Responses of Children Immunized with Capsular Polysaccharide of Hemophilus influenzae Type b, by David H. Smith, MD, et al, Pediatrics, 1973;52:637–644; and Haemophilus influenzae Type b Capsular Polysaccharide Vaccine in Children: A Double-blind Field Study of 100 000 Vaccinees 3 Months to 5 Years of Age in Finland, by Heikki Peltola, MD et al, Pediatrics, 1977;60:730–737

Comments by Georges Peter, MD

ABSTRACT OF ORIGINAL ARTICLE. One hundred forty-one children of 5 to 59 months of age were immunized with a single intramuscular dose of 0.67, 3.3, 17, or 67 μg polyribophosphate (PRP), the capsular antigen of Hemophilus influenzae, type b. The immunizations were well tolerated, particularly at doses of 0.67 to 17 μg. Antibody activity was measured by radioactive antigen binding, using 3H-labelled PRP. Doses of 3.3 and 17 μg produced significant antibody rises in nearly 90% of recipients; 0.67 and 67 μg in approximately half. The geometric mean titers were similar at three and six weeks after immunization and were greater with the middle doses.

The net antibody increase in responding children was strongly age dependent, but was not related to the preimmunization antibody concentration. Rises in serum bactericidal activity against H. influenzae type b generally accompanied rises in antibody concentration as measured by the antigen-binding assay.

ABSTRACT OF ORIGINAL ARTICLE. A recently developed Haemophilus influenzae type b capsular polysaccharide vaccine was given to 48,977 children 3 months to 5 years of age; an equal number of children receiving group A meningococcal vaccine served as controls. The protection as well as serum antibody response was strongly age dependent. Among children who had received the H. influenzae type b vaccine when 18 months of age or older, there were no cases of bacteremic disease caused by H. influenzae type b in the first year after vaccination. At the same time 11 such cases were seen in the control group of the same age, a highly significant difference. In the second year after vaccination two cases occurred in the H. influenzae type b-vaccinated group, five in the meningococcal-group A vaccinated group. No protection was seen among children who had been younger than 18 months when vaccinated, even if they received a booster dose of the vaccine.

The serum antibody response to the H. influenzae type b polysaccharide, measured by radioimmunoassay, was poor in children below 18 months of age and good in those above it. No effect of the vaccine could be seen on the nasopharyngeal carriage of H. influenzae type b, which was approximately 6% in this age group. Adverse effects of the vaccine were mild.

COMMENTARY

The introduction and widespread use of Haemophilus influenzae type b (Hib) vaccine has drastically reduced the incidence of bacterial meningitis in children and other invasive infections caused by this pathogen. This success again illustrates the immense potential of childhood immunizations. In children younger than 5 years of age during the prevaccine era, 70% of cases of bacterial meningitis were caused by Hib, and an estimated 1 in 200 children suffered invasive disease. An estimated 20,000 cases, including 10,000 to 12,000 cases of meningitis, occurred each year. While the mortality of Hib meningitis in the antibiotic era was ≤5%, Hib meningitis was a leading cause of acquired mental retardation, because neurologic sequelae occurred in 20% to 30% of survivors. In an editorial accompanying the article by Smith et al in Pediatrics in 1973, Dr Edward A. Mortimer summarized the evidence demonstrating the public health burden of Hib meningitis and concluded that “attempts to develop a safe, effective and logistically manageable immunization agent are warranted.” A quarter century later, epidemiologists from the Centers for Disease Control and Prevention reported that as a result of the vaccine-related decline in meningitis attributable to Hib, bacterial meningitis in the United States has become a disease predominately of adults rather than of infants and young children. The investigators further commented that “this achievement highlights the ultimate advantage of prevention over improvement in therapy and suggests the tremendous benefit for children throughout the world if access to the vaccine could be expanded.”

Research on an Hib vaccine had begun in the late 1960s in two independent but collaborating laboratories, directed by Drs David H. Smith and Porter.
Anderson in Boston, MA, and by Drs John B. Robbins and Rachel Schneerson at the National Institutes of Health. The vaccine immunogen was the purified Hib capsular polysaccharide, initially described as polyribophosphate and denoted as polyribophosphate, antibodies to which conferred protection against invasive disease. The results of the first Hib vaccine trial in children, performed in Salem, MA, were given in the 1973 publication in Pediatrics by Smith, Anderson, and their colleagues, and provided the basis for the subsequent large efficacy trial in Finland by Peltola et al, which was described in the 1977 publication.

Smith et al demonstrated that the Hib capsular polysaccharide was safe and immunogenic. The critical observation, however, was that antibody response was dependent on age. Whereas 87% of children older than 24 months responded to any dose of the vaccine, only 22% of infants did so. This age-dependent immunogenicity, as well as vaccine safety, was confirmed in the Finnish field trial in which 98,000 children between the 3 months and 5 years of age received either the Hib or a group A meningococcal vaccine. Vaccine efficacy correlated with the age-related immunogenicity noted previously. Vaccine was effective in preventing Hib bactereemic disease in children vaccinated at 18 months of age or older, but not in those who were younger. These findings also provided additional evidence for the protective role of serum anti-polyribophosphate antibody. Parenthetically, the primary purpose of this trial was to evaluate the efficacy of a group A meningococcal vaccine during a meningococcal epidemic in Finland, whereas the Hib vaccine served as the control vaccine.

