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Adverse events following Haemophilus influenzae type b (Hib) vaccines in the Vaccine Adverse Event Reporting System (VAERS), 1990-2013

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Abstract

Background: There are currently five *Haemophilus influenzae* type b (Hib) vaccines available in the United States for use in the primary vaccination series and/or for the booster dose. Few post-licensure safety studies of these vaccines have been conducted.

Objective: To characterize adverse events (AEs) after Hib vaccines reported to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods: We searched VAERS for US reports after Hib vaccines among reports received from January 1, 1990-December 1, 2013. We reviewed a random sample of reports and accompanying medical records for reports classified as serious. All reports of death were reviewed. Physicians assigned a primary clinical category to each reviewed report. We used empirical Bayesian data mining to identify AEs that were disproportionally reported following Hib vaccines.

Results: VAERS received 29,747 reports after Hib vaccines; 5,179 (17%) were serious, including 896 reports of deaths. Median age was 6 months (range 0-1022 months). Sudden infant death syndrome was the stated cause of death in 384 (51%) of 749 death reports with autopsy/death certificate records. The most common non-death serious AE categories were neurological conditions (80;37%), other non-infectious (46;22%) (comprised mainly of constitutional signs and

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Contributors' Statement

Pedro L. Moro: Dr. Moro conceptualized and designed the study, reviewed medical records and reports, conducted part of the analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Christopher Jankosky, David Menschik, Jonathan Duffy, Tom Shimabukuro: Drs. Jankosky, Menschik, Duffy, and Shimabukuro reviewed medical records and reports, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Paige Lewis, Brock Stewart: Ms. Lewis and Dr. Stewart conducted the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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symptoms); and gastrointestinal (39;18%). No new safety concerns were identified after clinical review of reports of AEs that exceeded the data mining statistical threshold.

Conclusions: Review of VAERS reports did not identify any new or unexpected safety concerns for Hib vaccines.

Keywords

Haemophilus influenzae type b (Hib) vaccines; epidemiology; surveillance; vaccine safety

Introduction

Haemophilus influenzae type b (Hib) polysaccharide vaccine was licensed in the United States in 1985 and used until 1988. Hib conjugate vaccines, which have superior immunogenicity in young children, were licensed in 1987 and 1989 and replaced the polysaccharide vaccine.[1] Other Hib and Hib-containing combination vaccines have subsequently been licensed and recommended by the Advisory Committee on Immunization Practices (ACIP) for prevention and control of Hib disease. [1,2] The three US licensed monovalent Hib vaccines are PedvaxHIB (Merck and Co., Inc., Whitehouse Station, New Jersey, 1990), ActHIB (Sanofi Pasteur, Inc., Swiftwater, Pennsylvania, 1993), and Hiberix (GlaxoSmithKline, Research Triangle Park, North Carolina, 2009). The three US licensed Hib-containing combination vaccines are Hib-HepB (COMVAX, Merck and Co., Inc., Whitehouse Station, New Jersey, 1996), DTaP-IPV/Hib (Pentacel, Sanofi Pasteur, Inc., Swiftwater, Pennsylvania, 2008), and Hib-MenCY (MenHibrix, GlaxoSmithKline, Inc, Rixensart, Belgium, 2012). [8-11] For simplicity, throughout this paper we refer to monovalent Hib and Hib-containing combination vaccines as “Hib vaccines.” Hib vaccines are recommended as a primary series for infants at 2, 4, and 6 months of age, and a booster dose given between 12 to 15 months of age. [1-6]

Pre-licensure studies showed that adverse reactions to PedvaxHIB, ActHIB, and Hiberix were usually mild, and generally resolved within 12-24 hours. [12-16] Rates of adverse reactions to Comvax, Pentacel, and MenHibrix were similar to those seen with separately administered vaccines. [17-19] Limited post-marketing evaluation of monovalent Hib vaccines has been conducted, while two post-marketing safety evaluations of Comvax and Pentacel showed no concerning safety patterns. [20,21] The scarcity of post-licensure safety evaluations prompted us to conduct a review of the safety of Hib vaccines in the Vaccine Adverse Event Reporting System (VAERS). We assessed VAERS reports involving the currently licensed Hib vaccines received from January 1, 1990 through December 1, 2013.

