

# Hypotonic–Hyporesponsive Episodes Reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998

Tracy S. DuVernoy, DVM, MPH; M. Miles Braun, MD, MPH; and the VAERS Working Group

**ABSTRACT.** *Background.* A hypotonic–hyporesponsive episode (HHE) is the sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis that occurs within 48 hours after childhood immunizations. This syndrome has been primarily associated with pertussis-containing vaccines administered to children <2 years of age, and has been estimated to occur once every 1750 diphtheria-tetanus-pertussis (DTwP) vaccinations. Previous studies of HHE were limited by small numbers of cases and, sometimes, by limited details of the event.

*Objectives.* To characterize a large number of HHE cases reported to the Vaccine Adverse Event Reporting System (VAERS), to assist clinicians in identifying HHE, and to assist researchers in investigating the risk factors, cause, and pathogenesis of this syndrome.

*Methods.* More than 40 000 VAERS reports received between 1996 and 1998 were screened for HHE by a computer algorithm and reviewed, and a telephone follow-up questionnaire was administered to the witness of HHE.

*Results.* There were 215 HHE cases, all nonfatal. The median age of onset of HHE was 4.0 months (range: 1.1–107 months). Over half of the reports (53%) concerned females. The median birth weight was 3.36 kg (range: 1.27–4.96 kg); 4.7% had a birth weight <2500 g. The median interval between vaccination and HHE was 210 minutes (range: 1 minute–2 days). Among children with HHE who were <24 months of age, the episode occurred within 5 minutes in only 8.5%, compared with 66.7% of children with HHE >24 months of age. There were no relevant findings regarding family medical history or the mothers' gestational history.

Nearly all of the children (98.6%) returned to their prevaccination state according to the telephone questionnaire; median time to return was 6 hours (range: 1 minute–4 months). The 3 children reported as not returning to their prevaccination state all had VAERS reports submitted after they developed conditions (autism, complex partial epilepsy, and developmental delays with infantile spasms) that are not known to be causally associated with immunization.

The vast majority of children (93%) with HHE received a pertussis-containing vaccine, either diphtheria-tetanus-acellular pertussis (DTaP, 28%), DTwP (11%), or diphtheria-tetanus-pertussis-*Haemophilus influenzae* type b (DTwP-HIB, 61%). During the HHE episode, 90.1% of the children had pallor and 49% had cyanosis. Because of the

HHE event, 6.8% of children had had all vaccines withheld as of the date of the interview. Of the remainder, 66.5% of children have had 1 or more subsequent vaccinations or vaccine components withheld, and 26.7% have not had any subsequent vaccinations withheld. Only 1 child was reported to have had a repeat episode of HHE, occurring after hepatitis B vaccination. From 1996 to 1998, the number of HHE reports decreased from 99 to 38, when the predominant pertussis vaccine administered to infants changed from whole-cell to acellular.

*Conclusion.* This study represents the largest published case series of children with HHE and supports the generally benign, self-limited, nonrecurrent nature of this syndrome. Although HHE has been less frequently reported to VAERS after increased use of DTaP, HHE does occur after the administration of DTaP and other nonpertussis-containing vaccines. Although most parents and pediatricians withheld the pertussis component of subsequent vaccinations, many did not, with no reported adverse events occurring in the children after the subsequent immunizations. Restricting the definition of HHE to a more narrow age range (eg, <2 years of age) is also proposed because most of the older children probably experienced vasovagal syncope rather than HHE within 5 minutes of immunization. *Pediatrics* 2000;106(4). URL: <http://www.pediatrics.org/cgi/content/full/106/4/e52>; hypotonic–hyporesponsive episode, childhood immunization, adverse event, vaccine safety.

ABBREVIATIONS. HHE, hypotonic–hyporesponsive episode; DTwP, diphtheria–tetanus–whole-cell pertussis vaccine; VAERS, Vaccine Adverse Event Reporting System; CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; DTwP-HIB, diphtheria–tetanus–whole-cell pertussis-*Haemophilus influenzae* type B vaccine; DTaP, diphtheria-tetanus-acellular pertussis vaccine; HIB, *Haemophilus influenzae* type B vaccine; OPV, oral polio virus vaccine; EEG, electroencephalogram; MMR, measles-mumps-rubella vaccine.

A hypotonic–hyporesponsive episode (HHE) is an adverse event after childhood immunization, usually with a pertussis-containing vaccine. Originally described by Hopper,<sup>1</sup> HHE has been defined as the sudden onset of limpness, decreased responsiveness, and pallor or cyanosis occurring within 48 hours after immunization, age 10 years or younger, and duration of event from 1 minute to 48 hours.<sup>2</sup> HHE has been estimated to occur once every 1750 diphtheria-tetanus-pertussis (DTwP) immunizations.<sup>3</sup> Although most HHE events have been associated with whole-cell pertussis-containing vaccines, HHE has been observed after immunization with acellular pertussis and other nonpertussis-containing vaccines.<sup>4</sup> According to sev-

From the Division of Epidemiology, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland.

Received for publication Feb 1, 2000; accepted May 22, 2000.

Reprint requests to (M.M.B.) Food and Drug Administration/Center for Biologics Evaluation and Research, HFM-220, 1401 Rockville Pike, Rockville, MD 20852-1428. E-mail: braunm@cber.fda.gov

PEDIATRICS (ISSN 0031 4005). Copyright © 2000 by the American Academy of Pediatrics.

eral small follow-up studies of HHE patients, there do not seem to be any negative sequelae of HHE.<sup>5-7</sup> Despite numerous studies of HHE, factors predisposing to HHE have not been determined, perhaps because of the small sample size of previous studies and, in some instances, their lack of detailed historical information.

