**Haemophilus influenzae type b**

*Haemophilus influenzae* is a cause of bacterial infections that are often severe, particularly among infants. It was first described by Pfeiffer in 1892. During an outbreak of influenza he found the bacteria in sputum of patients and proposed a causal association between this bacterium and the clinical syndrome known as influenza. The organism was given the name *Haemophilus* by Winslow, et al. in 1920. It was not until 1933 that Smith, et al. established that influenza was caused by a virus and that *H. influenzae* was a cause of secondary infection.

In the 1930s, Margaret Pittman demonstrated that *H. influenzae* could be isolated in encapsulated and unencapsulated forms. She identified six capsular types (a–f), and observed that virtually all isolates from cerebrospinal fluid (CSF) and blood were of the capsular type b.

Before the introduction of effective vaccines, *H. influenzae* type b (Hib) was the leading cause of bacterial meningitis and other invasive bacterial disease among children younger than 5 years of age; approximately one in 200 children in this age group developed invasive Hib disease. Nearly all Hib infections occurred among children younger than 5 years of age, and approximately two-thirds of all cases occurred among children younger than 18 months of age.

**Haemophilus influenzae**

*Haemophilus influenzae* is a gram-negative coccobacillus. It is generally aerobic but can grow as a facultative anaerobe. In vitro growth requires accessory growth factors, including “X” factor (hemin) and “V” factor (nicotinamide adenine dinucleotide [NAD]).

Chocolate agar media are used for isolation. *H. influenzae* will generally not grow on blood agar, which lacks NAD.

The outermost structure of *H. influenzae* is composed of polyribosyl-ribitol-phosphate (PRP), a polysaccharide that is responsible for virulence and immunity. Six antigenically and biochemically distinct capsular polysaccharide serotypes have been described; these are designated types a through f. In the prevaccine era, type b organisms accounted for 95% of all strains that caused invasive disease.

**Pathogenesis**

The organism enters the body through the nasopharynx. Organisms colonize the nasopharynx and may remain only transiently or for several months in the absence of symptoms (asymptomatic carrier). In the prevaccine era, Hib could be...
isolated from the nasopharynx of 0.5%–3% of normal infants and children but was not common in adults. Nontypeable (unencapsulated) strains are also frequent inhabitants of the human respiratory tract.

In some persons, the organism causes an invasive infection. The exact mode of invasion to the bloodstream is unknown. Antecedent viral or mycoplasma infection of the upper respiratory tract may be a contributing factor. The bacteria spread in the bloodstream to distant sites in the body. Meninges are especially likely to be affected.

The most striking feature of Hib disease is age-dependent susceptibility. Hib disease is not common beyond 5 years of age. Passive protection of some infants is provided by transplacentally acquired maternal IgG antibodies and breastfeeding during the first 6 months of life. In the prevaccine era peak attack rates occurred at 6–7 months of age, declining thereafter. The presumed reason for this age distribution is the acquisition of immunity to Hib with increasing age.

Antibodies to Hib capsular polysaccharide are protective. The precise level of antibody required for protection against invasive disease is not clearly established. However, a titer of 1 \( \mu g/mL \) 3 weeks postvaccination correlated with protection in studies following vaccination with unconjugated purified polyribosyl-ribitol-phosphate (PRP) vaccine and suggested long-term protection from invasive disease.

Acquisition of both anticapsular and serum bactericidal antibody is inversely related to the age-specific incidence of Hib disease.

In the prevaccine era, most children acquired immunity by 5–6 years of age through asymptomatic infection by Hib bacteria. Since only a relatively small proportion of children carry Hib at any time, it has been postulated that exposure to organisms that share common antigenic structures with the capsule of Hib (so-called “cross-reacting organisms”) may also stimulate the development of anticapsular antibodies against Hib. Natural exposure to Hib also induces antibodies to outer membrane proteins, lipopolysaccharides, and other antigens on the surface of the bacterium.

