

Immunization Safety Review

National Academy of Sciences
Institute of Medicine, FO 3031
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Washington, DC 20418

Dear Committee members,

SAFE MIND's recently obtained the transcribed minutes to the Simpsonwood meeting held June 7-8, 2000 in Norcross, Georgia where the finding of the Vaccine Safety Datalink analysis of Thimerosal containing vaccines and neurodevelopmental outcomes were reviewed by a panel of experts. There were a number of additional findings not previously reported that were contained in this document that I would like to share with the committee. A copy of the entire document is available for the committee's review along with a list of participants.

SAFE MIND's has summarized a number of comments made by the participants that we feel deserve special consideration by the committee. These comments will be categorized as introductory concerns related to the issue of thimerosal containing vaccines made by participants, CDC's presentations of the VSD data and discussion comments made after the presentations. The comments in *Italics* are that of SAFE MIND's made in reference to the discussion.

Introductory comments expressed by participants.

Dr. Johnston: Page 16 *comments made in reference to a prior meeting on thimerosal* "As an aside, we found cultural differences between vaccinologist and environmental health people in that many of us in the vaccine arena have never thought about uncertainty factors before. We tend to be relatively concrete in our thinking. Probably one of the big cultural events, at least for me, was when Dr. Clarkson repetitively pointed out to us that we just didn't get it about uncertainty (factors), and he was actually quite right."

Dr. Johnston: Page 20: *Referring to the mixture of both aluminum and mercury in vaccines...*there is absolutely no data including animal data, about the potential for synergy, additivity or antagonism, all of which can occur in binary metal mixtures that relate and allow us to draw any conclusions from the simultaneous exposure to these two salts in vaccines."

Dr. Clarkson: Page 21: "There is an issue that pharmacokinetics might be different too. Again this is all animal work, but the animal studies suggested, for example, a suckling animal does not eliminate methylmercury until the end of the suckling period, and there is a mechanism on the study for that. So there could be an age difference in the excretion rates."

Dr. Weil: Page 24: “One, up until this last discussion we have been talking about chronic exposure. I think it’s clear to me anyway that we are talking about a problem that is probably more related to bolus acute exposures, and we also need to know that the migration problems and some of the other developmental problems in the central nervous system go on for quite a period after birth. But from all of the other studies of toxic substances, 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, so that moving from one month or one day of birth to six months of birth changes enormously the potential for toxicity. **There are just a host of neurodevelopmental data that would suggest that we’ve got a serious problem. The earlier we go, the more serious the problem.** The second point I could make is that in relationship to aluminum, being a nephrologist for a long time, the potential for aluminum and central nervous system toxicity was established by dialysis data. To think there isn’t some possible problem here is unreal.”

CDC’s presentation of the VSD data by Dr. Verstraeten and Dr. Rhodes.

Dr. Verstraeten: Page 31: “ It is sort of interesting that when I first came to the CDC as a NIS officer a year ago only, I didn’t really know what I wanted to do, but one of the things I knew I didn’t want to do was studies that had to do with toxicology or environmental health. Because I thought it was too much confounding and it’s very hard to prove anything in those studies. Now it turns out that other people also thought that this study was not the right thing to do, so what I will present to you is the study that nobody thought we should do.”

Dr. Verstraeten: Page 40: “**...we have found statistically significant relationships between the exposures and outcomes for these different exposures and outcomes. First, for two months of age, an unspecified developmental delay, which has its own specific ICD9 code. Exposure at three months of age, Tics. Exposure at six months of age, an attention deficit disorder. Exposure at one, three and six months of age, language and speech delays which are two separate ICD9 codes. Exposure at one, three and six months of age, the entire category of neurodevelopmental delays, which includes all of these plus a number of other disorders.**”

Dr. Verstraeten: Page 42: “**But one thing that is for sure, there is certainly an under-ascertainment of all of these because some of the 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.**”

Dr. Verstraten: Page 44: “**Now for speech delays, which is the largest single disorder in this category of neurologic delays. The results are a suggestion of a trend with a small dip. The overall test for trend is highly statistically significant above one.**”

Dr. Verstraten: Page 45: “What this represents is the overall category of developmental delays, of which I have excluded speech delays because of the impression we had was some of the calculations were driven by this speech group, which was making up about

half of this category. After excluding this speech group, the trend is also apparent in this group and the test for trend is also significant for this category excluding speech.”

Dr Verstraeten: Page 68: “However, among prematures that becomes significant and we get relative risks up to two and three, whereby the ones that got more thimerosal are at a higher risk than the ones who got the combination vaccine.”

Dr. Weil: Page 75: “I think that what you are saying is in term of chronic exposure. I think that the alternative scenario is that this is repeated acute exposures, and like many repeated acute exposures, if you consider a dose of 25 micrograms on one day, then you are above threshold. At least we think you are, and then you do that over and over to a series of neurons where the toxic effect may be the same set of neurons or the same set of neurologic processes, it is conceivable that the more mercury you get, the more effect you are going to get.”

