at 65%, and also the highest speech delay rate. Meanwhile, at HMO A, the fully vaccinated rate was 60%, or four times greater than compliance at HMO B (15%), while the rate of all NDDs at HMO A was 5.7%, four times greater than the 1.3% rate found at HMO B.

	HMO A	HMO B	HMO C
Full vaccination rate	60%	15%	65%
NDD rate	5.7%	1.3%	n/a
Speech delay rate	3.9%	2.6%	4.5%

■ **Problems at Harvard Pilgrim** - There were questionable record keeping practices at Harvard Pilgrim (HMO C), and Massachusetts had been forced to take over after it declared bankruptcy. Even worse, the HMO used different diagnostic codes than the other two HMOs in Phase I. It wasn't surprising that the Harvard Pilgrim data was inconsistent. Also, the study population at Harvard Pilgrim was significantly smaller (15,000 kids). The smaller the population studied, the greater the margin of error, which lowers the study's “statistical power” and weakens the signal for outcomes.

■ **Undeclared conflict of interest.** After Verstraeten began work at GlaxoSmithKline, “the data, sampling and methodology of the study were altered, so that results would point to enough inconsistencies to cast doubt that mercury in vaccines causes autism,” critics alleged. Verstraeten had not been named as a GSK employee in the study and was misidentified as an employee of the CDC. It must be noted that GSK made thimerosal-containing vaccines included in the study, such as Hepatitis B and DTaP vaccines.

■ **Unavailability of data** - “The current practice of restricting access to the database to a limited group of possibly biased individuals is not acceptable,” SafeMinds declared. Their statement added that the *Pediatrics* report “cannot be accepted as final.” CDC rules had made the approval process long and arduous. Those who did gain access (the Geiers) could only “utilize a limited portion of the VSD data set, and their examination of the data is subject to constant monitoring by CDC staff.”

WHAT THE MEDIA SAID

Associated Press – Co-author Frank DeStefano “acknowledged that the early results suggested stronger links with some disorders, though not autism, but denied that there had been pressure or a cover-up. He said the final data reflect a more thorough recent analysis. Verstraeten, who left the CDC in July 2001, did not respond to an email request seeking a response, and company spokeswoman Nancy Pekarek said he did not wish to discuss the results, but provided a statement in which Verstraeten said that ‘since leaving the CDC he was only an adviser as the study was finalized and prepared for publication.’”⁵⁸

WHAT THE CDC SAID

CDC spokesman Von Roebuck told *Insight on the News* magazine that, “We pretty much looked into that [the manipulation of data] in the sense of how the information was presented, and we do stand behind it.” As for Verstraeten’s undisclosed employment at vaccine maker GSK, he said. “The one thing that we would want to happen differently is that would have been known before. But the work that Dr. Verstraeten did was for the CDC at the time the work was produced – the work that he did for the study was done when he worked for the CDC.”

WHAT LEADING VACCINE EXPERTS SAID

Dr. Neal Halsey, the national vaccine expert, along with colleagues Daniel A. Salmon and Lawrence H. Moulton, published a letter in the journal *Pediatrics* calling for further analysis of the data which included the following critiques:⁵⁹

■ **Changing Criteria** - By eliminating the combined umbrella outcome of NDDs, and dividing it into separate diagnoses, the authors “may have substantially reduced the power to find important relationships,” Halsey et al. said, adding that the later entry criteria “appear to have been more lax” than in a previous version.

■ **Excluding Diagnoses** - The requirement that diagnoses be made by an in-network specialist was also questioned. “Were diagnoses that were not made by a specialist excluded from analyses?” they asked, noting that primary care doctors are quite “capable of diagnosing ADD without input from a sub-specialist.”

■ **Unequal Population Sizes** – Halsey et al. also criticized the comparing of data from a large HMO with two much smaller ones.

WHAT VERSTRAETEN SAID

In a letter published in the April, 2004 issue of *Pediatrics*, Verstraeten wrote that, while his team had found a positive association between thimerosal and certain outcomes in Phase I, these findings could not be replicated in the second phase.⁶⁰

But this in no way disproved an association (at least for NDDs other than autism), he insisted in a declaration that is seldom, if ever quoted today. “The perception of the study changed from a positive to a neutral study,” he said. “Surprisingly, however, the study is being interpreted now as negative by many, including the anti-vaccine lobbyists. The article does not state that we found evidence against an association, as a negative study would. It does state, on the contrary, that additional study is recommended, which is the conclusion to which a neutral study must come.”

