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Safety of currently licensed hepatitis B surface antigen vaccines in the United States, Vaccine Adverse Event Reporting System (VAERS), 2005–2015

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ABSTRACT

Introduction: Currently four recombinant hepatitis B (HepB) vaccines are in use in the United States. HepB vaccines are recommended for infants, children and adults. We assessed adverse events (AEs) following HepB vaccines reported to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system.
Methods: We searched VAERS for reports of AEs following single antigen HepB vaccine and HepB-containing vaccines (either given alone or with other vaccines), from January 2005 - December 2015. We conducted descriptive analyses and performed empirical Bayesian data mining to assess disproportionate reporting. We reviewed serious reports including reports of special interest.
Results: VAERS received 20,231 reports following HepB or HepB-containing vaccines: 10,291 (51%) in persons <2 years of age; 2588 (13%) in persons 2–18 years and 5867 (29%) in persons >18 years; for 1485 (7.3%) age was missing. Dizziness and nausea (8.4% each) were the most frequently reported AEs following a single antigen HepB vaccine: fever (23%) and injection site erythema (11%) were most frequent following Hep-containing vaccines. Of the 4444 (22%) reports after single antigen HepB vaccine, 303 (6.8%) were serious, including 45 deaths. Most commonly reported cause of death was Sudden Infant Death Syndrome (197). Most common non-death serious reports following single antigen HepB vaccines among infants aged <1 month, were nervous system disorders (15) among children aged 1–23 months; infections and infestation (8) among persons age 2–18 years blood and lymphatic systemic disorders; and general disorders and administration site conditions among persons age >18 years. Most common vaccination error following single antigen HepB was incorrect product storage.
Conclusions: Review current U.S.-licensed HepB vaccines administered alone or in combination with other vaccines did not reveal new or unexpected safety concerns. Vaccination errors were identified which indicate the need for training and education of providers on HepB vaccine indications and recommendations.

1. Background

In the United States, there are five licensed recombinant hepatitis B surface antigen vaccines (HepB vaccines) available as single or multi-antigen formulations. The two single antigen HepB vaccines are Engerix-B® (GlaxoSmithKline Biologicals (GSK), 1983) [1] and Recombivax HB® (Merck, 1989) [2]. Both are recommended for all ages in a three doses series. Of the three combination vaccines containing HepB with other antigens, Comvax® and Pediarix® are for infants and children [3,4] while Twinrix® is used for adults [5]. Comvax® (Merck, 1997, currently not produced in the United States) [6] is a bivalent vaccine also containing *Haemophilus* B conjugate and was recommended for children aged 2, 4 and 12–15 months [3]. Pediarix® (GSK, 2002), also containing diphtheria and tetanus toxoid and acellular pertussis adsorbed (DTaP) and

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inactivated poliovirus, is recommended for children aged 2, 4, 6 months [4]. Twinrix® (GSK, 2002), also containing hepatitis A and B, is recommended for persons aged ≥18 years [5]. Infants should get their first dose of hepatitis B vaccine at birth and will usually complete the series at 6 months of age. All children and adolescents younger than 19 years of age who have not yet gotten the vaccine should also be vaccinated [7]. Hepatitis B vaccine is recommended for unvaccinated adults who are at risk for hepatitis B virus infection [8]. In 2015, 92.6% of U.S. children aged 19–35 months completed all three recommended doses of HepB vaccines [9].

In pre-licensure clinical trials, adverse events (AEs) following vaccination with HepB vaccines were mostly injection site reactions and mild systemic reactions [1–5]. Commonly reported mild AEs include local reactions, like pain (29%), erythema (3%), swelling (3%); and generalized reactions, like fever (6%) and headache (3%) [10].

Case reports in the early post-licensure period described temporal association with receipt of HepB vaccine and Guillain-Barré Syndrome (GBS), chronic illness such as chronic fatigue syndrome and other neurological disorders like optic neuritis, multiple sclerosis and diabetes mellitus [11], however, causal associations were not established. Studies have not demonstrated association with HepB vaccine and neonatal mortality and sepsis [12–14]. An extensive review by the Institute of Medicine (IOM) concluded that the evidence is inadequate to accept or reject a causal relationship between HepB vaccine and neurologic (e.g., encephalitis/encephalopathy, seizures, multiple sclerosis, GBS) and autoimmune diseases (e.g., systemic lupus erythematosus, vasculitis, rheumatoid arthritis) [15]. Studies from the CDC's Vaccine Safety Datalink [16] did not find associations between HepB vaccine and rheumatoid arthritis [17], Bell's palsy [18], autoimmune thyroid disease [19], anaphylaxis [20], optic neuritis [21], GBS [22] and sudden-onset sensorineural hearing loss [23].

