From Pandemic Suspect to the Postvaccine Era: The *Haemophilus influenzae* Story

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(See the article by Dworkin et al. on pages 810–6)

The history of the gram-negative coccobacillus, now known as *Haemophilus influenzae,* has several exciting chapters. In the frenzy of microbiologists' quest to identify the etiologic agent responsible for the devastating 1918 pandemic of influenza, the Pfeiffer's bacillus, or *Bacillus influenzae,* repeatedly occurred in pathology samples obtained from persons who died of fatal respiratory infections [1]. It is ironic that the organism, eventually designated *H. influenzae,* which was once so widely evident in laboratory tests (albeit, only fleetingly considered the cause of the "Spanish flu"), is now a rarely visible culprit that is still responsible for a huge toll of childhood illness in resource-poor countries. The story in between is one of progress and promise, with near elimination of serotype b disease in the United States and the emergence of new global initiatives for the poorest countries. Dworkin et al. [2], in this issue of *Clinical Infectious Diseases,* provide a new chapter in the *H. influenzae* story by describing 9 years of surveillance for invasive *H. influenzae* disease in Illinois during 1996–2004.

In 1987, *H. influenzae* type b polysaccharide-protein conjugate vaccines were licensed in the United States for children aged ⩾18 months, and before conjugate vaccines were even recommended for infants in the 2, 4, 6–month schedule in October 1990 by the Advisory Committee on Immunization Practices [3], a phenomenal herd effect was already occurring, as children who had been too young to be immunized began to experience significantly lower risk of disease [4]. The epidemiological trends were explained by the vaccine's ability to reduce acquisition of *H. influenzae* type b colonization, which led to interrupted transmission. The impact on *H. influenzae* type b disease was also evident among adults, although the vast majority of cases of *H. influenzae* type b disease had concentrated among children aged <5 years who were the primary beneficiaries of both direct and indirect vaccine effects. The incidence of invasive disease due to *H. influenzae* type b in the United States decreased by >99% (from >30 cases to <1 case per 100,000 children aged <5 years) [5]. These dramatic effects were replicated in wealthy countries throughout the world. By 1995, routine childhood vaccination against *H. influenzae* type b disease had reduced all bacterial meningitis by 55% and had shifted the median age of remaining patients from 15 months to 25 years [6]. More recent introduction of polysaccharide-protein conjugate vaccines for pneumococcal and meningococcal disease offers promise for this devastating clinical syndrome to become even rarer.

For too many years, progress in the control of *H. influenzae* type b disease was limited to industrialized countries, because cost of vaccine was an important barrier to widespread uptake. Another barrier was lack of recognition of the pathogen in many countries in which meningitis and sepsis are not routinely evaluated by microbiological testing, and limited resources in laboratories for detection of the organism have further hidden its role. Innovative studies that used the conjugate vaccine as a probe to uncover the preventable burden of *H. influenzae* type b have now demonstrated the major role that this bacterium plays in childhood meningitis and pneumonia on multiple continents [7–9]. There is now financial support for the procurement of the *H. influenzae* type b vaccine for the world's poorest countries through the Global Alliance for Vaccines and Immunization (GAVI; http://www.gavialliance.org). The *H. influenzae* type b vaccine has been introduced by 22 GAVI-eligible countries, and many more are requesting the vaccine. Routine childhood vaccination has now led to dramatic de-

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creases in invasive disease in several countries in Africa [10–12], including settings with a very high prevalence of HIV infection [13]. In 2005, GAVI funded the Hib Initiative to catalyze support of evidence-based decision-making regarding use of the *H. influenzae* type b vaccine (http://www.Hibaction.org). In 2006, the World Health Organization updated their position on the *H. influenzae* type b vaccine in support of global implementation [14].