“Did the CDC water down the original results?” Verstraeten asked, and then answered: “It did not.” Despite the fact that vaccine safety activists were charging that a “positive” study had been manipulated into a “negative” one, the study results were *neutral*; they proved nothing for either side of the debate. Presumably, the point he was making is that a deliberately manipulated study would have yielded a negative result, and not a neutral one.

“Did the CDC purposefully select a second phase that would contradict the first phase?” Verstraeten also asked. “Certainly not. The push to urgently perform the second phase at (Harvard Pilgrim) came entirely from myself, because I felt that the first-phase results were too prone to potential biases to be the basis for important public health decisions. (It) was the only site known to myself and my coauthors that could rapidly provide sufficient data that would enable a check of the major findings of the first phase in a timely manner.

And he added this:

The bottom line is and has always been the same: an association between thimerosal and neurological outcomes could neither be confirmed nor refuted, and more study is required.

WHAT A SPECIAL PANEL OF THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES SAID

On August 24, 2006, a special panel appointed by the NIEHS issued a report titled “Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink.”⁶¹ Among other things, the panel was asked to “Identify the strengths and weaknesses of the VSD for evaluating the possible association between exposures to thimerosal-containing vaccines and AD/ASD”

According to the panel, “a number of gaps were identified in the information available at the meeting. These involved business and medical practices at the MCOs that might impact data quality and interpretation of study results, and more generally, the completeness and validity of exposure and diagnostic data in the VSD and the ability to link across family members.” The panel recommended that these gaps be addressed prior to consideration of further studies of ASD and thimerosal using the VSD.

The panel also “identified several areas of weakness,” the report said. “The cumulative effect of these weaknesses was judged to reduce the usefulness of the VSD for addressing the potential association between exposure to the vaccine preservative thimerosal and risk of AD/ASD.”

The weaknesses of primary importance are summarized below.

Case ascertainment - “Of particular interest to the panel was the large proportion, around 25%, of births excluded from the analyses in the Verstraten study. These exclusions were intended to decrease confounding. The panel noted that these children may represent a susceptible population whose removal from the analysis might have had the unintended consequence of reducing the ability to detect an effect of thimerosal. A VSD study that relies exclusively on administrative data to identify cases of ASD is subject to both false positives and missed cases. This stems in part from the original design of the data systems that support the VSD; these systems were designed for administrative rather than research purposes. For example, the administrative record created for an outpatient visit of a child with AD/ASD who is being treated for another medical condition will reflect that other condition rather than the presence of autism. Entries of this type would lead to under-ascertainment of cases.”

Heterogeneity in business practices across and within MCOs (HMOs) – “Eight MCOs currently participate in the VSD and each relies on data systems designed to meet the specific business requirements of the MCO. In addition to obvious differences among MCOs in enrollment size and geographic location of the populations served, many other aspects of service delivery and tracking vary (e.g., developmental screening practices and specialist referral guidelines). Differences across clinics and other service providers affiliated with an individual MCO occur as well. The panel noted that these variations within and among VSD sites would complicate interpretation of a VSD study that combined data across clinics and sites by introducing heterogeneity in the completeness and quality of case ascertainment. Moreover, membership in an MCO might be influenced by an AD/ASD diagnosis. This could occur, for example, if children presenting with problems predictive of the development of AD/ASD (e.g., speech delay) are more likely to leave a MCO-administered plan because the parents believed that another model of service delivery would be more beneficial.”

Systematic changes over time – “The systems for creating medical records at the VSD sites are dynamic and change frequently in response to the evolution of the individual MCO business model. The panel noted that at least some of these changes would be expected to affect the observed rate of autism and could confound a trend analysis. One such change was the transition from paper to electronic medical records. This change occurred at different times for each of the participating MCOs.”

Estimation of mercury burden. “Panel members expressed a concern that thimerosal dose, administered through a series of vaccinations, may provide a poor surrogate measure of the cumulative exposure of a child to organic mercurials. Exposures through

diet or other environmental sources would not be documented reliably in either the VSD administrative data or medical charts.”

Transparency and Public Access – “The panel recognized the perception by some members of the public and the advocacy community that previous VSD analyses have not been conducted in an open manner. The panel recommended that the AD/ASD advocacy community participate meaningfully in all aspects of any future VSD study of AD/ASD, including design, analysis and interpretation.”

