

Safe Minds Assessment of the Pichichero Thimerosal Study

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INTRODUCTION

This analysis describes the concerns which Safe Minds has over a recently published study in *The Lancet* by Michael Pichichero *et al.*(1) in which blood measurements were taken of infants after administration of vaccines containing thimerosal. The article and accompanying commentary contain several sweeping statements about thimerosal safety:

- "Overall, the results of this study show that amounts of mercury in the blood of infants receiving vaccines formulated with thiomersal are well below concentrations potentially associated with toxic effects."
- "Administration of vaccines containing thimerosal does not seem to raise blood concentrations of mercury above safe values in infants."
- "This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines."

The design and results of the study do not support these statements. In fact, the results suggest that thimerosal exposure from vaccines may have caused neurological damage in some children. Safe Minds questions the objectivity of the study authors, due to their ties to vaccine research and vaccine manufacturers, which may have resulted in a biased study design and biased interpretation of the results.

OBJECTIVITY OF THE AUTHORS

- Pichichero has an acknowledged financial tie to Eli Lilly, the developer of thimerosal and the main target of thimerosal litigation. He has also claimed financial ties to a number of vaccine manufacturers, including manufacturers of thimerosal-containing vaccines.(2) For example, in an article in the American Academy of Family Physicians newsletter of April 2000, Dr. Pichichero makes this disclosure statement (3):

"The author has received research grants and/or honoraria from the following pharmaceutical companies: Abbott Laboratories, Inc.; Bristol-Myers Squibb Company; Eli Lilly & Company; Merck & Co.; Pasteur Merieux Connaught; Pfizer Labs; Roche Laboratories; Roussel-Uclaf; Schering Corporation; Smith Kline Beecham Pharmaceuticals; Upjohn Company; and Wyeth-Lederle."

- Pichichero's work has been cited in 21 vaccine patent applications He was involved in the recommendation for the Wyeth rotavirus vaccine and failed to anticipate its risks. (4) This vaccine was withdrawn soon after licensure due to adverse reactions.

- A substantial proportion of Dr. Pichichero's work involves vaccines. Safe Minds conducted a simple Medline search of publications listing M Pichichero as an author.(5) A breakdown of these publications by subject area shows that many focus on vaccines, especially those which contained thimerosal.

- 161 publications
- 23 DPT
- 7 Hib
- 1 HepB
- 1 Polio
- 3 Pneumococcal Conjugate
- 3 Rotavirus
- 4 New combination vaccines or general vaccine discussions
- The remainder deal with otitis media and use of antibiotics
- *Note some articles were counted more than once because they addressed more than one vaccine*

- Similarly, the University of Rochester web site provides biographical information on Dr. Pichichero, which describes his focus on vaccine research. (6) It describes him as an immunologist, not a toxicologist. None of his work involves safety assessment of a heavy metal or other toxicant. One paragraph cites his work on the Haemophilus influenzae type B vaccine, one of the thimerosal-containing vaccines that was added to the CDC/AAP-recommended infant schedule in 1991, nearly doubling the thimerosal load.

- John Treanor, another author, has also conducted substantial research into thimerosal-containing vaccines, and the University of Rochester is one of a few sites designated by NIH for evaluating new vaccines. Investigators at the University of Rochester helped develop the *Haemophilus influenzae* B vaccine. Per its web site, "Rochester has become a national model...in ensuring that as many people as possible are immunized." (7)

STUDY DESIGN ISSUES

Sample

- The sample size was small. Although the overall sample size was stated as 61 infants, there were only 33 exposed children who were used for the blood mercury assessment upon which the safety conclusions were made. One major shortcoming of a small sample size is the low chance of including infants who are especially sensitive to mercury's effects, or who may have detoxification difficulties. We know from the mercury literature that there is wide variability in the population in regard to mercury sensitivity and clearance. Since vaccines are given to virtually all infants, even if 1% retained mercury to

a much greater degree than the "norm", this would represent a large number of injured children.

