# Post-Licensure Impact of *Haemophilus influenzae* Type b and Serogroup C *Neisseria meningitidis* Conjugate Vaccines in Industrialized Countries

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## INTRODUCTION

Polysaccharide-protein conjugate vaccines are established tools for the prevention of serious disease caused by encapsulated bacteria. Conjugate vaccines to prevent disease caused by *Haemophilus influenzae* type b (Hib) and serogroup C meningococcus (MCC) have been used in routine national immunization programs over a number of years. In this chapter, we review development and implementation of these vaccines, and present data from industrialized countries demonstrating their striking impact and the continued need for effective enhanced surveillance post-vaccine introduction.

## THE BACTERIA

*H. influenzae* and *Neisseria meningitidis* are unrelated bacteria, which share a number of characteristics, the most obvious being their ability to cause bacterial meningitis and septicemia in humans.

*H. influenzae* is a gram-negative coccobacillus, which colonizes the human oropharynx. A minority of these organisms have polysaccharide capsules. The encapsulated strains are characterized on the basis of the antigenic properties of the capsule. Of the six serologically identified types (designated a–f), organisms with the type b capsule (Hib) are the most virulent.

Since humans are the only biologically relevant reservoir of *H. influenzae*, transmission of the organism occurs by person-to-person spread, usually through direct or indirect exchange of oropharyngeal secretions. After introduction into the oropharynx, *H. influenzae* may establish relatively long-term colonization (often lasting several months or more) or, primarily in the case of Hib, may invade through the mucosa and enter the bloodstream. Once the organism gains access to the bloodstream, it multiplies and may seed other sites, such as the meninges, joint spaces, or soft tissue. If Hib remains unchecked, clinical sepsis may follow, with or without manifestations of localized disease. Hib also causes lower respiratory tract infection, presumably by aspiration or direct extension from the oropharynx; only a minority of these lower respiratory tract infections result in bacteremia.

*N. meningitidis* is a gram-negative coccus with a polysaccharide capsule. The capsular polysaccharides of meningococcus define the serogroup. Thirteen serogroups have been identified, of which six (A, B, C, W135, X, and Y) commonly cause invasive human disease (1). Serogroups A, B, and C are the most important in terms of morbidity and mortality worldwide, accounting for 90% or more cases of clinical disease. All three of these serogroups may cause endemic disease. Serogroup A strains have caused most of the major outbreaks, especially in the African ''meningitis belt.'' Serogroups B and C have been associated with outbreaks in the developed world, usually with substantially lower incidence rates than those in the meningitis belt. Humans are the only recognized host for *N. meningitides*, and there is no known animal or environmental reservoir.

*N. meningitidis*, similar to Hib, colonizes the human oropharynx. Meningococcus is highly adapted to this commensal existence in humans, with a range of strategies for evasion of the immune response. The carrier state may last for a few days to months; it provides a reservoir for infection and enhances the immunity of the host. As with Hib, invasive disease—primarily meningitis and/or sepsis—may follow carriage, but meningococcus is a less common cause of pneumonia.

## EPIDEMIOLOGY OF DISEASE: HIB

In the 1940s, Hattie Alexander, a pediatrician and microbiologist working in New York City, demonstrated that if appropriate bacteriological methods were used, the fastidious bacterium Hib was commonly isolated from the cerebrospinal fluid (CSF) and blood of infants with purulent meningitis (2,3). With more widespread availability of appropriate bacteriological methods and the culturing of blood and ordinarily sterile body fluids (e.g., CSF, synovial fluid, etc.) from infants with focal infections and suspected sepsis as a standard of care, in the 1960s and 1970s, Hib came to be recognized as a major cause of severe invasive pediatric infections in industrialized countries in North America (4–6), northern and western Europe (7–13) and Australia (14), and New Zealand (15). Indeed, prior to the introduction of routine immunization of infants and toddlers with Hib conjugates in these industrialized countries, Hib was the most predominant agent responsible for bacterial meningitis and a major cause of various other invasive infections (e.g., septic arthritis, pericarditis, periorbital cellulitis), as well as pneumonia with empyema and epiglottitis among children less than five years of age. In the United States, for example, in 1987, prior to infant Hib conjugate vaccine introduction, the incidence of invasive Hib disease was 41 cases per 100,000 children <5 years of age, with a peak incidence from 6 to 11 months of age. In the late 1970s and early 1980s, approximately 20,000 invasive Hib cases occurred annually prior to the