**CRITIQUE BY IRVA HERTZ-PICCIOTTO, PHD, MPH, CHIEF OF THE
DIVISION OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH,
UNIVERSITY OF CALIFORNIA, DAVIS SCHOOL OF MEDICINE**

“The appropriateness of exclusions that amounted to nearly 25% of the birth cohort in the investigation by Verstraeten et al. (2003) was questioned in the NIEHS expert panel report, and (CDC Director) Dr. Julie Gerberding concurred that further work should be done using the VSD to address this weakness.”⁶² The VSD study “was not the last word... things need to be looked at again, perhaps with different methodology.”⁶³

WHAT A LEADING CRITIC IN CONGRESS SAID

Former Rep. Dave Weldon, MD (R-FL), who served as only one of two physician members of Congress, wrote to CDC Director Dr. Julie Gerberding about his “serious reservations about the four-year evolution and conclusions of this study.”⁶⁴

“I have read various emails from Dr. Verstraeten and coauthors. I have reviewed the transcripts of a discussion at Simpsonwood. I found a disturbing pattern which merits a thorough, open, timely and independent review by researchers outside of the CDC, HHS, the vaccine industry, and others with a conflict of interest in vaccine related issues (including many in University settings who may have conflicts), he wrote.

Instead of a “good faith effort” to investigate potential harm from thimerosal, “there may have been a selective use of the data to make the associations in the earliest study disappear,” he charged. “I cannot say it was the author’s intent to eliminate the earlier findings of an association. Nonetheless, the elimination of this association is exactly what happened and the manner in which this was achieved raises speculation.” The Simpsonwood transcripts, he added, “clearly indicated how easily the authors could manipulate the data and have reasonable sounding justifications for many of their decisions.”

WHAT THE IOM SAID

The IOM vaccine safety committee was not troubled by the changing criteria for entry and outcomes, nor did the total disappearance of an autism signal concern them.

“The difference in preliminary results can be attributed to three major reasons,” they said:

- “Investigators updated datasets with extended follow-up periods, which allowed for additional cases to be identified.”
- “They modified exclusion criteria based on scientific input from the (2001) IOM report and CDC and VSD investigators
- “They improved adjustments for health-care-seeking behavior.
- “Other reasons cited for the differences were a modification to the time of exposure, and inclusion of additional variables in the model.

The panel added this:

The committee notes that it is commonplace for large and important studies to be reviewed along the way, with adjustments often made to improve the eventual validity of the results; thus, it finds nothing inherently troubling in the fact that the VSD study underwent this process. The committee also notes that preliminary results are often misleading and can change substantially as methods are adjusted and more cases and controls are assembled. Indeed, the fact that a conference was held to discuss preliminary findings (Simpsonwood) would typically be interpreted as an attempt by researchers and their sponsors to “get it right,” given the high level of interest in the findings.

Under-ascertainment of cases? The IOM panel wrote that, for HMO A, the autism rate was 1 in 635, or 15.7-per-10,000, and HMO B had 1 in 523, or 19-per-10,000). “Several concerns were raised about the possibility of misclassification of cases with autism because of the way the age of the child was handled in the analyses,” they wrote. One worry was that “some cases of autism may have been missed with shorter follow-up.” But, the data “were adjusted for month and year of birth and time of follow-up,” a “statistical-analysis technique” that “should therefore take care of this concern,” the panel said, without explaining how.

Inclusion of younger children – “Another related concern was that inclusion of a younger group (who are less likely to be diagnosed with autism) in the study would bias the thimerosal effect toward zero,” the panel wrote. “Adjusting for age would reduce, but not eliminate, this tendency. However, if there were an effect of thimerosal, one still would anticipate a trend of increasing effect with age. In this study, there was no such association, even in the older age groups.”

Misdiagnosis of younger children – “The authors attempted to address this by determining the association between thimerosal and neurodevelopmental outcomes and found no consistent significant associations,” the panel said. But it conceded this very important point, often overlooked by the media: “If there are multiple pathways leading to these disorders, it would be difficult to detect the effect of any one cause—unless it occurred with high frequency and the sample size was large—because the tendency of misclassification of outcome is to dilute measures of effect.”

General Limitations cited by the IOM

- “The authors were unable to control completely for other potential confounding factors. In HMO B, the clinic that a child attended may have acted as a confounder.” In other words, inconsistencies between record keeping practices – even within the same HMO – render the data less reliable.
- “The HMO databases did not provide information on other possible confounders, such as maternal smoking, lead exposure, or fish consumption.” Total accumulated toxic exposure is probably more important than a single type of exposure from a single source (ie, mercury in vaccines). Background exposures should also be included.
- “Limitations include the study’s ability to answer whether thimerosal in vaccines causes autism because the study tests a dose-response gradient, not exposure versus non-exposure.” This study compared children who received the highest doses of thimerosal with children who received lower doses. Studying exposed versus non-exposed children might yield clearer data.
- “The small number of cases and instability of some of the risk estimates may affect the findings.” The number of autism cases found was quite low - far lower than what would be expected for such large HMOs.