The Vaccine Adverse Event Reporting System (VAERS), established in July 1990, provides a single system for the collection of reports regarding adverse events after the administration of any US-licensed vaccine.<sup>8</sup> This national, passive surveillance system, which receives 10 000 to 12 000 reports annually, is comanaged by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA).<sup>9</sup> Each reported event is coded using Coding Symbols for Thesaurus of Adverse Reaction Terms before being entered into the database.<sup>10</sup> VAERS documents events that are temporally, but not necessarily causally, related to vaccination.

This study characterizes the largest number of HHE cases reported to date. Its goal is to assist clinicians in identifying and understanding HHE and to assist researchers investigating the risk factors, cause, and pathogenesis of this syndrome.

## METHODS

All events reported to VAERS, as of April 1999, of childhood vaccinations administered between January 1, 1996 and December 31, 1998, and coded "hypotonia," "somnolence," "pallor," "apnea," "cyanosis," "syncope," or "stupor" were identified by a computer algorithm and then reviewed. Duplicate and foreign reports were excluded, as were any reports that mentioned urticaria, anaphylactoid reaction, seizure activity immediately preceding the hypotonic state, normal skin color throughout the event, or an interval from vaccination to HHE onset of >48 hours. Reports were followed up if they had the potential to meet the criteria of HHE as defined by the US Public Health Service workshop on HHE held in 1996 (see "Appendix").<sup>2</sup>

The reporter of the adverse event (generally a health care provider) was telephoned. Permission was obtained from the reporter allowing us to administer our questionnaire to the parent, legal guardian, or relative of the child who suffered the adverse event. If permission was not granted by the reporter, no further attempt was made to contact the parents. If telephone contact was unsuccessful, a letter was mailed to the parents at their last known address requesting voluntary participation in our study. When the reporter of the adverse event was the child's parent, the parent was contacted directly.

A questionnaire was administered by telephone to the person who witnessed the potential HHE event. Persons interviewed were advised that all information obtained would be kept strictly confidential and that their participation was entirely voluntary. The questionnaire sought the following information: signs and symptoms of the event, the vaccines administered before the event, medications administered around the time of vaccination, previous medical history of the child, family medical history, and details pertaining to gestation and delivery of the child. Three of the interviews were administered in Spanish by a native Spanish speaker. In addition, the mother of 1 potential case was deaf; the questionnaire was submitted to her and returned via e-mail.

A pilot study using a group of 20 potential cases was initially conducted, and because only minor revisions in the questionnaire resulted, the pilot data have been included in our study. The questionnaire data were double-entered and analyzed using the Epi-Info (CDC, Atlanta, GA) software package.

## RESULTS

### Overview

We attempted to follow-up on 435 reports of possible HHE submitted to VAERS. Permission to fol-

low-up with the parent of the child who experienced an HHE-like episode was granted by 400 of 403 reporters contacted (99.3%); 25 parents were the reporter of the event, and 7 reports did not list a reporter. We were unable to follow up on 123 reports; 104 parents could not be contacted, and 16 parents and 3 reporters declined our request for participation in this study. Of the 331 parents that we were able to contact, 312 telephone interviews (94.3%) were completed. Among the 312 telephone interviews, 91.6% of the respondents were the mother of the child (biologic, adoptive, foster, or step-mother), 5.6% were the father, and 2.8% of the respondents were the grandmother of the child. The episodes of 215 of 312 children (69%) met the case definition of HHE. The median follow-up time from the onset of HHE to telephone contact with the witness of the event was 16.5 months (range: 3.5-38.2 months).

Among the children with HHE, 122 (57%) received a diphtheria-tetanus-pertussis-*Haemophilus influenzae* type B vaccination (DTwP-HIB), 56 (26%) received diphtheria-tetanus-acellular pertussis (DTaP), 22 (10%) received DTwP, and 15 (7%) received another vaccination that did not contain pertussis antigen; 67% received a whole-cell pertussis-containing vaccine.

Ninety-nine of 215 reports (46.3%) of HHE occurred after the simultaneous administration of 3 vaccines; the most common combination was hepatitis B, polio (oral or injectable), and DTwP-HIB. The remaining children received 1, 2, or 4 different vaccines and 1 child received 5 vaccinations. Among the 200 individuals who received a pertussis-containing immunization (whole-cell or acellular), 55% of the HHE episodes occurred after the first vaccination within the childhood series of 5, 22% followed the second immunization, 14% followed the third, 7% followed the fourth, and 2% of the reports occurred after the fifth vaccination.

The largest number of reports of HHE (Fig 1) were observed during 1996 ( $n = 99$ ), with reports declining in 1997 ( $n = 78$ ), and 1998 ( $n = 38$ ). The proportion of HHE cases reported as having had a whole-cell pertussis vaccine declined from 88.9% (88/99) in 1996, to 62.8% (49/78) in 1997, and to 15.8% (6/38) in 1998. During the same 3-year time period, the per-

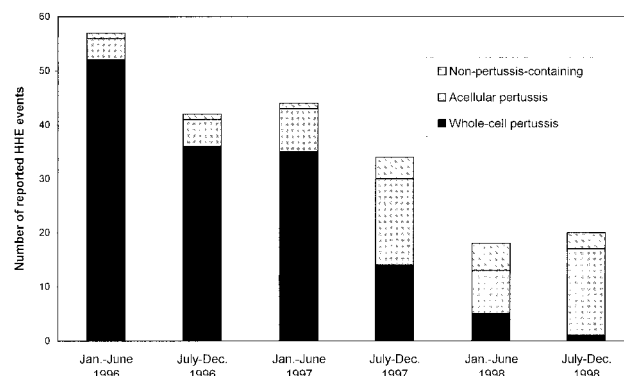


Fig 1. Events meeting the definition of HHE reported to VAERS, 1996-1998 ( $n = 215$ ).

centage of the total number of annual HHE reports involving DTaP increased from 9.1% in 1996 to 63.2% in 1998, while annual reports of HHE after a nonpertussis-containing vaccine increased from 2% to 21% during this same period.

