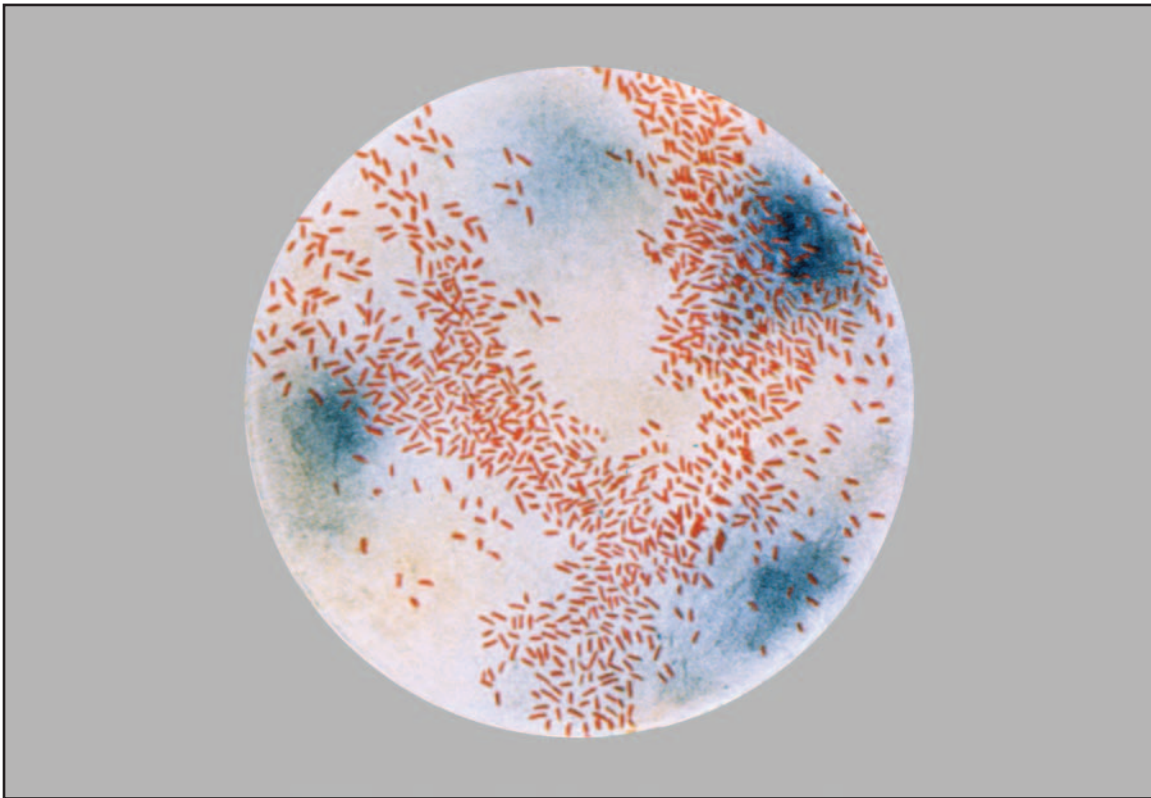


Prevention and Control of *Haemophilus influenzae* Type b Disease

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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CDC Adoption of ACIP Recommendations

ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of CDC on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for routine use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists. Recommendations for routine use of vaccines in adults are reviewed and approved by the American College of Physicians (ACP), AAFP, the American College of Obstetricians and Gynecologists, and the American College of Nurse-Midwives. ACIP recommendations adopted by the CDC Director become agency guidelines on the date published in *MMWR*.

Disclosure of Relationship

CDC, our planners, and our content experts wish to disclose that they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Content will not include any discussion of the unlabeled use of a product or a product under investigational use, with the following exceptions:

1. Hiberix can be administered as early as age 12 months, in accordance with Hib vaccination schedules for routine and catch-up immunization, to facilitate timely booster vaccination;
2. in certain situations, patients at increased risk for invasive Hib disease who are fully vaccinated need additional doses of Hib vaccine; and
3. unimmunized older children, adolescents, and adults with certain specified medical conditions should receive Hib vaccine.

Front cover photo: Photomicrograph of *Haemophilus influenzae* as seen using a Gram-stain technique (Photo/CDC).

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Prevention and Control of *Haemophilus influenzae* Type b Disease

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report compiles and summarizes all recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) regarding prevention and control of Haemophilus influenzae type b (Hib) disease in the United States. As a comprehensive summary of previously published recommendations, this report does not contain any new recommendations; it is intended for use by clinicians, public health officials, vaccination providers, and immunization program personnel as a resource. ACIP recommends routine vaccination with a licensed conjugate Hib vaccine for infants aged 2 through 6 months (2 or 3 doses, depending on vaccine product) with a booster dose at age 12 through 15 months. ACIP also recommends vaccination for certain persons at increased risk for Hib disease (i.e., persons who have early component complement deficiencies, immunoglobulin deficiency, anatomic or functional asplenia, or HIV infection; recipients of hematopoietic stem cell transplant; and recipients of chemotherapy or radiation therapy for malignant neoplasms). This report summarizes current information on Hib epidemiology in the United States and describes Hib vaccines licensed for use in the United States. Guidelines for antimicrobial chemoprophylaxis of contacts of persons with Hib disease also are provided.

