Report of a US Public Health Service Workshop on Hypotonic–Hyporesponsive Episode (HHE) After Pertussis Immunization

M. Miles Braun, MD, MPH*; Gina Terracciano, DO, MPH‡; Marcel E. Salive, MD, MPH*; Dean A. Blumberg, MD§; Patricia E. Vermeer-de Bondt, MD‖; Harald Heijbel, MD¶; Geoffrey Evans, MD#; Peter A. Patriarca, MD*; and Susan S. Ellenberg, PhD*

ABSTRACT. Hypotonic–hyporesponsive episode (HHE) is a term used to describe a somewhat heterogenous group of clinical disorders that have been reported primarily in association with whole-cell pertussis vaccination. A 1991 review by the Institute of Medicine determined that the evidence available was indeed consistent with a causal relation between whole-cell pertussis-diphtheria-tetanus immunization and HHE, but that the evidence was insufficient to indicate a causal relationship between HHE and the subsequent development of permanent neurologic damage. More recent data from clinical trials conducted in Europe suggest that HHE also occurs after vaccination with acellular pertussis vaccines.

The US Food and Drug Administration, in collaboration with the US Public Health Service, sponsored a workshop on HHE in Rockville, Maryland, on June 19, 1997. The primary goals of the workshop were to develop a case definition of HHE and to evaluate the general design and feasibility of possible studies of HHE using the federal Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. The goals of such studies would be to understand better the acute HHE event and to evaluate the possibility of long-term sequelae.

Case Definition. **There has been no generally accepted definition of HHE, and a standard definition would be useful for vaccine safety work and would potentially facilitate interstudy comparisons of the growing number of licensed vaccines containing acellular pertussis components.**

The workshop defined HHE as an event of sudden onset occurring within 48 hours of immunization, with duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age. All of the following must be present: 1) limpness or hypotonia, 2) reduced responsiveness or hyporesponsiveness, and 3) pallor or cyanosis or failure to observe or to recall skin coloration. HHE is not considered to have occurred if there is a known cause for these signs (eg, postictal), if urticaria is present during the event, if normal skin coloration is observed throughout the episode, or if the child is simply sleeping.

This inclusive (sensitive) case definition will allow investigators, through the technique of stratification according to certain characteristics (eg, time from vaccination to onset of HHE), to attempt to hone the definition and make it more specific. Refinement of the definition of HHE has been hindered by the lack of information on its pathophysiology and by the lack of pathognomonic signs, symptoms, and diagnostic tests. Another hindrance is that by the time the child presents for medical evaluation, the signs of HHE often have normalized. Moreover, different mechanisms may be involved in different individuals whose events meet this workshop's HHE definition.

Further Study of HHE. **Probably the most important question about HHE is whether it has any permanent sequelae. The workshop assessed the possible contribution VAERS-based studies could make to answering this question and found substantial methodologic problems; however, ongoing studies in Sweden and The Netherlands have the potential to provide useful information on this question. The most useful contribution of VAERS data would be in a descriptive study of HHE, with a possible case–control study of factors that may affect the risk of HHE after vaccination, rather than a study of possible permanent sequelae.**

The workshop participants felt that a detailed descriptive study of ~100 HHE events reported during a 1- to 2-year period could provide a more in-depth description of HHE cases in greater numbers than has been published previously, but the study would not address the issue of long-term sequelae of HHE. Better descriptive data may lead to new hypotheses concerning risk factors, etiology, and pathophysiology of HHE that might be evaluated further by studying subsequent cases and controls from VAERS or from other sources, depending on the hypotheses being tested.

