International Journal of Hygiene and Environmental Health xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

The risk of neurodevelopmental disorders following Thimerosal-containing Hib vaccine in comparison to Thimerosal-free Hib vaccine administered from 1995 to 1999 in the United States

David A. Geier[a,b], Janet K. Kern[a,b,c,*], Kristin G. Homme[d], Mark R. Geier[a,*]

[a] The Institute of Chronic Illnesses, Inc, Silver Spring, MD, USA
[b] CoMeD, Inc, Silver Spring, MD, USA
[c] CONEM US Autism Research Group, Allen, TX, USA
[d] International Academy of Oral Medicine and Toxicology, Champions Gate, FL, USA

ARTICLE INFO

Keywords:
Autistic
ADHD
Ethylmercury
Merthiolate
Language
PDD
Speech
Thiomersal

ABSTRACT

Investigators postulated that early-life exposure to organic mercury (Hg) significantly increases the risk of childhood neurodevelopmental disorders (NDs). The Vaccine Adverse Event Reporting System database was utilized to conduct a hypothesis testing case-control study by evaluating 3486 total adverse event reports reported following *Haemophilus influenza* type b (Hib) vaccination. Exposed subjects received a Thimerosal-containing formulation (HIBTITER™, Wyeth-Lederle), while unexposed subjects received a Thimerosal-free formulation (PEDVAXHIB™, Merck). Subjects were included if they received either of these two Hib vaccine formulations between 1995 and 1999. Cases were defined as adverse event reports with a reported outcome of autism, developmental delay, psychomotor delay, or NDs in general. Cases with reported outcomes of febrile convulsions, pyrexia, or injection site pain, all of which have no biologically plausible relation to Hg exposure, were also examined. Controls were defined as adverse event reports without any mention of the specific case outcome examined. Cases of reported autism (odds ratio (OR) = 2.75, $p < 0.02$), developmental delay (OR = 5.39, $p < 0.01$), psychomotor disorder (OR = 2.38, $p < 0.03$), and neurodevelopmental disorder in general (OR = 2.70, $p < 0.001$) were each significantly more likely than their respective controls to receive Thimerosal-containing Hib vaccine than Thimerosal-free Hib vaccine. Significant effects for neurodevelopmental disorder in general were observed for males (OR = 2.52, $p < 0.005$), but not females when separated by gender. For the outcomes that had no biologically plausible relation to Hg exposure, the cases were no more likely than their respective controls to receive Thimerosal-containing Hib vaccine than Thimerosal-free Hib vaccine. This study provides suggestive evidence of an association between Thimerosal and neurodevelopmental outcomes and provides support for carrying out additional well-designed studies examining the association between Thimerosal-containing vaccines and a wide range of neurodevelopmental outcomes.

1. Introduction

As reported by leading investigators, lifelong neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common and costly (Grandjean and Landrigan, 2006, 2014). These investigators reported that chemical exposure to compounds such as organic mercury (Hg) during early neurodevelopmental periods significantly increases the risk of children being diagnosed with a neurodevelopmental disorder (Grandjean and Landrigan, 2006, 2014).

A significant source of organic Hg exposure for many children in the United States (US) during the 1990s was from Thimerosal-containing childhood vaccines administered during infancy. Thimerosal is 49.55% Hg by weight and was added to many childhood vaccines at a dose of 12.5 μg Hg to 25 μg Hg per 0.5 mL vaccine dose (Kern et al., 2013). The organic Hg compounds, ethyl-Hg chloride and ethyl-Hg hydroxide, are the rapid breakdown products of Thimerosal in saline solutions (Tan and Parkin, 2000). Ethyl-Hg compounds easily cross cell membranes and significantly concentrate in intracellular environments, particularly, within mitochondria (Sharpe et al., 2012; Lohren et al., 2015). In addition, ethyl-Hg compounds are actively transported by the l-type neutral amino acid carrier transport (LAT) system into the brain (Zimmermann et al., 2013).

Overall, when considering environmental exposures to Hg and

* Corresponding authors at: 14 Redgate Ct, Silver Spring, MD, 20905, USA.
E-mail address: jkern@dfwair.net (J.K. Kern).

https://doi.org/10.1016/j.ijheh.2018.03.004
Received 19 November 2017; Received in revised form 27 December 2017; Accepted 13 March 2018

repeated bolus exposures from organic Hg from Thimerosal-containing vaccines, it was estimated that some infants in the 1990s received more than 50% of their total Hg exposure from Thimerosal-containing vaccines. It is well-documented that infants in the 1990s incurred exposures to ethyl-Hg from vaccines in bolus and cumulative doses that far exceeded multiple regulatory safety standards for similar toxicants (Kern et al., 2013; Bigham and Copes, 2005). Furthermore, exposure in infancy and childhood to multiple Thimerosal-containing vaccines continues unabated in many developing nations today. Furthermore, exposure to annual Thimerosal-containing influenza vaccines, including to pregnant women, infants, and children, continues to the present day in the US (Sykes et al., 2014).

Understanding the potential neurodevelopmental risks to infants is a critical public health issue today. Consequently, the aim of this study was to evaluate the potential adverse neurodevelopmental effects of increased organic Hg exposure from one particular series of Thimerosal-containing childhood vaccines (in comparison to the Thimerosal-free version), based upon an assessment of the Vaccine Adverse Event Reporting System (VAERS) database. In order to achieve this aim, the present hypothesis-testing study evaluated cases that were reported to the VAERS database with specific neurodevelopmental disorders, in comparison to controls (without such diagnoses), for exposure to organic Hg from a Thimerosal-containing *Haemophilus influenza* type b (Hib) vaccine in comparison to no exposure to organic Hg due to use of a Thimerosal-free Hib vaccine (i.e., a difference of 25 μg Hg/dose) administered in the same childhood vaccine schedule at 2, 4, 6, and 15 months of age (i.e., a total cumulative difference of 100 μg Hg) from 1995 through 2000.