Methods

Vaccine Adverse Events Reporting System (VAERS)

VAERS is a U.S. national vaccine safety surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), which receives spontaneous reports of adverse events (AEs) following immunization. [22] VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients and others. The VAERS report form collects information on age, gender,

vaccines administered, the AE experienced, and health history. Signs and symptoms of AEs are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology. [23] A VAERS report may be assigned one or more MedDRA preferred terms (PTs). Reports are classified as serious or non-serious. A report is considered serious based on the Code of Federal Regulations definition if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability. [24] For non-manufacturer serious reports, medical records are routinely requested and made available to VAERS personnel.

We analyzed VAERS reports received by December 1, 2013 for subjects vaccinated with any of the currently licensed Hib vaccines from January 1, 1990 through December 1, 2013. Non-US reports and duplicate reports were excluded. We described the most common MedDRA terms for serious and non-serious Hib vaccine reports.

Clinical review of serious reports

We conducted a clinical review of a random sample of 5% of non-death serious reports after Hib vaccines. A primary diagnostic category was assigned to each report, using a system previously described. [25] All reports of deaths after Hib vaccines were reviewed and the cause of death determined from information documented in the autopsy report, the death certificate, or the medical record. In this review we made no attempt to assess causality of the reported AEs. We also searched for all reports of anaphylaxis after Hib vaccines using the following specific MedDRA terms: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, and anaphylactoid shock. Reports of anaphylaxis were classified using the Brighton Collaboration case definition or noting a physician's diagnosis. [26]

Data mining

We used empirical Bayesian (EB) data mining [27] to identify AEs reported more frequently than expected following Hib vaccines by brand name for reports entered into the database as of December 1, 2013. We used published criteria [28, 29] to identify Hib vaccine-adverse event pairs 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). Through this data mining analysis, Hib reports for each vaccine brand were compared to all other vaccines in the VAERS database. We clinically reviewed the Hib vaccine reports with MedDRA PTs that exceeded the data mining threshold noted above. We excluded from this review reports of adverse events described in the vaccine package insert since these were AEs observed in pre-licensure studies and expected to occur during post-marketing safety surveillance. We reviewed all reports for PTs associated with disproportionate reporting if the total number of reports was ≤50. For PTs containing >50 reports, we reviewed a random sample of 20% of the total.

Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

Results

VAERS received 29,747 reports involving receipt of Hib vaccines (PedvaxHIB, ActHIB, Hiberix, Comvax, Pentacel) in the United States from January 1, 1990 through December 1, 2013 (Table 1); no reports after MenHibrix had been received for these dates. Of these reports, 26,978 (91%) involved children aged less than two years of age. Hib vaccines were administered concurrently with one or more other vaccines in 28,293 (95%) of case reports. Median onset time from vaccination to AE was one day [(range 0, 5105]. Among all Hib vaccine reports, 5,179 (17%) were coded as serious, which included 896 death reports. The most frequently reported PTs for all reports were fever (9,039;30%), crying (3,318;11%), injection site erythema (3,135;11%), irritability (2,957;10%), and rash (2,758;9%). Table 2 shows the ten most common PTs reported for serious and non-serious reports.

Non-death serious reports

Most reports (208;97%) involved children <2 years of age (median age 4 months). The most common diagnostic category among a sample of non-death serious reports (Table 3) were neurological conditions (80;37%), followed by other non-infectious (46;22%), and gastrointestinal (39;18%). Seizure was the most common neurological diagnosis in 55 of 80 (69%) reports; 19 of the 55 were febrile seizures. The most common gastrointestinal diagnosis was intussusception in 33 of 39 (85%) reports. In this sample of intussusception reports, rotavirus vaccine was always co-administered with Hib vaccine. Other non-infectious is a nonspecific category comprising diverse diagnoses (e.g., fever, diabetes mellitus type 1).

Deaths

Eight hundred ninety-six deaths were reported to VAERS after receipt of Hib vaccines. Death certificates, autopsy reports or medical records were obtained for 749 of the 896 (84%). Findings for confirmed causes of death from review of death certificates, autopsy reports, or medical records are shown in Table 4. Among reports with confirmed cause of death, the most frequent cause of death (384 of 749; 51%) was sudden infant death syndrome (SIDS). Most SIDS cases (201 of 384; 52%) occurred among males and the predominant age group affected were infants less than 6 months of age (352 of 384; 92%).