Workshop participants agreed that the question of possible long-term sequelae of HHE may currently be best answered in studies being conducted outside of the United States. A cohort of 82 892 infants was enrolled in the Stockholm II randomized, double-blind, controlled trial of one whole-cell and three acellular pertussis vaccines in Sweden in 1993–1994. In this trial, 101 infants developed HHE after vaccination. Of these children, 100 (1 had left Sweden) were evaluated subsequently at 18 months of age, using routine screening tests of motor and cognitive development intended to detect moderate to serious developmental problems. All 100 were found to be developing normally. At older ages, when more subtle developmental problems are detectable, comparison of the physical development and neurodevelopment of

From the *Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland; ‡National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia; §Department of Pediatric Infectious Diseases, University of California at Davis Medical Center, Sacramento, California; ‖Laboratory for Clinical Vaccine Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands; ¶Vaccine Safety Project, Swedish Institute for Infectious Disease Control, Stockholm, Sweden; and #Division of Vaccine Injury Compensation, Health Resources and Services Administration, Rockville, Maryland.

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Reprint requests to (M.M.B.) Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852.

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these children with a sample of trial participants without a history of HHE should be feasible. A protocol for a study to make such a comparison at ages 5½ and 8½ years is being prepared.

In The Netherlands, a case–control study of infants who had HHE reported in 1995 is ongoing. The HHE events were detected through national surveillance linked to the health care delivery system. Growth, health, and neurodevelopment are being assessed. Data presented at the workshop concerning children with HHE reported in 1994 indicate that all 101 children followed during the second year of life (mean age, 1.5 years) were in good health and developing normally. An interesting finding of this follow-up study was the low rate of recurrent collapse (subsequent HHE occurrences) after repeat doses of pertussis vaccine.

Summary. **Despite increasingly widespread use of acellular pertussis vaccine in infants, HHE will continue to occur. The HHE definition proposed by this workshop should facilitate interstudy comparisons of HHE incidence among in the growing number of vaccines containing acellular pertussis components and perhaps of other vaccines as well. This definition also may aid study in VAERS and elsewhere of the etiology, pathophysiology, and descriptive epidemiology of HHE. Ongoing investigations in Sweden and The Netherlands have the potential to expand substantially knowledge of the possibility of long-term sequelae of HHE.** *Pediatrics* **1998;102(5). URL: http://www.pediatrics.org/cgi/content/full/102/5/e52;** ***vaccine, pertussis vaccine, acellular pertussis vaccine, hypotonic–hyporesponsive episode, collapse, vaccine safety, adverse reaction.***

ABBREVIATIONS. HHE, hypotonic–hyporesponsive episode; VAERS, Vaccine Adverse Event Reporting System.

Hypotonic–hyporesponsive episode (HHE) is a term used to describe a somewhat heterogenous group of clinical disorders that have been reported primarily in association with whole-cell pertussis vaccination. A 1991 review by the Institute of Medicine determined that the available evidence was indeed consistent with a causal relation between whole-cell pertussis-diphtheria-tetanus immunization and HHE.[1] The improved safety profile of *acellular* pertussis vaccines with respect to more common vaccine reactions such as fever and injection site inflammation, now well-documented,[2] had led some to hope that vaccine-associated HHE would become a historical curiosity. However, more recent data from clinical trials conducted in Europe suggest that HHE also occurs after vaccination with acellular pertussis vaccines.[3] Consequently, interest in HHE continues among vaccinators, investigators involved with clinical trials or with postmarketing surveillance of vaccine safety, as well as parents.[4]

The US Food and Drug Administration, in collaboration with the US Public Health Service, sponsored a workshop on HHE in Rockville, Maryland, on June 19, 1997. A list of the participants is included in the Appendix. The primary goals of the workshop were to develop a case definition of HHE and to evaluate the general design and feasibility of possible studies of HHE using the federal Vaccine Adverse Event Reporting System (VAERS).[5] The goals of such studies would be to understand better the acute HHE event and evaluate the possibility of long-term sequelae. This report summarizes the main findings of this workshop.

CASE DEFINITION

Numerous studies of adverse events after pertussis vaccination during the last several decades have described events categorized as HHE,[4,6–8] "shock,"[9,10] "collapse,"[11] "anaphylaxis/collapse,"[12] "episodes of pallor or cyanosis,"[13] and so forth. Although many of these studies' categories had clinical features in common, the studies usually did not define the categories, and it is likely that inclusion criteria varied. Indeed, there has been no generally accepted definition of HHE, and a standardized definition would be useful for vaccine safety work and would potentially facilitate interstudy comparisons of the growing number of licensed vaccines containing acellular pertussis components. The proposed HHE definition is presented in Table 1.

