ARTICLE

Neonatal Deaths After Hepatitis B Vaccine

The Vaccine Adverse Event Reporting System, 1991-1998

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Objective: To evaluate reports of neonatal deaths (aged 0-28 days) after hepatitis B (HepB) immunization reported to the national Vaccine Adverse Event Reporting System (VAERS).

Design: Case series; review of autopsy reports.

Setting: Voluntary reports submitted to VAERS, a passive surveillance system, from the US population.

Patients: All US neonates (0-28 days of age) whose deaths after HepB vaccination given alone were reported to VAERS, occurring from January 1, 1991, through October 5, 1998.

Intervention: None (observational database).

Results: Of 1771 neonatal reports, there were 18 deaths in 8 boys and 9 girls (1 patient unclassified). The mean age at vaccination for these 18 cases was 12 days (range, 1-27 days); median time from vaccination to onset of symptoms was 2 days (range, 0-20 days); and median time from symptoms to death was 0 days (range, 0-15 days). The mean birth weight of the neonates (n = 15) was 3034 g (range, 1828-4678 g). The causes of death for the 17 autopsied cases were sudden infant death syndrome for 12, infection for 3, and 1 case each of intracerebral hemorrhage, accidental suffocation, and congenital heart disease.

Conclusion: Few neonatal deaths following HepB vaccination have been reported, despite the use of at least 86 million doses of pediatric vaccine given in the United States since 1991. While the limitations of passive surveillance systems do not permit definitive inference, these data suggest that HepB immunization is not causing a clear increase in neonatal deaths.

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Editor's Note: This report should help allay the fears of the antivaccine groups; it should, but will it?

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In 1991, hepatitis B (HepB) vaccine became the first vaccine recommended to be universally administered to neonates.[1] At the time of licensing of the recombinant HepB vaccines in 1986 (Recombivax; Merck & Co Inc, Whitehouse Station, NJ) and 1989 (Engerix; SmithKline Beecham Pharmaceuticals, Philadelphia, Pa), no serious reaction or death had been reported in infants (aged 0-12 months); however, the safety database was based on limited experience in approximately 2000 infants.[2-8]

Postmarketing surveillance is an important tool that may identify new or rare adverse events that are only observed after the vaccine is widely used after licensure.[9-15] The national Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system monitoring postmarketing vaccine safety.[15] It solicits reports of all events temporally related to immunization, some of which may be coincidental.[15] Despite limitations inherent in passive reporting systems such as biased reporting, incomplete reporting, and underreporting; lack of consistent diagnostic criteria; lack of a comparison group; and lack of data as to the number of vaccine doses administered,[15] VAERS has proved a useful tool in identifying and evaluating vaccine-related events such as thrombocytopenia after measles vaccine[12] and alopecia after immunization,[13] as well as providing further assurance about the safety of HepB[9,10] and hepatitis A vaccines.[11] Other strengths include the timely availability of data from a surveillance system that derives data from the entire US population.[15]

Neonatal Death Reports After Hepatitis B Vaccine Given Alone, US VAERS Reports, January 1, 1991, Through October 5, 1998 (n = 18)*

Case No./Age at Vaccine, d/Age at Death, d/Cause of Death	Birth Weight, g	Medical History†	Salient Findings at Autopsy
1/13/15/SIDS	. . .	. . .	. . .‡
2/27/28/SIDS	3203	. . .	. . .
3/13/15/SIDS	2608	Found with blood around nose	Moderate fatty change of liver
4/19/20/SIDS	2835	Found with blood around nose	Thymic cyst, right lobe; lungs: recent focus alveolar hemorrhage, focus squamous aspiration; liver: moderate microvascular changes, extramedullary hematopoiesis with focal neutrophilia; kidneys: urate deposit in collecting ducts, focal nephrosclerosis; adrenal glands: involution with focal calcification; pancreas: nesidiodysplasia; thymus: moderate eosinophil deposition
5/4/6/SIDS	. . .	. . .	
6/16/17/Intracerebral hemorrhage, sepsis?	2807	Baby fed, then choked, milk seen coming from nose, stopped breathing, went limp, parent "shook" child; CPR done, respirator support, declared "brain dead" 1-2 d later, respirator turned off; provisional diagnosis: subarachnoid hemorrhage ("CSF bloody" per family physician)	. . .§
7/14/24/SIDS	2523	Found with blood in mouth and nose; co-slept with mother in bed	. . .
8/1/16/*Enterobacter cloacae* pneumonia, acute necrotizing myocarditis	2438	2 h after vaccination: leg swollen, fever, vomiting, bloody diarrhea, taken to emergency department, Rx: fluid replacement, acetaminophin. 5 d later, fever (temperature, 40°C), tachypnea, hospitalized, Rx: antibiotics; died 11 d later: lung, nasopharynx, central line cultures: *E cloacea*–positive	Heart: acute necrotizing myocarditis, hypertrophy; lungs: pneumonia with *E cloacae*†, pleural adhesions, interlobar, ureter: focal stenosis, left; CNS: right lateral ventricle hemorrhage involving choroid plexus
9/6/8/Persistent fetal circulation, pneumonitis/ bronchopneumonia, aspiration of amniotic sac contents	4252	Congenital fracture of right clavicle; facial nerve palsy; amniotic membrane ruptured 12 h prior to birth; intermittent fever?	Persistent fetal circulation; lungs: pneumonitis/bronchopneumonia, aspiration of amniotic sac contents (possibly infected); congenital fracture right clavicle, facial nerve palsy
10/4/24/SIDS	4678	. . .	Lungs: occasional intra-alveolar hemorrhage; small bowel: autolytic changes; cerebellum: persistent external granular cell layer

