COMMENTS

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Questions About Thimerosal Remain

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Geier and Geier used a novel approach to investigate the role of thimerosal-containing diphtheria, tetanus, and pertussis vaccine as a risk factor for childhood neurodevelopmental disorders (1). Using data from the United States' Vaccine Adverse Events Reporting System, they compared the frequency of reported episodes of (presumably) vaccine-related neurodevelopmental disorders among thimerosal-containing DTAP vaccine recipients from 1992 through 2000, to reported cases associated with thimerosal-free DTAP vaccine from 1997 through 2000. Based on this analysis, they report that the thimerosal-containing vaccine was associated with a six-fold increase in the relative risk of autism and mental retardation. While Geier and Geier's work is important and may be corroborated by future findings, there are some significant problems with their approach that could diminish the veracity of their findings.

First, there is the potential for bias due to the different time periods of observation being employed. The authors state that this difference actually helps reduce the potential for bias because the observation period for thimerosal-containing vaccine extends far enough into the past to precede the media furor about a potential connection between thimerosal and developmental disorders. However, the latter part of the observation period occurred *after* the potential connection became well-publicized, and all the observation years were lumped together, so that a dramatic increase in (spurious) reported events during the most recent years could have biased the findings. Therefore, the problem of potential over-reporting in response to media reports is not adequately accounted-for. Further, the use of significantly different observation years could introduce additional bias, depending on secular trends in neurodevelopmental disorders, vaccine adverse events reporting, etc. . . It would have been preferable for the authors to provide data comparing the two vaccines for the overlapping 1997 through 2000 time period in addition to the overall comparison data, in order to answer the objection of potential time-related bias.

Second, by focusing only on thimerosal-containing DTaP, the authors ignore other potential sources of organic mercury exposure, including other thimerosal-containing vaccines. Hence, many of the children considered unexposed to thimerosal in this analysis may have actually been exposed at some point. This misclassification could lead to underestimating the strength of the potential link between thimerosal and autism. On the other hand, the great potential for misclassification may legitimately lead one to question the validity of the approach as a whole.

Third, there seems to be some confusion about the epidemiologic measure, "attributable risk." This is intended to be a measure of the *absolute* (not relative) difference in risk between people "exposed" and "unexposed" to a risk factor (2). Since it is based on absolute/actual risks rather than relative risks, it provides a measure of the true magnitude of the risk factor's impact in terms of morbidity. The authors appear to have calculated attributable risks incorrectly. They state that "the attributable risk value was determined by subtracting 1 from the RR value (RR – 1 = attributable risk)" (pg. 661). Making attributable risk a simple function of relative risk gives no indication of the impact of thimerosal in terms of absolute risk, and defeats the purpose of the measure.

Finally, there is also a problem with the authors' use of the epidemiologic measure, "relative risk." Relative risk is a measure of association that is calculated as the ratio of incidence in those exposed to the putative risk factor compared to incidence in those not exposed. Unfortunately, the

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authors' calculation of relative risk does not utilize true incidence rates and therefore is suspect. To appropriately measure incidence in those "exposed" and "unexposed" to thimerosal-containing DTaP vaccine, one would need to follow vaccinated children forward in time after receiving one or the other immunization to see what proportion of children in each group developed neurodevelopmental disorders. Instead, the authors compared the proportion of immunized children for whom a *perceived connection between vaccination and autism was reported* for thimerosal-containing DTaP vaccine versus thimerosal-free vaccine. This does not amount to a true comparison of incidence rates in the two groups, since there may have been numerous cases of developmental disorders for which no association with vaccination was suspected and which were therefore not reported. These incident cases were necessarily left out of the analysis. If all the unreported cases had been included, the calculated relative risk may have moved much closer to the null value of 1.0. For example, suppose that 1.2% of thimerosal-exposed children and 0.2% of non-thimerosal-exposed children had neurodevelopmental disorders reported to the VAERS—the relative risk would be 6.0 according to these data. But suppose that these disorders also occur at a more or less constant rate of 1% in young children in a manner that is NOT temporally associated with vaccination. By adding the additional 1% incidence to each of the groups, the relative risk would change from 6.0 to 1.83 (2.2% vs. 1.2%), indicating a much smaller strength of association. Given the design of this study, it would have been more appropriate to discuss the findings in terms of differences in the proportion of vaccine recipients reporting potentially vaccine-related disorders than in terms of relative risk.

All these issues aside, the authors' findings are interesting and potentially very important, as they do give some support to what the authors note is generally a skeptically-viewed theory about the possible connection between thimerosal-containing vaccines and neurodevelopmental disorders. Perhaps future research can build on their work. In the meantime, it seems prudent for clinicians to use thimerosal-free vaccines when possible.

1. Geier MR, Geier DA. Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. Exp Biol Med 3:228: 660–664, 2003.
2. Gordis L. Epidemiology. Philadelphia, PA: W.B. Saunders Co., p155–156, 1996.