Our safety review assesses AE reports to the Vaccine Adverse Event Reporting System (VAERS) following HepB vaccination, particularly those after administration of single antigen HepB.

2. Material and methods

2.1. Data source

VAERS is a national passive surveillance system for monitoring AEs following immunization and is co-administered by CDC and FDA. VAERS accepts reports from healthcare providers, vaccine manufacturers, vaccine recipients and others [24,25]. Signs and symptoms documented in reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) [26]; a VAERS report may be assigned more than one MedDRA PT. Reports are classified as serious if one or more of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability [27].

2.2. Descriptive analysis

We searched the VAERS database for reports following single antigen HepB and HepB-containing vaccines administered to children and adults in the United States from January 1, 2005 through December 31, 2015 (among reports received through April 30, 2016). Reports with unknown age or from foreign sources were excluded. We analyzed reports by age group, serious or non-serious status, most commonly reported MedDRA PTs, and type of HepB vaccine. Types included single HepB vaccine given alone (single vaccine) and HepB-containing vaccines (either single antigen or combination vaccine) administered with other vaccines (combination vaccines). We conducted descriptive analyses looking at age, sex, onset interval (from vaccination date [day 0] to onset of first symptoms), and the most common MedDRA PTs Data were analyzed using SAS (version 9.3, SAS Institute, Inc., Cary, NC).

2.3. Clinical review of serious reports and pre-specified conditions following single vaccine

CDC investigators (PM and BH) reviewed the original VAERS reports and available medical records for death and non-death serious reports of single vaccine. For death reports, we reviewed both single vaccines and combination vaccines. We verified the cause of death from the death certificate and/or autopsy report. We classified the cause of death into major ICD-10 groups as previously described [28]. For non-death serious reports, we determined the primary AE reported to VAERS and then assigned a primary diagnostic category using the MedDRA System Organ Class (SOC) [26]. We also reviewed reports of pre-specified conditions of interest based on prior post-licensure HepB vaccine safety monitoring and research including anaphylaxis and sepsis in infants aged <1 month and 1 to <2 months [29,30], and reports with MedDRA PTs (2) any terms which that met the statistical threshold for signaling in data mining analysis. To identify anaphylaxis reports, we used MedDRA PTs anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, and anaphylactoid shock [31]. we did not conduct formal causality assessment whether a vaccination error contributed to an AE.

2.4. Data mining

We used empirical Bayesian (EB) data mining to identify AEs that were reported more frequently than expected following HepB vaccines (compared to other vaccines) in the VAERS database, stratified by age and vaccine brand [32]. We used published criteria to identify vaccine-AE pairings that were reported at least twice as frequently as would be expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2) [33]. We reviewed all reports and available medical records for vaccine-AE pairings that met the statistical threshold for an EB data mining signal (EB05 > 2).

3. Results

From January 1, 2005 through December 31, 2015, VAERS received 20,231 reports following single and combination HepB vaccines; 51% were in females and 2958 (15%) were serious reports including 445 deaths (Tables 1a and 1b). Most reports (15,787, 78%), were following combination vaccines. The most commonly co-administered vaccines were *Haemophilus influenzae* type b-containing vaccines (HIBV) 5980 (38%), pneumococcal conjugate vaccine (PCV7) 5724 (36%), and rotavirus pentavalent vaccine (RV5) 4343 (28%). Forty-seven percent of single vaccine and 9% of combination vaccines were reported by the vaccine manufacturer (Tables 1a and 1b).

Among all ages, of 4444 reports of single vaccine, 2365 (53%) were among persons aged >18 years and 287 (6.5%) were classified as serious reports. Of the serious reports, 43 were death reports, of which 27 were infants <1 month of age. The most frequently reported MedDRA PT following single vaccine was incorrect product storage (22%), and following combination vaccines, fever was most frequently reported (23%) Table 2.

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