The genetic constitution of the host may also be important in susceptibility to infection with Hib. Risk for Hib disease has been associated with a number of genetic markers, but the mechanism of these associations is unknown. No single genetic relationship regulating susceptibility or immune responses to polysaccharide antigens has yet been convincingly demonstrated.
Clinical Features

Invasive disease caused by *H. influenzae* type b can affect many organ systems. The most common types of invasive disease are meningitis, epiglottitis, pneumonia, arthritis, and cellulitis.

Meningitis is infection of the membranes covering the brain and is the most common clinical manifestation of invasive Hib disease, accounting for 50%–65% of cases in the prevaccine era. Hallmarks of Hib meningitis are fever, decreased mental status, and stiff neck (these symptoms also occur with meningitis caused by other bacteria). Hearing impairment or other neurologic sequelae occur in 15%–30% of survivors. The case-fatality rate is 2%–5%, despite appropriate antimicrobial therapy.

Epiglottitis is an infection and swelling of the epiglottis, the tissue in the throat that covers and protects the larynx during swallowing. Epiglottitis may cause life-threatening airway obstruction.

Septic arthritis (joint infection), cellulitis (rapidly progressing skin infection which usually involves face, head, or neck), and pneumonia (which can be mild focal or severe empyema) are common manifestations of invasive disease.

Osteomyelitis (bone infection) and pericarditis (infection of the sac covering the heart) are less common forms of invasive disease. Otitis media and acute bronchitis due to *H. influenzae* are generally caused by nontypeable strains. Hib strains account for only 5%–10% of *H. influenzae* causing otitis media.

Nontypeable (unencapsulated) strains may cause invasive disease but are generally less virulent than encapsulated strains. Nontypeable strains are rare causes of serious infection among children but are a common cause of ear infections in children and bronchitis in adults.

Laboratory Diagnosis

A Gram stain of an infected body fluid may demonstrate small gram-negative coccobacilli suggestive of invasive *Haemophilus* disease. CSF, blood, pleural fluid, joint fluid, and middle ear aspirates should be cultured on appropriate media. A positive culture for *H. influenzae* establishes the diagnosis.

All isolates of *H. influenzae* should be serotyped. This is an extremely important laboratory procedure that should be performed on every isolate of *H. influenzae*, especially those obtained from children younger than 15 years of age. This test determines whether an isolate is type b, which is the only type that is potentially vaccine preventable. Serotyping
Haemophilus influenzae type b

Medical Management
Hospitalization is generally required for invasive Hib disease. Antimicrobial therapy with an effective third-generation cephalosporin (cefotaxime or ceftriaxone), or chloramphenicol in combination with ampicillin should be begun immediately. The treatment course is usually 10 days. Ampicillin-resistant strains of Hib are now common throughout the United States. Children with life-threatening illness in which Hib may be the etiologic agent should not receive ampicillin alone as initial empiric therapy.

Epidemiology

Occurrence
Hib disease occurs worldwide.

Reservoir
Humans (asymptomatic carriers) are the only known reservoir. Hib does not survive in the environment on inanimate surfaces.

Transmission
The primary mode of Hib transmission is presumably by respiratory droplet spread, although firm evidence for this mechanism is lacking.

Temporal Pattern
Several studies in the prevaccine era described a bimodal seasonal pattern in the United States, with one peak during September through December and a second peak during March through May. The reason for this bimodal pattern is not known.
Communicability

The contagious potential of invasive Hib disease is considered to be limited. However, certain circumstances, particularly close contact with a case-patient (e.g., household, childcare, or institutional setting) can lead to outbreaks or direct secondary transmission of the disease.

Secular Trends in the United States

*H. influenzae* infections became nationally reportable in 1991. Serotype-specific reporting continues to be incomplete.

Before the availability of national reporting data, several areas conducted active surveillance for *H. influenzae* disease, which allowed estimates of disease nationwide. In the early 1980s, it was estimated that about 20,000 cases occurred annually in the United States, primarily among children younger than 5 years of age (40–50 cases per 100,000 population). The incidence of invasive Hib disease began to decline dramatically in the late 1980s, coincident with licensure of conjugate Hib vaccines, and has declined by more than 99% compared with the prevaccine era.