The majority of HHE episodes (84.2%) occurred among infants <1 year of age; 22 (10.2%) were in children 1 to 2 years of age, and 12 (5.6%) were in children 3 to 9 years of age. Of 215 HHE reports, 170 (79.1%) occurred in children 6 months of age and younger; most reports of HHE were observed in children 1 to 2 months of age (Fig 2). The youngest vaccine recipient with HHE was 1.1 months of age and received only a hepatitis B vaccination. Of children receiving a pertussis-containing vaccination (DTwP-HIB, DTwP, or DTaP), the minimum age at vaccination was 1.5 months. Whole-cell pertussis products were involved in one half or more of the HHE events among individuals in the 3- to 4-month (68.1%), 5- to 6-month (81.3%), and 7- to 8-month (50.0%) age groups. A second, much smaller peak of reports involving whole-cell vaccine occurred within the 13- to 14-month and 15- to 16-month age groups.

The interval from vaccine administration to the observed HHE event ranged from 1 minute to 48 hours (Fig 3). Of 215 reports, 174 (82.1%) occurred within 12 hours after vaccination, with a peak (70.8%) occurring at <6 hours. HHE events after the administration of whole-cell pertussis vaccines accounted for 71.8% of the reports at <12 hours; acellular reports accounted for 23.0% and nonpertussis-containing made up 5.2%.

Figure 4 shows the 12-hour interval from pertussis vaccine administration to HHE onset. HHE reports associated with whole-cell pertussis vaccination showed a peak (37.8%) 3 to 4 hours after vaccination. In contrast, HHE events associated with acellular pertussis vaccination peaked in the first hour (41.9%) postimmunization.

### Clinical Signs

Clinical signs within 48 hours postimmunization, in addition to limpness and hyporesponsiveness reported by observers of the HHE cases, are listed in Table 1. More children who received nonpertussis-containing vaccines reported seizure activity after HHE than those who received whole-cell pertussis

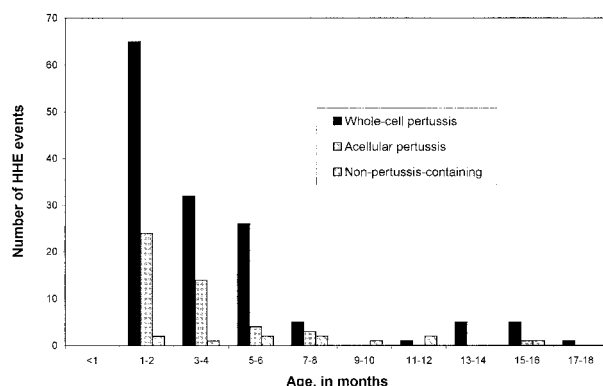


Fig 2. HHE events among children 18 months old and younger, by age and vaccine type ( $n = 197$ ).

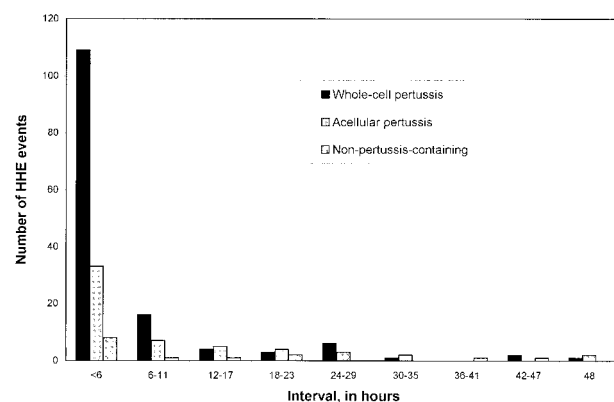


Fig 3. Time interval from vaccine administration to HHE onset ( $n = 212$ ).

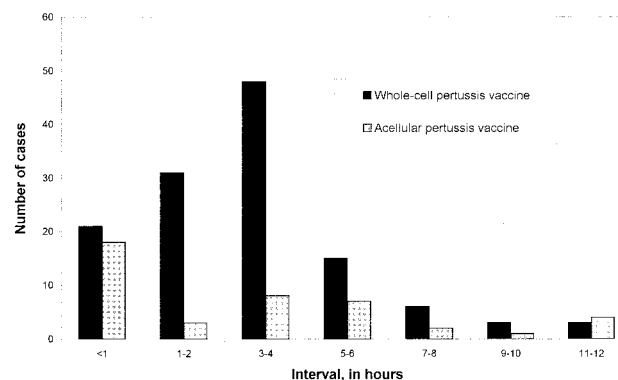


Fig 4. Time from vaccine administration to HHE onset for cases occurring within 12 hours after administration of a pertussis-containing vaccine.

immunization (13.3% and 4.9%, respectively). The median age of the children who received nonpertussis-containing vaccinations and seized was 7.5 months, compared with 7.3 months for those children who received whole-cell pertussis immunizations. Only 3 of the children had their seizure activity witnessed by a health care professional. Among the 14 persons with post-HHE seizures, 4 had documented fevers; the median temperature was 39.7°C. One 6-year-old child seized after head trauma during his hypotonic phase and the causes of the afebrile seizure activity of the remaining 9 children were unexplained.