- The small sample size means that the study lacks sufficient power to establish safety claims
- The sample was not randomly drawn, but was a convenience sample, and therefore not representative of all infants in terms of health status, socio-economic status, ethnicity, and other potentially important factors.

Dose

- Given that the half life of ethylmercury appears to be 6-7 days, virtually all, if not all, blood draws missed the peak blood concentrations of mercury. It is evident that earlier peaks existed because the feces contained high mercury values, and feces reflect earlier blood levels. It is impossible to state what the peak values are if they were not measured. It is also impossible to calculate average blood concentrations unless peak concentrations are measured. Standard methylmercury pharmacokinetic (PK) studies consider peak and average blood concentrations, along with tissue distribution, as necessary components of toxicity assessment. It is disingenuous to compare the blood levels in this study with past methylmercury ones without any type of adjustment factor, because the methylmercury studies incorporated peak levels into their values, whereas this study only included the smaller values.
- The dose of ethylmercury given to subjects varied greatly and was less than what a typical child in the 1990s could receive. In a rationally designed PK study, the dose is kept constant. In the Pichichero study, the 2 month old subjects were injected with between 37.5 mcg and 62.5 mcg of ethylmercury reflecting a 67% difference between the lowest and highest dose. The mean was 45.6 mcg. The typical child in the 1990s could receive 62.5 mcg of mercury at age 2 months and an additional 12.5 mcg at birth (from the Hepatitis B vaccine), or 37% and 64% more Hg, respectively, than the children in this study. The 6 month old subjects were injected with between 87.5 mcg and 175 mcg of ethylmercury reflecting a 100% difference between the lowest and highest dose. The mean was 111.3 mcg. By 6 months of age, the typical child in the 1990s would have received 187.5 mcg Hg, or 68% more than the Pichichero study group average.
- The total recorded dose of ethylmercury was not administered during the study data collection period. According to the national immunization schedule that existed during the data collection period (November 1999 to October 2000), it is not possible for a six month old infant to receive 175 mcg of ethyl mercury at only the six month visit. Rather, at 6 months of age, an infant would receive a maximum of 62.5 mcg Hg, from a DTaP, a HiB, and a Hep B vaccine. Thus, the Pichichero study, in calculating dose, included exposures which occurred months prior to the last injection. Thus, when the study characterizes blood draws as being "X" days after the mercury exposure, this is misleading, because it refers only to the last injection. Thus, the reader really doesn't

know how much dose any infant received at that last exposure from the data presented in the table in the study.

- In a properly designed PK study, multiple blood draws should be taken from each subject, and blood collection times should be consistent for all subjects. In this study, there was a single draw per child, and the collection times varied from 3 to 21 days for two month old infants, a 700% difference, and from 4 to 27 days for six month old infants, a 675% difference.

Modeling

- The single compartment model and safety assumptions looked at blood levels as the determinant of safety. However, a more important measure is mercury distribution into tissue, particularly the brain. Estimation of brain accumulation would require a two compartment model and measurement of peak blood levels, neither of which were components of this study. Yet it is apparent that the mercury is moving through the body and is redistributing because it is in the feces at substantial levels.

