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----- Original Message -----

From: Sumartojo, Esther (CDC/CCHP/NCBDDD)
To: Thompson, William (CDC/CCHP/NCCDPHP); Weintraub, Eric (CDC/OD/OCSSO)
Cc: Trevathan, Edwin (CDC/CCHP/NCBDDD); Sumartojo, Esther (CDC/CCHP/NCBDDD); Beltrami, Elise MD (CDC/CCID/NCPDCID)
Sent: Mon Apr 27 16:50:06 2009
Subject: FW: Thimerosal reanalysis paper

Bill and Eric,

Please see Ed Trevathan's comments on your manuscript. Ed will be out of the office until Wednesday; please contact me if you would like to discuss his concerns.

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-----Original Message-----

From: Trevathan, Edwin (CDC/CCHP/NCBDDD)
Sent: Saturday, April 25, 2009 8:24 PM
To: Sumartojo, Esther (CDC/CCHP/NCBDDD)
Subject: Thimerosal reanalysis paper

Esther,

Please pass this along to the appropriate person, including Bill Thompson and Elise, et. al.

I have reviewed this paper, and have major concerns that cannot be addressed with any revision or additional analysis. I have discussed these concerns previously with Bill. I apologize in advance for being so blunt, but there are major problems with the outcome measure.

The "tic" variables in this study were not the primary outcome variables. In fact it is clear that the outcome measures labeled as "tics" were designed without apparent involvement or consultation with neurologists or experts in movement disorders. While the authors use sophisticated statistical techniques, these techniques are used on these "tics" outcome measures that at best are of unknown or of limited validity.

The use of the term "tics" to describe the movements observed is probably inappropriate, and is potentially quite misleading and inaccurate. Tics are one of several different types of movement disorders in children, and these abnormal movements are often mistaken for normal variants by non-experts. Likewise, what a briefly trained observer believes may be tics are often not tics (and may be normal variants of movements) when evaluated by a qualified neurologist or psychiatrist - typically the medical specialists who do these sorts of evaluations. The children suspected of having tics by the trained observers were not later evaluated by a pediatric neurologist or a pediatric psychiatrist; in truth we do not really know whether these children had tics, other movement disorders, or no abnormal movements

whatsoever, or probably most likely some unknown combination of all of these possibilities. These are children suspected as having tics by observers who are not qualified to make the diagnosis of tics.

No doubt that parent self-report of tics is not reliable. In addition, the measure used by the authors is not of proven reliability compared to the clinical gold standard.

Unfortunately, the "tic" outcome measure is hopelessly flawed in this otherwise good data set. This is obviously not the fault of the authors, but this "tic" analysis is an analysis of an outcome that has an unknown relationship to true clinically diagnosed tics.

Furthermore, the authors are not able to distinguish between benign transient possible tics and true tic disorders (e.g., Tourette syndrome) - a major limiting problem. Without medical verification of the diagnosis of tics, and without any ability to accurately classify tics, these data are of very limited value, and offer the possibility of leading down a long, error-prone, and unproductive trail.

At the very least the authors should clearly state that the variables labeled "tics" are not tics diagnosed by qualified medical professionals, but are rather suspected tics identified by trained observers who are not those who would make a tic diagnosis accepted by any reasonable clinical research study of tics. So this is a pool of children who would typically be referred for possible tics to a pediatric neurologist, but are not children with tics.

I regret that I must strongly recommend against the publication of this analysis, for the reasons stated above.

Sorry,

Ed

Edwin Trevathan, MD, MPH

Director

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