In a previous study, we reviewed 1991 to 1994 VAERS data that revealed 6 neonatal deaths after HepB vaccination.[9] These deaths did not seem to be causally related to HepB immunization.[9] Recently, in response to an inquiry from the Institute of Medicine, we reviewed neonatal deaths after HepB vaccination reported to VAERS for the years 1991 to 1998. This updated review includes all US death reports after HepB vaccine given alone (rather than simultaneously with other vaccines) in neonates (aged 0-28 days), excluding duplicate and foreign reports.

CASE REPORTS

From January 1, 1991, through October 5, 1998, a total of 1771 neonatal (aged 0-28 days) events after receipt of HepB vaccine were reported to VAERS. Eighteen were death reports (**Table**). There were no reports of neonatal deaths in 1991, 1 death in 1992, 7 deaths in 1993, none in 1994 and 1995, 6 deaths in 1996, and 2 each in 1997 and 1998.

Neonatal deaths were reported in 8 boys and 9 girls (sex was not reported in 1 instance). The mean age at vaccination was 12 days (age range, 1-27 days). The median time from vaccination to onset of symptoms was 2 days (range, 0-20 days), and median time from onset of symptoms to death was 0 days (range, 0-15 days). The mean birth weight of the neonates (n = 15) was 3034 g (range, 1828-4678 g). Four cases were reported from New Hampshire, 3 from Pennsylvania, 2 from Texas, and 1 case each from California, Florida, Illinois, Maryland, Minnesota, Missouri, New York, South Carolina, and Virginia. Of 16 reports that included the vaccine manufacturer and lot number, only 2 cases received a dose from the same vaccine brand and lot; these deaths were diagnosed as sudden infant death syndrome (SIDS), and both cases resided in the same state. Cases were reported by physicians (n = 8), nurses (n = 4), state immunization program staff (n = 3), vaccine providers (unspecified) (n = 2), and a relative of the patient (n = 1).

Seventeen autopsy reports were available for review (1 case did not have an autopsy) (Table). The causes of death recorded by the medical examiner at autopsy were SIDS (n = 12); infections (1 case each of bronchopneumonia [no causative organism noted], pneumonitis/

Neonatal Death Reports After Hepatitis B Vaccine Given Alone, US VAERS Reports, January 1, 1991, Through October 5, 1998 (n = 18) (cont)*