From 1996 through 2000, an average of 1,247 invasive *H. influenzae* infections per year were reported to CDC in all age groups (range 1,162–1,398 per year). Of these, an average of 272 (approximately 22%) per year were among children younger than 5 years of age. Serotype was known for 76% of the invasive cases in this age group. Three-hundred forty-one (average of 68 cases per year) were due to type b.

There is evidence that Hib vaccines decrease the rate of carriage of Hib among vaccinated children, thereby decreasing the chance that unvaccinated children will be exposed.

Incidence is strikingly age-dependent. In the prevaccine era, up to 60% of invasive disease occurred before age 12 months, with a peak occurrence among children 6–11 months of age. Children 60 months of age and older account for less than 10% of invasive disease.

In 1998–2000, approximately 44% of children younger than 5 years of age with confirmed invasive Hib disease were younger than 6 months of age and too young to have completed a three-dose primary vaccination series. Fifty-six percent were age 6 months or older and were eligible to have completed the primary vaccination series. Of these age-eligible children, 68% were either incompletely vaccinated (fewer than 3 doses) or their vaccination status was unknown. Thirty-two percent of children aged 6–59 months with confirmed type b disease had received three or more doses of Hib vaccine, including 22 who had received a booster dose 14 or more days before onset of their illness. The cause of Hib vaccine failure in these children is not known.
In 2009, among children younger than 5 years of age, 35 cases of invasive disease due to Hib were reported in the United States. In addition, another 178 cases caused by unknown *H. influenzae* serotypes were reported, so the actual number of Hib cases could be between 35 and 213. Most cases were among unvaccinated or incompletely vaccinated children.

Risk factors for Hib disease include exposure factors and host factors that increase the likelihood of exposure to Hib. Exposure factors include household crowding, large household size, child care attendance, low socioeconomic status, low parental education levels, and school-aged siblings. Host factors include race/ethnicity (elevated risk among African Americans, Hispanics, Native Americans—possibly confounded by socioeconomic variables that are associated with both race/ethnicity and Hib disease), chronic disease (e.g., sickle cell anemia, antibody deficiency syndromes, malignancies, especially during chemotherapy), and possibly gender (risk is higher for males).

Protective factors (effect limited to infants younger than 6 months of age) include breastfeeding and passively acquired maternal antibody.

Secondary Hib disease is defined as illness occurring 1–60 days following contact with an ill child, and accounts for less than 5% of all invasive Hib disease. Among household contacts, six studies have found a secondary attack rate of 0.3% in the month following onset of the index case, which is about 600-fold higher than the risk for the general population. Attack rates varied substantially with age, from 3.7% among children 2 years of age and younger to 0% among contacts 6 years of age and older. In these household contacts, 64% of secondary cases occurred within the first week (excluding the first 24 hours) of disease onset in the index patient, 20% during the second week, and 16% during the third and fourth weeks.

Data are conflicting regarding the risk of secondary transmission among child care contacts. Secondary attack rates have varied from 0% to as high as 2.7%. Most studies seem to suggest that child care contacts are at relatively low risk for secondary transmission of Hib disease particularly if contacts are age-appropriately vaccinated.

**Haemophilus influenzae type b Vaccines**

**Characteristics**

A pure polysaccharide vaccine (HbPV) was licensed in the United States in 1985. The vaccine was not effective in children younger than 18 months of age. Estimates of efficacy in older children varied widely, from 88% to -69% (a negative efficacy implies greater disease risk for vaccinees
than nonvaccinees. HbPV was used until 1988 but is no longer available in the United States.

The characteristics of the Hib polysaccharide were similar to other polysaccharide vaccines (e.g., pneumococcal, meningococcal). The response to the vaccine was typical of a T-independent antigen, most notably an age-dependent immune response, and poor immunogenicity in children 2 years of age and younger. In addition, no boost in antibody titer was observed with repeated doses, the antibody that was produced was relatively low-affinity IgM, and switching to IgG production was minimal.

