Events Surrounding the DeStefano et al (2004) MMR-Autism Study

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Background

My primary job duties while working in the Immunization Safety Branch from 2000 to 2006 were to lead or co-lead three major vaccine safety studies.

1. VSD Thimerosal Neurodevelopment Study (Thompson et al, NEJM, 2007)
2. VSD Thimerosal Autism Study (Price, Thompson et al, Pediatrics, 2010)
3. MADDSP MMR-Autism Case-Control Study (DeStefano et al, Pediatrics, 2004)

The MADDSP MMR-Autism Cases Control Study was being carried out in response to the Wakefield (1998) Lancet study that suggested an association between the MMR vaccine and an autism-like health outcome. There were several major concerns among scientists and consumer advocates outside the CDC in the fall of 2000 regarding in the execution of the Verstraeten et al (2003) study[1]. The Verstraeten Study was the first study the CDC carried out to examine the association between thimerosal and neurodevelopmental outcomes including autism. Some of the major concerns included 1) many of the statistical analyses were carried out post-hoc after an initial set of analyses were run, 2) the study protocol evolved over time, and 3) the CDC did not share many of the internal study findings with individuals and constituents outside the CDC.

One of the important goals that was determined up front in the spring of 2001 before any of these studies started was to have all three study protocols vetted outside the CDC prior to the start of analyses so that consumer advocates could not claim that we were presenting analyses that suited our own goals and biases.

My primary responsibilities for the MADDSP MMR-Autism Study were:

1. Lead the large majority of the study-related meetings with all coauthors.
2. Write all the SAS programs for all the statistical analyses associated with the paper.
3. Summarize and present the statistical results to the coauthors on a regular basis.

In addition, all SAS programs and statistical analyses were reviewed by both Dr. Margarette Kolzcak and Dr. Andrew Autry. All data management work was led by Tanya Karapukar and she also reviewed the data management-related activities and decisions included in the SAS programs. All of my statistical analyses were run off of data sets cleaned and provided to me by Tanya Karapukar.

On September 5, 2001, we finalized the vetted study analysis plan for MADDSP MMR-Autism Study. (See Final Analysis Plan dated September 5, 2001). The study protocol included a timeline and the goal

[1] Thomas Verstraeten, et al., Safety of Thimerosal-Containing Vaccines: A Two-Phased Study of Computerized Health Maintenance Organization Databases (Verstraeten, et al., Pediatrics 112:5, 2003)

was to finish the analyses and submit the manuscript for publication to the New England Journal of Medicine by December 1, 2000. **The final analysis plan described analyses for the TOTAL sample and the BIRTH CERTIFICATE sample which included assessment of the RACE variable. (See pages 7 and 8 of the Final Analysis Plan). There were two primary endpoints for the study. One was using a threshold of 36 months (see Table 3a of Final Analysis Plan), and the second was a threshold of 18 months. (See Table 3b of Final Analysis Plan).** We hypothesized that if we found statistically significant effects at either the 18-month or 36-month threshold, we would conclude that vaccinating children early with the MMR vaccine could lead to autism-like characteristics or features. We never claimed or intended that if we found statistically significant effects in the TOTAL SAMPLE, we would ignore the results if they could not be confirmed in the BIRTH CERTIFICATE SAMPLE.

Timeline of Events:

1. In general, all coauthors attended the meetings I scheduled to discuss analyses with the exception of other conflicting meetings when one of us could not attend. The meetings began at least as early as March 2001.

2. On August 29, 2001, I outlined the method that would be used to code RACE for the TOTAL Sample and the Birth Certificate Sample. (See scanned notes from 2001-2002).

3. On September 5, 2001, we all met and finalized the study protocol and analysis plan. The goal was to not deviate from the analysis plan to avoid the debacle that accord with the Verstraeten Thimerosal Study published in Pediatrics in 2003. At the September 5th meeting we discussed in detail how to code RACE for both the TOTAL SAMPLE and the BIRTH CERTIFICATE SAMPLE. (See Page 7 of Agendas Attachment).

4. On October 15, 2001, I ran matched and unmatched analyses for whites and blacks. I would only do this if I had found statistically significant effects by RACE. (See 2001-2002 notes dated October 15, 2001).

