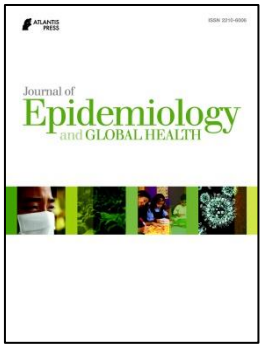

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ORIGINAL ARTICLE

A longitudinal cohort study of the relationship between Thimerosal-containing hepatitis B vaccination and specific delays in development in the United States: Assessment of attributable risk and lifetime care costs

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Abstract Epidemiological evidence suggests a link between mercury (Hg) exposure from Thimerosal-containing vaccines and specific delays in development. A hypothesis-testing longitudinal cohort study (n = 49,835) using medical records in the Vaccine Safety Datalink (VSD) was undertaken to evaluate the relationship between exposure to Hg from Thimerosal-containing hepatitis B vaccines (T-HBVs) administered at specific intervals in the first 6 months of life and specific delays in development [International Classification of Disease, 9th revision (ICD-9): 315.xx] among children born between 1991 and 1994 and continuously enrolled from birth for at least 5.81 years. Infants receiving increased Hg doses from T-HBVs administered within the first month, the first 2 months, and the first 6 months of life were significantly more likely to be diagnosed with specific delays in development than infants receiving no Hg doses from T-HBVs. During the decade in which T-HBVs were routinely recommended and administered to US infants (1991–2001),

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an estimated 0.5—1 million additional US children were diagnosed with specific delays in development as a consequence of 25 μg or 37.5 μg organic Hg from T-HBVs administered within the first 6 months of life. The resulting lifetime costs to the United States may exceed $1 trillion.

1. Introduction

Thimerosal is a mercury (Hg)-containing compound (49.55% Hg weight) used by pharmaceutical companies, and was developed in 1927. It has been added to a range of pharmaceutical products as an antimicrobial [1]. Following administration of Thimerosal-containing vaccines, Thimerosal rapidly dissociates into ethyl-Hg [2] which rapidly binds onto blood constituents [3] and is transported to many tissues in the body, including the brain [4]. Of particular concern, ethyl-Hg is actively transported across neuronal membranes [5], such as by the L-type neutral amino acid carrier transport system [6].

During the 1990s, US infants were exposed to significant amounts of organic Hg from Thimerosal-containing hepatitis B vaccine (T-HBV), diphtheria—tetanus—pertussis (DTP), and *Haemophilus influenzae* type B (Hib) vaccines administered at periodic intervals within the first 6 months of life. Typically, nominal concentrations of Thimerosal present in infant vaccines ranged from 0.005% to 0.01% (12.5 μg Hg/0.5 mL vaccine dose or 25 μg Hg/0.5 mL vaccine dose) [4]. Infants may have been exposed to bolus doses of organic Hg nominally ranging from 12.5 μg Hg to 62.5 μg organic Hg, collectively totaling up to nominally 200 μg organic Hg from Thimerosal-containing childhood vaccines during the first 6 months of life, representing >50% of all Hg exposure when considering environmental sources of Hg [4]. This dosing pattern continues unabated in many developing nations to the present day, and many US children continue to receive significant doses of organic Hg from the routinely recommended administration of Thimerosal-containing influenza vaccines (where >50% of all doses of influenza vaccine continue to contain 0.01% Thimerosal) given to pregnant women, infants, and young children [4].

In 2003, some of the co-authors of this article proposed that the hypothesis that exposure to Thimerosal-containing vaccines was associated with specific delays in development rested on indirect and incomplete information, primarily from analogies with methyl-Hg and levels of maximum Hg exposure from vaccines given to children [7]. It was suggested that the hypothesis was biologically plausible, but that the possible relationship bet ween Thimerosal-containing vaccines and specific delays in development was unproven at that time. As of 2003, no peer-reviewed epidemiological studies in the scientific literature had evaluated the potential association between Thimerosal-cont aining vaccines and specific delays in development. Our study was the first epidemiological study to report a significant association between the administration of tens of millions of doses of Thimerosal-containing diphtheria—teta nus—acellular-pertussis (DTaP) vaccines to US children and specific delays in development based upon assessment of the Vaccine Adverse Event Reporting System (VAERS) database.

Subsequent studies in the United States have revealed significant associations between specific delays in development and administration of Thimerosal-containing vaccines to infants in the VAERS [7,8], the Vaccine Safety Datalink (VSD) [9,10], and the National Health and Nutrition Examination Survey (NHANES) [11] databases.

The purpose of the present study was to extend previous research by conducting a longitudinal cohort study of prospectively collected automated medical records in the VSD database to further evaluate the relationship between organic Hg exposure from T-HBVs administered in the first 6 months of life, and the risk of a child being diagnosed with specific delays in development (or learning disability).

