第 40 回日本小児感染症学会招待講演

Haemophilus influenzae vaccine：the beginning of the immunization boom in the United States

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Introduction

Bacterial meningitis remains one disease feared by all parents. Its sudden onset, high mortality rate, and potential to cause lifelong disability are concerning not only for parents but also for physicians. One of the primary reasons that antibiotics are prescribed so liberally is because of concern that an initially localized infection like otitis media could lead to bacterial meningitis if it is not recognized and treated promptly. Pediatricians are taught from the early days of their training to be vigilant for the signs and symptoms of bacterial meningitis. Courtrooms are full of cases where physicians are blamed for not rapidly detecting and treating meningitis. Imagine the relief for families and doctors in the United States in 1985 when a vaccine to prevent the most common cause of bacterial meningitis in children, *Haemophilus influenzae*, type B (Hib) was developed and introduced into routine use. This vaccine, more than any other since polio vaccine, has dramatically impacted the lives of families and doctors who care for children. Now, just over 20 years later, residents in pediatrics may go through their entire training period without ever seeing a case of Hib meningitis. The success of the Hib vaccine program in the U. S. stimulated renewed enthusiasm among parents and physicians for immunizations and was the beginning of a 20-year expansion in the number of vaccines routinely given to American children.

Ⅰ. History of Hib disease and meningitis in U. S.

At its peak, Hib accounted for 20,000 cases of invasive disease per year in children under 5 years of age and Hib was the most common cause of serious bacterial infection in these young children. Many of those children had bacterial meningitis but others suffered from bacteremia, pneumonia, septic arthritis, cellulitis, and epiglotitis. Hib has the ability to colonize the nasopharynx of healthy children and at any given time 8-12% of children under 5 years of age carried the organism prior to the widespread use of Hib vaccine[1,2]. The polysaccharide capsule of Hib facilitates the maintainance of this carrier state and also allows the bacteria to avoid killing by the immature immune system of young children. The transition from a benign carrier state to invasive infection is often facilitated by the inflammation that accompanies upper respiratory tract viral infection. As a result, young children, who have frequent viral respiratory infec-

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Table 1 Comparison of the immunologic characteristics of polysaccharide and conjugate vaccines

Property	Polysaccharide	Conjugate
B-cell-dependent immune response	Yes	Yes
T-cell-dependent immune response	No	Yes
Immune memory	No	Yes
Lack of hypresponsiveness	No	Yes
Booster effect	No	Yes
Long-term protection	No	Yes
Reduction of carriage	No	Yes
Herd immunity	No	Yes

tions, are always at risk for invasive Hib disease.

The development and routine use of conjugated Hib vaccines in the United States changed this pattern dramatically. The conjugated vaccines reduce the percentage of young children carrying Hib in their nasopharynx. As a result even children who are not immunized are indirectly protected because they are no longer being exposed to Hib carriers and thus don't have the opportunity to develop invasive disease. The effect of this herd immunity is most dramatically illustrated by a study in a day care setting with young children that documented a reduction in carrier rates from 6.7% to 1.3% over a 4-year period[3].

Invasive Hib disease is now extremely rare in the United States. A recent report of five cases of invasive Hib disease in Minnesota was reported widely in the U. S. popular press because it was so unusual[4]. This report raised the concern among those working in the immunization field that the dramatic success achieved in the elimination of Hib disease was being threatened.

Ⅱ. Development of Hib vaccines

The first Hib vaccines manufactured in the U. S. became available in 1985 and consisted of the pure *Haemophilus influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP). This vaccine induced an immune response in 40-80% of children older than 18 months of age but that immune response was short-lived. Anti-PRP antibody titers waned to undetectable levels in many children immunized with these polysaccharide-based vaccines within a few years of immunization. These vaccines were recommended for routine use in the U. S. beginning at age 18 months but had little impact on rates of invasive Hib disease, presumably because vaccinated individuals continued to carry Hib in their nasopharynx and thus remained reservoirs of infection for contacts who were not immunized or whose antibody levels had declined following immunization.

