Critique of the 6 epidemiological studies used to exonerate thimerosal containing vaccines

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Six epidemiological studies have been used to "refute" the link between thimerosal and autism. These are:

1. "Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data" by Kreesten Madsen et al. 2003, published in the journal Pediatrics
2. "Autism and thimerosal-containing vaccines: lack of consistent evidence for an association" by Paul Stehr-Green et al., 2003, published in the American Journal of Preventative Medicine
3. "Association between thimerosal-containing vaccine and autism" by Anders Hviid et al., 2003, published in the Journal of the American Medical Association
4. "Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases" by Thomas Verstraeten et al., 2003, published in the journal Pediatrics
5. "Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association" by Nick Andrews et al., 2004, published in the journal Pediatrics
6. "Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism" by CS Price et al., 2010, published in the journal Pediatrics

This critique will consider each publication from two perspectives: (1) the scientific quality and (2) any anomalies based on information obtained from the Centers for Disease Control and Prevention via the Freedom of Information Act.

1. **"Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data" by Kreesten Madsen et al. 2003, published in** the journal Pediatrics

The publication reports an ecological study based on the reported autism incidence in Denmark as recorded in the Denmark National Center for Registry-based Research (NCRR) database. Denmark phased thimerosal containing vaccines out of circulation in 1992. The authors' premise is that if there is a causal relationship between autism and thimerosal containing vaccines, then the prevalence of autism should decrease in subsequent years. Instead, the study showed a dramatic increase in the number of new autism diagnoses in the years following thimerosal removal, in age groups 2-4, 5-6 and 7-9 years old.

This paper has two severe methodological flaws. First, the Denmark NCRR database changed diagnostic criteria for autism diagnoses in 1994 from ICD8 to ICD10. This led to a greater number of autism diagnoses overall. Second, the Denmark NCRR database changed the accounting of autism based on outpatient visits in 1995, whereas up to 1995, only inpatient (i.e., Hospital) visits were accounted. This led to a significant increase in autism cases counted beyond 1994. In a separate publication, the ratio of inpatients to outpatients accounted for by the NCRR database has been reported to be 13.5:1 (Madsen et al. 2002). These two data artifacts (changing diagnostic criteria and inpatient/outpatient reporting) show a misleading jump in the prevalence of autism after 1995. However, when these are corrected for, the actual autism rates in Denmark decreased by as much as 4 times upon the phase out of thimerosal-containing vaccines (Trelka et al. 2004). Although the raw data from the Madsen et al. 2003 publication has been requested, the authors chose not to release it, creating significant difficulty in confirming this decrease.

It is apparent from emails released by the CDC via the FOIA, that the lead author of the study, Dr. Kreesten Madsen, was well aware of the issues with the Denmark NCRR database. In fact, in a June 2001 email to then acting Deputy Director of the National Immunization Program (NIP) of the CDC, Diane Simpson, Dr. Madsen stated of the increases in autism rates after 1993, "Yes, but not very dramatically and there could be more reasons for that. First of all we had a change from ICD8 to ICD10 in 1994 and furthermore our outpatient clinics were registered in our surveillance from 1995." It wasn't until after Dr. Diane Simpson visited Denmark to forge a collaboration with Madsen's supervisor at Aarhus University that this publication went forward.

In addition, an additional email obtained from the CDC indicates that the autism rates in Denmark decreased between 1999-2001: from Dr. Marlene Lauritsen a coauthor from Aarhus University to Dr. Diana Schendel, a scientist in the National Center for Birth Defects and Developmental Disabilities (NCBDDD) of the CDC, "I need to tell you that the figures in the manuscript do not include the latest data from 2001. I only have these figures as a paper version and they are at work <redacted> But the incidence and prevalence are still decreasing in 2001. <redacted>" These data were excluded from the final publication.

Finally, although the CDC claims that this is an independent publication, co-author Dr. Poul Thorsen was in residence at the CDC at the time of the study. In addition, Dr. Thorsen made a specific request that Dr. Jose Cordero, then director of the NCBDDD write a letter to the editor of the journal Pediatrics for expedited review and publication of the Madsen et al. 2003 study. Dr. Thorsen in April, 2011 was indicted by the U.S. Attorney in Atlanta, Georgia for embezzlement of funds from a CDC grant to his institution, the North Atlantic Neuro-Epidemiology Alliance.

2. **"Autism and thimerosal-containing vaccines: lack of consistent evidence for an association" by Paul Stehr-Green et al., 2003, published in the American Journal of Preventative Medicine**

This paper is more of a "ecological review" of autism prevalence data obtained from California, Sweden and Denmark to deny a causal relationship between thimerosal containing vaccines and autism. The treatment of the California data was more of a critique of the Blaxill 2001 presentation to the Institute of Medicine Immunization Safety Review committee, where it was shown that increased uptake of thimerosal containing vaccines in California during the 1990's resulted in a corresponding increase in autism diagnoses. Here the authors criticized the reliability of the autism prevalence data, citing that the California data included autism spectrum disorder diagnoses such as Pervasive Development Disorder, which could account for the increase.