Anaphylaxis after Hib vaccines

During the period of this review, 56 reports of anaphylaxis after Hib vaccines were reported to VAERS. Medical records were available for 37 reports and the diagnosis of anaphylaxis was verified in 29 reports. In 2 reports there were other likely causes of anaphylaxis (cantaloupe and acetaminophen) leaving 27 reports with which vaccines were considered as a potential main contributor. Eleven reports met Brighton level one criteria, four level two, and two level three. Twelve did not meet Brighton criteria but a physician made the diagnosis of anaphylaxis. The median interval from vaccination to occurrence of symptoms was < 24 hours (range 0-3 days). In 25 reports a Hib vaccine was given in combination with one or more other vaccines. In two reports, one after Pentacel and one after ActHIB, these Hib vaccines were administered alone.

Data mining

Disproportionality analysis of Hib vaccines by specific brand revealed an elevated EB05 (>2) for the following MedDRA PTs:

Pentacel: ‘intussusception’, ‘enema administration’, ‘ultrasound abdomen abnormal’, ‘pertussis’, and ‘post-tussive vomiting’. In nearly all (N=201) intussusception reports (99%), rotavirus vaccine was administered concomitantly with Pentacel. Pentacel is the only Hib vaccine approved for the primary vaccination series that was licensed around the same time (2008) that the rotavirus vaccines, RotaTeq (2006) and Rotarix (2008), were licensed. Only two of 201 intussusception reports occurred in individuals who received Pentacel but not concomitant rotavirus vaccine. All the reports with the PT ‘ultrasound abdomen abnormal’ and 98% of the reports containing the PT ‘enema administration’ contained the PT ‘intussusception’. All reports with the PTs ‘pertussis’ or ‘post-tussive vomiting’ after Pentacel were submitted by the manufacturer of the vaccine and referred to patients who developed pertussis despite a prior history of vaccination (i.e., vaccination failure) and were identified by a disease surveillance system.

Comvax: ‘crying’, and ‘screaming’. Among reports with the PT ‘crying’ after Comvax, 79% (11/14) were non-serious and 64% (9/14) had recovered by the time the VAERS report was submitted. There were three serious reports of children for the PT ‘crying’: one was hospitalized for observation (reason for hospitalization not specified), another had gastritis as the discharge diagnosis and the third presented with a hyporesponsive episode of 10-15 minutes duration. Among Comvax reports with the PT ‘screaming’, 78% (7/9) were non-serious, with one serious report being the same report as the hyporesponsive episode mentioned above, and the other was a parental report of a child with delayed speech and language development.

PedvaxHIB: ‘meningitis’, ‘Haemophilus infection’, and the vaccination error code ‘wrong drug administered’. For PedvaxHIB reports containing the PT ‘meningitis’, most (73%; 8/11) referred to this adverse event described in a journal article, an abstract, or a separate post-marketing surveillance program. For the PT ‘Haemophilus’, 58% (11/19) were from a journal article, newspaper article or hearsay (i.e., second hand) reports. Reports of PedvaxHIB containing the vaccination error code ‘wrong drug administered’ (n=8) described children 11-16 years of age who received PedvaxHIB instead of meningococcal conjugate, Hepatitis A or quadrivalent human papillomavirus vaccines; no adverse events were reported.

For ActHIB or Hiberix reports there were no disproportionally reported PTs.

Discussion

We conducted a comprehensive review of AE reports after currently licensed Hib vaccines in VAERS using three levels of analysis: 1) automated analysis of all reports, 2) clinical review of serious reports, and 3) data mining analysis to assess for disproportionate reporting. Our analysis did not reveal any unexpected or concerning patterns of AEs after Hib vaccines. Some of the AEs noted were consistent with findings from pre-licensure trials for Hib