The development of protein conjugate Hib vaccines was a breakthrough in the science of pediatric immunization. The recognition that young children responded poorly to pure polysaccharide antigens led to the development of this new class of vaccines in which polysaccharide antigens are covalently conjugated to proteins. The immunologic effects of this linkage are many including the conversion of the immune response from a T cell independent response to a T cell dependent response (**Table 1**). Such responses are associated with long-term immunologic memory and a more robust immune response in general.

Ⅲ. Implementation of Hib vaccination program

Polysaccharide Hib vaccine was licensed for use in children in the U. S. in 1985. Although pediatricians had been anticipating this first opportunity to prevent the common invasive disease the use of vaccine was only modest. One of the reasons for the relatively low use was the fact that the first Hib vaccines were only recommended beginning at 18 months of age and pediatricians were aware that the majority of invasive Hib occurred in younger children.

The breakthrough for pediatricians was the licensure of the first protein conjugate Hib vaccine in

1987. This vaccine manufactured by Pasteur Merieux Connaught, was produced by covalently linking diphtheria toxoid protein to PRP polysaccharide (PRP-D). The immunologic superiority of this new conjugate vaccine allowed its use beginning at 2 months of age-an age at which pediatricians were used to seeing invasive Hib disease. The first large clinical trial of Hib conjugate vaccine involved 60,000 infants who were immunized at 2, 4, and 6 months of age[5]. This trial demonstrated a vaccine efficacy of 83%, a dramatic improvement over the efficacy of polysaccharide vaccines. Shortly after the first vaccine other Hib-conjugate vaccines were licensed in the U. S. (**Table 2**).

With all these vaccines available pediatricians had many options for immunizing their young infant patients and use of Hib conjugate vaccines rose steadily. By the early 1990's Hib vaccine coverage rates were high in young children and Hib disease began to disappear.

Ⅳ. Change in Hib epidemiology following vaccine program

Use of conjugated Hib vaccines increased very rapidly so that by 1997, Hib vaccine was being given to 93% of children under 2 years of age[6]. This widespread use of vaccine rapidly led to declines in rates of invasive Hib disease (**Figure 1**)[7]. Pediatricians celebrated this rapid elimination of meningitis, septic arthritis, and epiglottitis. Since 2000 the U. S. has had less than 40 reported cases of invasive Hib disease each year compared to 20,000 cases per year prior to the availability of Hib vaccines.

In a period of just 10 years Hib went from being the most common cause of meningitis in young children to a rare event (**Figure 2**)[8].

In fact, Hib has now become a disease of adults in the U. S. In one study of recent cases of invasive Hib, 75% of cases occurred in individuals 18 years of age and older[9]. Seniors 65 years of age

Table 2 History of Hib conjugate vaccine licensure in the U. S.

Conjugated protein	Vaccine Manufacturer	Year Licensed in U. S.
PRP-D	Pasteur Merieux Connaught	1987
PRP-HbOC	Wyeth Vaccines Inc.	1988
PRP-OMP	Merck Inc.	1989
PRP-T	Pasteur Merieux Connaught	1993