The treatment of Sweden autism prevalence data showed an increase in autism rates from 5-6 cases per 100,000 to a peak of 9.2 cases per 100,000 in 1993. Thimerosal was removed from vaccines in Sweden in 1987. The treatment of Denmark autism prevalence data was identical to that done in the Madsen et al. 2003 paper critiqued previously. The authors reported an astounding 20-fold increase in autism prevalence between 1990 and 1999, despite the removal of thimerosal from vaccines in 1992.

The most glaring flaws of this paper are the treatment of the Denmark prevalence data, which is discussed previously. In addition, the data from Sweden were based on inpatient (Hospital) visits only. 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. Also, the thimerosal exposure level based on the Sweden vaccination schedule during this time period was much less than that seen in California and the United States as a whole. Finally, concerning the California prevalence data, the study authors erred by citing PDD data inclusion. In fact, the California prevalence data reported by Blaxill in 2001 included only cases of "full blown" autism. The increase in autism prevalence in California has been since shown to be real by two separate peer reviewed studies.

Emails obtained from the CDC via the FOIA show that study co-authors Dr. Paul Stehr-Green (CDC consultant) and Dr. Diane Simpson (acting Deputy Director of the NIP) were scouring other countries from autism prevalence data to counter the October 2001 IOM ISR committee report citing that the relationship between thimerosal containing vaccines and autism is biologically plausible. Dr. Stehr-Green and Dr. Simpson traveled in Denmark and Sweden in August 2001 and very hastily formed collaborations with institutions in these countries that stewarded autism prevalence data. In an August 7, 2001 email prior to the trip, Dr. Simpson wrote, "I don't have any new data at the moment and am frantically trying to see what is available and how best to get it in time for the expected IOM report release (we have given up trying to submit it in time for the report as they are in the process of writing it)." In a separate email to Dr. Stehr-Green and Dr. Roger Bernier (Science Director of the NIP), Simpson writes "It is possible that the data won't help us at all, but we won't know until we see it." By this, she is inferring that "helpful" data would oppose the IOM ISR committee report and counter a causal relationship between thimerosal containing vaccines and autism. Thus, Dr. Simpson had a bias prior to writing the publication and demonstrated a vested interest in exonerating thimerosal using the Sweden and Denmark autism prevalence data.

3. **"Association between thimerosal-containing vaccine and autism" by Anders Hviid et al., 2003, published in the Journal of the American Medical Association**

This is a population-based cohort study comparing rates of autism prevalence among individuals who received thimerosal free vaccines versus those receiving thimerosal containing vaccines. The authors report that there was no evidence of increased autism prevalence with thimerosal exposure and that thimerosal seemed to have a "protective effect" against autism.

Criticisms of this study include the fact that the Denmark registry that holds the data allows 10-25% of diagnosed autism cases to be lost from its records each year. Thus, 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. This is seen in the study, which is skewed towards younger children that did not receive thimerosal containing vaccines (i.e., they were vaccinated after 1992). When a correction was applied (Safeminds, 2004), an increase in autism prevalence was 2.3 times greater in the group that received thimerosal containing vaccines.

4. **"Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases " by Thomas Verstraeten et al.,** 2003, published in the journal Pediatrics

This study comprised a comprehensive analysis of medical databases for three HMOs in a central data repository, the Vaccine Safety Datalink. This particular study was done in five separate phases. In the final phase (i.e., that reported in the publication), the authors claim there was no relationship between thimerosal exposure in vaccines and autism incidence. However, no data is reported to support this assertion.

Data from the first 4 phases of the study have been obtained (either via the FOIA or where the CDC directly reported the data). The first phase of the study (results obtained via FOIA) showed that infants that were exposed to 25 micrograms (ug) of mercury in their infant vaccines by age one month were 7.62 times more likely to have an autism diagnosis than those not exposed to any mercury. The study author, Thomas Verstraeten (then at the CDC) said of the correlation in an internal email, "It just won't go away".

In the second phase of the study, a different approach was taken: exposure was compared at 3 months of age, rather than one month. However, like the first phase, children exposed to the maximum amount of mercury in infant vaccines (62.5 ug) were 2.48 times more likely to have autism diagnosis compared to those not exposed to mercury in vaccines.

In the third phase of the study, more data stratification methods and exclusion criteria were applied to the analysis and the increase in risk for children at three months dropped to 1.69 times. At this point, it is evident that Verstraeten is receiving pressure within the CDC to apply methods to deny a causal relationship between thimerosal and autism. In an email written to a colleague outside of the CDC, Verstraeten states, "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 an unpleasant theory."