**Haemophilus influenzae type b Polysaccharide-Protein Conjugate Vaccines**

Conjugation is the process of chemically bonding a polysaccharide (a somewhat ineffective antigen) to a protein “carrier,” which is a more effective antigen. This process changes the polysaccharide from a T-independent to a T-dependent antigen and greatly improves immunogenicity, particularly in young children. In addition, repeat doses of Hib conjugate vaccines elicit booster responses and allow maturation of class-specific immunity with predominance of IgG antibody. The Hib conjugates also cause carrier priming and elicit antibody to “useful” carrier protein.

The first Hib conjugate vaccine (PRP-D, ProHIBIT) was licensed in December 1987. PRP-D is no longer available in the United States. HibTITER (HbOC) is also no longer available.

Two conjugate Hib vaccines are licensed for use in infants as young as 6 weeks of age (see below). A third Hib vaccine (Hiberix) is approved only for the last dose of the Hib schedule among children 12 months and older. The vaccines utilize different carrier proteins. Two combination vaccines that contain Hib conjugate vaccine are also available.

**Haemophilus influenzae type b Conjugate Vaccines**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Protein Carrier</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-T (ActHIB)</td>
<td>Tetanus toxoid</td>
<td>sanofi pasteur</td>
</tr>
<tr>
<td>PRP-T (Hiberix)</td>
<td>Tetanus toxoid</td>
<td>GSK</td>
</tr>
<tr>
<td>PRP-OMP (PedvaxHIB)</td>
<td>Meningococcal group B outer membrane protein</td>
<td>Merck</td>
</tr>
</tbody>
</table>

**Immunogenicity and Vaccine Efficacy**

Hib conjugate vaccines licensed for use in infants are highly immunogenic. More than 95% of infants will develop protective antibody levels after a primary series of two or three doses. Clinical efficacy has been estimated at 95% to 100%. Invasive Hib disease in a completely vaccinated infant is uncommon.
Haemophilus influenzae type b

Hib vaccine is immunogenic in patients with increased risk for invasive disease, such as those with sickle-cell disease, leukemia, or human immunodeficiency virus (HIV) infection, and those who have had a splenectomy. However, in persons with HIV infection, immunogenicity varies with stage of infection and degree of immunocompromise. Efficacy studies have not been performed in populations with increased risk of invasive disease.

Vaccination Schedule and Use
All infants, including those born prematurely, should receive a primary series of conjugate Hib vaccine (separate or in combination), beginning at 2 months of age. The number of doses in the primary series depends on the type of vaccine used. A primary series of PRP-OMP (PedvaxHIB) vaccine is two doses; PRP-T (ActHIB) requires a three-dose primary series (see table below). A booster is recommended at 12–15 months regardless of which vaccine is used for the primary series.

ACIP-Recommended Haemophilus influenzae type b (Hib) Routine Vaccine Schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>2 Months</th>
<th>4 Months</th>
<th>6 Months</th>
<th>12–15 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-T*</td>
<td>Dose 1</td>
<td>Dose 2</td>
<td>Dose 3</td>
<td>Booster</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>Dose 1</td>
<td>Dose 2</td>
<td></td>
<td>Booster</td>
</tr>
</tbody>
</table>

*Hiberix brand PRP-T vaccine is approved only for the last dose of the Hib series among children 12 months of age and older

The recommended interval between primary series doses is 8 weeks, with a minimum interval of 4 weeks. At least 8 weeks should separate the booster dose from the previous (second or third) dose. Hib vaccines may be given simultaneously with all other vaccines.

Limited data suggest that Hib conjugate vaccines given before 6 weeks of age may induce immunologic tolerance to subsequent doses of Hib vaccine. A dose given before 6 weeks of age may reduce the response to subsequent doses. As a result, Hib vaccines, including combination vaccines that contain Hib conjugate, should never be given to a child younger than 6 weeks of age.

With the exception of Hiberix, the conjugate Hib vaccines licensed for use in infants are interchangeable. A series that includes vaccine of more than one type will induce a protective antibody level. If a child receives different brands of Hib vaccine at 2 and 4 months of age, a third dose of either brand should be administered at 6 months of age to complete the primary series. Either vaccine may be used for the booster dose, regardless of what was administered in the primary series.