Introduction

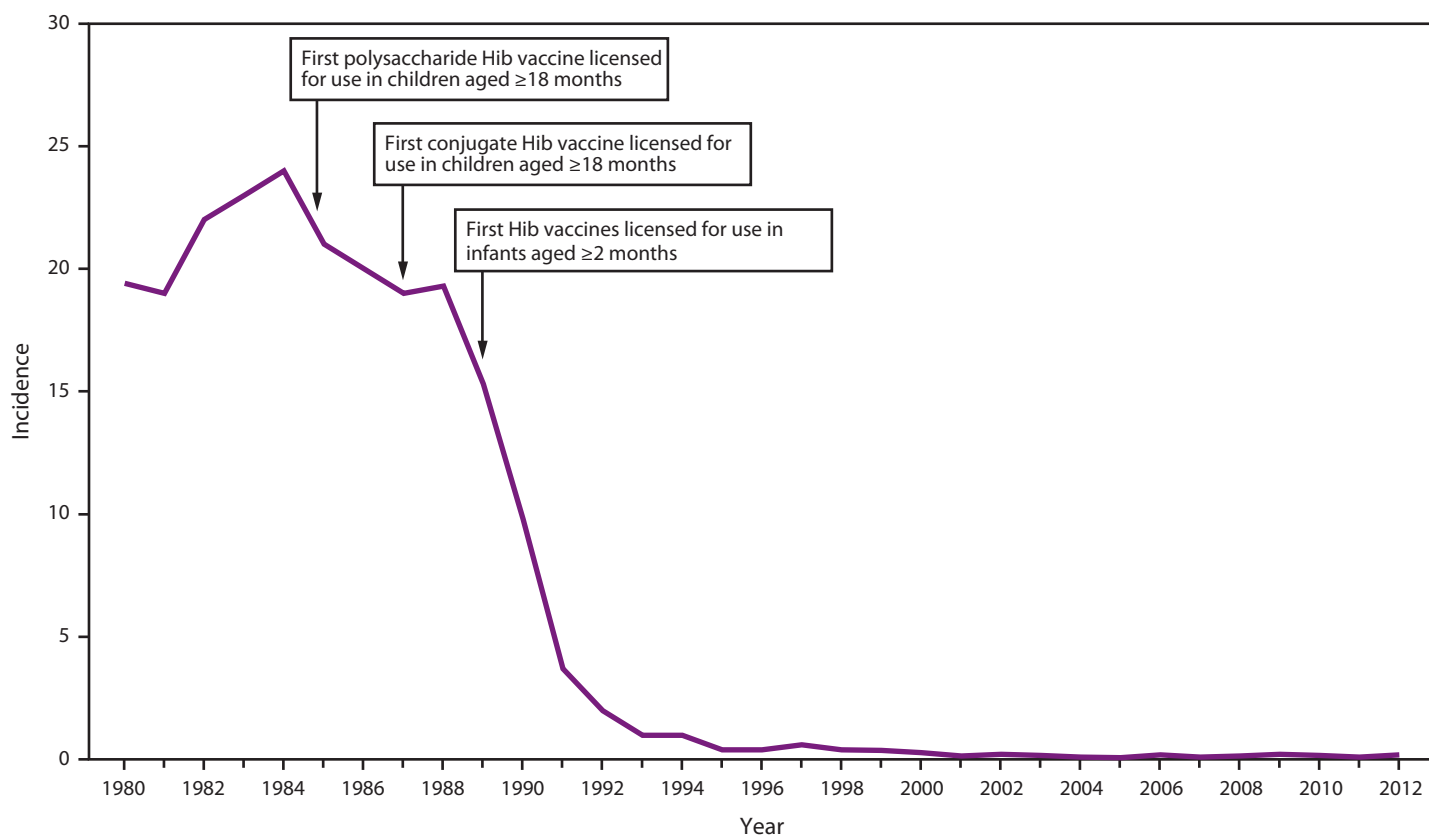
Before 1985, *Haemophilus influenzae* type b (Hib) was the leading cause of bacterial meningitis and a common cause of other invasive diseases (e.g., epiglottitis, pneumonia, septic arthritis, cellulitis, purulent pericarditis, and bacteremia) among U.S. children aged <5 years (1). Meningitis occurred in approximately two thirds of children with invasive Hib disease; 15%–30% of survivors had hearing impairment or severe permanent neurologic sequelae. Approximately 4% of all cases were fatal (2). The first polysaccharide Hib vaccine was introduced in the United States in 1985, followed by conjugate Hib vaccines in 1987 and 1989. During 1989–2000, the annual incidence of invasive Hib disease in children aged <5 years decreased by 99%, to less than one case per 100,000 children (3–7). During 2000–2012, the average annual incidence rate of invasive Hib disease in children aged <5 years

in the United States remained below the *Healthy People 2020* goal of 0.27/100,000 (8) (data available at <http://www.cdc.gov/abcs/reports-findings/surv-reports.html>) (Figures 1 and 2). Studies have demonstrated that vaccination with Hib conjugate vaccine leads to decreases in oropharyngeal colonization among both vaccinated and unvaccinated children (9–11); the prevalence of Hib carriage has decreased among preschool-aged children from 2%–7% in the prevaccine era to <1% in the vaccine era (9,12).

Several Hib-containing vaccines have been licensed since the initial Advisory Committee on Immunization Practices (ACIP) recommendations on prevention and control of Hib disease published in 1993 (13); subsequent publications have provided additional data and updated recommendations for these vaccines (14–17). This report summarizes previously published ACIP recommendations on prevention and control of Hib disease in immunocompetent and high-risk populations (14–18); it does not contain new recommendations and is intended as a resource for clinicians, public health officials, vaccination providers, and immunization program personnel. In addition, this report summarizes current information on Hib epidemiology in the

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FIGURE 1. Estimated annual incidence* of invasive *Haemophilus influenzae* type b (Hib) disease in children aged <5 years — United States, 1980–2012



Sources: 1980–1997: National Bacterial Meningitis Reporting System and National Notifiable Diseases Surveillance (NNDSS) data; Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood *Haemophilus influenzae* Type b (Hib) disease in the Hib vaccine era. *JAMA* 1993;269:221–6; CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1995. *MMWR* 1996;45:901–6; CDC. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1997. *MMWR* 1998;47:993–8. 1998–2009: NNDSS and Active Bacterial Core Surveillance (ABCs) data. 2010–2012: ABCs cases estimated to the U.S. population.

* Per 100,000 population.

United States and describes Hib vaccines licensed for use in the United States. Guidelines for antimicrobial chemoprophylaxis of contacts of persons with Hib disease also are provided.

Methods

ACIP's Meningococcal and *Haemophilus influenzae* type b Work Group* comprises a diverse group of health-care providers and public health officials. The Work Group includes professionals from academic medicine (pediatrics, family medicine, internal medicine, and infectious disease specialists), federal and state public health professionals, and representatives of professional medical organizations.

Published Hib vaccine recommendations were the primary sources of data used by the Work Group in summarizing recommendations for the prevention and control of Hib disease, including the evidence-based 2013 Infectious Diseases Society

of America clinical practice guideline for vaccination of the immunocompromised host (17–23). Surveillance data came from the Active Bacterial Core surveillance (ABCs) system and the National Notifiable Diseases Surveillance System (NNDSS) (24).