The fourth and fifth phase of the study incorporated a third HMO, Harvard Pilgrim, into the analysis. Some critics of the study questioned the use of Harvard Pilgrim as the HMO was riddled with questionable record keeping practices, 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 Phases 1 through 3. Other criticisms include that the study used younger children, from 0 to 3 years of age, even though the average age for an autism diagnosis at the time was at 4.4 years.

Finally, Dr. Verstraeten, who left the CDC and spent most of the two years prior to publication of the study as an employee of vaccine manufacturer GlaxoSmithKline, made a statement in 2004 that appeared in the journal Pediatrics 9 months after the publication of his study. In this statement, he says, ""The perception of the study changed from a positive to a neutral study," and continues "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."

5. "**Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United Kingdom does not support a causal association" by** Nick Andrews et al., 2004, published in the journal Pediatrics

This is a retrospective cohort study completed using records from the United Kingdom, where autism prevalence rates were compared for children receiving thimerosal containing DTaP and DT vaccines. The study authors report no correlation between the number of doses of vaccine and the incidence of autism and reported that thimerosal exposure had a protective effect against autism.

The main technical problem with this study is that the authors used a non-transparent, multi-variate regression technique to analyze vaccine uptake and autism prevalence data. The study included 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. Unfortunately, the authors of this study have refused to release their raw data. Accordingly, a single variable analysis cannot be completed.

Interestingly, emails obtained via FOIA indicate that Dr. Thomas Verstaeten at the CDC had decision authority as to whether this study would receive funding. Thus, this study, like the prior 4, may be tied directly to the CDC. In an email exchange with Dr. Robert Chen (also of the CDC), Verstraeten states the following about the UK study, ""The maximum exposure [in Britain] is indeed relatively low...my estimate is that you need at least >50 [mcg of mercury] by 3 months or >100 by 6 months to see an effect if there is one which you barely make...I hate to say this, but given these concerns, it may not be worth doing this after all. On the other hand, maybe the grant can be given to Harald in Sweden..."

In response to this, Elizabeth Miller (GPRD – UK), the study lead author, replies, "If this is true, then do we have sufficient exposure to ethyl Hg (i.e., thimerosal) by 4-6 months of age to pick up an effect? Do I have to give my GPRD money from WHO back???"

Again, this shows that Verstraeten and Chen of the CDC exerted financial control over the UK study. Also, this belies the fact that the UK thimerosal exposure was not comparable to that in the United States and that this study should not be extrapolated to autism-thimerosal correlation based on the US vaccination schedule.

6. **"Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism" by CS Price et al., 2010, published in the journal** Pediatrics

This study is comprised of the evaluation of the thimerosal exposure levels in a small study set of autistic children versus similar exposure in a control group of "neurotypical" children. The study was stratified into 4 exposure categories: prenatal, birth to one month, birth to seven months and birth to 20 months. No statistically significant difference was seen in the likelihood of receiving an autism diagnosis based on the level of mercury exposure within these categories.

The authors erroneously report that this is a study of the relative risk of autism with increasing levels of prenatal and postnatal thimerosal exposure. Instead, this is a study that determines the relative amount of thimerosal exposure between a group of autistic children and neurotypical children. This answers the wrong question. The question isn't whether autistic children received greater exposure to thimerosal. Instead, the question should be "does the risk of receiving an autism diagnosis increase with increasing thimerosal exposure." Such an analysis was not completed in this study.

Additionally, the study size is very limited (256 autistic and 752 control individuals). Within this group, further stratification is completed based on pre- and postnatal thimerosal exposure, further limiting the statistical power of the study. The data from this study were taken from the Vaccine Safety Datalink (VSD), which has been deemed inappropriate for this type of study by the 2006 National Institute for Environmental Health Studies 2006 committee "Thimerosal Exposure in Pediatric Vaccines: Feasibility of Studies Using the Vaccine Safety Datalink." This is due to problems with case ascertainment via administrative data which may lead to both false positives and missed cases, heterogeneity in business practices across the managed care organizations (MCOs) comprising the VSD (there were 3 different MCOs represented in the Price et al 2010 study), difficulties in linking children's records to their mothers' and poor estimation of total mercury burden.

Also, by considering prenatal and postnatal thimerosal burden separately, the study authors have not accounted for mercury exposure outside of the parameter study period. In other words, prenatal cohort analyses were not evaluated for postnatal exposures and vice versa. Finally, the covariate analysis completed on the cohort sets is ill conceived and runs the risk of introducing errors due to "multicollinearity". With these additional variables (birth weight, maternal age, birth order, breastfeeding duration, family income, maternal health care–seeking behavior, maternal exposures during pregnancy with study child, and early childhood health conditions), it becomes much easier to "fit" data to the desired outcome.