### Recurrent Seizure Activity

Respondents indicated that of the 14 children who seized after HHE and within 48 hours of vaccination, 3 children had subsequent seizure activity. The mother of a 7-month-old girl reported that her HHE episode occurred 2 hours after her third DTaP, *Haemophilus influenzae* type B (HIB), and oral polio virus (OPV) vaccinations. The infant then had 3 afebrile seizure episodes within 24 hours after her HHE event. Subsequently she had 2 normal electroencephalograms (EEGs). She had a febrile seizure episode 1 month after the HHE event and has remained seizure-free for at least 12 months. Another child, a 4-month-old boy, had a fever of 39.4°C to 40.6°C, 3 seizures, and was hospitalized in the 12 hours after his HHE event. An EEG study was not obtained. The



**TABLE 1.** Clinical Signs Within 48 Hours Postimmunization in Children With HHE

Clinical Signs of HHE Postimmunization	Whole-Cell Pertussis (n = 144) Percentage	Acellular Pertussis (n = 56) Percentage	Nonpertussis-Containing (n = 15) Percentage
Rash	10.1	2.0	14.3
Diarrhea	13.3	9.8	16.7
Wheezing	5.9	3.7	0
Seizure activity*	4.9	8.9	13.3
Fever	44.2	25.0	35.7
Median peak degrees (°C)	39.4	39.1	39.2
Skin color			
Pallor	92.9	92.2	64.3
Cyanosis	49.6	51.0	50.0
Both	39.6	39.3	13.3
Vomiting			
Before event	11.9	12.5	6.7
After event	6.3	12.5	20.0
Abnormal cry			
Before event	32.4	44.4	35.7
After event	16.9	22.2	21.4

\* All seizures occurred posthypotonia.

vaccinations that had been administered to this child included his second DTwP-HIB, second hepatitis B, and his first OPV. At follow-up, it was reported that this child experienced occasional febrile seizures for 5 months after HHE; however, 1 year after the HHE episode, he had been seizure-free for >9 months. The third child, an 8-month-old boy, experienced HHE 44 hours after his third hepatitis B immunization. Immediately after HHE, the child had an afebrile seizure. He had an abnormal 24-hour ambulatory EEG and was diagnosed with complex partial epilepsy 1 month after his reported HHE episode. This is the only child among the 14 children with seizures post-HHE who was diagnosed with a seizure disorder after the HHE event. The child continues to experience seizures despite anticonvulsant therapy. During telephone follow-up 8 months after the HHE event, the boy's mother indicated that he was developmentally normal. However, she reported 15 months post-HHE that he was beginning to regress developmentally.

Two other children among the 215 children with HHE (1.4%) were reported to have a diagnosis of epilepsy post-HHE. One child's VAERS report of HHE was submitted 1½ years after the event, around the time of her epilepsy diagnosis. At 2½ years post-HHE, this child is slowly being taken off anticonvulsants. The other child was diagnosed with epilepsy 1 month after his HHE event. His VAERS report preceded his diagnosis of epilepsy. This boy has been taken off of anticonvulsants and has been seizure-free for over 2 years. In addition, another child was diagnosed with epilepsy before the HHE event. Among the 4 children in our study with a diagnosis of epilepsy, the boy with complex partial epilepsy was the only child with seizure activity that occurred within 48 hours of immunization.

#### Other Medical History

Circulatory and cardiac problems and breath-holding spells were infrequently (<4%) reported to occur in the children who had HHE.

Among the group with HHE, 12 children (5.6%)

had a history of syncope according to the respondents but none of the fainting episodes were associated with vaccination. The most common reason reported for syncope was either injury or pain (eg, venipuncture).

#### Description of Children With HHE

The characteristics of children with HHE can be found in Table 2. More than one half were female (53%). The median birth weight was 3.4 kg; only 4.7% had a birth weight <2500 g. Only 1 child was a very low birth weight infant (<1500 g). The median age at onset of HHE after all vaccines was 4 months, but was 9.3 months for the group who had received a nonpertussis-containing vaccine.

Nearly all respondents (98.6%) indicated that their children had returned to normal after the HHE event; however, according to the respondents, 3 children did not. Of the 3 children, 1 boy was diagnosed with autism >16 months after his HHE event; the VAERS report of HHE in this child was submitted by his mother around the time of this boy's diagnosis with autism. Six hours after immunization with DTwP, OPV, HIB, and hepatitis B at 6 months of age, this boy began exhibiting signs and symptoms of HHE and had a fever of 39.4°C. At an unspecified interval after this HHE episode, the child began banging his head and rocking back and forth, and at 2 years of age, he did not speak. A diagnosis of autism was made at that time. All subsequent immunizations are being withheld from this child. The second child was diagnosed with infantile spasms at 6½ months of age, 2 weeks before her HHE event, which occurred 4 hours after her immunizations with pediatric diphtheria-tetanus vaccine, HIB, and hepatitis B. Because of the diagnosis of infantile spasms, the pertussis component of her vaccination was withheld. Eight months after HHE, the mother reported that the child still exhibited infantile spasms along with a lower level of mental development post-HHE compared with pre-HHE. The child's mother believed that her daughter had not returned to normal. Further immunizations are also withheld

**TABLE 2.** Characteristics of HHE Reports to VAERS Based Upon Type of Vaccine Administered, 1996–1998

Characteristics	Whole-Cell Pertussis <i>n</i> = 144	Acellular Pertussis <i>n</i> = 56	Nonpertussis- Containing Vaccine <i>n</i> = 15	Total <i>n</i> = 215
Sex				
% male	45.1	50.0	53.3	47
% female	54.9	50.0	46.7	53
Median birth weight, in kg	3.4	3.4	3.3	3.4
Range	1.3–4.9	1.6–4.9	2.4–3.9	1.3–4.9
Median age at onset of HHE, in mo	3.9	4.0	9.3	4.0
Range	1.5 mo–6 y	1.8 mo–6 y	1.1 mo–9 y	1.1 mo–9 y
% who returned back to prevaccination state	99.3	100	86.7	98.6**
Median time to return, in h	6	10	24	6
Range	5 min–4 mo	1 min–14 d	30 min–3 d	1 min–4 mo
% of cases who received acetaminophen*	64.0	59.3	20.0	58.9
% of events for which health care was sought	76.4	85.7	86.7	79.5
Median time to evaluation, in min	27.5	15	30	22.5
% with previous AE† postimmunization	2.8	0	20	3.3
% with subsequent AE postimmunization	0	0	15.3††	.9
% who have had some vaccinations withheld after HHE event	81.1‡‡	63.6§§	40	73.3
% with history of allergies‡	31.9	25.0	26.7	29.8
% with a negative change in overall level of development post-HHE§	3.7	0	6.7	2.9
% of cases who were ever hospitalized before HHE event	11.1	8.9	26.7	11.6
% of patients delivered by cesarean section	22.5	23.2	13.3	22.1
% of patients remaining in the hospital because of medical reasons after birth	9.8	19.6	6.7	12.1
Median age of mother at parturition, in y	29.5	28.5	28	29
Range	16–42	17–40	20–36	16–42
% of biologic mothers with medical problems during gestation#	19.4	16.1	20	18.6

