Epidemiology

A cross-sectional study of the relationship between infant Thimerosal-containing hepatitis B vaccine exposure and attention-deficit/hyperactivity disorder

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a marked pattern of inattention and/or hyperactivity-impulsivity that is inconsistent with developmental level and interferes with normal functioning in at least two settings. This study evaluated the hypothesis that infant Thimerosal-containing hepatitis B vaccine (T-HepB) exposure would increase the risk of an ADHD diagnosis. This cross-sectional study examined 4393 persons between 13 and 19 years of age from the combined 1999–2004 National Health and Nutritional Examination Survey (NHANES) by analyzing demographic, immunization, socioeconomic, and health-related variables using the SAS system. Three doses of T-HepB exposure in comparison to no exposure significantly increased the risk of an ADHD diagnosis using logistic regression (adjusted odds ratio = 1.980), linear regression (adjusted beta-coefficient = 0.04747), Spearman's rank (Rho = 0.04807), and 2 × 2 contingency table (rate ratio = 1.8353) statistical modeling even when considering other covariates such as gender, race, and socio-economic status. Current health status outcomes selected on an *a priori* basis to not be biologically plausibly linked to T-HepB exposure showed no relationship with T-HepB. The observed study results are biologically plausible and supported by numerous previous epidemiological studies, but because the NHANES data is collected on a cross-sectional basis, it is not possible to ascribe a direct cause-effect relationship between exposure to T-HepB and an ADHD diagnosis. During the decade from 1991 to 2001 that infants were routinely exposed to T-HepB in the United States (US), an estimated 1.3-2.5 million children were diagnosed with ADHD with excess lifetime costs estimated at US $350-$660 billion as a consequence of T-HepB. Although Thimerosal use in the HepB in the US has been discontinued, Thimerosal remains in the HepB in developing countries. Routine vaccination is an important public health tool to prevent infectious diseases, but every effort should be made to eliminate Thimerosal exposure.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a brain disorder characterized by a marked and ongoing pattern of inattention and/or hyperactivity-impulsivity that is inconsistent with developmental level and interferes with functioning in at least two settings (e.g., at home and at school) [1,2]. For most children in this category, the diagnostic term ADHD is used. The diagnostic term attention deficit disorder (ADD) is also used, but to a lesser extent. ADHD is considered a chronic condition in which a large proportion of these children continue to meet the diagnostic criteria into adulthood [3]. The mean age of initial diagnosis is approximately 6 ± 2 years of age [2]. Boys are more

affected than girls, such that the male to female ratio is typically reported to be about 5–1 [4].

Prevalence reports reveal an increase in the rates of ADHD over the past few decades. For example, Child Trends, a non-profit research organization, reports that in 1996, 1 in 18 children had a diagnosis of ADHD, and in 2012, 1 in 8 children had a diagnosis of ADHD. This represents an increase of about 75% [5]. According to the US Centers for Disease Control and Prevention (CDC) the percentage of children with an ADHD diagnosis continues to increase, from 7.8% in 2003 and 9.5% in 2007 and to 11.0% in 2011 [6]. However, some researchers suggest that the increase in the ADHD prevalence is partially explained by methodological characteristics of different studies [7]. The annual

cost of ADHD in the US is estimated to be between US $36 and US $52 billion [8].

To date, there is no consensus on the underlying cause of ADHD [9]. Heavy metals, such as lead (Pb) and mercury (Hg) have been implicated [10,11]. A recent meta-analysis of epidemiological studies evaluating the relationship between prenatal and early infancy exposures to Hg on the long-term risk of a child being diagnosed with ADHD revealed that the risk of an ADHD diagnosis was increased by Hg exposure (odds ratio (OR) = 1.60, 95% confidence interval (CI) = 1.10-2.33), and that the risk remained similar after excluding studies not adjusted for confounders [12]. In considering the sources of Hg exposure for infants, it was previously reported that the routine administration of Thimerosal-containing childhood vaccines was and continues to be a significant source of potentially dangerous Hg exposure for many infants in the US and worldwide [13]. Thimerosal is an organic Hg-containing compound (49.55% Hg by weight) that is rapidly broken down into ethyl-Hg chloride, ethyl-Hg hydroxide, and thiosalicylate in aqueous solutions [14]. It has been reported that about 50% of the Hg dose that some infants received was from Thimerosal-containing vaccines, with breast milk being the other major source [15]. Thimerosal-containing vaccine and environmental exposures resulted in some infants receiving bolus and cumulative doses of Hg in excess of Hg safety limits established by the US Environmental Protection Agency (EPA), the US Food and Drug Administration (FDA), the CDC's Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO) [13,15].

In this study, the National Health and Nutrition Examination Survey (NHANES) was examined. The NHANES is a major program of the National Center for Health Statistics (NCHS) of the CDC designed to assess the health and nutritional status of adults and children in the US. The NHANES examines a nationally representative sample of about 5000 Americans located in counties across the US each year, combining interviews with physical and laboratory examinations. As described by NCHS, NHANES is supposed to be used in epidemiological studies to determine the prevalence of major diseases and risk factors for diseases, which help develop sound public health policy.