2. Methods

The VAERS is an epidemiological database that has been maintained jointly by the US Centers for Disease Control and Prevention (CDC) and US Food and Drug Administration (FDA) since 1990 as a surveillance tool to evaluate vaccine safety. Specific adverse events following vaccination are required to be reported to this database as mandated by law, but other adverse events that occur following vaccine administration are passively reported to VAERS. Reports are submitted to VAERS using a standardized form by healthcare providers and/or parents. The VAERS Working Group of the CDC has previously acknowledged that less than 5% of the total adverse events reported to VAERS are reported by parents. Specific serious adverse events and deaths reported to VAERS are followed-up by the CDC/FDA.

The VAERS Working Group notes that VAERS is simple to use and flexible by design, and the data are available in a timely fashion, but it also warns that the potential limitations may include systematic error due to underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes and lack of precise denominators for the numbers of doses of each type of vaccine administered to patients. In addition, when evaluating data from VAERS, it is important to note that, for any reported event, no cause and effect relationship has been established. VAERS is interested in all potential associations between vaccines and adverse events. Therefore, VAERS collects information on any adverse event following vaccination reported by an individual who associates the adverse event with vaccination, be it coincidental or truly caused by a vaccine (Singleton et al., 1999; Geier and Geier, 2004). Nevertheless, the CDC' and the FDA' joint VAERS Working Group and independent investigators have repeatedly analyzed and published epidemiologic studies based upon VAERS using appropriate analysis methods (Singleton et al., 1999; Geier and Geier, 2004).

2.1. Determining the population at risk

An analysis of the VAERS database updated through January 14, 2017 was undertaken using the CDC Wonder online computer interface (http://wonder.cdc.gov/vaers.html). This portal provides a direct method for independent investigators to rapidly analyze current data in VAERS. The cases and controls examined in this study were selected from adverse event reports associated with *Haemophius influenzae* type b (Hib) vaccine. The Hib vaccine adverse event reports examined in this study only included those with reported Thimerosal-containing HIBTITER™ (Wyeth-Lederle, Pearl River, NY, USA, VAERS Code = 35) vaccine or Thimerosal-free PEDVAXHIB™ (Merck, Whitehouse Station, NJ, US, VAERS Code = 129) vaccine, administered from January 1995 through December 1999, with a listed residence in the United States and a specified gender. A total of 3486 subjects with adverse event reports in the VAERS database were identified for inclusion in the present study. Of the total of 3486 adverse event reports, 1853 were in males and 1633 were in females.

2.2. Determining cases

The cases were selected from the 3486 total adverse event reports examined and identified as having outcomes for which a link to Hg exposure was biologically plausible, i.e., outcomes of neurodevelopmental disorders, namely: autism (VAERS code: 10003805), developmental delay (developmental delay, VAERS code: 10012559; intellectual disability, VAERS code: 10067989, learning disability, VAERS code: 10024092; learning disorder, VAERS code: 10061265; or severe mental retardation, VAERS code: 10040443), psychomotor disorder (aphasia, VAERS code: 10002948; hyperkinesia, VAERS code: 10020651; psychomotor disorders, VAERS codes: 10037211, 10037213, 10037214, or 10049215; or speech disorders, VAERS code: 10041466), and neurodevelopmental disorders in general (aphasia, VAERS code: 10002948; autism, VAERS code: 10003805; developmental delay, VAERS code: 10012559; hyperkinesia, VAERS code: 10020651; intellectual disability, VAERS code: 10067989, learning disability, VAERS code: 10024092; learning disorder, VAERS code: 10061265; psychomotor disorders, VAERS codes: 10037211, 10037213, 10037214, or 10049215; severe mental retardation, VAERS code: 10040443; or speech disorders, VAERS code: 10041466). To validate the methodology, a second group of cases were selected from the 3486 total adverse event reports examined that were defined as having outcomes that lacked a biologically plausible link to Hg exposure, namely, febrile convulsions (VAERS code: 10022116), pyrexia (VAERS code: 10037660), and injection site pain (VAERS code: 10022086). Table 1 summarizes the gender breakdown for each type of case examined in this study.

2.3. Determining controls

The controls were selected from the 3486 total adverse event reports examined. The controls were selected for each type of case outcome examined by including as controls only those adverse event reports that did not report the specific type of case outcome under study. For example, when examining autism cases, the controls comprised all of the reports where autism was not listed among the adverse event symptoms. Table 1 summarizes the gender breakdown of controls for each case outcome examined.

2.4. Determining exposure

Exposure was determined in the present study based upon the type of Hib vaccine examined. Table 2 provides an overview of the components of the two formulations of Hib vaccine examined in the present study (Committee on Infectious Diseases and Committee on Environmental Health, 1999). It was determined from the manufacturer's product materials that each HIBTITER™ vaccine recipient was exposed to 25 μg Hg from the Thimerosal present as a preservative in each dose, whereas each PEDVAXHIB™ vaccine a recipient was exposed to 0 μg Hg per dose. Each study subject included in the present study received at least one dose of HIBTITER™ or PEDVAXHIB™. The dates of