\* Medication (Tylenol or Temptra) was given before onset of HHE.

† Adverse event.

‡ Includes medication, food, environmental, and/or other (insects, animals) allergies.

§ Parents were asked whether their child's overall level of development (includes mental and physical) had changed in a negative way post-HHE in comparison to pre-HHE.

|| Does not include immediate hospitalization following birth.

||| Prematurity not included.

# Includes diabetes, high blood pressure, or epilepsy.

\*\* Three cases did not return back to normal according to the respondents. One child was diagnosed with a seizure disorder post-HHE, 1 child was diagnosed with autism, and the third child demonstrated a decreased level of mental development and concomitant infantile spasms.

†† *n* = 2. One child exhibited seizure activity after vaccinations given at 1 year of age. The other child experienced hypotonia and pallor subsequent to his third hepatitis B immunization.

‡‡ *n* = 107. Most common vaccine withheld was pertussis (79.4%).

§§ *n* = 35. Most common vaccine withheld was pertussis (77.1%).

||| *n* = 6. Most common vaccine withheld was hepatitis B (33.3%) and all vaccines (33.3%).

from this child. The third child is the 8-month-old boy diagnosed with complex partial epilepsy 1 month after his HHE episode. The VAERS report for this child was completed by a health care professional 5 months after the event. It was reported that no subsequent immunizations would be withheld from this child, although he did have a seizure after his DTaP, measles-mumps-rubella vaccine (MMR), and varicella vaccinations at 1 year of age.

Only 3.3% of the children had experienced a vaccine adverse event before HHE. The 7 adverse events were fever (1), pallor (1), somnolence (2), hypotonia (2), and seizure activity (1). Of the children who received subsequent vaccinations, <1% experienced a vaccine adverse event after the reported HHE episode. One child who developed HHE after his second hepatitis B immunization experienced a similar HHE event after his third hepatitis B vaccination at 6 months of age.

Of the children with HHE, 148 (73.3%) had some

subsequent vaccinations or vaccine component withheld by their parents or their physicians. The most common vaccine withheld was pertussis (whole-cell or acellular; 84.4%). Of the 124 children for whom a pertussis-containing vaccination was initially withheld, 12 (9.7%) subsequently were immunized with DTaP; adverse events were reported for none of these children after subsequent DTaP immunization.

Nearly all of the respondents (94.6%) reported that their children's overall level of development remained unchanged after the HHE event. Developmental improvement was reported by 2.5% of respondents and 2.9% believed that their children's overall level of development had been adversely affected.

Table 3 lists the 15 HHE events (7%) reported to VAERS after the administration of nonpertussis-containing vaccines. The most common vaccine administered to this group was hepatitis B (8/15; 53.3%), given singly or in combination with other vaccines.

**TABLE 3.** Characteristics of HHE Reports to VAERS After Administration of Nonpertussis-Containing Vaccine(s), 1996–1998 (*n* = 15)

Vaccine(s) Administered	Age (Months)	Sex	Interval to HHE (Minutes)†	Return to Normal‡	Previous Adverse Event§	Vaccines Withheld
Hepatitis B	1.1	F	180	3600	No	HepB
Hepatitis B	1.3	M	5	30	No	None
Hepatitis B	3.1	M	300	4320	No	HepB
Hepatitis B	7.8	M	2640	No¶	No	None
Hepatitis B	9.3	F	1200	360	No	None
Hepatitis B	85.8	F	5	60	Pallor	None
Hepatitis A	107.5	M	Unknown	4320	No	HepA
IPV	6.6	F	45	60	No	All
Pediatric DT	15.6	F	900	2160	Seizure	DT and P
Varicella	12.3	F	1200	1320	No	None
Varicella	19.7	M	2460	120	No	None
MMR, HIB	12.8	M	600	4320	No	None
DT, HepB, HIB	7.6	F	240	No#	No	All
OPV, HepB, HIB	6.9	M	1	1440	No	None
*DT, OPV, MMR	60.8	M	60	2160	Somnolence	None

HepB indicates hepatitis B vaccine; IPV, injectable polio virus vaccine; DT, diphtheria and tetanus toxoid.

\* Child also received purified protein derivative.

† Time in minutes from vaccine administration to when HHE was first noticed.

‡ Time in minutes for the child to return to their prevaccination state after the HHE event as determined by the respondent.

§ Did the patient have a similar adverse event after vaccinations before this described event? If yes, what symptom(s) was(were) evident?

¶ A list of subsequent vaccine(s) withheld from the patient after the HHE event.

# Seizure disorder diagnosed post-HHE.

# Child exhibits a decreased level of development in combination with preexisting infantile spasms.

Six children received a solo hepatitis B vaccination; 5 of these reports were among children <1 year of age.

A description of children older than 2 years of age who experienced HHE postimmunization can be found in Table 4. The median time from immunization to HHE was 5 minutes (range: 1 minute–18.5 hours) in this older age group, compared with 215 minutes (range: 1 minute–48 hours) for children 2 years of age and younger.