vaccines that described injection site reactions (e.g., injection site erythema) and certain systemic reactions (e.g., fever, crying, irritability). [2, 3-10] In our clinical review of non-death serious reports we noted that seizures were the most common neurological event reported. Consistent with this finding was the observation that the MedDRA PT 'convulsion' was the third most common PT among serious reports. Seizures were observed sporadically during some of the prelicensure clinical trials for PedvaxHIB, and Pentacel [3,10], although seizures did not occur more frequently among the vaccinated than the comparison groups. Febrile convulsions are common in childhood, occurring in 2-4% of individuals. [30] Febrile convulsions may be related to febrile infections and have also been associated with Diphtheria, Tetanus, and Pertussis (DTP) whole-cell, 13-valent pneumococcal conjugate, and trivalent inactivated influenza (TIV) vaccines. [31] Among death reports, SIDS was the leading cause of death (52%), which is consistent with infant mortality data that places SIDS as the third leading cause of death in the United States among infants. [32] SIDS occurs rarely during the first month of life, buts peaks between 2-3 months of age. [33] SIDS deaths in the United States have been declining since the early 1990s for a variety of factors that include recommended changes in sleeping position and environment, clarification of the case definition, and diagnostic coding shifts. [34-36] There is a large body of evidence that vaccination is not causally associated with SIDS. [37-39] Because SIDS peaks at a time when children are receiving a relatively large number of recommended vaccinations, it would not be uncommon to observe a coincidental close temporal relationship between vaccination and SIDS. [39] A previous study on death reports in VAERS found that SIDS was the most common cause of death reported in almost half of all deaths reported. [40] The combination of Hib vaccines, DTP and oral polio (OPV) vaccine was the most common vaccine combination given in 1266 deaths reported to VAERS during 1990-1997. [40]

Through data mining, we found higher disproportional reporting for certain PTs associated with different Hib-containing products. For Pentacel, disproportionate reporting for 'intussusception', 'enema administration', and 'ultrasound abdomen abnormal' appear to be related to concomitantly administered rotavirus vaccine, which has a known association with intussusception. [41,42] Through our clinical review of a sample of serious Hib reports we also noted that intussusception was the most common diagnosis among gastrointestinal events and in all these reports rotavirus vaccine was given concomitantly with a Hib vaccine. Pentacel was licensed in the US in 2008 [9], two years after rotavirus vaccines were reintroduced into the recommended vaccine schedule, which might explain why the association of Pentacel with intussusception is more likely to be confounded by coadministration with a rotavirus vaccine than the other Hib vaccines (Hiberix was licensed in 2009 but is not given at the same age as rotavirus vaccine). Data mining findings involving the PTs 'pertussis' and 'post-tussive vomiting' are difficult to interpret since all the reports in question were submitted by the Pentacel manufacturer as part of a manufacturer sponsored study with this vaccine [44] and thus may represent reporting bias. For other PTs (e.g., meningitis, haemophilus), the source for the reports were journal or newspaper articles or another surveillance system. These reports indicate vaccine failure rather than a vaccine adverse event.

The Vaccine Safety Datalink (VSD) conducted an observational study of the combination Hib vaccine, DTaP-IPV-Hib (Pentacel), for the period September 2008 through January

2011. [21] Compared to children who received a DTaP-containing vaccine without Hib, children aged 1-2 years who received DTaP-IPV-Hib vaccine had an elevated risk of fever (RR = 1.83, 95% CI: 1.34, 2.50). However, no increased risk for fever was observed among children less than 1 year of age (RR = 0.83, 95% CI: 0.73, 0.94). No increased risk was observed for seizure, meningitis/encephalitis/myelitis, or nonanaphylactic allergic reaction. Although our study cannot be compared to this prospective assessment in the VSD, we did observe that fever was the most common PT for both serious and non-serious reports for all Hib vaccines studied.

A postmarketing safety study of Hib-HepB (Comvax) was conducted by an integrated healthcare organization using a large-linked data base for the period July 1997 through December 2000. [20] Using ICD-9 codes, the study evaluated outcomes occurring during the 1-30 days following administration of Hib-HepB, compared with two control groups (historical control group and self-comparison group). A total of 127 codes had statistically elevated risks and 66 had statistically decreased risks. On medical record review, there was no consistent pattern of respiratory or gastrointestinal illnesses. The authors concluded there was no consistent association between serious adverse events and vaccination with Hib-HepB and the vaccine had a favorable safety profile.

VAERS has strengths such as its broad national scope and timeliness. However, any finding in VAERS needs to be interpreted with caution given the inherent limitations of passive surveillance systems, such as over- or under-reporting, biased reporting, and inconsistency in quality and completeness of reports. [22] VAERS generally cannot assess if a vaccine caused an AE. VAERS does not collect data on the number of individuals vaccinated, therefore with no denominator data it is not possible to calculate incidence rates of AEs.