SUMMARY: This highly controversial study is considered the most important by people who reject any link between thimerosal and ASD, yet it is fraught with severe limitations, methodological weaknesses and questionable analyses. Data collected from the HMO’s was repeatedly re-analyzed – at least five times across three years of study. During that time, entry criteria were changed, children too young to have an ASD diagnosis were added, and other questionable methods of analysis were used. The relative risk for autism fell from 11.35 to zero during that time. As for other NDDs, even the lead author wrote that this was a “neutral” study and could not be used to support or refute a link.

5) “Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association.”⁶⁵

Authors: [Andrews N](#), [Miller E](#), [Grant A](#), [Stowe J](#), [Osborne V](#), [Taylor B](#).

Publication & Date: *Pediatrics*, September, 2004

Online at: <http://pediatrics.aappublications.org/cgi/content/full/114/3/584>

Details – This study was “designed to investigate whether there is a relationship between the amount of thimerosal that an infant receives via diphtheria-tetanus-whole-cell pertussis (DTP) or diphtheria-tetanus (DT) vaccination at a young age and subsequent neurodevelopmental disorders.” It was a retrospective cohort study of 109,863 children born in the UK from 1988 to 1997. Outcomes studied were general developmental disorders, language or speech delay, tics, attention-deficit disorder, autism, unspecified developmental delays, behavior problems, and others. “Exposure was defined according to the number of DTP/DT doses received by 3 and 4 months of age and also the cumulative age-specific DTP/DT exposure by 6 months.”

Results: “Only in 1 analysis for tics was there some evidence of a higher risk with increasing doses (HR: 1.50 per dose at 4 months). Statistically significant negative associations with increasing doses at 4 months were found for general developmental disorders (HR: 0.87), unspecified developmental delay (HR: 0.80) and attention-deficit disorder (HR: 0.79; 95% CI: 0.64-0.98). For the other disorders, there was no evidence of an association with thimerosal exposure.”

Authors’ Conclusions: “With the possible exception of tics, there was no evidence that thimerosal exposure via DTP/DT vaccines causes neurodevelopmental disorders.” For general developmental disorders, unspecified developmental delay, and ADD, there was an apparent protective effect from increasing thimerosal exposure.

CRITIQUES OF THE STUDY

■ **Mercury is Not Protective** - Many observers felt that the “protective effect” of organic mercury exposure found in young children was biologically implausible. According to this study, higher thimerosal exposure at 4 months of age reduced the risk of ADD and unspecified developmental delay by at least 20 percent compared to children with lower exposures. There is no biological evidence to suggest that a known neurotoxin like ethylmercury can be beneficial to neurodevelopment.

■ **A Deceptive Study Design** – When researchers try to determine if there is a cause-and-effect relationship between two different things – in this case thimerosal exposure and autism outcomes – they make their calculations using something called a “regression analysis,” which, in its simplest form, most people know of as a “curve.” A simple regression analysis has two variables. In this case, thimerosal (the potential causative

agent) would be the “independent variable,” and autism (the potential effect of the agent) would be the “dependent variable.” It is important to note as well that this is not an analysis of exposure or not, but only the timing of vaccination. *All* of the children in this study were exposed to thimerosal

But in Andrews et al., the authors used a model that was a bit more complicated, something called a “multiple regression analysis,” which had one dependent variable (autism), and multiple independent variables, including *two* independent variables (thimerosal exposure levels, and year of birth) that were “correlated” with each other, since thimerosal exposures went up with time. This creates a well-known problem in regression known as “multicollinearity” It is illogical to include both variables unless you believe the increases over time are only due to improved awareness. If there is no logic to including a variable in a regression model, it simply doesn’t belong there. In this case, since the time variable and the vaccine exposure variable are correlated, they actually compete to explain the outcome effect. Inclusion of the time variable reduces the significance of the exposure variable. Yet the authors never explained why they included a time variable that correlates and competes with the exposure variable. Instead, the Andrews model assumes implicitly that increased autism rates are due to time trends alone.