STUDY INTERPRETATION

- Improper use of methylmercury safety levels as a marker for ethylmercury risk: the Pichichero study compares ethylmercury blood levels with levels from methylmercury risk assessments, but obviously, ethylmercury is a different molecule than methylmercury, and therefore it needs its own safety assessment. A slight change in molecular structure can have very different effects in the body. There has never been a full safety assessment of thimerosal, as the FDA has admitted. The only way to do this is to conduct a series of cellular or molecular level studies as well as population studies consisting of either (a) animal studies which measure behavioral, neuropsychological, or physiological outcomes (that is, does "x" dose result in "y" aberrant behavior or "z" reduction on memory tests, etc.), or (b) human studies on exposed populations, again looking at behavioral, neuropsychological, or physiological outcomes. These types of studies have been done extensively for methylmercury, and this is why methylmercury blood levels can be correlated with certain outcomes or risk, but it has never been done thoroughly for thimerosal. The Pichichero study does not address adverse outcomes at all, and therefore does not constitute a true safety assessment.
- Improper interpretation of 1994 Grandjean study to assess safety: the Lancet study authors cite a 1994 article by Philippe Grandjean as saying that a 29 nMol/L blood concentration is the level for methylmercury which is thought to be safe, since it is ten times lower than the levels at which adverse effects have been found in methylmercury research. (Ten times 29 nMol/L equates to 290 nMol/L, or 59 part per billion.) Actually, as the EPA explains (8), the EPA incorporated a ten-fold factor into their safety assessments due to "uncertainty factors" because the methylmercury studies are small, have a high margin of error, and there is immense variability in human response to mercury. Thus, to be truly protective of the population, blood levels should not exceed 29 nMol/L (which equates to 5.8 parts per billion, or the 6 mcg/L the EPA refers to in their

document). The EPA was concerned when a national study (NHANES) showed that 10% of the US women of child bearing age had blood mercury over 6 ppb. Thus, a level of 6 ppb or over, equivalent to 29+ nMol/L, is considered by EPA to be cause for alarm.

- In the Pichichero study, there is one infant blood level out of the 17 2-month old blood samples (12%) which was 20.55 nMol/L, or 4.1 ppb. This infant had its blood drawn at day 5, received 37.5 mcg/Hg, and weighed 5.3 kg.
- a) Day 5 is past the peak value in blood, meaning that at days 1-3, levels would be much higher.
- b) A 37.5 mcg dose is (conservatively) 60% of what a typical 1990s infant may have received ($37.5/62.5=60\%$).
- c) A 5.3 kg infant is at the 95th percentile of weight for a 2 month old, that is, a large, heavy baby. Since blood Hg concentrations are in part dependent on weight, a child with a lower weight than this infant (that is, 95% of the 2 month old population) would have had a higher blood level than this infant.
- The implications of points a, b, and c are that (1) if the study infant's blood were taken at 1-3 days, it is more than likely that the Hg levels would have exceeded 6 ppb; (2) it is likely that the peak levels of more than 12% of 2 month old children children given the full 62.5 mcg of mercury would exceed 6 ppb; and (3) a larger percentage of smaller infants - but still those of "normal" weight - would be likely to have blood levels exceeding 6 ppb.
- In addition, there were two other 2 year olds with mercury levels at between 10 and 15 nMol/L. These values are with 1/2-1/3 of the EPA margin of safety, with blood draws on days 6-7.
- For these reasons alone, the results of the Pichichero study are anything but "reassuring" to parents whose children were exposed to thimerosal as infants.

LEARNING FROM THE STUDY

- Despite its many limitations, the Pichichero study does provide new or confirming information about the pharmacokinetics of ethylmercury injected into infants.
- The half life of ethylmercury in infants appears to be shorter than methylmercury, approximately 6-7 days. Pharmacologically, this period would be considered a very long half life and a long time for a toxic substance to be circulating in the body. In fact, the single blood draw after 20 days for which mercury quantitation could be made showed mercury being circulated at about 5 nMol/L. In a developing brain a few days are significant time periods for an agent that interferes with cell division and organization.
- The control group had no detectable mercury, indicating that the mercury in the exposed group was due to the thimerosal in the vaccines

SUMMARY

- The Pichichero is a small-scale descriptive study with many design limitations, which has moderate value in advancing understanding of ethylmercury

pharmacokinetics. It has little if no value as a safety assessment of thimerosal from vaccines, and its conclusions are overreaching, perhaps reflecting a bias on the part of its lead author towards absolving licensed vaccines of any adverse effects.

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