5. On October 24th, I wrote in my notes that we have selected the New England Journal of Medicine as the target journal for the manuscript. (See 2001-2002 notes dated October 24th, 2001).

6. On October 31, 2001, all coauthors discussed the study initial results. (See page 8 of Agendas Attachment).

7. On November 2nd, I wrote in my notebook to run analyses for whites and blacks for the early-vaccinated and late-vaccinated subjects. These analyses were run for the TOTAL sample. I would have only run those types of analyses if we had been attempting to explore why we had found significant RACE effects. (See 2001-2002 notes dated November 2, 2001)

8. On November 6, 2001, I have written notes instructing myself to run 4 group analyses and BLACK analyses. Again, I would have only been doing this if we had found concerning results for blacks. (See 2001-2002 notes dated November 6, 2001).

9. On November 8, 2001, I continued to write that the Black/White comparisons need to be continued. (See 2001-2002 notes dated November 8, 2001).

10. On February 20, 2002, all coauthors met and discussed statistical analyses for the Total Sample and the Birth Certificate Sample. (See page 14 of agendas attachment).

11. On May 22, 2002, all coauthors met and discussed analysis of the 24 month threshold for the Total Sample. We did this because there were many statistically significant effects at the 24 month threshold. (See page 16 of Agendas Attachment).

12. On June 28, 2002, all coauthors met and examined subgroup analyses by RACE for Whites and Blacks. (See page 17 in the Agendas Attachment and handout that includes Table 5).

13. In the Excel File named "describe_results_2002_0702.xls", Table 7 shows the RACE analyses that I had run using ONLY the BIRTH CERTIFICATE Sample --- the unadjusted RACE effect was statistically significant. (OR=1.51, [95%CI 1.02 - 2.24]). At the bottom of Table 7, it also shows that for the NON-BIRTH Certificate Sample, the adjusted RACE effect statistically significance was HUGE. (OR=2.94 [95%CI 1.48 - 5.81). That is the main reason why we decided to report the RACE effects for ONLY the BIRTH Certificate Sample.

14. In the Excel File named "describe_results_2002_0801.xls", I split Table 7 into three different Tables (Table 7a, Table 7b, and Table 7c) to further investigate the RACE subgroup analyses.

15. All the coauthors met and decided sometime between August 2002 and September 2002 not to report any RACE effects for the paper.

16. Sometime soon after the meeting where we decided to exclude reporting any RACE effects, also between August 2002 and September 2002, the coauthors scheduled a meeting to destroy documents related to the study. Dr. Coleen Boyle was not present at the meeting even though she was involved in scheduling that meeting. The remaining 4 coauthors all met and brought a big garbage can into the meeting room and reviewed and went through all our hard copy documents that we thought we should discard and put them in the large garbage can. However, because I assumed this was illegal and would violate both FOIA laws and DOJ requests, I kept hard copies of all my documents in my office and I retained all the associated computer files. This included all the Word files (agendas and manuscript drafts), Excel files with analysis and results, and SAS files that I used to generate the statistical findings. I also kept all my written notes from meetings. All the associated MMR-Autism Study computer files have

been retained on the Immunization Safety Office computer servers since the inception of the study and they continue to reside there today.

17. On or about September 3, 2002, I informed Dr. Melinda Wharton, the Division Chief for the Branch I worked in, that we had concerning results from the MMR-Autism Study that we would like to discuss with her.

18. Dr. Melinda Wharton formally reprimanded Dr. Bob Chen, my Branch Chief, on September 18, 2002. As I stated in my e-mails to both Dr. Melinda Wharton and to Dr. Walt Orenstein, I believe this was an intimidating personnel action and threatened the credibility of the entire branch. It also put a big black cloud over our branch and demoralized many of the staff.

19. On October 9, 2002, Dr. Margarette Kolczak, an extremely reputable biostatistician, reviewed my SAS programs and made a suggestion for testing the RACE Interaction. This was a post-hoc decision and an attempt to absolve us from reporting the RACE effects.

20. On October 16, 2002, I asked Dr. Walt Orenstein to remove the formal reprimand of Dr. Chen because I said there was false information included in it. (See e-mail RE Dr. Robert Chen's Reprimand).

