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contents:

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ACIP RECOMMENDATION: POLYSACCHARIDE VACCINE FOR PREVENTION OF HAEMOPHILUS INFLUENZAE TYPE B DISEASE

The following recommendations from the Immunization Practices Advisory Committee first appeared in the Centers for Disease Control publication Morbidity and Mortality Weekly Report, Vol. 34/No. 15, April 19, 1985.

A polysaccharide vaccine* against invasive (bacteremic) disease caused by Haemophilus influenzae type b recently has been licensed in the United States. The purposes of this statement are to summarize available information about this vaccine and to offer guidelines for its use in the prevention of invasive H. influenzae type b disease.

HAEMOPHILUS INFLUENZAE DISEASE

H. influenzae is a leading cause of serious systemic bacterial disease in the United States. It is the most common cause of bacterial meningitis, accounting for an estimated 12,000 cases annually, primarily among children under 5 years of age. The mortality rate is 5%, and neurologic sequelae are observed in as many as 25% to 35% of survivors. Virtually all cases of H. influenzae meningitis among children are caused by strains of type b (Hib), although this capsular type represents only one of the six types known for this species. In addition to bacterial meningitis, Hib is responsible for other invasive diseases, including epiglottitis, sepsis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia. Nontypeable (noncapsulated) strains of H. influenzae commonly colonize the human respiratory tract and are a major cause of otitis media and respiratory mucosal infection but rarely result in bacteremic disease. Hib strains account for only 5% to 10% of H. influenzae causing otitis media.

Several population-based studies of invasive Hib disease conducted within the last ten years have provided estimates of the incidence of disease among children under 5 years of age, the major age group at risk. These studies have demonstrated attack rates of meningitis ranging from 51 cases per 100,000 children to 77/100,000 per year and attack rates of other invasive Hib disease varying from 24/100,000 to 75/100,000 per year. Thus, in the United States, approximately one of every 1,000 children under 5 years of age develops systemic Hib disease each year, and a child's cumulative risk of developing systemic Hib disease at some time during the first five years of life is about one in 200. Attack rates peak between six months and 1 year of age and decline thereafter. Approximately 35% to 40% of Hib disease occurs among children 18 months of age or older, and 25% occurs above 24 months of age.

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*Official name: Haemophilus b Polysaccharide Vaccine.

Incidence rates of Hib disease are increased in certain high-risk groups, such as Native Americans (both American Indians and Eskimos), blacks, individuals of lower socioeconomic status, and patients with asplenia, sickle cell disease, Hodgkin's disease, and antibody deficiency syndromes. Recent studies also have suggested that the risk of acquiring primary Hib disease for children under 5 years of age appears to be greater for those who attend day-care facilities than for those who do not.

The potential for person-to-person transmission of systemic Hib disease among susceptible individuals has been recognized in the past decade. Studies of secondary spread of Hib disease in household contacts of index patients have shown a substantially increased risk of disease among exposed household contacts under 4 years of age. In addition, numerous clusters of cases in day-care facilities have been reported, and recent studies suggest that secondary attack rates in day-care classroom contacts of a primary case also may be increased.

HAEMOPHILUS b POLYSACCHARIDE VACCINE

The Hib vaccine is composed of the purified, capsular polysaccharide of H. influenzae type b . . . . Antibodies to this antigen correlate with protection against invasive disease. The Hib vaccine induces an antibody response that is directly related to the age of the recipient; infants respond infrequently and with less antibody than do older children or adults. Improved responses are observed by 18 months of age, although children 18 to 23 months of age do not respond as well as those 2 years of age or older. The frequency and magnitude of antibody responses reach adult levels at about 6 years of age. Levels of antibodies to the capsular polysaccharide also decline more rapidly in immunized infants and young children than in adults.

In a manner similar to other polysaccharide antigens, revaccination with Hib vaccine results in a level of antibody comparable to that for a child of the same age receiving a first immunization. Such polysaccharide antigens have been termed "T-cell independent" because of their failure to induce the T-cell memory response characteristic of protein antigens.

Limited data are available on the response to Hib vaccine in high-risk groups with underlying disease. By analogy to pneumococcal vaccine, patients with sickle cell disease or asplenia are likely to exhibit an immune response to the Hib vaccine. Patients with malignancies associated with immunosuppression appear to respond less well. Additional data are needed on the immune response to Hib vaccine in these groups.

A precise protective level of antibody has not been established. However, based on evidence from passive protection in the infant rat model and from experience with agammaglobulinemic children, an antibody concentration of 0.15 µg/ml correlates with protection. In the Finnish field trial, levels of capsular antibody greater than 1µg/ml in three-week postimmunization sera correlated with clinical protection for a minimum of 1 1/2 years. Approximately 75% of children 18 to 23 months of age tested achieved a level greater than 1 µg/ml, as did 90% of 24- to 35-month-old children. Measurement of Hib antibody levels is not routinely available, however, and determination of antibody levels following vaccination is not indicated in the usual clinical setting.