Inclusion Criteria

The proposed definition for HHE is a postvaccination event of sudden onset characterized by pallor (or cyanosis), limpness, and reduced responsiveness. These are the core clinical criteria reported in the literature and noted by the workshop participants with specific experience in this area. With respect to the age range at which HHE occurs, the time between vaccination and occurrence of HHE, and the duration of the episode, we chose age and time limits that were very inclusive. For example, although the vast majority of reports of HHE involve children 18 months of age or younger, our proposed age criterion is <10 years. Similarly, with respect to the time elapsed from vaccination to the onset of HHE, although the vast majority of reports involved periods of <12 hours, we set the limit at 48 hours. It is hoped that in the future, research advances may allow these criteria to be made more specific (ie, more narrow). For now, however, workshop participants appreciated the advantage of a more inclusive definition that potentially would capture additional cases of HHE.

Toward a More Refined Definition

An inclusive definition could permit investigators, through the technique of stratification according to specific characteristics (eg, time from vaccination to onset of HHE), to attempt in the future to hone the

TABLE 1. Proposed Definition of HHE

Inclusion criteria
Sudden onset of
Limpness or hypotonia
Reduced responsiveness or hyporesponsiveness
Pallor or cyanosis (or failure to observe or to 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

definition and make it more specific. Such an approach also could be useful to aid etiologic research and to permit more precise comparisons of HHE rates among different vaccines. Potential stratifications might include, for example, age <1 year, age <18 months, onset of HHE between 1 and 12 hours after vaccination, duration of HHE ≥5 minutes, and so forth.

Etiology, Pathophysiology, and Differential Diagnosis

Refinement of the definition of HHE is hindered in part by the lack of information on its pathophysiology and by the lack of pathognomonic signs, symptoms, and diagnostic tests. Another hindrance is that by the time the child presents for medical evaluation, the signs of HHE often have normalized. Workshop participants discussed in some detail possible cardiovascular, neurologic, and allergic/immunologic pathophysiologic mechanisms, with potential age-dependent host responses; however, data to support or refute these mechanisms are sparse.[4] Moreover, different mechanisms may be involved in different individuals whose events meet the proposed HHE definition.

Many clinical conditions, when occurring in the postvaccination period, may sometime be difficult to distinguish clinically from HHE: Dysfunctional neurologic or cardiovascular reactivity may lead to a *syncopal episode* with onset temporally related to the (stressful) vaccine injection; in the postinfancy period, *vasovagal reaction* is a leading cause of syncope, particularly during the 15 minutes after vaccination.[14] Arrhythmia, obstructive cardiomyopathy, aortic stenosis, or other congenital cardiac conditions may result in *insufficient cardiac output* during the fever, pain, or intense crying that sometimes follows immunization. *Cyanotic* or *pallid breath-holding spells* also may follow intense postvaccination crying or pain. The *postictal state*, when it follows nonobserved seizures, and *atonic convulsions* may mimic the limpness and hyporesponsiveness of HHE. Convulsions often are associated with fever as well as with a family history of seizures. *Deep sleep* or *narcolepsy–cataplexy* also may result in limpness and unresponsiveness. *Anaphylaxis* may produce signs similar to HHE but typically will be accompanied by skin or respiratory signs such as urticaria, angioedema, or wheezing. Many of these diagnoses, as well as others (eg, intoxication, endocrine or metabolic disorders such as hypoglycemia) can be differentiated from HHE by preceding and associated signs, subsequent clinical course, and diagnostic testing.

HHE: PROBLEMS WITH ITS NAME

Workshop participants agreed that the phrase hypotonic–hyporesponsive episode had several drawbacks as a name for events meeting the criteria noted above. First, the skin color changes of pallor and cyanosis, part of our proposed definition, are not included in the term. Second, there is a misconception, evidenced by reports to the VAERS and one published article,[15] that one "H" in HHE is an abbreviation for hypotensive. Third, the acronym HHE also can denote another neurologic condition: hemiconvulsions, hemiplegia and epilepsy.

