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Commentary: A Link Between Mercury Exposure, Autism Spectrum Disorder, and Other Neurodevelopmental Disorders? Implications for Thimerosal-Containing Vaccines

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Abstract

Autism is a multisystem developmental disorder characterized by dysfunctional immunity and impaired brain function. Although autism is partly determined by genetic susceptibility factors, reported dramatic increases in the prevalence of autism in developed countries have intensified scientific focus on environmental exposures. Pre- and perinatal immunotoxic insults are now strongly suspected as contributors to this increase. Mercury (Hg) is both a neuro- and an immunotoxin and continues to be used in some pediatric vaccines in the form of the preservative thimerosal. Although currently there are no direct human studies on the risks of Hg exposure from thimerosal-containing vaccines (TCVs), animal studies show that doses relevant to human TCV exposure can result in adverse neurodevelopmental outcomes. To date, TCVs continue to be administered on a regular basis to potentially the most vulnerable populations: pregnant women and children. In light of existing experimental evidence, the rationale for using this known immunotoxic and neurotoxic substance in human vaccines should be reconsidered.

Given the dramatic and rapidly-growing reported prevalence of autism spectrum disorder (ASD) (Newschaffer, Falb, & Gurney, 2005), a clear answer to the etiology of this apparent epidemic would serve parents as well as the medical community entrusted with the health of all children. The focus of this commentary is on the possible involvement of thimerosal (49% ethylmercury (EtHg)) in neurodevelopmental disorders. In the past, thimerosal was used worldwide as a preservative in vaccines. Although this practice has largely been discontinued due to safety concerns (Offit & Jew, 2003), thimerosal continues to be used in less-developed and developing countries (Dórea, Marques, & Brandao, 2009)), as well as in the preservation of multi-dose vaccine vials in Canada and the United States (Centers for Disease Control and Prevention, 2011; Public Health Agency of Canada, 2011). The use of thimerosal-containing vaccines (TCVs) continues to be a highly contentious issue. The fact that a causal link between thimerosal exposure and neurodevelopmental disorders in children is not supported by many studies (Andrews et al., 2004; Hviid, Stellfeld, Wohlfahrd, & Melbye, 2003; Parker, Schwartz, Todd, & Pickering, 2004; Verstraeten et al., 2003) fails to put this issue at rest.

One side of the continuing debate is fuelled by 70-years worth of research that has demonstrated the detrimental effects of human exposure to EtHg (summarized in Geier et al., 2007). Specifically, significant association between exposure to TCVs and neurodevelopmental disorders in children including autism, speech disorders, mental retardation, thinking abnormalities and personality disorders has been reported in some studies (Gallagher & Goodman, 2008; Geier & Geier, 2006; Young, Geier, & Geier, 2008; Gallagher & Goodman, 2010).

The other side of the debate is grounded in two main assumptions. The first is that the level of Hg in TCVs is too low to cause harm (Eldred, Dean, McGuire, & Nash, 2006; Offit, 2000). The second is, as pointed out by Hviid, Stellfeld, Wohlfahrd, & Melbye (2003), "The hypothesis of an association between thimerosal and autism has primarily been based on biological plausibility through analogies with methylmercury (MetHg). EtHg, however, is *thought* to have a shorter half-life in the human body than MetHg" [emphasis added]. In other words, EtHg is thought to be efficiently excreted from the body and therefore the *assumption* is that it does not represent a risk to the developing child, unlike MetHg which has been recognized as an important risk-factor for neurodevelopmental delays (Corbett & Poon, 2008; Freire et al., 2009).

Assumptions, however, are not an adequate substitute for the lack of experimental data, especially in thorny issues such as vaccine safety. In that context, animal experiments created to model vaccine schedules in rodents and infant macaques have produced adverse neurodevelopmental outcomes resulting from very low EtHg exposures (i.e., equivalent of a single TCV) (Dórea, 2011; Hewitson et al., 2010)). Furthermore, in a landmark study comparing the toxicokinetics of EtHg and MetHg in infant macaques, Burbacher et al. (2005) demonstrated that although EtHg indeed shows more efficient blood-clearance than MetHg, there was a much higher proportion of inorganic Hg in the brains of EtHg-exposed monkeys than in the brains of those exposed to MetHg (up to 71% vs. 10%). In addition, the average brain-to-blood concentration ratio was slightly higher for the EtHg-exposed monkeys. Notably, there was also a large difference in the blood Hg half-life compared with the brain half-life for the EtHg-exposed monkeys (6.9 days vs. 24 days), indicating that blood Hg may not be a good indicator of risk of adverse effects on the brain (Burbacher et al., 2005). Overall, Burbacher et al.'s (2005) data suggest that although the accumulation of Hg in the blood from TCV exposure is relatively small, accumulation in the brain from such exposures may still occur at potentially hazardous levels.