Dr. Verstraeten: Page 78: “Then the last slide I wanted to show, there was a question of if there was any way from this data that we could estimate what would happen in the future if there is Thimerosal-free HepB and Thimerosal-free haemophilus influenza vaccine and only DTP has Thimerosal.” Page 79 “The second column would be the same scenario but now at six months. Assuming they have received two additional DTPs, so between three and six months of age they have increased their ethylmercury amounts by 50 micrograms. If I do in this current cohort with all its limitations, because there is also the HepB that exists in this cohort*, I can’t really take it out. It is significant for this one disorder which is language delay and it is quite high. Together with that, speech or language delay which is a combination of these two disorders, also becomes significant.” * *Dr. Verstraeten could not determine which children got HepB at birth in some cases so it was difficult to back the birth dose of Hep B out of the data.*

Dr. Davis: Page 88: “Now one might imagine that [relative risk of 1.018] would just disappear once we actually confirmed these diagnoses from chart review, but in fact it did not. You see if the diagnosis was mentioned in the chart, the relative risk increases ever so slightly.”

Dr. Rhodes: Page 93: “I think I had two purposes in mind going through the analyses I’ve done. One was a very quick verification that there wasn’t some crucial missing statement in 4,000 lines of programming, and there wasn’t. Tom’s programming was perfectly clear. I also wanted to try to take a different look at the data because I think sometimes we make choices in our analyses. We conceptualize the problem very quickly and then everything else kind of depends on those initial choices and we don’t always go down other pathways...I think we will see that I will approach the data analysis in somewhat of a different way, and I will talk about what some of the results are when I look at the data in somewhat of a different fashion.”

Dr. Rhodes; Page 99: When you take the three month classification and see what happens to these kids a little later on...even seven to fourteen days later, you can see that there has been substantial movement from zero and the 12.5 mcg group. For example, after seven

days at NCK, fully 27% of the zero group has received some sort of vaccination the next seven days and 42% have received some vaccination in the next 14 days. *This finding would argue that the proposed thimerosal cohort study involving neurodevelopmental testing should classify exposure by actual exposures the first year of life and not just on the first three months of life.*

Dr. Rhodes: Page 104: “I am not advocating totally throwing them [the low mercury exposure group] away and never considering them in any analysis, but at least for now let’s think if we can establish if there are differences in this group of 37 to 75, then in a sense we really don’t need them.”

Dr. Rhodes: Page 105: **“The other thing that happens at NCK is that even a year or two years after the policy change has been made and all kids are supposedly receiving the combination, there is an odd, small group of kids that supposedly receives separate DTP and Hib (note: with more thimerosal) and an unusually high percentage of those kids are outcomes.”**

Dr. Rhodes Page 106 **“For example, if 1,500 kids were receiving one vaccine combination in that month of birth and 20 were receiving some other, I have removed the 20 completely from the analyses.**

Dr Rhodes: Page 107. **“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.”** *Dr. Rhodes recommends excluding the lowest exposure cases, claiming that the fact that their exposures were low suggested family behavior that made them unusual. The low rate of outcomes in this group, of course, added significance. He also suggests excluding some cases that had unusually high exposures and outcomes at the same time, as any high exposure, high outcome group would support the signal.*

Dr. Verstraeten: Page 142: “But if I can have the next slide, here instead of the proportional hazard model, we did a logistic regression model. I didn’t use person time here and it’s a bit tough to define exactly the control group. However, if I do it for all ages and not looking at different years, and this is for speech, the outcome is almost identical to the proportional hazard model, which suggests to me that it is not a question of bringing the diagnosis forward, but it is really the overall number that drives this estimate.”

Dr. Chen: Page 151: “One of the reasons that led me personally to not be so quick to dismiss the findings was that on his own Tom independently picked three different outcomes that he did not think could be associated with mercury (conjunctivitis, diarrhea and injury) and three out of three had a different pattern across different exposure levels as compared to the ones that again on a priority basis we picked as biologically plausible to be due to mercury exposure.”

Dr Brent: Page 161: **“Wasn’t true that if you looked at the population that had 25 micrograms you had a certain risk and when you got to 75 micrograms you had a higher risk.”**

Dr. Verstraeten: Page 161: “Yes, absolutely, but these are all at the same time. Measured at the same age at least.”

Dr. Brent: Page 161: “I understand that, but they are different exposures.”

Dr. Verstraeten: Page 161: “Yes”.

Dr. Brent: Page 161: “What is your explanation? What explanations would you give for that?”

Dr. Verstraeten: Page 161: **“Personally, I have three hypotheses. My first hypotheses is it parental bias. The children that are more likely to be vaccinated are more likely to be picked up and diagnosed. Second hypothesis, I don’t know. There is a bias that I have not recognized, and nobody has yet told me about it. Third hypothesis. It’s true, it’s Thimerosal. Those are my hypotheses.”**

Dr. Brent: Page 161: “If its true, which or what mechanisms would explain the finding with?”