Although many resource-poor countries still await realization of the benefits of disease prevention through use of the *H. influenzae* type b conjugate vaccine, the analysis by Dworkin et al. [2] of *H. influenzae* surveillance trends in Illinois gives a glimpse into the postvaccine era. Using statewide passive reporting complemented by hospital discharge data, Dworkin and colleagues confirm a low incidence of total *H. influenzae* invasive disease among children aged <5 years, fluctuating between <1 case to nearly 3 cases per 100,000 children; one-fourth of cases in this age group were caused by serotype b.

Of interest, Dworkin et al. [2] describe a significant increase in the reporting of invasive *H. influenzae* disease in people aged ⩾65 years from 1.1 to 3.9 cases per 100,000 persons, which corresponds to an increase from 16 to 58 cases statewide per year. Of the 96 isolates available for typing from this age group, serotype f caused 36.5% of cases, serotypes b and e each caused 21.9% of cases, and only 13.5% of cases were due to nontypeable *H. influenzae*. Age-specific serotype trends over time were not reported.

Surveillance analyses sometimes generate more questions than they answer. Dworkin et al. [2] have already pursued several questions. Does the increase in reported cases represent a real increase in disease occurrence? Passive surveillance systems can be vulnerable to changes in reporting behavior. Hospital discharge records were reviewed to assess this possibility, and a similar total number of cases was found, although the authors note the inability to remove duplicate reports or validate administrative coding. Even if reporting of laboratory-confirmed cases is comprehensive or sensitivity has not differed over time, changes in clinical or laboratory practices could also artifactually increase the observed incidence of invasive *H. influenzae* disease. Collection of blood or CSF samples for culture is needed for detection of *H. influenzae*. Blood culture practices strongly influence rates of pneumococcal bacteremia [15]. It is possible that temporal changes in specimen collection (e.g., increased blood volume), transportation, or laboratory processing that result in higher yields could reveal more cases than previously detected without a true change in disease occurrence. Of particular note are the discrepancies in serotype determination that have become more common during the vaccine era [16]. Confirmation of capsular type by PCR testing is used in some reference laboratories.

It is also quite possible that there has been a real increase in the incidence of invasive *H. influenzae* disease among adults in Illinois. What might account for this trend? Well-known risk factors for serious disease due to *H. influenzae* include advanced age, immunosuppression, and, for pulmonary manifestations, chronic lung disease. The authors ruled out an important role of HIV infection among their surveillance population. Increased longevity may be expanding the pool of seniors at highest risk. Although reports frequently describe rates in persons aged ⩾65 years, risk continues to increase with each decade; therefore, further age standardization of rates may be needed for temporal comparisons. Waning immunity from childhood exposure to *H. influenzae* type b disease or other capsular types of the disease might account for the age-specific increases, and it is interesting that the proportion of nontypeable cases was lowest among the oldest population in Illinois. In addition to age, changes in living situations, such as more nursing home dwellers, or enhanced contact with young children might account for some increased risk.

Concern about the potential for vaccination to lead to an increase in invasive disease caused by nonvaccine types, or "replacement disease," is not new. Although there are a few reports of increase in *H. influenzae* disease due to serotypes a and f [17, 18], the magnitude of increase in *H. influenzae* disease due to non-b encapsulated strains has been small compared with the huge decrease in *H. influenzae* type b disease. For the pneumococcal conjugate vaccine, emergence of nonvaccine types has started to occur—both among the target age group of young children [19, 20] and among HIV-infected adults [20]—but for both pneumococcal and *H. influenzae* type b conjugate vaccines, the substantial net benefit in disease reduction is still evident relative to the small increase of replacement types.

The intriguing surveillance analysis of Dworkin et al. [2] will be complemented by exploration of other surveillance populations, and it highlights the value of long-term monitoring of immunization programs through laboratory-based surveillance efforts that can differentiate vaccine-preventable disease from other cases. This is especially important as new vaccines, including combination vaccines, become available. Clinical and public health laboratories play a critical role in deciphering the evolving stories that microbes tell.

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