EFFECTIVENESS OF VACCINE

In 1974, a randomized, controlled trial of clinical efficacy was conducted in Finland among children 3 to 71 months of age. Approximately 98,000 children, half of whom received the Hib vaccine, were enrolled in the field trial and followed for a four-

year period for occurrence of Hib disease. Among children 18 to 71 months of age, 90% protective efficacy (95% confidence limits, 55%-98%) in prevention of all forms of invasive Hib disease was demonstrated for the four-year follow-up period. Although no disease occurred among over 4,000 children 18 to 23 months of age immunized with Hib vaccine and followed for four years, only two cases occurred in the control vaccine recipients in this age group. As a result, vaccine efficacy in the subgroup of children immunized at 18 to 23 months of age could not be evaluated statistically. The vaccine was not efficacious in children under 18 months of age.

REVACCINATION

Limited data regarding the potential need for revaccination are available at present. Current data show that children who have received the Hib vaccine 2 to 42 months previously have an immune response to the vaccine similar to that in previously unvaccinated children of the same age. No immunologic tolerance or impairment of immune response to a subsequent dose of vaccine occurs. As with other polysaccharide vaccines, the shorter persistence of serum antibodies in young children given Hib vaccine, compared with adults, suggests that a second dose of vaccine may be needed to maintain immunity throughout the period of risk, particularly for children in the youngest age group considered for vaccination (those 18 to 23 months of age). A second injection following the initial dose is likely to increase the protective benefit of vaccination for this high-risk group, because antibody titers 18 months after vaccination, although detectable in most vaccine recipients, are no longer significantly different from those in unvaccinated children of the same age.

RECOMMENDATIONS FOR VACCINE USE

Recently published data regarding vaccine efficacy and the risk of Hib disease among young children strongly support the use of Hib vaccine in the United States in high-risk persons for whom efficacy has been established. Specific recommendations are as follows:

1. Immunization of all children at 24 months of age is recommended. The precise duration of immunity conferred by a single dose of Hib vaccine at 24 months of age is not known, although, based on available data, protection is expected to last 1 1/2 to 3 1/2 years. Until further data are available to determine whether an additional dose of vaccine may be necessary to ensure long-lasting immunity, routine revaccination is not recommended.

2. Immunization of children at 18 months of age, particularly in known high-risk groups, may be considered. Although the precise efficacy of the vaccine among children 18 to 23 months of age is not known, this age group accounts for approximately 12% of all invasive Hib disease among children under 5 years of age, and Hib vaccine has been shown by serologic methods to be immunogenic in most children of this age group. However, physicians and parents should be informed that the vaccine is not likely to be as effective in this age group as in older children. These younger children may need a second dose of vaccine within 18 months following the initial dose to ensure protection. Additional data regarding the duration of the antibody response are needed to define the timing of a second dose more precisely.

   Children who attend day-care facilities are at particular risk of acquiring systemic Hib disease. Initial vaccination at 18 months of age for this high-risk group should be considered.

Children with chronic conditions known to be associated with increased risk for Hib disease should receive the vaccine, although only limited data on immunogenicity and clinical efficacy in this group are available. These conditions include anatomic or functional asplenia, such as sickle cell disease or splenectomy, and malignancies associated with immunosuppression.

3. Immunization of individuals over 24 months of age who have not yet received Hib vaccine should be based on risk of disease. The risk of invasive Hib disease decreases with increasing age over the age of 2 years. Because the vaccine is safe and effective, however, physicians may wish to immunize previously unvaccinated healthy children between 2 years and 5 years of age to prevent the Hib disease that does occur in this age group. The potential benefit of this strategy in terms of cases prevented declines with increasing age of the child at the time of vaccination. Therefore, children 2 to 3 years of age who attend day-care facilities should be given a higher priority than day-care attendees who are 4 to 5 years old.

4. Insufficient data are available on which to base a recommendation concerning use of the vaccine in older children and adults with the chronic conditions associated with an increased risk of Hib disease.

5. Vaccine is not recommended for children under 18 months of age.

6. Simultaneous administration of Hib and DTP vaccines at separate sites can be performed, because no impairment of the immune response to the individual antigens occurs under these circumstances.

SIDE EFFECTS AND ADVERSE REACTIONS

Polysaccharide vaccines are among the safest of all vaccine products. To date, over 60,000 doses of the Hib polysaccharide vaccine have been administered to infants and children, and several hundred doses have been given to adults. Only one serious systemic reaction has been reported thus far -- a possible anaphylactic reaction that responded promptly to epinephrine. High fever (38.5°C [101.3°F] or higher) has been reported in fewer than 1% of Hib vaccine recipients. Mild local and febrile reactions were common, occurring in as many as half of vaccinated individuals in the Finnish trial. Such reactions appeared within 24 hours and rapidly subsided. Current preparations appear to result in fewer such local reactions. Simultaneous administration with DTP does not result in reaction rates above those expected with separate administration.