Using the NHANES data, this study evaluated the potential relationship between infant exposure to Thimerosal-containing hepatitis B vaccine and the risk of an ADHD diagnosis. It was hypothesized in this study that infant exposure to Hg from Thimerosal-containing hepatitis B vaccines would significantly increase the risk of an ADHD diagnosis. Then, based upon the results observed, additional analyses were undertaken to determine the numbers and costs associated with ADHD diagnoses in the US as a consequence of infant exposure to Thimerosal-containing hepatitis B vaccines.

2. Methods

This study employed the Statistical Analysis Software (SAS) system version 9.00 for Windows, (Cary, NC, USA) running on a 64-bit based PC with dual-core Intel® (Santa Clara, CA, USA) Xeon® CPU x5680 at 3.33 GHz, 6 cores, and 12 logical processors, with 44.0 GB of RAM, and utilizing Microsoft (Redmond, WA, USA) Windows 7 Ultimate operating system to examine the NHANES data. The NHANES is a program of studies designed to assess annually the health and nutritional status of adults and children in the United States based on questionnaires and physical examinations and to track changes over time. The present study utilized demographic, socioeconomic, immunization, and health-related data within the NHANES database.

2.1. Study participants

A total of 31,126 persons were examined by combining data from the 1999–2000, 2001–2002, and 2003–2004 NHANES program. Among these persons, a sub-group was identified of 4393 teenage persons (between 13 years and 19 years of age) with non-missing values for the

demographic, immunization, and medical condition variables examined in this study.

Within the NHANES demographic dataset, the variables examined were as follows: gender (variable: RIAGENDR, male = 1, female = 2]), age in years at screening (variable: RIDAGEYR, values = 13 to 19), race (variable: RIDRETH2, non-Hispanic White = 1, non-Hispanic Black = 2, and Hispanic = 3 [Mexican American + Other Hispanic]), and socioeconomic status (variable: INDFMPIR, values = 0 to 5, poverty income ratio (PIR) — a ratio of family income to poverty threshold).

2.2. Outcomes

The NHANES medical conditions dataset was examined for ADHD-diagnosis status as follows. Each person included had an identified diagnostic status for the outcome of ADHD (variable: MCQ060 [Yes = 1, No = 2], survey question, "Has a doctor or health professional ever told {you/study participant} that {you/she/he/study participant} had attention deficit disorder?"). In addition, the current health status of each person was determined by evaluating the NHANES current health status dataset. Each person had an identified diagnostic status for the following outcomes: stomach or intestinal illness in the last 30 days (variable: HSQ510 [Yes = 1 or No = 2], survey question, "Did {you/study participant} have a stomach or intestinal illness with vomiting or diarrhea that started during those 30 days?") and flu, pneumonia, or ear infections within the last 30 days (variable: HSQ520 [Yes = 1 or No = 2], survey question, "Did {you/study participant} have flu, pneumonia, or ear infections that started during those 30 days?"). The current health status outcomes were selected *a priori* as not having a biologically plausible link to increased Hg exposure from infant Thimerosal-containing hepatitis B vaccines, and were selected to reflect the general health status of the exposed/unexposed persons examined.

2.3. Exposures

The immunization exposure variable was identified from within the NHANES immunization dataset. The variable examined was hepatitis B vaccine (variable: IMQ020, survey question, "Have you/has study participant ever received the 3-dose series of the hepatitis B vaccine?"). Persons identified as receiving 3 doses of hepatitis B vaccine (variable: IMQ020 = 1) and persons identified as receiving no doses of hepatitis B vaccine (variable: IMQ020 = 3) were included in this study. Exposed persons were composed of those persons receiving 3 doses of Thimerosal-containing hepatitis B vaccine and born from 1991 onwards (variable: hepatitis B vaccine exposure = 1). A birth date from 1991 onwards was selected because hepatitis B vaccine was for the first time routinely recommended for administration to American infants by the Advisory Committee on Immunization Practices (ACIP) in 1991 [16]. Specifically, the ACIP recommendations called for the administration of the first dose of hepatitis B vaccine between birth and 2 months of age, the second dose between 1 and 4 months of age, and the third dose between 6 and 18 months of age. The unexposed persons were composed of those persons receiving no doses of hepatitis B vaccine and those persons receiving 3 doses of hepatitis B vaccine born before 1991 (these persons presumably received the hepatitis B vaccine after infancy) (variable: hepatitis B vaccine exposure = 2).

2.4. Statistical analyses

In all statistical analyses, the statistical package in SAS was utilized, and a two-sided p-value < 0.05 was considered statistically significant. The null hypothesis was that there would be no relationship between infant Thimerosal-containing hepatitis B vaccine exposure and the risk of any of the three outcomes studied — an ADHD diagnosis; stomach or intestinal illness within the last 30 days; and flu, pneumonia, or ear infections within the last 30 days.