The reported association between TCV's and neurodevelopmental delays in various epidemiological studies as quoted above (Geier & Geier, 2006; Gallagher & Goodman, 2008; Gallagher & Goodman, 2010; Young et al., 2008), is not sufficient to claim a causal relationship. However, given the fact that compelling data exist on the capacity of low-dose exposure to EtHg (in vaccine-relevant exposures) to harm the developing nervous system in a manner consistent with the pathology of autism (Hewitson et al., 2010; Hornig, Chian, & Lipkin, 2004; Olczak et al., 2011a,b), the safety of TCVs appears to stand on uncertain ground. Furthermore, despite claims to the contrary (Eldred et al., 2006; Offit & Jew, 2003), the presence of thimerosal in vaccines should not be disregarded as a health risk for the following reasons. First, the many so-called controls in vaccine studies are not really controls in a scientific sense at all. For example, the vast majority of studies on vaccine safety compare the full vaccine in question to either another vaccine (e.g., Hviid, Stellfeld, Wohlfahrd, & Melbye, 2003; Verstraeten et al., 2003), or to a vaccine containing an adjuvant such as aluminum (Al) (Exley, 2011). Such an experimental design is inadequate for two major reasons. First, Al on its own is a neurotoxin implicated in ASD (Lopes & Caldas, 2011; Tomljenovic & Shaw, 2011a; Tomljenovic & Shaw, 2012). Second, as shown in Table 1 which lists the levels of Hg in vaccines in relation to U.S. Environmental Protection Agency (EPA) and World Health Organization (WHO) limits, even thimerosal-free vaccines contain Hg in levels which are potentially toxic to humans. Note also that the EPA and the WHO limits refer to dietary sources of Hg. This is of added concern because only a very small fraction of the ingested Hg is absorbed through the gastrointestinal tract (0.01-10%; WHO, 2003), unlike injected Hg which is expected to be more or less completely absorbed in the systemic circulation.

Table 1. Levels of Some Environmental Sources of Hg with References to the U.S. Environmental Protection Agency (EPA) and World Health Organization Safety Limits

Hg Concentration (ppb)	*Form*	*Biological Significance*
0.4	MetHg	Median chronic weekly intake of contaminated fish (0.4 µg/kg body weight), causes delayed speech and autistic like symptoms in male children (Corbett & Poon, 2008)
1.6	MetHg	Provisional Tolerable Weekly Intake (PTWI) based on body weight for infants and pregnant women (1.6 µg/kg; Food and Agriculture Association/World Health Organization, 2006)
2	Inorganic mercury	U.S. EPA limit for drinking water (U.S. EPA, 2011)
200	Mercury, various	Level in liquid the U.S. EPA classifies as hazardous waste based on toxicity characteristics (U.S. EPA, 2010)
600	EtHg	Concentration in vaccines containing trace amounts of thimerosal (0.3 µg/0.5 mL dose, or 600 µg/L; Halsey, 1999)
25,000–50,000	EtHg	Concentration in thimerosal-containing multi-dose influenza, meningococcal pneumococcal polysaccharide and diptheria-tetanus vaccines (Offit & Jew, 2003)