#### Family Medical History

Respondents were queried regarding their family's and their own medical history. Over 37% of the biologic mothers reported a history of fainting during their lifetime; only 13.4% of the biologic fathers reported this same history. Over one quarter of the biologic mothers had a history of either medication (27.4%) or any other type of allergy (27.8%). In comparison to the biologic mothers, biologic fathers and full and half siblings reported much lower percent-

ages of medication allergies (12.6%, 18.6%, and 6.3%, respectively) but similar results regarding any other allergies. Approximately 18.4% of biologic mothers and 4.8% of biologic fathers reported physician-diagnosed migraines. Seizure activity, breath-holding spells, and heart problems were infrequently (all <5%) reported for family members.

#### DISCUSSION

This study is the first descriptive epidemiologic study of a large case series of children with HHE. From July 31, 1996, when the first acellular pertussis vaccine was licensed for infants in the United States, to the end of our study period (December 31, 1998), acellular pertussis vaccines became the predominant pertussis-containing vaccines in the United States. During the time of our study (1996–1998), pertussis vaccination coverage rates were stable.<sup>11</sup> Concurrently, numbers of HHE reports to VAERS decreased from 99 in 1996 to 38 in 1998. This decrease could

**TABLE 4.** Characteristics of HHE Events Among Children Older Than 2 Years of Age Reported to VAERS, 1996–1998 (*n* = 12)

Age at Onset (Months)	Sex	Vaccines Administered	Interval to HHE (Minutes)*	Return to Normal?†	Previous Adverse Event‡	Vaccines Withheld§
51.2	M	HepB, OPV, MMR, DTaP	5	1	No	None
52.6	F	OPV, MMR, DTaP	1	1440	No	None
55.7	M	HepB, OPV, MMR, DTwP-HIB	2	240	No	None
58.8	F	OPV, DTaP	1110	120	No	None
59.1	F	OPV, MMR, DTaP	1	1440	No	None
59.9	F	HepB, OPV, MMR, DTaP	1	30	No	None
60.8	M	OPV, MMR, DT, PPD	60	2160	Somnolence	None
66.0	F	OPV, MMR, DTaP	30	1440	No	None
71.9	M	OPV, DTwP	300	60	No	None
72.4	M	OPV, MMR, DTaP	5	30	No	None
85.8	F	HepB	5	60	Pallor	None
107.5	M	HepA	Unknown	4320	No	Hepatitis A

HepB indicates hepatitis B vaccine; HepA, hepatitis A vaccine; DT, diphtheria and tetanus toxoid; PPD, purified protein derivative.

\* Time in minutes from vaccine administration to when HHE was first noticed.

† Time in minutes for the patient to return to their prevaccination state after HHE event as determined by the respondent.

‡ Did the patient have a similar adverse event after vaccinations before this described event?

§ A list of subsequent vaccine(s) withheld from the patient after the HHE event.

suggest that HHE occurs less frequently after vaccination with DTaP than after whole-cell pertussis, which is similar to what has been observed in clinical trials with respect to more common adverse events, such as injection site reactions, fever, and fussiness.<sup>12–16</sup> Our finding of a decrease in HHE during a time of increasing DTaP usage is consistent with a summary by Heijbel et al<sup>4</sup> of HHE rates in 8 pertussis vaccine studies; however, the difference between DTaP and whole-cell pertussis vaccines in number of HHE reports in our study is greater than the differences summarized by Heijbel et al.<sup>4</sup> Whether the greater difference we observed is real or reflects, in some degree, reporting bias could only be determined by population-based incidence studies.

Our findings generally concur with previous studies finding a lack of long-term sequelae of HHE.<sup>3,5–7</sup> Nearly all respondents stated that their children returned to their prevaccination state relatively quickly (range: 6–24 hours) and that their overall level of development had not been adversely affected post-HHE; only 3 respondents indicated that their children did not return to normal. The 3 children were diagnosed with autism, complex partial epilepsy, and developmental delays in association with infantile spasms, respectively. In the first 2 instances, the reports to VAERS were submitted 17 months and 5 months, respectively, after HHE. In contrast, the median time from HHE to submitting a report to VAERS for the other HHE reports in our study was 5 days. It is unlikely that children not developing chronic problems would have their HHE reported to VAERS several months after the event. Therefore, the proportion of our case series (assembled from passive surveillance data) reporting chronic problems may be greater than that found in active follow-up of a cohort of children experiencing HHE. In the third child, the diagnosis of infantile spasms preceded HHE. Infantile spasms have been found not to be associated with DTwP vaccine in an Institute of Medicine review.<sup>17</sup>

The American Academy of Pediatrics<sup>18</sup> and the Advisory Committee for Immunization Practices<sup>13</sup> previously considered HHE as a contraindication to further vaccinations containing pertussis antigen; since 1991, HHE has been considered a precaution. While most parents and physicians withheld the whole-cell or acellular pertussis component of subsequent immunizations after HHE, 24.1% did not; based on the results of our telephone questionnaire, there were no reported adverse events after the subsequent immunizations. The lack of recurrent HHE within our study is consistent with 2 recent studies. One study by Vermeer-de Bondt and colleagues<sup>19</sup> reported no cases of recurrent HHE after the administration of whole-cell pertussis vaccine among 84 children who had experienced a previous HHE episode. Goodwin et al<sup>20</sup> studied 66 children who experienced HHE, 59 of whom were subsequently vaccinated with primarily acellular pertussis vaccine with no recurrent collapse. The 1 individual experiencing recurrent HHE in our study had been immunized with hepatitis B on both occasions.