Dr. Verstraeten: Page 162: **“You are asking for biological plausibility?”**

Dr. Brent: Page 162: “Well, yes”

Dr. Verstraeten: Page 162: **“ When I saw this, and I went back through the literature, I was actually stunned by what I saw because I thought it is plausible.** First of all there is the Faeroe study, which I think people have dismissed too easily, and there is a new article in the same Journal that was presented here, the Journal of Pediatrics, where they have looked at PCB. They have looked at other contaminants in seafood and they have adjusted for that, and still mercury comes out. That is one point. Another point is that in many of the studies with animals, it turned out that there is quite a different result depending on the dose of mercury. Depending on the route of exposure and depending on the age at which the animals were exposed. Now, I don’t know how much you can extrapolate that from animals to humans, but that tells me mercury at one month of age is not the same as mercury at three months, at 12 months, prenatal mercury, later mercury. There is a whole range of plausible outcomes from mercury. On top of that, I think that we cannot so easily compare the U.S. population to Faeroe or Seychelles populations. We have different mean levels of exposure. We are comparing high to high in the Seychelles, high to high in the Faeroe and low to low in the U.S., so I am not sure how easily you can transpose one finding to another one. So basically to me that leaves all the options open, and that means I can not exclude such a possible effect.”

Discussion comments made by participants after the presentations .

Dr. Johnson: Page 198: **“This association leads me to favor a recommendation that infants up to two years old not be immunized with Thimerosal containing vaccines if suitable alternative preparations are available.** I do not believe the diagnoses justifies compensation in the Vaccine Compensation Program at this point. I deal with causality, it seems pretty clear to be that the data are not sufficient one way or the other. My gut feeling? It worries me enough. Forgive this personal comment, but I got called out a eight o'clock for an emergency call and my daughter-in-law delivered a son by C-Section. Our first male in the line of the next generation, and I do not want that grandson to get a Thimerosal containing vaccine until we know better what is going on. It will probably take a long time. **In the meantime, and I know there are probably implications for this internationally, but in the meantime I think I want that grandson to only be given Thimerosal-free vaccines.”**

Dr. Weil: Page 207: **“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 positive relationships are those that one might expect from the Faroe Islands studies. They are also related to those data we do have on experimental animal data and similar to the neurodevelopmental tox data on other substances, so that I think you can't accept that this is out of the ordinary. It isn't out of the ordinary. The Seychelles Island studies and somebody said the Faeroe Islands studies both, were chronic exposures. We are not talking necessarily about chronic exposure. We are talking about a series of acute exposures and at one point in time that exposure is much greater on one day than any of the Seychelles Islands. **The increased incidence of neurobehavioral problems in children in the past few decades is probably real...I work in the school system where my effort is entirely in special education and I have to say that the number of kids getting help in special education is growing nationally and state by state at a rate we have not seen before.**

Dr. Weil: Page 208: **“The rise in the frequency of neurobehavioral disorders whether it is ascertainment or real, is not too bad. It is much too graphic. We don't see that kind of genetic change in 30 years.”**

Dr. Brent: Page 229: **“The medical legal findings in this study, causal or not, are horrendous and therefore, it is important that the suggested epidemiological, pharmacokinetic, and animal studies be performed. If an allegation was made that a child's neurobehavioral findings were caused by Thimerosal containing vaccines, you could readily find a junk scientist who would support the claim with “a reasonable degree of certainty”. But you will not find a scientist with any integrity who would say the reverse with the data that is available. And that is true. So we are in a bad position from the standpoint of defending any lawsuits if they were initiated and I am concerned.”**

Dr. Clements: Page 247: **“I am really concerned that we have taken off like a boat going down one arm of the mangrove swamp at high speed, when in fact there was not enough**

discussion really early on about which way the boat should go at all. And I really want to risk offending everyone in the room by saying that perhaps this study should not have been done at all, because the outcome of it could have, to some extent, been predicted, and we have all reached this point now where we are left hanging, even though I hear the majority of consultants say to the Board that they are not convinced there is a causality direct link between Thimerosal and various neurological outcomes. I know how we handle it from here is extremely problematic. The ACIP is going to depend on comments from this group in order to move forward into policy, and I have been advised that whatever I say should not move into the policy area because that is not the point of this meeting. But nonetheless, we know from many experiences in history that the pure scientist has done research because of pure science. But that pure science has resulted in splitting the atom or some other process which is completely beyond the power of the scientists who did the research to control it. And what we have here is people who have, for every best reason in the world, pursued a direction of research. **But there is now the point at which the research results have to be handled, and even if this committee decides that there is no association and that information gets out, the work that has been done and through the freedom of information that will be taken by others and will be used in ways beyond the control of this group. And I am very concerned about that as I suspect it is already too late to do anything regardless of any professional body and what they say...**

Dr. Bernier: Page 113: **“We have asked you to keep this information confidential.** We do have a plan for discussing these data at the upcoming meeting of the Advisory Committee on Immunization Practices on June 21 and June 22. At that time CDC plans to make a public release of this information, so I think it would serve all of our interests best if we could continue to consider these data. The ACIP work group will be considering also. If we could consider these data in a certain protected environment. So we are asking people who have a great job protecting this information up until now, to continue to do that until the time of the ACIP meeting. **So too basically consider this embargoed information.** That would help all of us to use the machinery that we have in place for considering these data and for arriving at policy recommendations.”