These and subsequent studies led in 1985 to the licensure of the first Hib vaccine and resulting recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention for routine immunization of all children at 24 months of age. However, because Hib disease was most common in children in the first year of life, the demonstration of age-related immunogenicity and lack of efficacy of this first generation vaccine in infants necessitated development of a vaccine that would be effective in the first 6 months of life. Smith, Anderson, Robbins, and Schneerson continued their work, preparing conjugate Hib vaccines of the capsular polysaccharide covalently bound to a protein carrier that converted the polysaccharide hapten into a T-lymphocyte independent to a T cell-dependent antigen that would induce humoral antibody responses in young infants. In December 1987, the first of these conjugates was approved by the US Food and Drug Administration for use beginning at 18 months of age. Subsequent trials demonstrated immunogenicity and efficacy of different Hib conjugate vaccines in infants beginning as early as 2 months of age and, in late 1990, infant immunization was introduced.

The impact of these conjugate vaccines on the incidence of Hib-invasive disease in the United States has been dramatic. From 1987 to 1994, the incidence in children younger than 5 years of age decreased by >95% and prompted the Childhood Immunization Initiative goal of elimination of invasive Hib disease in young children. The occurrence of bacterial meningitis from 1986 to 1995 decreased by 55% and, in children between 1 month and 5 years of age, by 87%, resulting in an increase in the median age of patients with bacterial meningitis from 15 months to 25 years.

This success in preventing Hib disease is attributable to widespread vaccination of infants and young children. Among those 19 to 35 months of age in the United States, 92% in 1996 were estimated to have received three or more doses of Hib vaccine. The effect in infants, however, preceded vaccination in this age group and the subsequent achievement of this high rate of immunization. The explanation of this unexpected development is the decrease in the rate of Hib pharyngeal carriage in vaccinees, a finding that indicates that elimination of the disease may be possible.

Marked decline in Hib disease also has occurred in other countries that have adopted infant vaccination. H influenzae type b is a common cause of meningitis and other invasive infections throughout the world, supporting the need for widespread infant vaccination and indicating further the immense potential of this vaccine for the health of children. In fact, in developing countries, the incidence of disease is greater than that in industrialized countries, and Hib is a common cause of severe pneumonia. Vaccination has been demonstrated recently to be effective in preventing invasive Hib disease in a large trial in the Gambia. As a result of these findings, introduction of Hib vaccine in the Expanded Programme for Immunization currently is under consideration by the World Health Organization. The major obstacle appears to be vaccine cost and the resulting economic challenge for countries with limited public health resources.

These 1973 and 1977 publications in Pediatrics of the results of the early trials of the first generation Hib vaccine were the beginning of a relatively rapid and ultimately extraordinarily successful immunization program. Although the initial vaccine was only moderately effective, this limitation emphasized the need for more effective vaccine and fostered the development of conjugate vaccines. In addition, the conjugate vaccine technology has become the basis for development of effective vaccines for infants and children against pneumococcal, meningococcal, and group B streptococcal infections, and promises to have continuing, significant impact on the prevention of infectious diseases in the 21st century.

For their work on H influenzae vaccination and its resulting importance to children, Smith and Anderson shared the prestigious 1997 Albert Lasker Medical Research Award with Robbins and Schneerson.

REFERENCES


2. Smith DH, Peter G, Ingram DL, Harding AL, Anderson P. Responses of children immunized with the capsular polysaccharide of Hemophilus
COMMENTARY


Comments by Richard D. Krugman, MD

Reviewing the past 50 years of publications related to the field of child abuse and neglect in *Pediatrics* is clearly less daunting a task than one would face if the field were infectious disease or neonatology. In part, this is true because the field is relatively new, has suffered from a stunning lack of interest from National Institutes of Health and, with some exceptions, there is a paucity of professional interest in academic departments of pediatrics. It also has been perceived by many as a “social” or “legal” problem that was not amenable to medical intervention or study. Kempe’s landmark article,1 which was published in *JAMA* in 1962, is acknowledged as the catalyst for modern day pediatric interest in child abuse and neglect. Most of the publications in *Pediatrics* have recounted the medical findings of physically and, more recently, sexually abused children in an effort to assist in the differential diagnosis of “accidental” and “nonaccidental” injury. Some, including Helfer and Slovis’ brief communication2 in 1977, Billmire and Myers 1985 article3 in physical abuse, and McCann and colleagues work4,5 in the area of sexual abuse have been very useful, especially in the courtroom.

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Received for publication Mar 19, 1998; accepted Mar 19, 1998.
Address correspondence to: Richard D. Krugman, MD, Department of Pediatrics, University of Colorado School of Medicine, C-290, 4200 E 9th Ave, Denver, CO 80262. *PEDIATRICS* (ISSN 0031 4005). Copyright © 1998 by the American Academy of Pediatrics.

It was Caffey’s article,6 “The Infant Whiplash Shaking Syndrome,” which has to be considered as the first landmark article in *Pediatrics*. This work was enormously important. It provided an explanation for how subdural hematomas in infants occur, it started the slide to extinction for the term “spontaneous subdural hematoma”, which was in vogue in the 1960s, and it has formed the conceptual basis for how pediatricians today understand broadly the etiology of one of the leading causes of infant morbidity and mortality from trauma. Caffey stated that the theme of his report was fourfold: “1) it presents the essential clinical manifestations of the whiplash shaken infant syndrome; 2) it presents evidence that so-called battered babies are really shaken babies; 3) it emphasizes the high vulnerability of the infant head, brain, and eyes to habitual, manual whiplash stresses of ordinary shaking by the extremities; and 4) it supports the hypothesis that casual, habitual manual whiplash shaking of infants is a substantial, primary frequent cause of later mental retardation and permanent brain damage.”

Of the hundred or so articles on child abuse and neglect that have been published in *Pediatrics* over the past 50 years, two other papers stand out that should have landmark status. I have chosen them because they fit the twin responsibilities of pediatricians who confront children with various forms of maltreatment every day in their practices. These responsibilities are recognition (including diagnosis) and prevention.

Southall and his colleagues published my second

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*Pediatrics* 1998;102:252
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