■ **Lack of Transparency** – The authors have repeatedly declined to make their data available to others for independent verification, and they fail to state why they chose such an erroneous method that would produce multicollinearity. “It’s a flaw of the peer review process, because someone should have called them on it,” said Mark Blaxill of SafeMinds. “But Pediatrics wants the outcome they report, so no one requires them to be transparent.” The AAP and its journal *Pediatrics* receive millions of dollars a year in advertising and other funds from major pharmaceutical companies, including vaccine makers. This clear conflict of interest was never mentioned in mainstream media coverage of this subject.

■ **Potential Conflicts of Interest** – Some of the authors have ties to vaccine manufacturers and/or the national immunization program of the United Kingdom. For example, Elizabeth Miller, FRCP, was the architect of the UK vaccine program and has testified in court in defense of drug companies in vaccine injury lawsuits.

■ **Results Not Applicable to US** - Where infant exposures to mercury from vaccines was considerably higher.

WHAT THE AUTHORS SAID

The authors acknowledged several limitations in their study:

■ The outcomes measured occurred “at a relatively young age” and were “more likely to be affected by confounding factors that are also associated with delayed or incomplete vaccination.”

■ Another limitation was the “inability to adjust for many potential confounding factors, such as unrecorded medical conditions and socioeconomic factors.”

■ “If the increased risk in the US study were attributable only to the additional thimerosal exposure after 4 months of age, then it is possible that our study may not have been able to detect the risks found in the US study.”

■ Validation exercises found that 20% of the diagnoses were invalid or questionable. “This lack of specificity is a limitation of the study because it biases against finding an association.”

■ As for the risk of minor transient tics, “the possibility of a true effect cannot be ruled out,” although it was more plausible that the association “is a chance effect or the result of confounding.”

WHAT THE IOM SAID

The IOM panel noted the differences in mercury exposure rates in the US and UK vaccines scheduled. “With the (UK’s) 2-3-4 month schedule, children could have received a maximum of 50mcg of mercury at 3 months of age and 75mcg of mercury at 4 and 6 months of age. This amount is less than the maximum amount received by U.S. children. U.S. children could have received 75 mcg of mercury after 3 months, 125 mcg after 4 months, and 187.5 mcg after 6 months.

What Irva Hertz-Picciotto, PhD, MPH, Chief of the Division of Environmental and Occupational Health, University of California, Davis School of Medicine, said:

Andrews et al. (2004) examined a specific hypothesis, namely, that autism risk would be increased from early administration of thimerosal-containing vaccines, based on the number of vaccines received prior to 3 months, prior to 4 months, and the timing and number of vaccines prior to 6 months of age. The unexplained oddity that three of the nine categories of developmental disorders (general developmental disorders, attention deficit disorders, and unspecified developmental delay) were significantly reduced in those with early vaccines would suggest the possibility that confounding (acknowledged by the authors as a problem) could have resulted in a 'healthy vaccinee' effect. In other words, the healthiest babies would be those who were vaccinated at the earliest times.⁶⁶

SUMMARY: This study used a statistical sleight of hand to make any association disappear. The authors included a time variable that competes with the exposure variable. Such a model assumes *a priori* that increased autism rates are due to time trends alone. This study also suffered from some of the most serious undisclosed conflicts of interest among all the thimerosal ASD epidemiological investigations.

6) “Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years”⁶⁷

Authors: Thompson WW, Price C, Goodson B, Shay DK, Benson P, Hinrichsen VL, Lewis E, Eriksen E, Ray P, Marcy SM, Dunn J, Jackson LA, Lieu TA, Black S, Stewart G, Weintraub ES, Davis RL, DeStefano F; Vaccine Safety Datalink Team.

Publication & Date: *New England Journal of Medicine*, September 26, 2007

Online at: <http://content.nejm.org/cgi/content/full/357/13/1281>

Details: Although autism was not included in this study, it is still presented as evidence against any association between thimerosal in vaccines and certain immune-globulins given during pregnancy and adverse outcomes.

Investigators studied 1,047 children between 7 and 10 years of age enrolled in participating HMOs of the VSD database. The children were given standardized tests for 42 neuropsychological outcomes, including speech and language disorders, verbal memory, achievement, fine motor coordination, visuospatial ability, attention and executive-functioning tasks, behavior regulation, tics, and general intellectual functioning.

Attention, hyperactivity and executive functioning were based on reports from parents and teachers, while motor tics, phonic tics and stuttering evaluations combined ratings by evaluators with reports from parents and teachers.

Mercury exposure from thimerosal was determined from computerized immunization records, medical records, personal immunization records, and parent interviews. The authors “assessed the association between current neuropsychological performance and exposure to mercury during the prenatal period, the neonatal period (birth to 28 days), and the first 7 months of life.”