2. Methods

The study protocol was approved by the US Centers for Disease Control and Prevention (CDC), the Institutional Review Board of Kaiser Permanente North-West (KPNW; ID: NW-05MGeie-01), and the Institutional Review Board of Kaiser Permanente Northern California (KPNC; ID: CN-03MGeie-01-H). Data were analyzed at the secure Research Data Center of the National Center for Health Statistics in Hyattsville, MD, USA. The views expressed in this study do not necessarily reflect those of the CDC or those of Kaiser Permanente.

The VSD project was created in 1991 by the National Immunization Program of the CDC, and VSD data collection and study methods have been previously described [12–16]. The project links medical event information, specific vaccine history, and selected demographic information from the computerized databases of several health maintenance organizations (HMOs).

2.1. Study participants

An overall cohort of over 1.9 million children enrolled in the VSD project (updated through the end of 2000) from KPNW, Kaiser Permanente Colorado, and KPNC was examined using SAS software (SAS Institute Inc., 100 SAS Campus Drive, Cary, NC 27513-2414, USA). Among the overall cohort of children, a subset of children with nonmissing date of birth and nonmissing sex (who were HMO-enrolled from their date of birth) was further examined.

The outcome files (inpatient and outpatient diagnoses) from this subset of children were then reviewed to find the first instance of International Classification of Disease, 9th revision (ICD-9)-diagnosed specific delays in development, including: reading disorder, unspecified (315.00), alexia (315.01), developmental dyslexia (315.02), specific spelling difficulty (315.09), dyscalculia (315.1), disorder of written expression (315.2), expressive language disorder (315.31), mixed receptive–exp ressive language disorder (315.32), speech and language developmental delay due to hearing loss (31 5.34), developmental articulation disorder (31 5.39), developmental coordination disorder (315.4), mixed development disorder (315.5), other specified delays in development (315.8), and unspecified delay in development (315.9). If there were multiple instances of the same diagnosis in a child, only the first instance was counted.

The records of the children diagnosed with specific delays in development were then reviewed to determine the mean age of initial diagnosis (2.63 years of age) and the standard deviation age of mean initial diagnosis (1.59 years of age). Then, using this information, we required that every member of the cohort assembled for our study had to be continuously enrolled from birth for at least 5.81 years (mean age of initial diagnosis + 2 × standard deviation of initial diagnosis). As a result, a cohort of 49,835 children (males = 25,624 and females = 24,210; male to female ratio = 1.06), born between 1991 and 1994, was examined in the present study.

2.2. Hepatitis B vaccine exposure

The vaccine file for the cohort was then reviewed to determine the exact dates of hepatitis B vaccine administration. Those members of the cohort receiving no doses of hepatitis B vaccine were also included in the present study. Overall among members of the cohort, Hg exposure was assigned as 12.5 μg organic Hg/dose for those receiving a pediatric hepatitis B vaccine or 0 μg organic Hg/dose for those receiving either combined *Haemophilus influenzae* type B (Hib)-hepatitis B vaccine or neither of the aforementioned vaccines (0 μg organic Hg/dose from T-HBV). In addition, to allow for a potential association between exposure and outcome, individuals diagnosed with specific delays in development before administration of the vaccines examined in the present study were excluded.

2.3. Statistical analyses

In all statistical analyses, the StatsDirect statistical software (Version 2.8.0, StatsDirect Ltd., 9 Bonville Chase, Altrincham, Cheshire WA 14 4QA, UK) was utilized, and a two-sided p value < 0.05 was considered statistically significant.

In the first set of experiments, the Fisher's exact test statistic was utilized to examine the relationship between increasing amounts of organic Hg exposure from T-HBV administration and the frequency of diagnosed specific delays in development. In the first experimental group (Experiment I), the data were examined to determine the frequency of diagnosed specific delays in development among the cohort of children exposed to 12.5 μg organic Hg from T-HBV administered in the first month of life, in comparison with the frequency of diagnosed specific delays in development among the cohort of children exposed to 0 μg organic Hg from T-HBV administered in the first month of life. In the second experimental group (Experiment II), the data were examined to determine the frequency of diagnosed specific delays in development among the cohort of children exposed to 25 μg organic Hg from T-HBV administered in the first 2 months of life, in comparison with the frequency of diagnosed specific delays in development among the cohort of children exposed to 0 μg organic Hg from T-HBV administered in the first 2 months of life. In the third experimental group (Experiment III), the data were examined to determine the frequency of diagnosed specific delays in development among the cohort of children exposed to 37.5 μg organic Hg from T-HBV administered in the first