Unvaccinated children 7 months of age and older may not
require a full series of three or four doses. The number of
doses a child needs to complete the series depends on the
child's current age.

**Detailed Vaccination Schedule for *Haemophilus influenzae* type b Conjugate Vaccines**

| Vaccine          | Age at 1st Dose (Months) | Primary Series | Booster
|------------------|--------------------------|---------------|---------
| PRP-T (ActHIB)   | 2–6                      | 3 doses, 2 months apart | 12–15 months* |
|                  | 7–11                     | 2 doses, 2 months apart | 12–15 months* |
|                  | 12–14                    | 1 dose         | 2 months later |
|                  | 15–59                    | 1 dose         | —        |
| PRP-OMP (PedvaxHIB) | 2–6                      | 2 doses, 2 months apart | 12–15 months* |
|                  | 7–11                     | 2 doses, 2 months apart | 12–15 months* |
|                  | 12–14                    | 1 dose         | 2 months later |
|                  | 15–59                    | 1 dose         | —        |

‡ Hiberix brand PRP-T vaccine is approved only for the last dose of the Hib series among children 12 months of age and older
*At least 2 months after previous dose

**PRP-T (ActHIB)**

Previously unvaccinated infants aged 2 through 6 months
should receive three doses of vaccine administered 2
months apart, followed by a booster dose at age 12–15
months, administered at least 2 months after the last dose.
Unvaccinated children aged 7 through 11 months should
receive two doses of vaccine 2 months apart, followed by
a booster dose at age 12–15 months, administered at least
2 months after the last dose. Unvaccinated children aged
12 through 14 months should receive one dose of vaccine
followed by a booster at least 2 months later. Any previously
unvaccinated child aged 15 through 59 months should
receive a single dose of vaccine.

**PRP-OMP (PedvaxHIB)**

Unvaccinated children aged 2 through 11 months should
receive two doses of vaccine 2 months apart, followed by
a booster dose at 12–15 months of age, at least 2 months
after the last dose. Unvaccinated children aged 12 through
14 months should receive one dose of vaccine followed by a
booster at least 2 months later. Any previously unvaccinated
child 15 through 59 months of age should receive a single
dose of vaccine.

Children with a lapsed Hib immunization series (i.e., children
who have received one or more doses of Hib-containing
vaccine but are not up-to-date for their age) may not need
all the remaining doses of a three- or four-dose series.
Vaccination of children with a lapsed schedule is addressed
in the catch-up schedule, published annually with the child-
hood vaccination schedule.
**Haemophilus influenzae type b**

Hib invasive disease does not always result in development of protective anti-PRP antibody levels. Children younger than 24 months of age who develop invasive Hib disease should be considered susceptible and should receive Hib vaccine. Vaccination of these children should start as soon as possible during the convalescent phase of the illness. The schedule should be completed as recommended for the child's age.

**Vaccination of Older Children and Adults**

In general, Hib vaccination of persons older than 59 months of age is not recommended. The majority of older children are immune to Hib, probably from asymptomatic infection as infants. However, some older children and adults are at increased risk for invasive Hib disease and may be vaccinated if they were not vaccinated in childhood. These include those with functional or anatomic asplenia (e.g., sickle cell disease, postsplenectomy), immunodeficiency (in particular, persons with IgG2 subclass deficiency), immunosuppression from cancer chemotherapy, infection with HIV, and receipt of a hematopoietic stem cell transplant (HSCT). Previously unvaccinated persons older than 59 months of age with one of these high-risk conditions should be given at least one pediatric dose of any Hib conjugate vaccine.

**Combination Vaccines**

Two combination vaccines that contain *H. influenzae* type b are available in the United States–DTaP-IPV-Hib (Pentacel, sanofi pasteur) and hepatitis B–Hib (Comvax, Merck). A third combination, TriHiBit, is no longer available in the U.S.