Data on the immunogenicity and safety of current licensed and available Hib vaccines were summarized on the basis of findings from a literature search of PubMed and Web of Science databases that was completed on April 2, 2012. A nonsystematic review was conducted for studies on safety, effectiveness, and immunogenicity of the current Hib vaccines published from the time of vaccine licensure through March 2012. Because MenHibRix was licensed in June 2012, studies published before licensure also were reviewed. The literature search included clinical trials, randomized controlled trials, controlled clinical trials, evaluation studies, and comparative studies conducted worldwide and published in English. The Vaccine Adverse Events Reporting System (VAERS) (available at <http://www.vaers.hhs.gov>) also was searched for postlicensure safety

* A list of the members of the Work Group appears on page 14.

data for the currently licensed and available Hib vaccines.

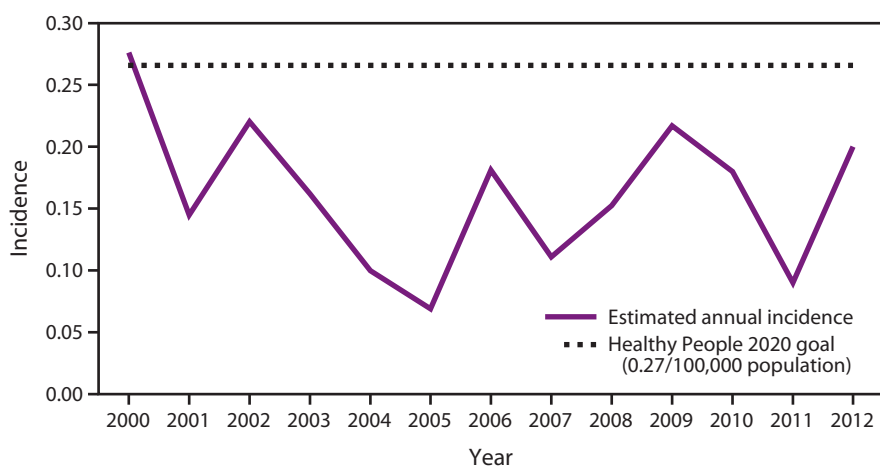
During December 2012–February 2013, the Work Group held one teleconference meeting and the members communicated with each other via e-mail messages to review current recommendations and to consider potential revisions to the statement. A summary of data reviewed, Work Group discussions, and the current description of Hib epidemiology was presented at the ACIP's February 2013 meeting. On February 20, 2013, ACIP members approved the Hib Vaccine Recommendations Statement. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the report.

Background

H. influenzae is a species of bacteria that has encapsulated (typeable) or unencapsulated (nontypeable) strains. Encapsulated strains express one of six antigenically distinct capsular polysaccharides (types a, b, c, d, e, or f). Encapsulated *H. influenzae* nontype b strains, particularly type a, can cause invasive disease similar to Hib disease (25,26). Nontypeable strains also can cause invasive disease but more commonly cause mucosal infections such as otitis media, conjunctivitis, and sinusitis. Hib vaccines only protect against *H. influenzae* type b strains; no vaccines against nontype b or nontypeable strains currently are available. *H. influenzae* colonizes the upper respiratory tract of humans and is transmitted person-to-person by inhalation of respiratory droplets or by direct contact with respiratory tract secretions.

The majority of Hib disease in the United States occurs among unimmunized and underimmunized infants and children (those who have an incomplete primary series or are lacking a booster dose) and among infants too young to have completed the primary immunization series (27) (Figure 3). Although rare, Hib disease after full vaccination with the primary series and booster dose does occur; among Hib case-patients aged <5 years with age-appropriate vaccine status reported during 2002–2012 in the United States, 16% had completed the primary Hib series, and 43% had completed the full Hib series (Figure 3). Hib disease is uncommon in adults and in children aged >5 years. Additional information about *H. influenzae* disease is available at <http://www.cdc.gov/hi-disease>.

FIGURE 2. Estimated annual incidence* of invasive *Haemophilus influenzae* Type b infection in children aged <5 years — United States, 2000–2012



Sources: National Notifiable Diseases Surveillance and Active Bacterial Core Surveillance (ABCs) data.
* Per 100,000 population.

Persons with certain immunocompromising conditions are considered at increased risk for invasive Hib disease; these conditions might include:

- functional or anatomic asplenia,
- HIV infection,
- immunoglobulin deficiency including immunoglobulin G2 subclass deficiency,
- early component complement deficiency,
- receipt of a hematopoietic stem cell transplant, or
- receipt of chemotherapy or radiation therapy for malignant neoplasms.

Children who develop Hib disease despite appropriate vaccination should be evaluated for an immunological deficiency that predisposes them to Hib disease (28).

Historically, American Indian/Alaska Native (AI/AN) populations have had higher rates of Hib disease and colonization than the general U.S. population, with a peak in disease at a younger age (4–6 months) than among other U.S. infant populations (6–7 months) (29–31). Before introduction of vaccine in 1985, rates among AN children were five times higher than rates among non-AN children in Alaska (4). Although rates of Hib disease among AI/AN children have decreased in the postvaccine era, they remain higher than among non-AI/AN children. During 1998–2009, the average annual incidence of Hib disease in children aged <5 years in the United States was 8–10 times higher among AI/AN children (1.3/100,000) than it was among white (0.16/100,000) and black (0.12/100,000) children, respectively (27).

Development of Hib Vaccines

The first Hib vaccine licensed for use in the United States in 1985 was a monovalent vaccine consisting of purified polyribosylribitol phosphate (PRP) capsular material from type b strains. Although the vaccine was highly effective in trials in Finland among children aged ≥ 18 months, postmarketing effectiveness studies in the United States demonstrated variable effectiveness (-69%–88%) (32). PRP vaccines were ineffective in children aged < 18 months because of the T lymphocyte-independent nature of the immune response to PRP polysaccharide (13). Conjugation of the PRP polysaccharide with protein carriers that contain T-lymphocyte epitopes confers T-lymphocyte-dependent characteristics to the vaccine. This conjugation enhances the immunologic response to the PRP antigen, particularly in young infants, and results in immunologic memory (e.g., anamnestic response) (33). Studies have suggested that long-term protection from invasive Hib disease is correlated with the presence of anti-PRP levels ≥ 0.15 $\mu\text{g}/\text{ml}$ in unvaccinated children and anti-PRP levels ≥ 1.0 $\mu\text{g}/\text{ml}$ in vaccinated children (34,35).