Of the 215 reports of HHE on which follow-up

information was obtained, 14 indicated seizure activity after HHE and within 48 hours of immunization. Four of the 14 reported fever concomitant with the seizure; 9 were reported as afebrile, and 1 child (5 years old) seized after a fall. Only 2 of the 14 children (14.3%) had a personal or family history of febrile seizures. Febrile seizures after immunizations are considered relatively benign events.<sup>21,22</sup> There is no evidence that they develop into epilepsy,<sup>23,24</sup> and they generally remit spontaneously without specific therapy. The cumulative incidence of febrile convulsions to age 5 years is ~2% to 4%.<sup>25</sup> Previously published scientific evidence suggests that whole-cell pertussis vaccine is causally related to either febrile seizures or HHE<sup>23,24,26–28</sup> but we are unaware of published reports of the 2 adverse events combined. Only 2 children among the 9 who exhibited afebrile seizures had a recurrence of seizure activity; as described by the respondents, 1 child had subsequent febrile seizures, and 1 child (described above) was diagnosed with complex partial epilepsy.

The difference in the median time interval between immunization and the HHE event among children >2 years old (5 minutes) compared with those <2 years of age (215 minutes or 3.6 hours) is substantial and may relate to an increased proportion with vasovagal reactions among the older population. In an article describing syncope after immunization, the second most common age group for postvaccination syncope was children in the 4- to 6-year age group.<sup>29</sup> According to this study, 63.2% of the cases of syncope occurred within 5 minutes or less after immunization.<sup>29</sup> Therefore, consideration should be given to restricting the definition of HHE to a more narrow age range (eg, <2 years of age) because most of the older children may actually have experienced vasovagal syncope instead of HHE.

HHE occurred in 15 children who received a non-pertussis-containing immunization. The median age of this group of 15 children (9.3 months) was slightly older in comparison to those receiving pertussis-containing vaccines. Although vaccine or vaccine component reactions may play a role, alternative causal explanations include vasovagal syncope (as a result of injection per se), breath-holding spells, febrile reactions, transient illnesses unrelated to vaccination, or other processes.

No clues about the cause of HHE were found with regard to family medical history or the mothers' gestational history. The rate of fainting and migraine headaches among the biologic mother group is similar to the national rates; ~30% to 50% of the adult population is prone to syncope, and 20% of women have a history of migraines at any time in their lives.<sup>30,31</sup> Within our study, the 4.8% rate of migraine development in the biologic fathers is lower than the rate in women and consistent with the rate within the general male population.<sup>31</sup>

Our study has several limitations. The clinical information submitted to VAERS or obtained during telephone follow-up may not be fully accurate because parents were queried about their children's events occurring a median of 16.5 months earlier. Medical records were not obtained for this study;



however, HHE is rarely observed by health care providers and often has resolved by the time of an emergency department or office visit. Underreporting is an important feature of passive surveillance systems such as VAERS. Although there are some specific events after pertussis immunization that are legally required to be reported to VAERS, such as anaphylaxis and encephalopathy within specified time frames after vaccination, HHE is not one of these specified events. According to Rosenthal and Chen,<sup>32</sup> the percentage of HHE episodes that are reported to VAERS after immunization with DTwP may be as low as 3%. Underreporting would be expected to bias a case series such as ours if the underreporting were related to characteristics that we analyzed. For example, parents may be more inclined to report HHE if their children develop a chronic condition. The long duration between HHE and VAERS report for the 2 children with such conditions, compared with the other reports, may represent an example of such bias.

## CONCLUSION

This is the largest known case series of children with HHE. Our findings support the relatively benign, self-limited nature of this syndrome. Although we observed a decrease in the overall number of HHE reports from 1996 to 1998 as acellular pertussis became the predominant pertussis vaccine, HHE will continue to be reported because it also occurs after administration of vaccines other than whole-cell pertussis. Finally, consideration should be given to restricting the definition of HHE to a more narrow age range (eg, <2 years of age) because most of the older children experienced vasovagal syncope instead of HHE.

## APPENDIX

### Inclusion criteria

- Sudden onset of
  - Limpness or hypotonia
  - Reduced responsiveness or hyporesponsiveness
  - Pallor or cyanosis (or failure to observe or recall skin coloration)
- Age <10 y
- Onset of event within 48 h of vaccination
- Duration of episode from 1 min to 48 h

### Exclusion criteria

- Known cause of above signs (eg, postictal)
- Urticaria, wheezing, or anaphylaxis during episode
- Sleep
- Normal skin coloration throughout episode

## ACKNOWLEDGMENTS

This research was supported in part by the appointment of Dr DuVernoy to the Research Participation Program at the Center for Biologics Evaluation and Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the FDA.

We thank Drs Robert Ball, Zarifa Reed, Robert Wise, and Manette Niu for critical review of the manuscript.

We also greatly appreciate the efforts of the VAERS Working Group for their dedication to the maintenance of VAERS. The members of the VAERS Working Group include: Susan Ellenberg, Suresh Rastogi, Robert Wise, Manette Niu, Frederick Varricchio, Robert Ball, Carol Krueger, David Davis, Linda Silvers, and Phil Perucci (FDA); Robert Chen, Gina T. Mootrey, Penina Haber, Vitali Pool, Wendy Wattigney, Tara Strine, Robert Pless, and Jane

Seward (CDC); and Vito Caserta and Geoffrey Evans (Health Resources and Services Administration).

We also gratefully appreciate the efforts of Dr Rosalie Trevejo to design the initial questionnaire.