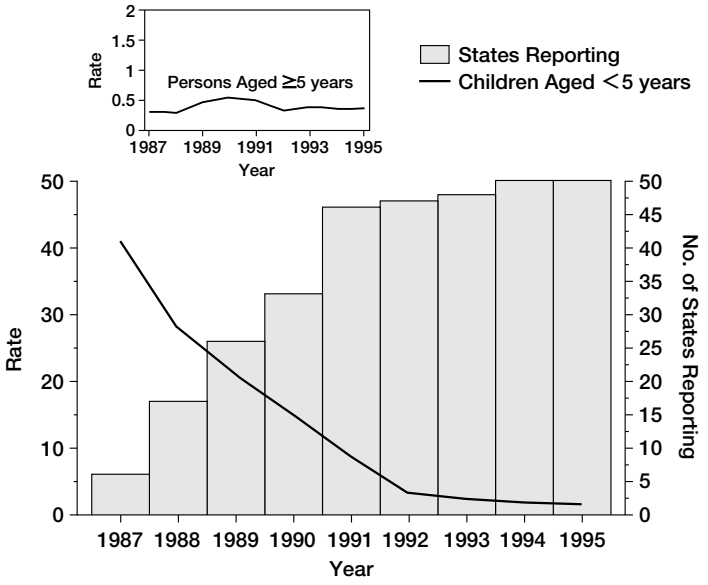

Figure 1 Incidence rate* of invasive *Haemophilus influenzae* (Hi) disease among children <5 years, incidence rate† of invasive Hi disease among persons aged ≥5 years, and number of states reporting Hi surveillance data-United States, National Notifiable Diseases Surveillance System, 1987-1995

*Per 100,000 children aged <5 years.
†Per 100,000 persons aged ≥5 years.
§Because of the low number of states reporting surveillance data during 1987-1990, rates for those years were race-adjusted using the 1990 U. S. population.

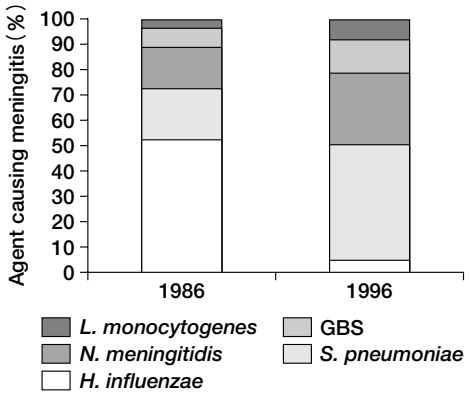

Figure 2 Pathogenic agents of bacterial meningitis in the United States, 1986 vs 1996 (quote from reference 8)

and older were affected in 44% of cases.

V. Developments in the Hib vaccination program since 1985

The road forward with Hib vaccination has not been completely smooth in the U. S. Beginning in late 2007 shortages of vaccine began to occur with the PRP-OMP (Merck, Inc) vaccine not being available[10]. This shortage required a modification of the routine immunization schedule in which the 12-18 month booster dose of vaccine was not provided. The hope was that immunity would be sufficient with the primary vaccine series and disease still prevented. The first indication that this might not be the case occurred with a report in early 2009 of 5 cases of invasive Hib disease in the state of Minnesota[4]. Each of the affected children were either unimmunized, incompletely immunized, or had an immunodeficiency that may have led to a poor response to vaccine. However, the fact that they developed disease raised the concern that asymptomatic nasopharyngeal carriage was increasing in the community as a result of the reduced immunization schedule being used in all children. If that was the case, other unimmunized children would be at increased risk of exposure to the organism and at risk for the development of invasive disease.

VI. Implications for other vaccines

The dramatic success of the Hib immunization program in the U. S. stimulated the development of other conjugated vaccines. Once Hib disease had been largely eliminated, Pneumococcus became the most common cause of invasive bacterial infection in young children. In 2000 the first conjugated Pneumococcal vaccine was licensed in the U. S. and rapidly incorporated into the routine immunization schedule. By 2004 73% of children under 2 years of age were receiving pneumococcal conjugate vaccine and rates of invasive pneumococcal disease began to decline[11]. Active surveillance programs have documented a significant decline in rates of pneumococcal disease in children as a result of widespread use of pneumococcal conjugate vaccine (**Figure 3**)[12].

The latest conjugate vaccine to be developed is a vaccine to prevent *Neiseria meningiditis*. This vaccine became available in the U. S. in 2005 and is currently being given routinely to all children at 11-12 years of age. Studies have now also demonstrated the efficacy of conjugated meningococcal vaccines in infants as young as 2 months of age and it is anticipated that the age for routine immunization with this class of vaccines will be lowered in the next few years.