Case No./Age at Vaccine, d/Age at Death, d/Cause of Death	Birth Weight, g	Medical History	Salient Findings at Autopsy
11/23/29/ Bronchopneumonia	2637	"Died suddenly"	Lungs: broncopneumonia (no organism specified); fallopian tube: serous cyst
12/17/18/Accidental suffocation	3062	Nasal congestion; heat rash; co-slept with parents and sibling (aged 1 y) on sofa bed	Skull: small contusions on surface of skull (no small fracture)
13/13/22/SIDS	1829	34 wk gestation; apnea of prematurity, feeding problems of prematurity; hospitalized 18 d after birth, discharge weight 2100 g; co-slept with mother on couch, found on back on floor beside couch	Lungs: scattered acute intra-alveolar hemorrhage; cerebellum: persistent external granular cell layer
14/16/20/SIDS	3232	2 ½ h postvaccine: vomiting for 4 h, fever (temperature, 38°C), Rx: acetaminophin; next morning appeared fine 1 h before found limp, no respirations but with heartbeat, CPR, hospitalized on ventilator, ventilator support withdrawn 2 d later (no clinical signs of brain activity)	Heart: massive myocardial infarction; CNS: diffuse ischemic encephalopathy; lungs: interstitial pulmonary edema, atelectasis, small foci of hemorrhage; kidneys: early acute tubular necrosis; thymus: lymphocytic depletion; blood and urine cultures: no growth
15/1/16/SIDS	3090	Congenital epidural cyst of right maxillary sinus; "sniffles/sneezing" 2-3 d; co-slept with mom in bed, found on left side	Liver: multifocal areas of extramedullary hematopoiesis, brisk acute and chronic triaditis with focal extension through limiting plate, hepatic infarct with hyperemic border; maxilla: right epidural cerebrospinal cyst
16/1/19/SIDS	2240	35 wk gestation, perinatal jaundice; mother heavy smoker; co-slept with mother in bed, found on left side	Lungs: diffuse intra-alveolar acute hemorrhage; liver: chronic, eosinophilic triaditis; spleen: mild eosinophila; gastric/small/large bowel wall: autolysis; cerebellum/dentate nucleus: persistent external granular cell layer, mild peripheral eosinophilia
17/20/21/SIDS	3317	. . .	Liver: extramedullary hematopoiesis; heart: patent ductus arteriosus, patent foramen ovale
18/18/18/Coarctation of the aorta, mitral stenosis, chronic biventricular heart failure	2977	Seen in pediatrician's office for "well-baby" visit, no reported symptoms; child died in car on the way home from office	Heart: severe coactation of the aorta, parachute mitral valve (mitral stenosis), persistent left superior vena cava to coronary sinus, patent ductus arteriosus, patent foramen ovale, cardiomegaly, chronic biventrivular heart failure

**VAERS indicates Vaccine Adverse Event Reporting System; SIDS, sudden infant death syndrome; ellipses, data not available; CPR, cardiopulmonary resuscitation; CSF, cerebrospinal fluid; Rx, prescription given; and CNS, central nervous system.*

†*Data abstracted from initial of follow-up VAERS report.*

‡*Cause of death at autopsy per family physician (patient's name not provided on VAERS report).*

§*Cause of death as listed on death certificate (autopsy not performed).*

bronchopneumonia/aspiration of amniotic sac contents in a neonate with persistent fetal circulation, and *Enterobacter cloacea* pneumonia/sepsis); and 1 case each of intracerebral hemorrhage (presumptive diagnosis based on "bloody cerebrospinal fluid" obtained prior to death in a "shaken" baby—this was the case where an autopsy was not performed), accidental suffocation, and congenital heart disease (Table).

COMMENT

This review reveals 18 neonatal deaths after HepB vaccine reported to VAERS during an interval in which at least 86 million doses of pediatric HepB vaccine were distributed in the United States (Centers for Disease Control and Prevention, unpublished data, 1999). There were 12 reports of SIDS; coincidental SIDS deaths are expected following any infant vaccination, however, given the extent of vaccine coverage and the incidence of SIDS.[15] Three reports (bronchopneumonia, pneumonitis/bronchopneumonia/aspiration of amniotic sac contents, congenital heart disease) were initially reported as possible SIDS cases because the infant did not exhibit significant symptoms. The unexpected cause of death was determined at autopsy. At this time, there is no way to prove or disprove a causal relation between HepB immunization and SIDS using individual autopsy reports; however, in cases of unexplained infant deaths, detailed review of autopsy materials by pediatric pathologists should be considered, as causes other than SIDS may be revealed.

Since the 1991 Advisory Committee on Immunization Practices recommendation of universal HepB immunization of infants, no evidence of either an increased trend in the overall number of neonatal deaths[16] or in neonatal deaths after HepB vaccination reported to VAERS was found. From 1985 (before universal HepB immunization of infants) to 1996, the total number of neonatal deaths in the United States decreased from 7.0 to 4.8 deaths per 1000 live births.[16] During the years 1992 to 1996, the number of SIDS cases (the predominant cause of infant deaths) reported to VAERS decreased by nearly 50% (US Food and Drug Administration, unpublished data, 1998). The overall decline in neonatal deaths most likely is due to improvements in prenatal and obstetric care and advances in neonatal intensive care for low-

birth-weight infants[17-19]; the decrease in SIDS cases reported to VAERS may reflect declining SIDS rates after the American Academy of Pediatrics' 1992 recommendation to put infants to sleep on their backs[20] and the 1994 "Back to Sleep" campaign.[21] However, only an estimated 1% of SIDS cases occur in neonates.[16] These indirect indices, despite their limited interpretability, do provide some reassurance that HepB vaccination is not causing a clear increase in unexplained neonatal or infant deaths.

As events reported to VAERS may be coincidental, detailed epidemiologic studies are needed for more definitive evaluation of potential causal relationships between vaccination and serious events or death.[15]

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