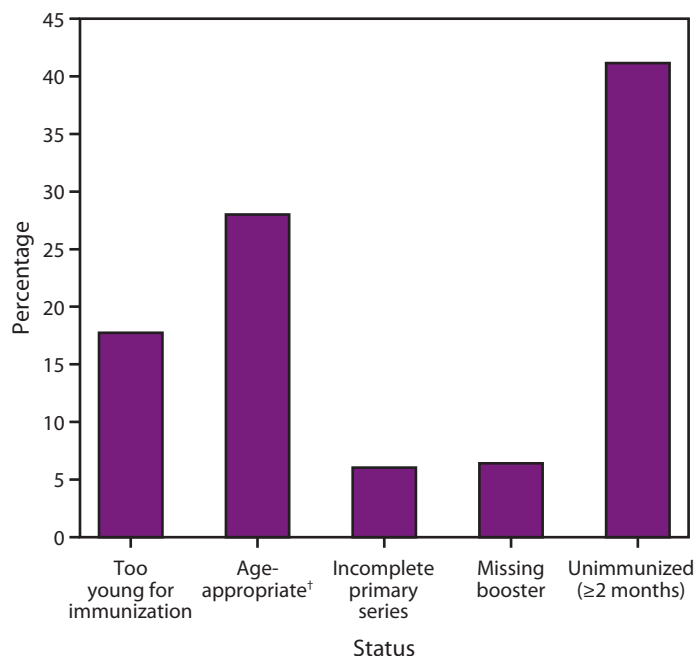
By 1989, three monovalent Hib conjugate vaccines were licensed for use among children aged ≥ 15 months (29). In late 1990, two of these conjugate vaccines were licensed for use among infants (36,37). Since 1990, additional Hib vaccines from numerous manufacturers have been licensed and are currently used in the United States, including monovalent Hib conjugate vaccines and combination vaccines that contain a Hib conjugate vaccine. No polysaccharide Hib vaccines are used currently in the United States.

Current Licensed and Available Hib Monovalent Conjugate Vaccines

As of January 1, 2014, three monovalent PRP polysaccharide-protein conjugate vaccines had been licensed by the Food and Drug Administration (FDA) and were available in the United States: PRP-OMP (PedvaxHIB, Merck and Co., Inc., Whitehouse Station, New Jersey), PRP-T (ActHIB, Sanofi Pasteur, Inc., Swiftwater, Pennsylvania), and PRP-T (Hiberix, GlaxoSmithKline, Research Triangle Park, North Carolina) (38) (Table 1).

In December 1990, PRP-OMP (PedvaxHIB) was licensed by FDA as a 2-dose primary series for infants at ages 2 and 4 months, with a booster dose (dose 3) at age 12 months (39). PRP-OMP contains purified PRP conjugated with an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. Further information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM253652.pdf>.

FIGURE 3. Percentage of children aged < 5 years with cases of invasive *Haemophilus influenzae* type b (Hib) disease,* by vaccine status — United States 2002–2012



Sources: Active Bacterial Core surveillance system and National Notifiable Diseases Surveillance System.

* N = 265. An additional 57 children aged < 5 years with Hib had unknown vaccine status and were excluded.

[†] Among those with age-appropriate vaccine status, 41% were too young to complete the primary series, 16% completed the primary series, and 43% completed the full series.

In March 1993, PRP-T (ActHIB) was licensed by FDA as a 3-dose primary series for infants at ages 2, 4, and 6 months, with a booster dose (dose 4) at age 15 months (40). This vaccine contains purified PRP conjugated with tetanus toxoid. Further information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109841.pdf>.

In August 2009, PRP-T (Hiberix) was licensed by FDA for use as the booster dose (which will be dose 3 or 4, depending on vaccine type used for primary series) of the Hib vaccine series for children aged 15 months through 4 years who have received a Hib primary series (16). This vaccine contains purified PRP conjugated with tetanus toxoid. Further information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM179530.pdf>.

Current Licensed and Available Hib Combination Conjugate Vaccines

As of January 1, 2014, three combination vaccines that contain an *H. influenzae* type b conjugate vaccine had been licensed by

TABLE 1. *Haemophilus influenzae* type b (Hib) conjugate vaccines licensed and available in the United States as of January 2014

Vaccine product	Manufacturer	Trade Name	Components	Primary series	Booster dose
Monovalent vaccine					
PRP-OMP* [†]	Merck & Co, Inc	PedvaxHIB	PRP conjugated to OMP	2, 4 mos	12–15 mos
PRP-T	sanofi pasteur	ActHIB	PRP conjugated to tetanus toxoid	2, 4, 6 mos	12–15 mos
PRP-T	GlaxoSmithKline	Hiberix	PRP conjugated to tetanus toxoid	Not licensed for primary series	12–15 mos [§]
Combination vaccine					
PRP-OMP-HepB* [†]	Merck & Co, Inc	Comvax	PRP-OMP + hepatitis B vaccine	2, 4 mos	12–15 mos
DTaP-IPV/PRP-T	sanofi pasteur	Pentacel	DTaP-IPV + PRP-T	2, 4, 6 mos	15–18 mos [¶]
MenCY/PRP-T**	GlaxoSmithKline	MenHibRix	MenCY + PRP-T	2, 4, 6 mos	12–15 mos

Source: Adapted from American Academy of Pediatrics. *Haemophilus influenzae* infections. Pickering L, Baker C, Kimberlin D, Long S, eds. Red book: 2012 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012:345–52.

* If a PRP-OMP vaccine is not administered as both doses in the primary series, or if there is uncertainty about which products were administered previously, a third dose of Hib conjugate vaccine is needed to complete the primary series.

[†] Preferred vaccine for American Indian/Alaska Native children.

