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Infant Environmental Exposure to Thimerosal and Neuropsychological Outcomes at Ages 7 to 10 Years

Technical Report Volume I

Executive Summary

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The interpretations of results presented in this report represent the views of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

Executive Summary

The current study was conducted to investigate whether there are relationships between prenatal and/or early childhood exposure to thimerosal-containing vaccines and immune globulins and neurodevelopmental functioning at ages seven to ten years. The study utilized a retrospective cohort design wherein computerized medical records were used to select a sample of children who had been exposed to varying amounts of thimerosal-containing vaccines and immune globulins during infancy. The children were assessed at ages 7 to 10 years using a battery of neurodevelopmental assessments administered in a clinical setting. Results are based on data obtained from 1,047 study participants.

There are three major strengths of the study. The first is that we were able to compute accurate measures of each child's prenatal and early childhood exposures to ethylmercury from thimerosal-containing vaccines and immune globulins. We used three sources of data on vaccination and immune globulin receipt to develop measures of exposure levels. The first source was computer-automated records maintained by the HMOs as part of the Vaccine Safety Datalink system and as part of their administrative record keeping systems. The second source was from detailed abstractions of medical charts of children and their mothers. These data were collected by a team of experienced chart abstractors. The third source was from personal records and responses to survey items provided by parents during a detailed interview with each child's biological mother.

The second major strength of the study was that outcomes were measured in a clinical setting using a battery of standardized assessment tools. Outcome measures spanned domains of speech and language, verbal memory, reading achievement, fine motor coordination, visual spatial ability, attention/executive functioning, behavior regulation, tics, and general intellectual functioning.

The third major strength of the study is that we were able to obtain detailed information for each child on potential confounding factors. These included data on other prenatal and early childhood exposures, on other diagnoses and medical conditions of children and their mothers, and on whole range of child and family characteristics. These included income, maternal education, birth order, plurality, family size/structure, language spoken in the home, maternal age, duration of breastfeeding, and maternal diagnoses of neuropsychological disorders. These data were obtained from parent interview, from medical record abstraction, and from the computer-automated records.

The primary weakness of the current study is that exposure levels were not determined in a randomized, controlled trial (RCT) design. Although the study measured and controlled for a wide range of potential confounders, it is impossible to know with certainty whether the threat of selection bias has been eliminated. Selection bias will have affected the results if one or more unmeasured factors have causal effects on both the amount of exposure that children receive, and on outcome measures. Given this important limitation of the design of the study, results can only be judged as informative, not conclusive. The study was intended to be an important contribution to a growing literature regarding the possible effects of ethylmercury, and was not intended to be a definitive concluding

statement of whether the ethylmercury in thimerosal-containing vaccines and immune globulins does or does not cause harm.

Associations between each of 42 outcome measures and exposure to thimerosal-containing vaccines and immune globulins were estimated from linear and logistic regression models that controlled for potential confounding effects of family demographics and other factors. Models were fit to each of the 42 outcome measures to estimate the effects of:

- Prenatal exposure;
- Neonatal exposure (cumulative exposure birth to one month);
- Birth to 7 months exposure (cumulative exposure birth to seven months);
- For males - Prenatal exposure;
- For males – Neonatal exposure;
- For males – Birth to 7 months exposure;
- For females - Prenatal exposure;
- For females – Neonatal exposure;
- For females – Birth to 7 months exposure;
- Interaction effects of prenatal exposure and cumulative exposure birth to seven months;
- Interaction effects of antibiotic treatment concurrent with receipt of thimerosal-containing vaccines or immune globulins birth to one month;
- Interaction effects of antibiotic treatment concurrent with receipt of thimerosal-containing vaccines or immune globulins birth to seven months.

Across the models for the 42 outcome measures we found small numbers of statistically significant effects that were roughly balanced between findings where increased exposure was associated with better outcomes, and findings where increased exposure was associated with worse outcomes. For example, in the model used to estimate main effects on the combined group of males and females, higher prenatal exposure was associated with better scores on one outcome measure, and worse scores on another. Cumulative exposure birth to one month was associated with a better outcome on one measure, and a worse outcome for another. Cumulative exposure birth to seven months was associated with better outcomes for two measures. This pattern of results is consistent with what would be expected to occur by chance if exposure had no relationship to outcomes. Using a $p < 0.05$ criterion, the expected number of false rejections of the null hypothesis for 42 tests for a single exposure measure (e.g., birth to seven months) is obtained as the product of 0.05 and 42, which is equal to three. The three false rejections of the null hypothesis are expected to be roughly equally distributed between positive and negative associations.

The pattern of finding small numbers of beneficial effects, approximately equally balanced with findings of harmful effects was replicated over all sets of analyses. This type of pattern was found for prenatal, neonatal (birth to 1 month) and birth to 7 months exposure effects for the full sample, for boys, for girls, for interaction effects of prenatal with birth to 7 months exposures, and for interaction effects of antibiotic treatment concurrent with neonatal and birth to 7 months receipt of thimerosal-containing vaccines or immune globulins. For example, the evaluation of three exposure measures (prenatal,

neonatal, birth to 7 months) across the 42 outcome measures, for each of the two sexes required 152 hypothesis tests. Among those tests, 13 were significant at the $p < 0.05$ level. The associations were in the direction of increased exposure being associated with better outcomes for seven of the significant tests. The remaining five were in the direction worse outcomes. Under a null hypothesis of no association between exposure and outcomes, the expected number of false rejections of the null hypothesis for 152 tests at the $p < 0.05$ level is 13.

Results of two large studies conducted in Great Britain indicated mixes of beneficial and harmful associations between exposure to ethylmercury from vaccines and outcomes similar to those measured in the current study (Heron et al., 2004; Andrews et al., 2004). Results from the current study showing significant associations between exposures in birth to 7 months and assessor rated motor and phonic tics in boys appear to support two sets of findings from previous studies. The study by Verstraeten et al (2003) found a significant association between exposure and tics at one of three HMOs. And Andrews et al. (2004) found a significant harmful association between exposure and tics in a special sub-analysis. However, Heron et al. (2003) reported a beneficial association between exposure and tics. And among the findings of the current study was a beneficial association between parent reported motor tics and neonatal exposure for girls.

The beneficial associations between exposures and outcomes in the fine motor domain found in the current study coincide with a finding reported by Heron et al. (2003) of a beneficial association between exposure and fine motor skills. However, these findings do not align with the estimated harmful effects of methylmercury exposure from fish consumption on performance on the finger tapping test, as reported by Grandjean et al. (1997).

The results of models used to test interaction effects between prenatal and postnatal exposure did not support the hypothesis that prenatal exposure would exacerbate the effects of postnatal exposure. Nor did the results of this study support the hypothesis that antibiotic treatment would worsen the effects of postnatal exposure.

We conclude that we did not find clear and convincing evidence of harm. While studies of the sort conducted here cannot disprove the null hypothesis, we consider the pattern of positive and negative associations to be consistent with what we would expect to occur by chance if exposure had no relationship to outcomes. We note, however, that the previously stated caution regarding the threat of selection bias should not be ignored. We urge the reader to consider the results of this study as one piece of evidence in the context of a growing literature on the effects of exposure to ethylmercury.