A further bias in vaccine studies is that they tend to deliberately exclude vulnerable populations of individuals with a variety of pre-existing conditions (e.g., chromosomal abnormalities, neurological disorders such as convulsions, malnutrition etc; see Appendix 1 of Verstraeten et al., 2003). Ironically, these same conditions are considered as "false-contraindications to vaccinations" by medical health authorities worldwide (Epidemiological Unit Ministry of Health, 2009), despite the fact that cases of autistic regression as well as deaths following vaccination in children with underlying susceptibilities (that fall under both "exclusion" and "false contraindication criteria"), have been reported in the scientific literature (Ottaviani, Lavezzi, & Matturri, 2006; Poling, Frye, Shoffnes, & Zimmerman, 2006; Yang et al., 2006). That the exclusion of those populations, which are most likely to suffer adverse neurological outcomes due to exposure to an established neurotoxin such as Hg, from vaccine trials is a method biased towards generating Type 2 errors (false negatives) should be fairly obvious. Yet, such practices continue to the present and appear to be a pillar on which "one-size fits all" vaccination policies are based (Tomljenovic & Shaw, 2011b). It is of interest, however, that the very notion of "one-size fits all" has been amply discounted by Poland, Ovsyannikova, & Jacobson (2008) who showed that immune responses to vaccines depend on individual's genetic makeup. Notably, the findings of Poland et al. (2008) have equally important implications for both vaccine safety and efficacy (Tomljenovic & Shaw, 2011b).

While it is true that the exact cause(s) of autism remain elusive, multiple lines of research suggest that it results from an interplay between genetic and environmental factors (Pardo, Vargas, & Zimmerman, 2005; Perry et al., 2011; Theoharides, 2009; Theoharides, Kempuraz, & Redwood, 2009). Furthermore, in a recent review of 450 original papers on epidemiology, possible pathogenesis and treatment of ASDs, Theoharides et al. (2009) have found that autism, which they termed as an emerging "neuroimmune disorder," is characterized by increased oxidative stress, immune dysregulation, gut–blood–brain barrier disruption and brain inflammation. To note is that aluminum (Al) hydroxide is used as an adjuvant in vaccines to increase the body's response to vaccines. In this regard, it has been reported that Hg and Al both affect the same biochemical pathways that are

shown to be disrupted in autism. Importantly, both Al and Hg are: (i) brain barrier neurotoxins (Zheng, 2001); (ii) pro-oxidants (Monnet-Tschudi, Zurich, Boschar, Corbaz, & Honegger, 2006; Nehru & Anand, 2005; Verstraeten, Golub, Keen, & Oteiza, 1997; Yin et al., 2007), destructive to the actions of crucial antioxidant enzymes, including glutathione (Gstraunthaler, Pfaller, & Kotanko, 1983; Jyoti, Sethi, & Sharma, 2007; Murakami & Yoshino, 2004;), superoxide dismutase and catalase (Gstraunthaler et al., 1983; Nehru & Anand, 2005); (iii) potent activators of microglia and brain inflammation (Li, et al., 2009; Monnet-Tschudi et al., 2006; Platt, Fiddler, Riedel, & Henderson, 2001); and, (iv) potent neurotoxins (Bishop, Morley, Day, & Lucas, 1997; Dórea, 2011; Geier et al., 2007; Geier, Sykes, & Geier, 2007; Tomljenovic, 2011; Tomljenovic & Shaw, 2011a; Tomljenovic & Shaw 2012), as well as stimulators of immune responses (Cribbs et al., 2003; Exley, Siesjo, & Eeriksson, 2010; Fournie et al., 2001; Tomljenovic & Shaw, 2011a; Tomljenovic & Shaw 2012).

Given the above evidence, the possibilities for toxic synergistic interaction between Al and Hg in vaccines is not only possible, but likely. Moreover, both vaccine compounds appear to have all the necessary biochemical properties to induce neuroimmune disorders. In this regard it should be emphasized that there is a tight and delicate connection between development of the immune system and that of the central nervous system, thus underscoring the plausibility that disruption of critical events in immune development may play a role in neurobehavioral disorders including those of the autism spectrum (Belmonte et al., 2004; Dietert & Dietert, 2008; Hertz-Picciotto et al., 2008; Tomljenovic & Shaw, 2011a; Tomljenovic & Shaw, 2012). Indeed, early-life immune challenges in critical windows of developmental vulnerability have been shown to produce long-lasting, abnormal cognitive and behavioural responses, including increased fear and anxiety, impaired social interactions, deficits in object recognition memory and sensorimotor gating deficits (Hornig, Chian, & Lipkin, 2004; Ibi et al., 2009; Konat, Lall, Toth, & Salm 2011; Olczak et al., 2011a; Spencer, Heida, & Pittman, 2005). These symptoms are highly characteristic of ASD. Although autism is partly determined by genetic susceptibility factors, reported dramatic increases in the prevalence of ASD in developed countries (particularly the United States, United Kingdom, Canada & Australia) have intensified scientific focus on environmental exposures. The latter are being recognized as being increasingly important as genetic drift and/or changes in gene penetrance alone cannot explain the sharp rise in autism prevalence observed in the last two to three decades (Theoharides et al., 2009; Tomljenovic & Shaw 2011a). Both pre- and perinatal immunotoxic insults are now strongly suspected as contributors to this increase (Dietert, & Dietert, 2008; Hornig, Chian, & Lipkin, 2004; Tomljenovic & Shaw, 2011a; Tomljenovic & Shaw, 2012).