[§] To facilitate timely booster vaccination, Hiberix can be administered as early as age 12 months, in accordance with Hib vaccination schedules for routine and catch-up immunization (CDC. Licensure of a *Haemophilus influenzae* type b [Hib] vaccine [Hiberix] and updated recommendations for use of Hib vaccine. MMWR 2009;58:1008–9).

[¶] The booster dose may be administered as early as age 12 months, provided that at least 6 months have elapsed since the third dose.

** Recommendations for the MenCY component of MenCY/PRP-T have been published previously (CDC. Infant meningococcal vaccination: Advisory Committee on Immunization Practices (ACIP) recommendations and rationale. MMWR 2013;62:52–4).

FDA and were available in the United States: PRP-OMP/HepB (Comvax, Merck and Co., Inc., Whitehouse Station, New Jersey), DTaP-IPV/PRP-T (Pentacel, Sanofi Pasteur, Inc., Swiftwater, Pennsylvania), and MenCY/PRP-T (MenHibRix, GlaxoSmithKline, Inc., Rixensart, Belgium) (38) (Table 1).

In October 1996, PRP-OMP/HepB (Comvax) was licensed by FDA for vaccination against invasive Hib disease and hepatitis B infection in infants at ages 2, 4, and 12 through 15 months (14). This vaccine includes the antigenic components used in PedvaxHIB (PRP-OMP) and Recombivax HB (hepatitis B surface antigen). Further information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109869.pdf>.

In June 2008, DTaP/IPV/PRP-T (Pentacel) was licensed by FDA for vaccination against invasive Hib disease, diphtheria, tetanus, pertussis, and poliomyelitis in infants at ages 2, 4, 6, and 15 through 18 months (15). It is not indicated for the DTaP/IPV booster dose at age 4 through 6 years. The vaccine includes the antigenic components used in ActHIB (PRP-T) and Poliovax. Further information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109810.pdf>.

In June 2012, MenCY/PRP-T (MenHibRix) was licensed by FDA for vaccination against invasive Hib disease and *N. meningitidis* serogroups C and Y disease in infants at ages 2, 4, 6, and 12 through 15 months (17). Infants at increased risk for meningococcal disease[†] should be vaccinated with a 4-dose

series of MenCY/PRP-T. Routine meningococcal vaccination is recommended only for infants who are at increased risk for meningococcal disease. However, MenCY/PRP-T may be used in any infant for routine vaccination against Hib. Further recommendations for use of the MenCY component of MenCY/PRP-T have been published previously (17). Further vaccine information is available in the package insert at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM308577.pdf>.

Immunogenicity of Current Licensed and Available Hib Vaccines

Protective antibody levels are detected for both PedvaxHib and ActHib after a primary series (41–43). However, the vaccines differ in the timing of antibody response. PedvaxHib produces a substantial antibody response after the first dose with an additional boost in geometric mean antibody concentration after the second or third dose (41,42,44–46). Therefore, PedvaxHib is licensed as a 2-dose primary series. PedvaxHib effectiveness was 93%–100% in Navajo infants vaccinated with a 2-dose series (13,41,47).

Geometric mean antibody concentrations remain at or below 1.0 µg/ml after the first and second dose of ActHIB, but a protective antibody response is seen after the third dose (41,42,45,48,49). Effectiveness studies for ActHIB were terminated early in the United States with licensure of the first Hib conjugate vaccine; no cases of invasive Hib disease were reported among vaccinees at the time of study termination (13,47). A prospective controlled trial of PRP-T among 56,000 subjects in the United Kingdom found an effectiveness of 95% (95% confidence interval [CI] = 74%–100%) (47).

[†] Infants with persistent complement component deficiencies, those with functional or anatomic asplenia (including sickle cell disease), healthy infants in communities with a meningococcal disease outbreak for whom vaccination is recommended, and infants traveling to or residing in areas with hyperendemic or epidemic meningococcal disease.

Antibody levels decline after completion of the primary series with PRP-T and PRP-OMP vaccines and a booster dose at age 12–15 months is necessary to maintain protective antibody levels. Booster doses of PedvaxHib, ActHib, and Hiberix at age 12–15 months provide levels of antibody that are protective against invasive Hib disease (16,44,46,48,50,51).

Protective antibody responses comparable to those detected after receipt of separately administered PedVaxHIB and Recombivax HB vaccines are seen after the second primary dose and booster dose of Comvax vaccine (14,52). Pentacel and MenHibRix induce protective antibody responses that are noninferior to separately administered PRP-T vaccines after the third primary dose and booster dose (53–59).

No clinically significant immune interference has been observed with any of the available monovalent or combination Hib vaccines and concomitant administration of other routine childhood vaccines (51,52,60–67; ACIP, unpublished data, 2009).

Safety of Current Licensed and Available Hib Vaccines

In prelicensure trials, adverse reactions to PedvaxHib, ActHib, and Hiberix were uncommon, usually mild, and generally resolved within 12–24 hours (16,41,43,46,49,50). Rates of adverse reactions to Comvax, Pentacel, and MenHibRix were similar to those seen with separately administered vaccines (14,52–54,68).

Postmarketing surveillance for adverse events following receipt of Hib vaccines has been conducted primarily by two systems in the United States: VAERS and the Vaccine Safety Datalink (VSD). VAERS is a national passive surveillance system operated jointly by CDC and FDA that receives reports of adverse events following vaccination from health-care personnel, manufacturers, vaccine recipients, and others (69). VAERS can generate, but not test, vaccine safety hypotheses and is subject to several limitations, including reporting biases and inconsistent data quality (69). VSD is a collaboration between CDC and nine integrated health-care organizations that conducts population-based vaccination safety studies to assess hypotheses that arise from review of medical literature, reports to VAERS, changes in immunization schedules, or introduction of new vaccines (70).

Safety Data Reported to VAERS

During January 1, 1990–May 31, 2013, VAERS received 29,047 reports involving receipt of Hib vaccines (PedvaxHIB, ActHIB, Hiberix, Comvax, and Pentacel) in the United States; 26,375 (91%) reports involved children aged <2 years.

Hib vaccines were administered concurrently with one or more other vaccines in 95% of case reports. The median time from vaccination to onset of an adverse event was 1 day. The most frequently reported adverse events were fever (31%), crying (11%), injection site erythema (11%), irritability (10%), and rash (9%).

