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Experience of *H. influenzae* Type b (Hib) and Pneumococcal Conjugate Vaccine in Korean Children

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Abstract *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* are important pathogens in children. The introduction of Hib and 7-valent pneumococcal conjugate vaccine (PCV7) into childhood immunization schedule contributed to a substantial reduction in the burden of related diseases. However, in Korea, these vaccines are not included in the national immunization program although they have been used since 1993 or 2004, respectively. Because the disease burden and the effectiveness of each vaccine might vary by geographical region or ethnicity, a study was conducted to determine the optimal immunization strategy in Korea.

The Hib and pneumococcal meningitis incidence was 6.0/100,000 <5 years and 2.1/100,000 <5 years, respectively in a defined population in Korea. According to data obtained from hospital records from 1986 through 2005, pneumococci and Hib were found to be the major causes of invasive bacterial disease in children, although invasive Hib disease has decreased after introduction of vaccine. The serotype coverage of PCV7 is about 70% for invasive pneumococcal diseases <5 years in Korea. Immunogenicity studies of Hib vaccine were meta-analyzed and showed excellent response in Korean children. PCV7 was highly immunogenic in infants, too. After two and three PCV7 vaccinations, 63-98 and 97-100% of infants achieved protective antibody level, respectively. According to these data, adopting two doses for a primary series could be a feasible option for facilitating vaccine coverage rate for these two vaccines. In a cost benefit analysis, Hib vaccine would be cost benefit at 2+1 doses, each costing approximately \$20 even with the underestimated diseases burden. There is no available data for PCV7. In 2007, the vaccination rates of Hib vaccine and PCV7 were about 60% and 10%, respectively. In conclusion, for disease control of invasive Hib and pneumococcal diseases in Korea, routine immunization of Hib and PCV7 as 2 doses and a booster can be recommended.

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Introduction

Haemophilus influenzae type b (Hib) and *Streptococcus pneumoniae* are bacteria which cause serious diseases often life-threatening illnesses such as meningitis, sepsis and severe pneumonia in young children. Resistance to these infections depends on the integration of a variety of host defenses, including mucosal factors, complement, specific antibodies, phagocytosis and cell-mediated immunity. Among these, antibodies have been the focus of vaccine research. Antibodies are responsible for immunity to these bacterial infection through inducing protective opsonophagocytic and bactericidal activities in infants and young children who show inability to mount antibodies to the capsular polysaccharides of these organisms.

The limited immunogenicity of the capsular polysaccharides of Hib and pneumococcus in infants and young children led to the development of the protein conjugate vaccine which employs the carrier-hapten principles of antigen presentation.

Hib conjugate vaccines were developed in the 1980s and after routine use of Hib vaccines, the incidence of invasive Hib diseases has decreased dramatically. From 1998, WHO recommended including Hib vaccination as part of routine national immunization programs (NIP). Recently more than one hundred countries introduced Hib vaccine in infant immunization schedule.

Over 25 years of international experience with Hib vaccines has demonstrated that they are safe and effective. Routine use of Hib conjugate vaccine has consistently led to decreases in the incidence of invasive Hib disease of 90% or more across a wide range of epidemiologic situations in industrialized countries. In some countries, the vaccine has caused a near-disappearance of invasive Hib disease through a combination of direct protection and herd immunity.

According to the successful use of Hib vaccine, the same conjugation method was applied to pneu-

mococcal vaccine. The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2000. By 2007, PCV7 was launched in about 70 countries and was included in NIP in 17 countries. PCV showed good effectiveness for the prevention of invasive pneumococcal diseases in children. According to ABC surveillance in US, the incidence of invasive pneumococcal diseases was dramatically decreased in children¹. PCV showed efficacy for about 80% of vaccine type (VT) invasive pneumococcal diseases (IPDs), 58% of all serotypes IPD and 27% of pneumonia². However after introduction of PCV7, serotype changes were noticed³. Whereas a great decrease of IPD was seen with VT serotypes, IPD caused by non-vaccine type (NVT) or vaccine related type 19A were increased. This observation made people to urge to develop new conjugate vaccines which includes more serotypes such as 1, 5, 7F as well as vaccine related serotypes (VRT) 6A and 19A.

In Korea, Hib vaccine was introduced from early 1990s and PCV7 from 2003. The optimal Hib vaccination strategy will depend on many factors, including information on the local burden of Hib disease, local epidemiology of Hib disease, local dynamics of Hib transmission, characteristics of the different vaccines, results of different vaccination schedules and immunogenic responses to Hib vaccine.

In this background, the studies about Hib and pneumococcal disease and their vaccines were performed in Korea from 1999 with funds from the government such as Korean Food and Drug Administration, Korean Center for Disease Control and Prevention and other sources to understand the epidemiology, disease characteristics, immunogenicity and efficacy of vaccine and cost effectiveness.