PRECAUTIONS AND CONTRAINDICATIONS

The Hib vaccine is unlikely to be of substantial benefit in preventing the occurrence of secondary cases, because children under two years old are at highest risk of secondary disease. Because the vaccine will not protect against nontypeable strains of *H. influenzae*, recurrent upper respiratory diseases, including otitis media and sinusitis, are not considered indications for vaccination.

NEW VACCINE DEVELOPMENT

New vaccines, such as the Hib polysaccharide-protein conjugate vaccines, are being developed and evaluated and may prove to be efficacious for children under 18 months of age.

PDN Editorial Note: From 1980 to 1984, 1,704 cases of Haemophilus influenzae meningitis, including 131 deaths, were reported to the Texas Department of Health. Eighty percent (1,356) of the cases and 74% (97) of the deaths were in children less than 2 years of age and, as such, would not have been preventable with the newly licensed vaccine. During 1984, 521 cases were reported in Texas. Of the 247 cases for whom surveillance forms were received, 66 (27%) were enrolled in day-care centers.

At a cost of $6.85/dose, the direct vaccine costs for immunizing all Texas children between 24 and 35 months of age would be about $1.9 million. If the vaccine efficacy rate were 90%, 101 (19%) of the 521 cases reported in 1984 could have been prevented by universal immunization at 24 months of age.

Although the Texas Department of Health supports these ACIP recommendations on Hib vaccine, no funds have been allocated to support the use of Hib vaccine in public health clinics.

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DISSEMINATED MYCOBACTERIUM BOVIS INFECTION FROM BCG VACCINATION OF A PATIENT WITH ACQUIRED IMMUNODEFICIENCY SYNDROME

This article first appeared in the Centers for Disease Control (CDC) publication, Morbidity and Mortality Weekly Report, Vol. 34/No. 16, April 26, 1985.

In December 1982, Kaposi's sarcoma and acquired immunodeficiency syndrome (AIDS) were diagnosed in a 29-year-old white homosexual man. A trial of vinblastine sulfate failed to decrease the progression of his skin lesions. In February 1984, when seen in a clinic in Tijuana, Mexico, he was given a BCG vaccination. The expected local lesion from the BCG vaccination healed normally within the next few weeks. In June, he developed chills and fever to 39.4° C (103°F), weakness, fatigue, anorexia, and a mild headache. In July, the site of BCG vaccination on his left arm ulcerated, draining a small amount of pus and blood. A previously enlarged lymph node in the left axilla increased substantially in size and became very tender. Because of the possibility of disseminated BCG infection, treatment was begun with INH 300 mg/day, ethambutol 25 mg/kg/day, and pyridoxine. He rapidly became afebrile and regained his feeling of well-being. The ulcer healed slowly, and the enlarged lymph node decreased in size and tenderness. Two blood cultures taken June 28 and a culture of the ulcerating lesion taken July 16 grew Mycobacterium bovis, BCG strain. A blood culture taken July 23, just before therapy, grew M. fortuitum.

MMWR Editorial Note: BCG vaccine contains live mycobacteria derived from a strain of M. bovis attenuated through years of serial passage in culture by Calmette and Guerin at the Pasteur Institute, Lille, France. Although BCG has been widely used throughout the world, its use in the United States is limited to those uncommon situations in which uninfected persons are repeatedly exposed to infectious tuberculosis, and other means of preventing infection cannot be applied. BCG has also been used to stimulate the immune system of patients with various cancers, especially malignant melanoma, with the objective of causing regression of the tumors. As with any vaccine containing live organisms, however, it is contraindicated in persons with severely impaired immune responses, including those with AIDS, because disseminated infection with the organism contained in the vaccine may result.

M. bovis and M. tuberculosis (the M. tuberculosis complex) are pathogenic for man and are distinct from the "atypical" mycobacteria that tend to be opportunistic. Infection with M. bovis or M. tuberculosis, even if disseminated, is generally not

considered opportunistic and is, therefore, not used as a marker for AIDS in CDC's surveillance definition of AIDS. The BCG strain of M. bovis, however, being attenuated and not usually a cause of disease, may be considered an opportunist.

Of the 9,760 AIDS patients in the United States reported to CDC as of April 24, 1985, 2.7% were reported to have tuberculosis. Disseminated atypical mycobacterial infection, used as a marker for AIDS, was reported in 3.7%. Another 0.9% were reported to have disseminated infection with an undetermined species of mycobacteria. The true cumulative incidence of mycobacterial infections in AIDS patients is undoubtedly higher. The opportunistic infections reported to CDC's AIDS surveillance program are largely limited to those present at the time AIDS is diagnosed. Disseminated mycobacterial infections are not common among the initial opportunistic infections in AIDS patients, but in one series of 71 AIDS patients, 24 (34%) reportedly developed infection with M. avium complex organisms at some time during their illness. The great majority (94%) of the atypical mycobacterial infections reported to the AIDS surveillance program have been due to M. avium complex; 4% were due to M. kansasii; and 2%, to other species. Besides the patient reported here, only one other AIDS patient had disseminated M. fortuitum reported; the M. fortuitum cannot be explained by the BCG vaccine and may represent a contaminated culture rather than a true infection.

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