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Invited critical review

Making sense of epidemiological studies of young children exposed to thimerosal in vaccines

José G. Dórea

C.P. 04322, Universidade de Brasilia, 70919-970 Brasilia, DF, Brazil

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ABSTRACT

Objective: To compare epidemiological studies dealing with neurological issues (compatible with Hg toxicity) linked to exposing newborns and infants to intramuscular doses of preservative-Hg resulting from vaccination with thimerosal-containing vaccines (TCV).
Methods: Major databases were searched for studies that addressed neurodevelopment outcomes other than autism. Eight studies were identified and compared.
Results: Information extracted from the studies done in the USA, the UK, and Italy is important in understanding the complex interplay of variables but insufficient to establish non-toxicity for infants and young children still receiving TCV: a) there is ambiguity in some studies reporting neurodevelopment outcomes that seem to depend on confounding variables; b) the risk of neurotoxicity due to low doses of thimerosal is plausible at least for susceptible infants; c) there is a need to address these issues in less developed countries still using TCV in pregnant mothers, newborns, and young children.
Conclusions: Since the use of TCV is still inevitable in many countries, this increases the need to protect vulnerable infants and promote actions that strengthen neurodevelopment. Developing countries should intensify campaigns that include breastfeeding among efforts to help prime the central nervous system to tolerate exposure to neurotoxic substances, especially thimerosal-Hg.
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Contents

1. Introduction

It is estimated that 3% of neurodevelopmental disabilities (NDD) are directly linked to environmental neurotoxic substances and that 25% of these disabilities may arise as a result of interaction with individual genetic susceptibilities [1]. Outside a handful of rich countries, organic mercury (Hg) in the form of ethylmercury (EtHg) may be the first exposure a vaccinated infant has to a potentially neurotoxic substance such as mercury. EtHg is the metabolite of thimerosal widely used to preserve immunoglobulins (used by Rh-negative pregnant women) and vaccines that are given to pregnant mothers, newborns, infants, and young children.

Because the child is healthy when he/she takes vaccines, adverse events caused by vaccination are monitored to insure vaccine safety. Neurological syndromes and diseases may appear as a result of vaccine's antigens [2–4]; however, in the case of vaccine-thimerosal

E-mail address: dorea@rudah.com.br.

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doses (0.01%), the possible central nervous system (CNS) effects of EtHg may be transient or may appear years after the exposure and only under circumstances that have not as yet been clearly characterized.

Neurological and other adverse events subsequent to vaccines are closely monitored by a Vaccine Adverse Event Reporting System (VAERS in the USA) in many countries. Serious events like neurological diseases [5] and illnesses [6] are rare but have been detected in adults by the VAERS. In children the most common clinical post-vaccine events are mild fever, chills, and discomfort with favorable outcome; adverse events that require medical attention are hypotonic–hyporesponsive episodes, fever, and convulsions which are cured without any sequel in 98.4% of the cases [7]. None of these events are ascribed to Hg toxicity. Nevertheless, the most controversial debate surrounding vaccines and neurological disabilities has resulted from the assumption that the MMR (measles, mumps, and rubella) vaccine could be related to autism. Long before the Lancet paper was withdrawn, the debate had already shifted from vaccine reaction to the neurological effect of EtHg as a provoking agent [8]. For this specific issue the reader is referred to recent reviews by expert neurotoxicologists [9,10].

Hg neurotoxicity involves long latencies and atypical responses between low and high doses [11], which makes it a recurrent issue open to investigation. Autism, however, is not the object of this review; instead, the focus is the few epidemiological studies that have addressed the crucial neurological issues (compatible with recognizable Hg toxicity) linked to exposing newborns and infants to intramuscular doses of thimerosal-Hg after immunization with TCV.

2. Thimerosal-Hg and infants' CNS integrity

2.1. Contextualization

Vaccination has made it possible to eradicate or control infectious disease that otherwise would be devastating to children, and large-scale dispensation of vaccines in multidose containers requires the use of preservatives. The safety profile of thimerosal used as a vaccine preservative was not an issue until the late 1990s; however, after 60 years of mandatory use public health professionals in the USA raised concerns about exposure of newborns and infants to Hg doses above the maximum recommendation (0.1 μg/kg b.w.) set by the Environmental Protection Agency [12].