Results: Among the 42 outcomes studied, only a few significant associations with exposure to thimerosal were detected. These associations were “small and almost equally divided between positive and negative effects.” For example:

- Higher prenatal mercury exposure was associated with better performance on one measure of language and poorer performance on one measure of attention and executive functioning.
- Increasing levels of mercury exposure from birth to 7 months were associated with better performance on one measure of fine motor coordination and on one measure of attention and executive functioning.

■ Increasing mercury exposure from birth to 28 days was associated with poorer performance on one measure of speech articulation and better performance on one measure of fine motor coordination.

Conclusions “Our study does not support a causal association between early exposure to mercury from thimerosal-containing vaccines and immune globulins and deficits in neuropsychological functioning at the age of 7 to 10 years.

Critique by Mark D. Noble, PhD - Professor of Genetics and of Neurobiology and Anatomy, University of Rochester Medical Center: ⁶⁸

Poor Confirmation of Cases – “One of the most critical problems with the studies of Andrews et al. is the very poor validation for the data that they analyzed. Validation responses were received from 162 of 166 general practices that were queried, of which it appears that each was asked about a single child. Of this group, 19% of diagnoses could not be confirmed. Of those with a confirmed diagnosis, 39% were considered to be transient problems (which is not a description that would normally be applied to autism) and the duration of the problem could not be determined for an additional 35% of cases. Thus, only 26% of the validation attempts established that problems were long-term in children with a confirmed diagnosis.”

Low Number of Unexposed Children – “The number of individuals reported to receive no thimerosal exposure during the first 4 months of life was very low, representing only 3.4% of infants delivered at term and 5.8% of pre-term infants.”

“The small numbers of children with behavioral differences were spread in unspecified distributions across the ten years of information, and attempts at validation provided confirmation of long-term problems in only 20.5% of cases. (This) renders analysis of the data base of Andrews and colleagues fraught with uncertainty. In the specific context of autism, any decreased representation in the zero-exposure cohort (i.e., less than a total of 3 cases identified) seems unlikely to be suitable for accurate statistical comparisons.”

Mercury As “Neuro-protective”?: “Claims made that increased exposure to thimerosal was associated with equal or even lower levels of hazard thus appear to be conjectural. Moreover, children also exposed to hepatitis B and/or influenza vaccinations in the first six months of life were excluded from the analysis, thus excluding those children known to have still higher levels of thimerosal exposure and further limiting the values of the comparisons conducted.”

Critique by Mary Catherine DeSoto, PhD, and Robert T. Hitlan, PhD, Department of Psychology, University of Northern Iowa: ⁶⁹

Seven of the authors had received fees from Merck, Kaiser Permanente and other pharmaceutical companies that may have or had an interest in disproving any link to thimerosal and/or mercury exposure and developmental disorders. First, it is important to be very clear that we do not believe that authors would

purposefully change their data, or consciously misstate conclusions. Not only would this be unethical, but the stakes are very high. But this does not mean there is no bias; the bias would be subtle and far less nefarious than any sort of purposeful altering of data. If a person has publicly staked his/her career on a certain position being right, it may become harder to keep a truly open mind, even when new data become available and even when the original intent was to be objective. A way this bias might manifest itself is an overstatement or slight misstatement of results. We feel that both sides have been guilty of this, and this happens when a person becomes so confident in the correctness of his/her own view that he/she no longer reviews evidence to the contrary. Unconscious bias may exist even in the best scientists

This is the sort of bias, whether conscious or unconscious, that occurs. Because some of the authors of the Thompson study have publicly aligned with opposing a mercury-autism link (by taking consulting fees), they may be unconsciously more prone to review studies that support their view, less likely to review opposing viewpoints, and may eventually become unaware of relevant research (e.g., Newland et al. 2008). By using 42 measures and finding only a small handful of effects, it is easy to say the obtained relations are chance occurrences. Then, another scholar summarizes the study and slightly changes the results based on a world view that there is no effect of thimerosal, “found no evidence of neurological problems in children exposed to mercury containing vaccines” (Offit 2007, p. 1279). Then this assessment gets quoted by those who do not bother to look carefully at the original study, and scientific advancement becomes stifled.

OTHER CRITIQUES OF THE STUDY

■ The response rate was extremely low. Of 3,648 children selected for recruitment only 1,107 (30.3%) were tested. Among those not responding, 1,026 could not be located, while the mothers of 959 children refused participation. 68% of those refusing cited lack of time, but 13% reported “distrust of or ambivalence toward research

■ Mothers with special needs kids are usually those with the least amount of free time. With such a low response rate, the children studied were likely healthier than the general population.