Although the United States and the European Union countries reduced or eliminated thimerosal from most vaccines in 1999, TCVs continue to be used in less-developed and developing countries (Dórea, Marques, & Brandao, 2009). Furthermore, in the United States and Canada, it is recommended that all pregnant women, infants, and children receive annual influenza vaccination (starting with two doses of influenza vaccine in the first year of life; Dórea, Marques, & Brandao, 2009; Public Health Agency of Canada, 2011), most of which still contain the full amount of thimerosal (Table 1). In Canada, the commonly used multi-dose vials for hepatitis B vaccine (which is routinely given to newborn babies), similarly contain thimerosal (Public Health Agency of Canada, 2011).

In conclusion, when evaluating the relation between Hg exposures and neurodevelopmental disorders, including ASD, it is important to recognize that the lack of evidence does not necessarily imply absence of evidence. Similarly, neither does the *quantity* of research on one side substitute for a lack of its *quality* (Cobigo et al., 2012; Demicheli, Jefferson, Rivetti, & Price, 2005). Currently, the absence of direct human studies on the risks of EtHg exposure from TCVs is a gap that has been filled with the experimentally unsupported assumption that TCV Hg is safe. This assumption should be now reconsidered in view of the following: (i) animal studies have shown that exposure to EtHg can lead to accumulation of inorganic Hg in brain (Burbacher et al., 2005), and that doses relevant to TCV exposure can negatively impact neurodevelopment (Dórea, 2011; Hewitson et al., 2010; Hornig, Chian, & Lipkin, 2004; Olczak et al., 2011a, b); (ii) evidence from several (although

not all) epidemiological studies supports the link between TCV exposure in children and adverse neurodevelopmental outcomes including autism; and, (iii) there is a striking correspondence between symptoms of autism and Hg-poisoning (Bernard, Enayati, Redwood, Roger, & Binstock, 2001; Hornig, Chian, & Lipkin, 2004; Olczak et al., 2011a, b). To date, TCVs continue to be administered on a regular basis to potentially the most vulnerable populations: pregnant women and children (especially in developing countries). Given this, we believe it is high time to reassess the rationale for using thimerosal, a known immune and neurotoxic substance, in human vaccines. In this context, the results and conclusion of Cobigo et al. (2012) are important as a guidance to the design of much needed new studies that will have the capacity to resolve this crucial issue.

Key Messages From This Article

People with disabilities: There is no data on safety of TCVs in people with autism or developmental disabilities. Historically, vaccine trials have routinely excluded individuals with a variety of pre-existing conditions. These include personal or family history of developmental delays or neurological disorders (i.e., epilepsy/seizures; Tomljenovic & Shaw 2011b). This lack of relevant safety data should be of concern, since cases of deaths following vaccination in children with developmental disabilities (i.e., psychomotor retardation) have been established in the scientific literature (Yang et al., 2006).

Professionals: The medical community has, at large, largely rejected examples of vaccine injury by citing a "greater good" argument, namely that the number of those negatively affected is trivial in relation to those prevented from the hazards of infectious disease. The entire argument thus hinges on the actual safety of various vaccine components and this argument is hindered by a general lack of appreciation of the actual data on the subject. It is our goal in this letter to broaden the perspective that some vaccine components indeed have the capacity to do harm and that only rigorous research, not mere assumptions of safety, will be needed to finally resolve the issue.

Policymakers: The use of thimerosal in vaccines should be reconsidered, especially in those vaccines intended for pregnant women and children. There is sufficient evidence to show that low-level exposure to Hg can be hazardous to vulnerable populations, particularly developing foetuses, infants and children. Moreover, the persisting use of TCV in developing countries is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products.

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