Despite these drawbacks, nearly all the participants agreed that the term HHE should continue to be used for two main reasons. First, the term is now reasonably well established, after a period when a number of different terms had been used. Second, it is possible that with additional study, our understanding of the condition may improve, and subsequent change of the name could reflect deletions, additions, or modifications of clinical criteria.

POSSIBLE ADDITIONAL STUDY OF HHE USING VAERS

Probably the most important question about HHE is whether it has any permanent sequelae. This question has been examined in one study of 6 children followed 6 to 7 years after HHE.[7] The investigators concluded that "it is unlikely that such reactions lead to significant neurological impairment." The small size of the study, and the finding of neurodevelopmental abnormalities not considered by the authors to be significant, makes it reasonable to study further the question of possible permanent sequelae. The workshop assessed the possible contribution VAERS-based studies could make to answering the question and found substantial methodologic problems described in part below. Workshop participants found that the most useful contribution of VAERS data would be in a descriptive study of HHE, with a possible case–control study of factors that may affect risk of HHE after vaccination, but not a study of possible permanent sequelae.

VAERS

VAERS is the US passive surveillance system that receives reports of adverse events after immunization. Established in 1990, VAERS is administered by the Centers for Disease Control and Prevention and the Food and Drug Administration.[5,16,17] Approximately 50 to 100 reports to VAERS each year could be expected to include details that meet our definition of HHE.[18]

Case–Control Study of Possible Permanent Sequelae of HHE

Workshop participants discussed options for a study of long-term sequelae of HHE in VAERS. Such a study would involve identifying cases of HHE reported to VAERS since its inception in 1990. Attempts would be made to contact the parents of the children affected and, with the parents' consent, to obtain information from school, medical, and other records—as well as from the parents' observations—to try to gauge the children's development. Workshop participants highlighted several major problems with this study approach. One such problem was that assessment of the children's development, unless performed by identically administered standardized developmental examinations (extremely complex for a national study), would be so imprecise as to prevent detection of possible associations of mild to moderate developmental impairments with HHE.

Another difficult issue is the selection of appropriate controls. Controls should represent the population of children without HHE who would have been reported to VAERS had they developed HHE. A potential problem is that controls selected from VAERS may not meet this criterion. This is at least in part because VAERS is a passive surveillance system that is known to be subject to underreporting, and the degree of underreporting varies substantially with respect to the type of adverse event[19] and probably other factors. The determinants of this underreporting are not well understood. As a result, there is a real possibility of selection bias and recall bias, as well as confounding in a VAERS case–control study of possible permanent sequelae of HHE. For these, and other, reasons, workshop participants doubted whether a VAERS-based case–control study would have sufficient precision and validity to determine, for example, whether a child's problems with reading in second grade were associated with an HHE reaction in the first year of life.

Descriptive Study of HHE With Possible Case–Control Study to Identify Risk Factors

This is the approach supported by the workshop participants. The first step would involve a detailed descriptive study of approximately 100 HHE events reported during a 1- to 2-year period. Information on medical history of the child, obstetric history, family history, and so forth, also would be gathered (Table 2). Such a study could provide a more in-depth description of HHE cases in greater numbers than has been published previously, but the study would not address the issue of long-term sequelae of HHE. The descriptive data may lead to new hypotheses concerning risk factors, etiology, or pathophysiology of HHE. Such hypotheses potentially could be evaluated further by studying cases and controls reported to VAERS subsequent to those enrolled in the descriptive study, or by studying cases and controls from other sources, depending on the hypotheses being tested.

STUDY OF POSSIBLE LONG-TERM SEQUELAE OF HHE IN SWEDEN AND THE NETHERLANDS

Workshops participants agreed that the question of possible long-term sequelae of HHE may currently be best answered in studies being conducted outside of the United States.