I. Epidemiology

The epidemiology study of bacterial meningitis was performed in the Jeonbuk province in Korea from 1999 to 2001⁴. It was a prospective population based study. In children less than 5 years old,

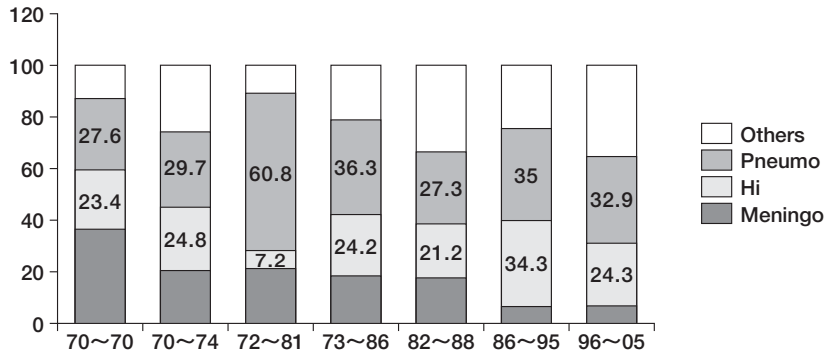


Figure 1 Relative etiology of bacterial meningitis from 1970 through 2005 in 7 studies performed in Korea

the incidence of invasive Hib disease was 6.8/100,000 and meningitis was 6.0/100,000. Because this study was performed with a 16% Hib immunization rate in the population, the true incidence may be higher than the results. Moreover this study was focused on Hib disease and the incidental finding of pneumococcal meningitis of 2.1/100,000 is not fully reliable.

Since asymptomatic nasopharyngeal carriers of Hib and *S. pneumoniae* are responsible for transmission of these organisms and is the reservoir of bacteria for invasive disease, carriage rate study in a population is important. The *Haemophilus influenzae* carriage rate was 13.4% in children less than 5 years old in Seoul, Korea⁵⁾. Pneumococcal carriage rate was about 30–35% in same age group^{6,7)}. VT and VRT of pneumococci was about 60–80.5% among nasopharyngeal isolates^{6,7)}.

II. Clinical Characteristics of Hib and pneumococcal diseases

Since basic epidemiologic information on bacterial meningitis in children is limited in Korea, an analysis of the bacteriologically proven meningitis from 1986–2005 in terms of the relative frequency of causative organisms, mortality rate, and age distribution beyond the neonatal period was performed. The first 10 years data was analyzed for 1986 through 1995⁸⁾. Data was obtained from

hospital records of patients diagnosed with bacterial meningitis. *S. pneumoniae* was the most common bacteria responsible for 35.0%, followed by *H. influenzae* for 34.3% and *Neisseria meningitidis* 6.4% (Figure 1). The case fatality rate was 20.0%, 17.1%, and 16.7% for *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*, respectively.

Another study was done for the recent 10 years 1996 through 2005⁹⁾. According to recent 10 years results, *S. pneumoniae* was the cause in 32.9%, the most common etiology of bacterial meningitis in children less than 18 years. Hib was the cause of 24.3% of bacterial meningitis (Figure 1). As for the etiology of invasive bacterial diseases, *S. pneumoniae* was responsible for 30% of the cases and Hib 10%. The decreased proportion of Hib may be attributable to the effects of increased Hib vaccination coverage in Korea.

For the invasive pneumococcal diseases, bacteremia, meningitis and bacteremic pneumonia were about 30% each respectively. For the invasive Hib diseases, however, meningitis was attributable to 82%. Although this result is a little different with other studies performed in other countries, it was assumed that the clinical manifestations of these 2 bacteria are different.

The cumulative proportion of Hib meningitis cases by age is similar with that of US¹⁰⁾. About 60% of meningitis occurred in infants and 77% in

children less than 24 months.

The serotype distribution of pneumococci was studied in Korea¹¹. The proportion of PCV7 vaccine type serotypes decreased from 76% of all isolates to 57% before the introduction of PCV7.

Interestingly, even before the introduction of the vaccine, the proportion of 19A serotype showed an increase, also. The serotype distribution of pneumococcal disease should be studied continuously to monitor the vaccine impact.

III. Immunogenicity of Hib and Pneumococcal Vaccines

Many studies were done for the immunogenicity of various Hib vaccines in Korea. In a meta-analysis of these reports, it was found that Hib vaccines showed a good antibody response in Korean infants after vaccination at 2, 4 and 6 months of age¹². When the possibility of implicating a 2-dose schedule in infants was examined, it was found that more than 70% of the infants showed seroconversion after 2 doses of Hib vaccine instead of 3 dose schedule as a primary series, which complies with the guidelines of the WHO for Hib vaccines¹³.