**Comvax**

Comvax (Merck) is a combination hepatitis B–Hib vaccine, licensed in October 1996. The vaccine contains a standard dose of PRP-OMP (PedvaxHIB), and 5 mcg (pediatric dose) of Merck’s hepatitis B vaccine. Comvax is licensed for use when either or both antigens are indicated. However, because of the potential of immune tolerance to the Hib antigen, Comvax should not be used in infants younger than 6 weeks of age (i.e., the birth dose of hepatitis B, or a dose at 1 month of age, if the infant is on a 0-1-6-month schedule). Comvax is not licensed for infants whose mothers are HBsAg positive or whose HBsAg status is unknown. However, the vaccine contains the same dose of Merck’s hepatitis B vaccine recommended for these infants, so response to the hepatitis B component of Comvax should be adequate. The Advisory Committee on Immunization Practices (ACIP) has approved off-label use of Comvax in children whose mother is HBsAg positive or whose HBsAg status is unknown. See http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/1003hepb.pdf.
Recommendations for spacing and timing of Comvax are the same as those for the individual antigens. In particular, the third dose must be given at 12 months of age or older and at least 2 months after the second dose, as recommended for PRP-OMP.

**Pentacel**

Pentacel (sanofi pasteur) is a combination vaccine that contains lyophilized Hib (ActHIB) vaccine that is reconstituted with a liquid DTaP-IPV solution. The vaccine was licensed by FDA in June 2008. Pentacel is licensed by FDA for doses 1 through 4 of the DTaP series among children 6 weeks through 4 years of age. Pentacel should not be used for the fifth dose of the DTaP series, or for children 5 years or older regardless of the number of prior doses of the component vaccines.

The DTaP-IPV solution is licensed only for use as the diluent for the lyophilized Hib component and should not be used separately. If the DTaP-IPV solution is inadvertently administered without being used to reconstitute the Hib component the DTaP and IPV doses can be counted as valid. However, PRP-T (ActHib) must be reconstituted only with the DTaP-IPV diluent supplied in the Pentacel package, or with a specific 0.4% sodium chloride ActHib diluent. If DTaP-IPV diluent is not available then the provider must contact the manufacturer (sanofi pasteur) to obtain the ActHib diluent. Any dose of ActHib reconstituted with a diluent other than DTaP-IPV or specific ActHib diluent should not be counted as valid and must be repeated.

**Contraindications and Precautions to Vaccination**

Vaccination with Hib conjugate vaccine is contraindicated for persons known to have experienced a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of that vaccine. Vaccination should be delayed for children with moderate or severe acute illnesses. Minor illnesses (e.g., mild upper respiratory infection) are not contraindications to vaccination. Hib conjugate vaccines are contraindicated for children younger than 6 weeks of age because of the potential for development of immunologic tolerance.

Contraindications and precautions for the use of Pentacel and Comvax are the same as those for its individual component vaccines (i.e., DTaP, Hib, IPV, and hepatitis B).

**Adverse Reactions Following Vaccination**

Adverse reaction following Hib conjugate vaccines are not common. Swelling, redness, or pain have been reported in 5%–30% of recipients and usually resolve within 12–24
Haemophilus influenzae type b

Vaccine Adverse Reactions
- Swelling, redness, or pain in 5%-30% of recipients
- Systemic reactions infrequent
- Serious adverse reactions rare

hours. Systemic reactions such as fever and irritability are infrequent. Serious adverse reactions are rare.

All serious adverse events that occur after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS) (http://vaers.hhs.gov/).

Vaccine Storage and Handling
All Hib conjugate vaccines should be shipped in insulated containers to prevent freezing. Unreconstituted or liquid vaccine should be stored at refrigerator temperature (35°–46°F [2°–8°C]). Hib vaccine must not be frozen.

ActHIB should be used within 24 hours of reconstitution.

Surveillance and Reporting of Hib Disease
Invasive Hib disease is a reportable condition in most states. All healthcare personnel should report any case of invasive Hib disease to local and state health departments.

Selected References


CDC. Licensure of a Haemophilus influenzae Type b (Hib) Vaccine (Hiberix) and Updated Recommendations for Use of Hib Vaccine. MMWR 2009;58:1008-9.

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