Among all Hib vaccines reports, approximately 17% were coded as serious as defined in the Code of Federal Regulations (71) (i.e., report contained information that the event led to death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability). Among the 5,062 reports coded as serious, the most frequent adverse events were fever (37%), vomiting (21%), convulsion (20%), irritability (17%), and intussusception (11%). In 97% of the intussusception reports, rotavirus vaccine was administered concomitantly and might have prompted reporting of this adverse event.

VAERS received reports of 878 deaths following Hib containing vaccines that occurred during January 1, 1990–May 31, 2013. An autopsy report or other medical records was available for 620 (71%) of these deaths, among which the most frequent cause of death was sudden infant death syndrome (52%). Other causes of death included respiratory (9%), cardiovascular (5%), infectious (5%), neurologic (3%), and gastrointestinal (2%) conditions. In 14% of reports, the cause was undetermined, and in 11% of reports, various other causes were reported (e.g., asphyxia and blunt force trauma).

The reporting frequencies for Hib containing vaccines are similar to what has been observed with other recommended childhood vaccines. No unusual or unexpected safety patterns were observed in VAERS data for any Hib vaccines.

Population-Based Safety Findings

No postlicensure safety studies of monovalent Hib vaccines were identified by the literature review. However, the VSD conducted an observational study of the combination Hib vaccine, DTaP-IPV-Hib (Pentacel), for the period September 2008–January 2011 (55). Compared with children who received DTaP-containing control vaccine (i.e., without Hib), children aged 1–2 years who received DTaP-IPV-Hib vaccine had an elevated risk for fever (RR = 1.83; 95% CI = 1.34–2.50). DTaP-IPV-Hib vaccine was not associated with any other medically attended adverse health event.

An independent postmarketing safety evaluation of Hib-HepB (Comvax) was conducted by a managed care organization in Seattle, Washington, for the period July 1997–December 2000 (72). Using ICD-9 codes, the retrospective cohort study evaluated adverse events reported 1–30 days

following administration of Hib-HepB, compared with rates of adverse events among two control groups (historical control group and self-comparison group). A total of 27,802 vaccine doses were administered during the study period with 111,129 diagnoses recorded within 0–30 days following administration of Comvax in any health-care setting. There were 127 separate adverse event codes with significant elevated relative risks and 66 codes with significantly decreased relative risks ($p < 0.5$). On medical record review, there was no consistent pattern to respiratory or gastrointestinal illnesses; fever findings appeared to be explained by changes in data collection or by concomitant vaccination with measles, mumps, and rubella virus vaccine. Two deaths occurred within the study period, both of which were considered unrelated to vaccination. No consistent association was identified between serious adverse events and vaccination with Hib-HepB, and the vaccine had a favorable safety profile.

Recommendations for Hib Vaccine Use

Recommendations for Routine Vaccination

ACIP recommends routine administration of a conjugate Hib vaccine series (monovalent vaccine [PedvaxHib (PRP-OMP) or ActHib (PRP-T)] or Hib vaccine in combination with HepB [Comvax], DTaP/IPV [Pentacel], or MenCY [MenHibRix]) beginning at age 2 months. Infants aged 2–6 months should receive a 3-dose series of Hib PRP-T as ActHib, Pentacel, or MenHibRix or a 2-dose series of Hib PRP-OMP as PedvaxHib or Comvax (Table 1). The first dose can be administered as early as age 6 weeks. A booster dose (which will be dose 3 or 4 depending on vaccine type used in primary series) of any licensed conjugate Hib vaccine (monovalent vaccine [PedvaxHib (PRP-OMP), ActHib (PRP-T), or Hiberix (PRP-T)] or Hib vaccine in combination with HepB [Comvax] or DTaP/IPV [Pentacel] or MenCY [MenHibRix]) is recommended at age 12 through 15 months and at least 8 weeks after the most recent Hib vaccination (Table 1).

Hib vaccine has been found to be immunogenic in patients with immunocompromising conditions although immunogenicity varies with the degree of immunocompetence (13,73–84). Patients at increased risk for invasive Hib disease who are vaccinated (have received a Hib primary series and a booster dose at age ≥ 12 months) do not need further routine immunization, except in certain situations (Table 2).

Guidance for Hib Vaccine Use

Guidance for Routine Vaccination

Doses for either primary series (2-dose or 3-dose) should be administered 8 weeks apart; however, if necessary, an interval of 4 weeks between doses is acceptable. If a PRP-OMP vaccine (PedvaxHIB or Comvax) is administered for both doses in the primary series, a third primary dose is not indicated. If a PRP-OMP vaccine (PedvaxHib or Comvax) is not administered for both doses in the primary series or there is uncertainty about which products were administered previously, a third primary series dose of a Hib conjugate vaccine is needed to complete the primary series. Any monovalent or combination Hib conjugate vaccine is acceptable for the booster dose (dose 3 or 4 depending on vaccine type used in primary series), regardless of the product used for the primary series. Hiberix should be used only for the booster dose (dose 3 or 4, depending on the vaccine type used for primary series) in children aged 12 months through 4 years who have received at least 1 dose of Hib vaccine previously.

Guidance for Catch-up Schedules

If the first vaccination is delayed by >1 month, the recommended catch-up schedule (available at <http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html>) should be followed.

- For unvaccinated infants receiving the first dose at age <7 months, 2 doses of PRP-OMP or 3 doses of PRP-T vaccine should be administered with a minimum of a 4-week interval between doses. A booster dose (dose 3 or 4 depending on vaccine type used for primary series) at age 12 through 15 months is necessary only if 2 or 3 primary doses (depending on vaccine type used) were administered before age 12 months.
- For unvaccinated infants receiving the first dose at age 7 through 11 months, a second dose should be administered at least 4 weeks later (regardless of Hib conjugate vaccine [PRP-T or PRP-OMP] used for first dose). A third (and final) dose should be administered at age 12 through 15 months or 8 weeks after the second dose, whichever date is later.
- For unvaccinated children receiving the first dose at age 12 through 14 months, a second dose of any monovalent or combination Hib conjugate vaccine should be administered 8 weeks after the first dose. A third dose is not necessary.
- For unvaccinated children receiving the first dose at age 15 through 59 months, no further doses of any monovalent or combination Hib conjugate vaccine are indicated.