Conclusion

In addition to stimulating the development of other conjugate vaccines, the success of Hib vaccine also set the stage for many other vaccines to be adopted in the U. S. When Hib vaccine was introduced it was only the 4th vaccine routinely used in young children. By 2000 that number had expanded to 6 including vaccines for hepatitis B and Varicella and now 10 vaccines are given to all young children. It was the dramatic elimination of Hib disease that illustrated the power of immunizations for both the general public and physicians.

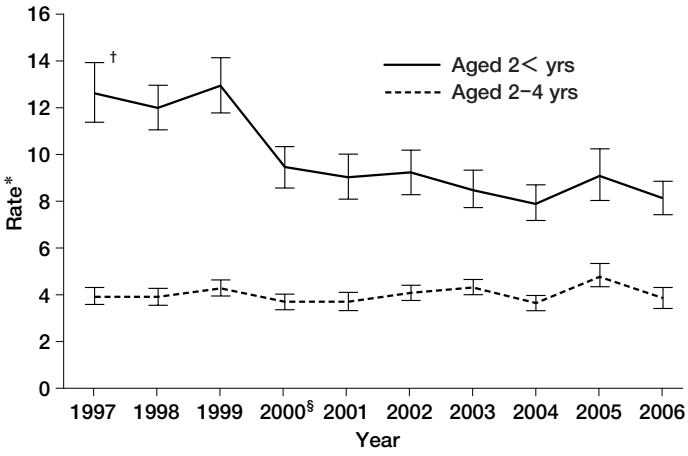

Figure 3 Annual all-cause pneumonia hospitalizations rates among children aged <2 years and 2-4 years-nationwide inpatient sample, United States 1997-2006

*Per 1,000 population.

†95% confidence interval.

§7-valent pneumococcal conjugate vaccine licensed in February 2000.

The use of conjugate vaccines for Hib, pneumococcus, and *N. meningiditis* has the potential to eliminate all but the most rare causes of bacterial meningitis in children. Future generations of doctors will be able to practice without the fear of missing a case of early infection because all children will be protected from invasive disease through immunization.

REFERENCES

1) Barbour ML, Mayon-White RT, Coles C, et al：The impact of conjugate vaccine on carriage of *Haemophilus influenzae*, type B. J Infect Dis 171：93-98, 1995
2) Kelly DF, Moxon ER, Pollard AJ：*Haemophilus influenzae* type b conjugate vaccines. Immunology 113：163-174, 2004
3) Heath P：The UK Hib vaccine experience. Arch Dis Child 86：396-399, 2002
4) CDC：Invasive *Haemophilus influenzae* type B disease in five young children-Minnesota, 2008. MMWR 58：58-60, 2009
5) Eskola J, Peltola H, Takala AK, et al：Efficacy of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 317：717-722, 1987
6) CDC：Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children-United States, 1987-1997. MMWR 47 (46)：993-998, 1998
7) CDC：Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children-United States, 1987-1995. MMWR 45：901-906, 1996
8) Schuchat A, Robinson K, Wenger JD, et al：Bacterial meningitis in the United States in 1995. N Engl J Med 337：970-976, 1997
9) Dworkin M, Park L, Borchardt SM：The changing epidemiology of invasive *Haemophilus influenzae* disease, especially in persons>65 years old. Clin Infect Dis 44：810-816, 2007
10) CDC：Interim recommendations for the use of *Haemophilus influenzae* type b (Hib) conjugate vaccines related to the recall of certain lots of Hib-containing vaccines. MMWR 56：1318-1320, 2007
11) CDC：National, State, and urban area vaccination coverage among children aged 19-35 months-United States, 2004. MMWR 54：717-721, 2005
12) CDC： Pneumonia hospitalizations among young children before and after introduction of pneumococcal conjugate vaccine-United States, 1997-2006. MMWR 58：1-4, 2009

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