Although thimerosal is considered one of the most prevalent contact allergens [13], it is widely used in pharmaceutical products; despite its wide use in multidose vaccine vials as a preservative, there are instances where it may fail to prevent short-term bacterial contamination [14] or destabilize antigens [15,16]. Clinical vaccine trials and surveillance of post-license TCV safety have always focused on issues other than thimerosal (or EtHg) toxicity. Although thimerosal has been cautioned in relation to significant side effects in therapeutic agents [17] and in vaccines [18], specific issues related to infant-CNS effects have only recently received some attention [19]. A full vaccination schedule with TCV can expose newborns and infants to Hg levels above the maximum limit recommended by WHO; as a result the plausibility of untoward neurological events is now intensely debated and has already moved rich countries to phase out its use in vaccines for pregnant mothers and young children. As a consequence, eight epidemiological studies have been conducted dealing with neurodevelopment after a full schedule with TCV and are summarized in Table 1.

The developing CNS of foetus, infants and young children is particularly vulnerable to neurotoxic substances [20]. Mercury's most widely recognized effects are neurological; lately, alarming reports have appeared linking environmental Hg exposure and risk of diminished cognitive function [21–25]. Therefore, environmental health and safety professionals have attributed neurologic risks to Hg contamination. Methylmercury-MeHg (from dietary seafood) and EtHg (from TCV) are the organic Hg forms to which young children are likely to be exposed [26].

2.2. Plausibility of neurological effects of ethylmercury exposure during early life

We know little about the mechanisms of EtHg transport but it is believed to move throughout the body like MeHg [27]. The rise in Hg concentrations (derived from a single shot of TCV) in an infant's blood seems to be faster and to last longer [28] than blood-EtHg measured in adults [29]; 50% of blood-Hg samples measured 12 h after TCV (hepatitis B) in newborns were above safe limits of 5 ng/mL [28]. Clarkson and Strain [30] pointed out that a peak value of blood mercury appears to be a determinant of toxic effect in population studies. Magos et al. [31] recognized that the circulation time between Hg absorption site and brain is an important toxicity factor. Ceccatelli et al [32], discussed how the binding of Hg to blood cells modulates toxicokinetics (and toxicodynamics): a stronger binding of Hg to blood cells can retard its diffusion by fecal elimination or brain uptake. A post-natal rise in total hair-Hg has been reported and partly attributed to TCV-Hg [33,34]. Indeed, EtHg has been found in hair of infants that had been immunized with TCV [35].

A wide spectrum of tissue growth and differentiation determines the often unrecognized gradient of anatomic-physiological complexity (stages of maturity) of young children referred to as infants. Infancy, from birth to 6 months, is the post-natal period's most vulnerable time to CNS effects of neurotoxic substances. Infants are not just small children, but a heterogeneous subset of this population with a wide range of physiological, metabolic and anatomical differences — notably, structural and functional CNS development [26]. A comprehensive discussion of such issues is presented elsewhere [26]; briefly, between a 1-day-old neonate and a 6-month-old infant (who has doubled its original body mass and already acquired functional abilities) differences brought by growth, tissue differentiation and brain development (including complex functions) set them apart in terms of the TK and TD of EtHg exposure. Indeed it is recognized that the half-life of some drugs administered on the first post-natal day is significantly correlated with gestational age [36].

The complex physiological and functional CNS variability among neonates and neurodevelopment outcomes of the sub-clinical effects of EtHg is an important but unaddressed issue [37,38]; this is compounded by the timing, dose, and duration of EtHg exposure. The possible outcome of an unanticipated CNS untoward (secondary) effect due to EtHg may appear only after immunization's collateral (primary) effects attributed to the antigens and not captured by the vaccines' adverse effect systems [39]. The greater the time elapsed after the TCV-Hg challenge and neurodevelopment assessment, the greater the chances that the measured outcome can be affected by confounding variables. This illustrates the intractable task of determining TD and TK of thimerosal-EtHg exposure during the first 24 post-natal weeks especially when exposure to EtHg occurs in the perinatal period. This is further compounded when mothers have been liberally immunized with TCV against tetanus, hepatitis B, common flu and pandemic H1N1.

The TK of EtHg in newborns and infants has been inferred [40] from a few animal and human studies [41,42]. However, because of ethical issues, EtHg TD research in infants requires special circumstances and may only be inferred from properly conducted epidemiological studies. Coupled with that, co-exposure to other neurotoxic substances (especially during pregnancy) may increase children's susceptibility to vaccine-EtHg exposure, particularly if the ability to detoxify Hg has been compromised by additional unsuspected circumstances related to Hg metabolism: glutathione S-transferases (GST) polymorphisms [43,44] and Hg elimination [45].

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