## REFERENCES

1. Hopper JMH. Illness after whooping cough vaccination. *Med Officer.* 1961;106:241–244
2. Braun MM, Terracciano G, Salive ME, et al. Report of a US Public Health Service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. *Pediatrics.* 1998;102(5). URL: <http://www.pediatrics.org/cgi/content/full/102/5/e52>
3. Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics.* 1981;68:650–659
4. Heijbel H, Ciofi degli Atti M, Harzer E, et al. Hypotonic hyporesponsive episodes in eight pertussis vaccine studies. *Dev Biol Stand (Basel).* 1997; 89:101–103
5. Baraff LJ, Shields WD, Beckwith L, et al. Infants and children with convulsions and hypotonic-hyporesponsive episodes following diphtheria-tetanus-pertussis immunization: follow-up evaluation. *Pediatrics.* 1988;81:789–794
6. Gold R, Scheifele D, Halperin S, et al. Hypotonic-hyporesponsive episodes in children hospitalized at 10 Canadian pediatric tertiary-care centres, 1991–1994. *Can Comm Dis Rep.* 1997;23:73–77
7. Blumberg DA, Lewis K, Mink CM, Christenson PD, Chatfield P, Cherry JD. Severe reactions associated with diphtheria-tetanus-pertussis vaccine: detailed studies of children with seizures, hypotonic-hyporesponsive episodes, high fevers, and persistent crying. *Pediatrics.* 1993;91:1158–1165
8. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine.* 1994;12:542–550
9. Niu MT, Salive ME, Ellenberg SS. Post-marketing surveillance for adverse events after vaccination: the national Vaccine Adverse Event Reporting System (VAERS). MEDWATCH Continuing Education article, November 1998
10. Food and Drug Administration. *COSTART—Coding Symbols for Thesaurus of Adverse Reaction Terms.* 4th ed. Rockville, MD: Food and Drug Administration; 1994
11. Centers for Disease Control and Prevention. Notice to readers: national vaccination coverage levels among children aged 19–35 months—United States, 1998. *MMWR Morb Mortal Wkly Rep.* 1999;48:829–830
12. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics.* 1995; 96(suppl):557–566
13. Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 1997;46(RR-7):1–25
14. Deloria MA, Blackwelder WC, Decker MD, et al. Association of reactions after consecutive acellular or whole-cell pertussis vaccine immunizations. *Pediatrics.* 1995;96(suppl):592–594
15. Blumberg DA, Mink CM, Cherry JD, et al. Comparison of acellular and whole-cell pertussis-component diphtheria-tetanus-pertussis vaccines in infants. *J Pediatr.* 1991;119:194–204
16. Rosenthal S, Chen R, Hadler S. The safety of acellular pertussis vaccine vs whole-cell pertussis vaccine: a postmarketing assessment. *Arch Pediatr Adolesc Med.* 1996;150:457–460
17. Institute of Medicine. *Adverse Effects of Pertussis and Rubella Vaccines.* Washington, DC: National Academy Press; 1991
18. American Academy of Pediatrics. Appendix II. In: Peter G, ed. 1997 *Red Book: Report of the Committee on Infectious Diseases.* 24th ed. Elk Grove Village, IL: American Academy of Pediatrics; 1997:677
19. Vermeer-de Bondt PE, Labadie J, Rümke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. *Br Med J.* 1998;316:902–903
20. Goodwin H, Nash M, Gold M, Heath T, Burgess M. Vaccination of children following a previous hypotonic-hyporesponsive episode. *J Paediatr Child Health.* 1999;35:549–552
21. Hirtz DG, Nelson KB, Ellenberg JH. Seizures following childhood immunizations. *J Pediatr.* 1983;102:14–18
22. Prensky AL. History of convulsions and use of pertussis vaccine. *J Pediatr.* 1985;107:244–245
23. Golden GS. Pertussis vaccine and injury to the brain. *J Pediatr.* 1990;116: 854–861



24. Shields WD, Nielsen C, Buch D, et al. Relationship of pertussis immunization to the onset of neurologic disorders: a retrospective epidemiologic study. *J Pediatr*. 1988;113:801–805
25. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med*. 1998;338:1723–1728
26. Cherry JD, Holtzman AE, Shields WD, et al. Pertussis immunization and characteristics related to first seizures in infants and children. *J Pediatr*. 1993;122:900–903
27. Walker AM, Jick H, Perera DR, Knauss TA, Thompson RS. Neurologic events following diphtheria-tetanus-pertussis immunization. *Pediatrics*. 1988;81:345–349
28. Wentz KR, Marcuse EK. Diphtheria-tetanus-pertussis vaccine and serious neurologic illness: an updated review of the epidemiologic evidence. *Pediatrics*. 1991;87:287–297
29. Braun MM, Patriarca PA, Ellenberg SA. Syncope after immunization. *Arch Pediatr Adolesc Med*. 1997;151:255–259
30. Manolis AS, Linzer M, Salem D, Estes NA III. Syncope: current diagnostic evaluation and management. *Ann Intern Med*. 1990;112:850–863
31. Waters WE, O'Connor PJ. Prevalence of migraine. *J Neurol Neurosurg Psychiatry*. 1975;38:613–616
32. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *Am J Public Health*. 1995;85:1706–1709

## Hypotonic–Hyporesponsive Episodes Reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998

Tracy S. DuVernoy, M. Miles Braun and the VAERS Working Group  
*Pediatrics* 2000;106:e52

### Updated Information & Services

including high resolution figures, can be found at:  
<http://pediatrics.aappublications.org/content/106/4/e52>

### References

This article cites 26 articles, 9 of which you can access for free at:  
<http://pediatrics.aappublications.org/content/106/4/e52#BIBL>

### Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):  
**Infectious Disease**  
[http://www.aappublications.org/cgi/collection/infectious\\_diseases\\_sub](http://www.aappublications.org/cgi/collection/infectious_diseases_sub)  
**Vaccine/Immunization**  
[http://www.aappublications.org/cgi/collection/vaccine:immunization\\_sub](http://www.aappublications.org/cgi/collection/vaccine:immunization_sub)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Hypotonic–Hyporesponsive Episodes Reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998**

Tracy S. DuVernoy, M. Miles Braun and the VAERS Working Group  
*Pediatrics* 2000;106:e52

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/106/4/e52>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2000 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

## American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