Conclusion

Our review of the safety of Hib vaccines did not find any new or unexpected safety concerns and was reassuring on the safety of PedvaxHIB, ActHIB, Hiberix, Comvax, and Pentacel. CDC and FDA will continue to monitor adverse events following Hib vaccination in VAERS.

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What's known on this subject:

Pre-licensure studies showed that adverse reactions to the three US licensed monovalent Hib vaccines (PedvaxHIB, ActHIB, and Hiberix) were usually mild, and generally resolved within 12-24 hours. Rates of adverse reactions to the Hib-containing combination vaccines (Comvax, and Pentacel) were similar to those seen with separately administered vaccines.

What this study adds:

Post-licensure surveillance of adverse events after the five currently licensed Hib vaccines did not find any new or unexpected safety concerns in the Vaccine Adverse Event Reporting System.

Table 1.

Characteristics of all reports after currently licensed Haemophilus influenza type b (Hib) vaccines in VAERS among reports received from January 1, 1990 through December 1, 2013

Characteristics	No. (%)
Total reports	29,747
Serious	5,179 (17)
Male	15,327 (52)
Median onset interval (range) in days	1 (0 – 5,105)
Type of reporter (N= 28,273)	
Vaccine provider	18,330 (65)
Manufacturer	2,215 (8)
Parent	1,423 (5)
Other [b]	6,305 (22)
Unknown reporter	1,474 (5)
Median age (range) in months	6 (0 – 1022)
Age less than 2 years	26,978 (91)
Subject recovered by the time the VAERS form was submitted	20,352 (68)

[a] Total Hib vaccines given = 29,826 (some individuals received more than one Hib vaccine at a time)

[b] Secretary, office assistant, etc

Table 2.

The most frequent serious and non-serious adverse events following Haemophilus influenza type b (Hib) vaccines reported to VAERS, 1990-2013

MedDRA Preferred Terms by Serious/Non-serious status[a]	N (%)
Serious	5,179
Pyrexia	1,894 (37)
Vomiting	1,121 (22)
Convulsion	1,053 (20)
Irritability	884 (17)
Intussusception	600 (12)
Diarrhoea	590 (11)
Crying	583 (11)
Hypotonia	489 (9)
Lethargy	486 (9)
Apnoea	483 (9)
Nonserious	24,568
Pyrexia	7,145 (29)
Injection site erythema	3,046 (12)
Crying	2,735 (11)
Rash	2,457 (10)
Irritability	2,073 (8)
Screaming	1,691 (7)
Urticaria	1,644 (7)
Injection site swelling	1,586 (7)
Agitation	1,577 (6)
Erythema	1,521 (6)

[a]The MedDRA preferred terms reflect the 10 most frequent terms coded in serious and nonserious reports after receipt of Hib vaccines. A report may contain more than one MedDRA preferred term.

Table 3.

Diagnostic categories for a random sample (N=214) of non-death serious reports after all currently licensed Haemophilus Influenza Type b (Hib) vaccines[a] in VAERS among reports received from January 1, 1990 through December 1, 2013

Body System Category	N (%)
Neurological	80 (37)
Seizures/epilepsy	55
Hypotonic-hyporesponsive	7
Other noninfectious	46 (22)
Fever	12
Hematological	5
GastrointestinaI [b]	39 (18)
Intussusception [c]	33
Other infectious	22 (10)
Allergy	8 (4)
Respiratory	7 (3)
Local reaction	6 (3)
Cardiac	5 (2)
Musculoskeletal	1 (1)

[a](PedvaxHIB, ActHIB, Hiberix, Comvax, Pentacel)

[b]35 of 39 Gastrointestinal reports also received a rotavirus vaccine with the Hib vaccine

[c]All intussusception reports reviewed received rotavirus vaccine on the same date as Hib vaccine

Table 4.

Confirmed cause of death among death reports following administration of Haemophilus influenza type b (Hib) vaccines in VAERS

Cause of death [†]	N (%)
Sudden Infant Death Syndrome	384 (51)
Undetermined	106 (14)
Respiratory	66 (9)
Pneumonia	36
Trauma	60 (8)
Cardiovascular	35 (5)
Other infectious	33 (4)
Other non-infectious	31 (4)
Neurological	20 (3)
Gastroenterological	12 (2)
Intussusception[‡]	7
Total	**749**

[†]Confirmed by review of death certificate, autopsy report or medical record

[‡]Four reports received Rotavirus vaccine concomitantly