21. On October 20, 2002, I described to Dr. Orenstein the dilemma I was in regarding the concerning MMR-Autism Study results and the reprimand of Dr. Chen. I told him I felt intimidated by the move and I linked it to them knowing the results would be problematic if they were shared outside the CDC.

22. On October 22, 2002, Dr. Boyle was assigned to brief Dr. Orenstein and Dr. Jose Cordero (the new Center Director for the National Center of Birth Defects and Developmental Disabilities).

23. Between October 22, 2002 and January 2004, there were significantly fewer hand written notes for the MMR-Autism Study because we had finalized the results and were writing the manuscript up for publication. I have many draft manuscripts that were written and are dated.

24. On January 8, 2004, I began to present draft PowerPoint presentations of the MMR-Autism Study for the Institute of Medicine meeting that I was scheduled to present on February 9, 2004 in Washington DC. I have copies of each of those PowerPoint presentations. During the next 30 days, I presented the results to the Division Director of ESD in the National Immunization Program, and the Director of the National Immunization Program. I would also present the results in the offices of Dr. Julie Gerberding.

25. On January 27, 2004, I had lunch with Dr. Marshalyn Yeargin-Allsopp. She told me that Dr. Frank DeStefano still currently reported to her.

26. On February 2, 2004, I met with Dr. Steve Cochi (the new Director of the National Immunization Program) and Dr. Melinda Wharton. During that meeting I provided Dr. Cochi with a draft of my letter to Dr. Julie Gerberding and sought his input. He requests that I remove any criticism of NIP in the letter.

27. During the February 2 meeting with Dr. Cochi and Dr. Wharton, I also requested that Dr. Walter Orenstein be brought into the meeting because he had arrived in the building that morning. Dr. Cochi suggested that Dr. Orenstein was "heading off into the sunset" and that we shouldn't bother him with these issues. Although Dr. Orenstien had announced his retirement in January 2004, he was still coming for meetings on a regular basis.

28. On this same day, Brooke Barry, a CDC public health analysis and someone I trusted very much, informed me that the "autism caucus" was meeting on February 3rd and that they were initiating or requesting a formal investigation of the National Immunization Program.

29. On February 2, 2004, after meeting with Dr. Cochi and Dr. Wharton, I delivered my letter for Dr. Julie Gerberding regarding my concerns regarding results from the MMR-Autism Study just before I had to present them to the Institute of Medicine on February 9, 2004. (See scanned letter to Dr. Gerberding dated February 2, 2004).

30. On March 9th, I was put on administrative leave. In the Annex to the memorandum, they provided a list of my "inappropriate and unacceptable behavior in the work place" which included "you criticized the NIP/OD for doing very poor job of representing vaccine safety issues, claimed that NIP/OD had failed to be proactive in their handling of vaccine safety issues, and you requested that Dr. Gerberding reply to your letter from a congressional representative before you made your presentation to the IOM." (See scanned Memorandum dated January 9, 2004.). I stand by that statement and I do not think it was unacceptable to convey that to Dr. Gerberding.

Conclusion

I believe we intentionally withheld controversial findings from the final draft of the DeStefano et al (2004) Pediatrics paper. We failed to follow the final approved study protocol and we ran detailed in depth RACE analyses from October 2001 through August 2002 attempting to understand why we were finding large vaccine effects for blacks. The fact that we found a strong statistically significant finding among black males does not mean that there was a true association between the MMR vaccine and autism-like features in this subpopulation. This result would have probably have led to designing additional better studies if we had been willing to report the findings in the study and manuscript at the time that we found them. The significant effect of early vaccination with the MMR vaccine might have also been a proxy for the receipt of thimerosal vaccines early in life but we didn't have the appropriate data to be able to code the level of thimerosal exposure from the MADDSP school records.

In addition to significant effects for black males, we also found significant effects for “isolated autism cases” and for the threshold of 24 months of age. If we had reported the 24 month effects, our justification for ignoring the 36 month significant effects would not have been supported. In the discussion section of the final published manuscript, we took the position that service seeking was the reason we found a statistically significant effect at 36 months. This was a post-hoc hypothesis regarding the findings after we confirmed one of our primary hypotheses. Because we knew that the threshold for 24 months was also statistically significant, reporting it would have undermined the hypothesis that service seeking was the reason we found an effect at 36 months. (See published paper).