■ Among a population of 1,026 children, one could expect to find about 45 students on medication for ADD/ADHD. Was that the case? “There were a small number of kids” with ADD/ADHD, Dr. Thompson said, without providing a number.

■ It is possible that low birth-weight kids had increased deficits, but children born below 5.5lbs were excluded from the study.

■ Some children had probably received years of therapy to treat outcomes they were being tested for. An unreported number had been treated with prescription drugs, speech

therapy, psychotherapy and/or other forms of treatment. Investigators conceded that prior therapy "may have ameliorated the potential negative effects of thimerosal exposure," and "could have biased the results toward" finding nothing.

- Despite the mix of positive and negative associations, there remained a "higher likelihood" of motor and phonic tics in boys, something found in previous studies, including Verstraeten (US) and Andrews (UK).

- Boys exposed to the highest amounts of mercury by 7 months of age were 2.19 times more likely to have motor tics, and 2.44 times more likely to have phonic tics than boys in the lowest exposure rates.

- The authors failed to differentiate between "transient" tics, which go away within a year, and "chronic" tics, which can last a lifetime. Nor did they distinguish between "simple" and "complex" tics. "We did not categorize them, and some of them may have been chronic," Dr. Thompson said.

- In fact, "The replication of the (2003) findings regarding tics suggests the potential need for further studies," the authors wrote.

- There were also small but negative associations with speech-articulation in children, and lower verbal IQs among girls, which together "suggest a possible adverse association between neonatal exposure to mercury and language development," the authors said. A similar "increased risk of language delays at one HMO associated with thimerosal-containing vaccines," was found in Verstraeten's 2003 VSD study.

- It is illogical to cite an increased risk for tics (one replicated in a prior study and which may need "further study") and increased language deficits (also found in the same prior study), but still conclude that there is "no causal association" between thimerosal neuropsychological deficits.

- Sallie Bernard of SafeMinds, the only consumer representative on the study's panel of advisors, said the final conclusions were mere "conjecture." The many limitations "preclude any reasonable determination of the 'truth.' The authors' arbitrary selection of one explanation for their conclusion risks misleading the reader into thinking that the absence of a relationship has been proved."⁷⁰

- Dr. Lawrence Rosen, a pediatrician who treats ASD in Tappan, NJ, said the mixed results and severe limitations "make the study kind of worthless. They are picking and choosing what they want to report. It's not a well-designed study. So either don't publish it; or do so with all sorts of explanations. You can't have it both ways. This study doesn't answer any questions. It makes things even muddier."⁷¹

- Extremely few children received no thimerosal: the investigators largely compared medium-to-high exposures to low exposures, instead of zero exposure.

DEFENSE OF THE STUDY

■ Dr. Ted Schettler, science director of the Science and Environmental Health Network, said there were “only a few significant associations, small and equally divided. When looking at multiple outcomes, some favorable and some unfavorable, it’s very common for authors to conclude that chance variability is the reason.”⁷²

■ Dr. Thompson said tics were “likely to be transient,” and not of clinical importance. They were also detected by trained experts, not parents, meaning they were “probably” not severe enough for parents to notice. “And given that kids that age (7-10) have the greatest degree of transient tics,” he added, “we believe these were transient.”⁷³

■ Although a 30% response rate “could have an impact on selection bias,” it’s impossible to know which way the bias may have gone. Parents with concerns about their child’s development might be more likely to participate.

SUMMARY: The response rate to this study was extremely low, suggesting possible selection bias in the recruitment of patients. Moreover, the children were examined years after their thimerosal exposure, and many of them had presumably received medical and behavioral treatments in the intervening period. It is illogical to conclude there is “no causal association” between thimerosal neuropsychological deficits, and then cite an increased risk for tics (one replicated in a prior study “further study”) and increased language deficits (also found in the same prior study).

7) “Continuing increases in autism reported to California's developmental services system: mercury in retrograde.”⁷⁴

Authors: Schechter R, Grether JK.

Publication and Date: *Archives of General Psychiatry*, January, 2008

Online at: <http://archpsyc.ama-assn.org/cgi/content/full/65/1/19>

Details: “The exclusion of thimerosal from childhood vaccines in the United States was accelerated from 1999 to 2001.” This study was designed to see if trends in California’s Department of Developmental Services (DDS) autism client data “support the hypothesis that thimerosal exposure is a primary cause of autism.” The authors investigated trends in autism cases by age and birth cohort in children with autism who were DDS clients from January 1, 1995, through March 31, 2007.