TABLE 2. Guidance for *Haemophilus influenzae* type b (Hib) vaccination in high-risk groups

High-risk group*	Hib vaccine guidance
Patients aged <12 mos	Follow routine Hib vaccination recommendations
Patients aged 12–59 mos	If unimmunized or received 0 or 1 dose before age 12 mos: 2 doses, 8 wks apart If received ≥2 doses before age 12 mos: 1 dose 8 wks after last dose If completed a primary series and received a booster dose at age ≥12 mos: no additional doses
Patients aged <60 months undergoing chemotherapy or radiation therapy†	If routine Hib doses administered ≥14 days before starting therapy: revaccination not required If dose administered within 14 days of starting therapy or given during therapy: repeat doses starting at least 3 mos following therapy completion
Patients aged ≥15 mos undergoing elective splenectomy	If unimmunized:‡ 1 dose prior to procedure¶
Asplenic patients aged >59 mos and adults	If unimmunized:‡ 1 dose
HIV-infected children aged ≥60 mos	If unimmunized:‡ 1 dose
HIV-infected adults	Hib vaccination is not recommended
Recipients of hematopoietic stem cell transplant, all ages	Regardless of Hib vaccination history: 3 doses (at least 4 wks apart) beginning 6–12 mos after transplant

* Persons with functional or anatomic asplenia, HIV infection, immunoglobulin deficiency including immunoglobulin G2 subclass deficiency, or early component complement deficiency, recipients of a hematopoietic stem cell transplant, and those receiving chemotherapy or radiation therapy for malignant neoplasms.

† Some experts suggest conducting serologic testing for these patients (Source: Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2013;[Epub ahead of print] doi: 10.1093/cid/cit684).

‡ Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months are considered unimmunized.

¶ Some experts suggest vaccination at least 14 days before the procedure (Sources: CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2011;60[No. RR-2]; CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. *MMWR* 1993;42[No. RR-4]; Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2013;[Epub ahead of print] doi: 10.1093/cid/cit684.) Some experts suggest administering a dose prior to elective splenectomy regardless of prior vaccination history (Source: American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Pickering L, Baker C, Kimberlin D, Long S, eds. Red book: 2012 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012:345–52).

- Previously unvaccinated children aged ≥60 months who are not considered high-risk generally are immune to Hib disease and do not require catch-up vaccination.

The recommended catch-up schedule should be followed for children aged <12 months who are at increased risk for Hib disease and have delayed or no Hib vaccination. Catch-up guidance for children aged 12 through 59 months who are at increased risk for Hib disease and who have delayed or no Hib vaccination is described below (see “High-risk groups”; Table 2).

Guidance for Vaccinating Special Populations

American Indians/Alaska Natives

Hib meningitis incidence peaks at a younger age (4–6 months) among AI/AN infants than among other U.S. infant populations (6–7 months) (29–31). Vaccination with a 2 dose primary series of a Hib vaccine that contains PRP-OMP (PedvaxHIB or Comvax) is preferred for AI/AN infants to provide early protection because these vaccines produce a protective antibody response after the first dose (41–43,51,52,85). If the first vaccination dose is delayed by >1 month, the recommended catch-up schedule (available at <http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html>) should be followed. A booster dose (dose 3)

of Hib vaccine is recommended at age 12 through 15 months; for the booster dose, there is no preferred vaccine formulation (i.e., any licensed Hib conjugate vaccine is acceptable). The importance of this early protection was demonstrated in Alaska (30,86). During July 1991–January 1996, a PRP-OMP vaccine was used statewide in Alaska and a >90% decrease in Hib disease rates occurred among AN and nonnative children (30,86). During 1996–1997, after the statewide vaccine was changed to a combination vaccine that included a non-OMP Hib component, Hib incidence increased significantly (19.8 to 91.1 cases/100,000 children aged <5 years, $p<0.001$) among AN children while remaining unchanged among nonnative children (30,86). Disease reappearance seemed to be attributable to the use of a Hib vaccine that did not achieve early protective antibody concentrations in children who had ongoing exposure to Hib via oropharyngeal colonization among close contacts. After returning to the use of PRP-OMP containing vaccines in Alaska, the incidence of Hib disease in AN children decreased to rates of fewer than six cases per 100,00 children aged <5 years (30,86).

Children Aged <24 Months with Invasive Hib Disease

Children aged <24 months who develop invasive Hib disease can remain at risk for developing a second episode because natural infection in this age group does not reliably result in development of protective antibody levels. These children

should be considered unvaccinated regardless of previous Hib vaccination and should receive Hib vaccine doses according to the age-appropriate schedule for unimmunized children (28,87–89). Children aged <24 months who develop invasive Hib disease should receive primary vaccination or re-vaccination with a second primary series beginning 4 weeks after onset of disease.

Preterm Infants

Medically stable preterm infants[§] should be vaccinated beginning at age 2 months according to the schedule recommended for other infants, on the basis of chronological age.

High Risk Groups

Persons considered at increased risk for invasive Hib disease include those with functional or anatomic asplenia, HIV infection, immunoglobulin deficiency (including immunoglobulin G2 subclass deficiency), or early component complement deficiency, recipients of a hematopoietic stem cell transplant, and those receiving chemotherapy or radiation therapy for malignant neoplasms. A single dose of any licensed Hib conjugate vaccine should be administered to unimmunized older children, adolescents, and adults who are asplenic or who are scheduled for an elective splenectomy. Some experts suggest administering a dose prior to elective splenectomy regardless of prior vaccination history (22). On the basis of limited data on the timing of Hib vaccination before splenectomy, experts suggest vaccination at least 14 days before the procedure (18,19,23) (Table 2).

Unimmunized children aged ≥60 months who have HIV infection should receive 1 dose of Hib vaccine. Whether HIV-infected children who have received a full 3 or 4 dose vaccine series (depending on the vaccine type used for the primary series) will benefit from additional Hib doses is unknown. Because the incidence of Hib infections among HIV-infected adults is low, Hib vaccine is not recommended for adults with HIV infection (21,23) (Table 2).