TABLE 2. Suggested Information to Gather for Study of HHE Risk Factors*

Information included in case definition (see Table 1)
Including degree of limpness, hyporesponsiveness, and pallor or cyanosis
All vaccines administered
Posture and activity before episode
Peak temperature before and during episode, vital signs
Antipyretic administered before HHE? If so, note number of hours prior
Excessive crying or abnormal crying before HHE?
Vomiting before, during, or after HHE?
Medical and obstetric history
Developmental level before HHE event
Family history of syncope, seizures, or migraine, or HHE
Results of physical examination and laboratory/diagnostic testing
Description of method of HHE ascertainment

* Not an exhaustive list

Sweden

A cohort of 82 892 infants was enrolled in the Stockholm II randomized, double-blind, controlled trial of one whole-cell and three acellular pertussis vaccines in 1993–1994.[3] In this trial, 101 infants developed HHE after vaccination. Of these children, 100 (1 had left Sweden) were subsequently evaluated at 18 months of age using routine screening tests of motor and cognitive development that are intended to detect moderate to serious developmental problems. All 100 were found to be developing normally. At older ages, when more subtle developmental problems are detectable, comparison of the physical development and neurodevelopment of these children with a sample of trial participants without a history of HHE should be feasible. A protocol for a study to make such a comparison at 5½ and 8½ years of age is currently being prepared.

The Netherlands

In The Netherlands, a case–control study of infants who had HHE reported in 1995 is ongoing. The HHE events were detected through national surveillance linked to the health care delivery system. Growth, health, and neurodevelopment are being assessed. Data presented at the workshop concerning children with HHE reported in 1994 indicate that all 101 children followed during the second year of life (mean age, 1.5 years) were in good health and developing normally. An interesting finding of this follow-up study was the low rate of recurrent collapse (subsequent HHE occurrences) after repeat doses of pertussis vaccine.[20]

SUMMARY

Despite increasingly widespread use of acellular pertussis vaccine in infants, HHE will continue to occur. The HHE definition proposed by this workshop should facilitate interstudy comparisons of HHE incidence among the growing number of vaccines containing acellular pertussis components and perhaps of other vaccines as well. This definition also may aid study in VAERS and elsewhere of the etiology, pathophysiology, and descriptive epidemiology of HHE. Ongoing investigations in Sweden and The Netherlands are expected to expand substantially knowledge of the possibility of long-term sequelae of HHE.

APPENDIX

Workshop Participants

Bascom Anthony, MD, Food and Drug Administration, Rockville, MD; Dean Blumberg, MD, University of California–Davis, Sacramento, CA; M. Miles Braun, MD, MPH, Food and Drug Administration, Rockville, MD; Vito Caserta, MD, MPH, Health Resources and Services Administration, Rockville, MD; Robert Chen, MD, MA, National Immunization Program/CDC, Atlanta, GA; Robert Davis, MD, MPH, University of Washington & Group Health Cooperative, Seattle, WA; Susan Ellenberg, PhD, Food and Drug Administration, Rockville, MD; Geoffrey Evans, MD, Health Resources and Services Administration, Rockville, MD; Marsha Gerdes, PhD, Children's Hospital of Philadelphia, Philadelphia,

PA; Harald Heijbel, MD, Swedish Institute for Infectious Disease Control, Stockholm, Sweden; Deborah Hirtz, MD, National Institute of Neurologic Disorders and Stroke, Bethesda, MD; David Klein, PhD, National Institute of Allergy and Infectious Diseases, Bethesda, MD; Jennifer Pinto-Martin, PhD, University of Pennsylvania School of Medicine, Philadelphia, PA; Bruce Meade, PhD, Food and Drug Administration, Rockville, MD; Jeffrey Moak, MD, George Washington University School of Medicine, Washington, DC; Karin Nelson, MD, National Institute of Neurologic Disorders and Stroke, Bethesda, MD; Peter Patriarca, MD, Food and Drug Administration, Rockville, MD; Regina Rabinovich, MD, MPH, National Institute of Allergy and Infectious Diseases, Bethesda, MD; Marcel Salive, MD, MPH, Food and Drug Administration, Rockville, MD; Gina Terracciano, DO, MPH, National Immunization Program/CDC, Atlanta, GA; and Patricia Vermeer, MD, National Institute for Public Health and Environment, Bilthoven, The Netherlands.

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