Results: “The estimated prevalence of autism for children at each year of age from 3 to 12 years increased throughout the study period. The estimated prevalence of DDS clients aged 3 to 5 years with autism increased for each quarter from January 1995 through March 2007. Since 2004, the absolute increase and the rate of increase in DDS clients aged 3 to 5 years with autism were higher than those in DDS clients of the same ages with any eligible condition including autism.

Authors’ Conclusions: The DDS data do not show any recent decrease in autism in California despite the exclusion of more than trace levels of thimerosal from nearly all childhood vaccines. The DDS data do not support the hypothesis that exposure to thimerosal during childhood is a primary cause of autism.

CRITIQUES OF THE STUDY

Thimerosal Removal Not Complete Until 2003 – The authors’ statement that “The exclusion of thimerosal from childhood vaccines in the United States was accelerated from 1999 to 2001” is inaccurate. Vaccine makers were asked to voluntarily remove thimerosal from childhood vaccines in July of 1999, a process that took a few years. Likewise, the authors claim their study is inconsistent with a thimerosal association because “the prevalence of autism in children reported to the DDS has increased consistently for children born from 1989 through 2003, inclusive of the period when exposure to TCVs has declined.” The last TCVs (with the exception of the influenza vaccine) were manufactured in 2001, but expired in 2003.

Youngest Cohort Data is Unreliable – The study states that there were more 3-5-year olds in the first quarter of 2007 (children born from 2002-2004) than among 3-5 year olds in the first quarter of 2006 (born from 2001-2003). But diagnoses among younger children can vary, depending especially on the average age of diagnosis in any given area. This is why the CDC waits until children are 8 years of age in order to conduct its own autism surveillance studies, which are considered to be the most accurate in the

United States. Unfortunately, the CDC surveillance system does not include children in California.

Falling Age of Diagnosis Creates Artificial Increase – One reason that CDC waits until children are 8 years of age is because each year, the average age of autism diagnoses goes down. The result is that, each year, more and more three-year-olds are diagnosed as compared to prior years. This is supported by a study published in the December 2008 issue of *Archives of Pediatric and Adolescent Medicine*.⁷⁵ “Shifts in age at diagnosis inflated the observed prevalence of autism in young children in the more recent cohorts compared with the oldest cohort,” the authors wrote. “This study supports the argument that the apparent increase in autism in recent years is at least in part attributable to decreases in the age at diagnosis over time.”

IOM: California Data Not Reliable For Incidence Studies – In its 2004 report on thimerosal and autism, the IOM Immunization Safety Committee discussed two reports from California’s DDS system (from 1999 and 2003) that showed a large increase in autism cases from 1987 to 2002. Those data were “widely cited as evidence of an increase in the incidence of ASD in the United States,” the panel wrote. But, it cautioned: “The report stresses that the study was not designed to measure trends in autism incidence, and the data should therefore be interpreted with caution. Several methodological limitations have been cited, including the failure to account for changes over time in the population size or composition, in diagnostic concepts, in case definitions, or in *age of diagnosis*.” (Emphasis added).

DDS: Be Careful Drawing Conclusions – On a webpage titled “Data Interpretation Considerations and Limitations,” the DDS cautions: “Although information published by DDS in the Quarterly Client Characteristics Report is often used by media and research entities to develop statistics and draw conclusions some of these findings may misrepresent the quarterly figures.” In addition, it says, “Increases in the number of persons reported from one quarter to the next do not necessarily represent persons who are new to the DDS system.”⁷⁶

Authors: Findings Must Be Confirmed – The authors concluded that “Continuing evaluation of the trends in the prevalence of autism for children born in recent years is warranted to confirm our findings.” Unfortunately, that will never be possible in California, where entry criteria for DDS services were broadly expanded to include children with PDD-NOS and Asperger’s Disorder in January, 2008. “Information from these new items will not be comparable to prior information,” a DDS statement says.

SUMMARY – The conclusions of this study rely solely on one year of data in one state among the youngest children who presumably received markedly less thimerosal in their vaccines. Basing such a conclusion on the youngest cohort data is unreliable, partly because the falling age of diagnosis creates an artificial increase. The IOM said the California data is not reliable for incidence studies, the California Department of Developmental Services cautioned against drawing conclusions from the database, and

the authors themselves warned that their findings must be confirmed from later data, something that has not happened – and cannot happen.

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