Children aged 12–59 months who are at increased risk for Hib disease (persons with asplenia, HIV infection, immunoglobulin deficiency, early component complement deficiency, or chemotherapy or radiation therapy recipients) and who received no doses or only 1 dose of Hib conjugate vaccine before age 12 months should receive 2 additional doses of vaccine 8 weeks apart; children who received 2 or more doses of Hib conjugate vaccine before age 12 months should receive 1 additional dose, at least 8 weeks after the last dose (Table 2).

Hib vaccination during chemotherapy or radiation therapy should be avoided because of possible suboptimal antibody

response. Patients vaccinated within 14 days of starting immunosuppressive therapy or while receiving immunosuppressive therapy should be considered unimmunized, and doses should be repeated beginning at least 3 months following completion of chemotherapy. Patients who were vaccinated more than 14 days before chemotherapy do not require revaccination, with the exception of recipients of a hematopoietic stem cell transplant who should be revaccinated with a 3-dose regimen 6–12 months after successful transplant, regardless of vaccination history (80); at least 4 weeks should separate doses (Table 2).

Guidance for Vaccine Administration

Hib vaccines are administered intramuscularly in individual doses of 0.5 mL. Adverse events occurring after administration of any vaccine should be reported to VAERS. Reports can be submitted to VAERS online, by facsimile, or by mail. More information about VAERS is available by calling 1-800-822-7967 (toll-free) or online at <http://vaers.hhs.gov>.

Interchangeability of Vaccine Product

Studies have demonstrated that any combination of licensed monovalent Hib conjugate vaccines for the primary and booster doses provide comparable or higher antibody levels than with the same monovalent product (33,44–46,51,91–93). Therefore, licensed monovalent Hib conjugate vaccines are considered interchangeable for the primary as well as the booster doses (dose 3 or 4, depending on vaccine type used for primary series) (18,94). Data on the interchangeability of combination vaccines with other combination vaccines or with monovalent vaccines are limited (52,63). Whenever feasible, the same combination vaccine should be used for the subsequent doses; however, if a different brand is administered, the dose should be considered valid and need not be repeated.

Precautions and Contraindications

Adverse reactions to Hib-containing monovalent vaccines are uncommon, usually mild, and generally resolve within 12–24 hours (41–43,49). Rates of adverse reactions to Hib combination vaccines are similar to those observed with separately administered vaccines (14,33,52–54). More complete information about adverse reactions to a specific vaccine is available in the package insert for each vaccine and from CDC at <http://www.cdc.gov/vaccines/vac-gen/side-effects.htm>.

Vaccination with a Hib-containing vaccine is contraindicated in infants aged <6 weeks. Vaccination with a Hib-containing vaccine is contraindicated among persons known to have a severe allergic reaction to any component of the vaccine. The

[§] Infants who do not require ongoing management for serious infection, metabolic disease, or acute renal, cardiovascular, neurologic, or respiratory tract illness and who demonstrate a clinical course of sustained recovery and pattern of steady growth (90).

tip caps of the Hiberix prefilled syringes might contain natural rubber latex, and the vial stoppers for Comvax, ActHib, and PedvaxHIB contain natural rubber latex, which might cause allergic reactions in persons who are latex-sensitive. Therefore, vaccination with these vaccines is contraindicated for persons known to have a severe allergic reaction to dry natural rubber latex (48,50–52). The vial stoppers for Pentacel and MenHibRix do not contain latex (63,95). Vaccination with Comvax is contraindicated in patients with a hypersensitivity to yeast (52).

As with all pertussis-containing vaccines, benefits and risk should be considered before administering Pentacel to persons with a history of fever $\geq 40.5^{\circ}\text{C}$, hypotonic-hyporesponsive episode, persistent inconsolable crying lasting ≥ 3 hours within 48 hours after receipt of a pertussis-containing vaccine, or seizures within 3 days after receiving a pertussis-containing vaccine (63).

Hib monovalent and combination conjugate vaccines are inactivated vaccines and may be administered to persons with immunocompromising conditions. However, immunologic response to the vaccine might be suboptimal (18).

Guidance for Chemoprophylaxis

Secondary cases of Hib disease (illness occurring within 60 days of contact with a patient) occur but are rare. Secondary attack rates are higher among household contacts aged <48 months (2.1%), especially those aged <12 months (6%) and <24 months (3%) (29). Data are conflicting on the risk for secondary illness among child care contacts, but it is thought to be lower than among household contacts (29). Rifampin is recommended for chemoprophylaxis because it achieves high concentrations in respiratory secretions and eradicates nasopharyngeal carriage in $>95\%$ of carriers (96–99). There are no guidelines for control measures around cases of invasive nontype b *H. influenzae* disease. Chemoprophylaxis is not recommended for contacts of persons with invasive disease caused by nontype b *H. influenzae* because cases of secondary transmission of disease have not been documented (100,101).

Index Patients with Invasive Hib Disease

Index patients who are treated with an antibiotic other than cefotaxime or ceftriaxone and are aged <2 years should receive rifampin prior to hospital discharge (22). Because cefotaxime and ceftriaxone eradicate Hib colonization, prophylaxis is not needed for patients treated with either of these antimicrobials.

Household Contacts

Rifampin chemoprophylaxis is recommended for index patients (unless treated with cefotaxime or ceftriaxone) and all household contacts in households with members aged <4 years

who are not fully vaccinated or members aged <18 years who are immunocompromised, regardless of their vaccination status (22).

Child Care Contacts

Rifampin chemoprophylaxis is recommended in child care settings when two or more cases of invasive Hib disease have occurred within 60 days and unimmunized or underimmunized children attend the facility (22). When prophylaxis is indicated, it should be prescribed for all attendees, regardless of age or vaccine status, and for child care providers.

Conclusion

Hib disease was once a leading cause of bacterial meningitis among U.S. children aged <5 years. As a result of the introduction of Hib vaccines in the United States and sustained high vaccine coverage, Hib disease is now rare, with rates below the Healthy People 2020 objective. However, the risk for invasive Hib disease continues among unimmunized and underimmunized children, highlighting the importance of full vaccination with the primary series and booster doses. Although Hib disease is uncommon, continued *H. influenzae* surveillance with complete serotyping data is necessary so that all Hib cases are identified and appropriate chemoprophylaxis measures can be taken.

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