Recently the immunogenicity study of PCV7 was done in Korean infants. The infants showed good antibody responses to all VT serotypes. When the geometric mean antibody titer was compared among children vaccinated with 3 doses of PCV7 from different countries, the data indicated that Korean infants showed better immune response than other population for all VT serotypes¹⁴.

The reverse cumulative curve of antibody titers in infants vaccinated with 3 doses of PCV7 showed all infants have a good immune response to the vaccine.

When the functional opsonic activity was examined, all subjects showed good functional activity after the vaccine, as well¹⁵.

IV. Immunization Rates of Hib and PCV

Hib and PCV vaccines are not included in the NIP in Korea. A survey on the vaccination rate of these vaccines among more than 1,500 children throughout Korea was performed. The primary vaccination rate for Hib vaccine was 65.2%, booster vaccination rate was 54.8%¹⁶.

The vaccination rate for PCV7 was much lower and there was a great difference of vaccination rate of PCV7 according to different regions in Korea¹⁶.

V. Change of Clinical Diseases or Carriage Rate after Introduction of Vaccines

According to the bacterial meningitis study results in Korea, Hib meningitis decreased significantly as vaccination rates increased in Korea⁹.

To confirm the effect of PCV7, pneumococcal nasopharyngeal (NP) carriage was compared between fully vaccinated children and nonvaccinated controls. Pneumococcal carriage rate was 18.0% and 31.5% for the vaccinated and control group, respectively. Among those vaccinated, 41.7% of the serotypes were vaccine-related type (VRT : 6A, 6C, 19A) with the most common serotype 6C. In contrast, 52.4% of the isolates in the control group were vaccine type. Resistance rates for penicillin and erythromycin were lower in the vaccine group. Multi-resistant drug proportion was also lower in vaccinated subjects. PCV7 reduces carriage in VT which may lead to replacement of pneumococci by antibiotic susceptible VRT or nonvaccine type strains¹⁷.

VI. Cost Benefit Analysis of Hib and Pneumococcal Vaccines

In Korea, for the cost-benefit analysis of the Hib vaccine, the total Hib disease burden including incidence, rate of admission and mortality for the following diseases were analyzed and based on these factors an estimate of the cost for treating these diseases was done¹⁸.

In the previous meta-analysis it was found that the immunogenic response to a 2 dose and 3 dose primary series was tolerable and therefore the cost-benefit of a total 3-dose and 4-dose schedule (including the booster dose) was analyzed. In conclusion it can be concluded that Hib vaccine showed a definite cost-benefit for both a 3- and 4-dose schedule in Korea. As for the cost-benefit analysis for pneumococcus, the burden and cost of pneumococcal disease was analyzed. This data proves that pneumococcus has a high burden in children and adults in Korea¹⁹⁾.

Hib vaccine has been an optional vaccine up to 2007 and is highly recommended by the Korean Pediatric Society, but is not-yet an NIP vaccine in Korea. PCV vaccine was introduced in 2003 and is currently an optional vaccine.

At this point, further studies on epidemiology on pneumococcal diseases in Korea are needed for an accurate estimate on disease burden. The appropriate vaccine schedule for PCV in Korea should be established based on immunogenicity data. And a cost-benefit analysis in accordance with PCV vaccine schedule is needed for making important decisions in vaccination policies.

VII. Hib and Pneumococcal Vaccine Evaluation Center in Korea

In Korea, the immunogenicity analysis of Hib vaccine and PCVs can be performed in the Center for Vaccine Evaluation and Study, Medical Research Institute, Ewha Womans University School of Medicine, Seoul. The quantitative and qualitative analysis of antibodies induced by Hib and pneumococcal vaccines are performed at this center.

The quantitative response of Hib vaccines is analyzed by ELISA with PRP antigen²⁰⁾.

The function of antibodies elicited by Hib vaccines is evaluated by the serum bactericidal assay using Hib Egan strain.

Pneumococcal ELISA to quantify specific IgG to

pneumococcal serotype specific capsular polysaccharides is performed according to a protocol established by WHO pneumococcal serology reference laboratories in University of Alabama at Birmingham, AL, USA. The Center for Vaccine Evaluation and Study at Ewha Womans University has a network for correspondence with this laboratory.

The functional assay for pneumococci, opsonophagocytic killing assay (OPKA) is performed for evaluation of PCVs as well as pneumococcal polysaccharide vaccines (PPV).

With these assays, many Hib vaccines, PCVs and PPV were evaluated in Korea²¹⁾.

Recently, we have studied the immune response of the VRT after PCV7 in infants¹⁵⁾. It has been assumed that because 19F and 19A have similar capsular structure, the PCV7 which includes 19F would induce protective effect against VRT 19A also. However, it was found that although antibodies are elicited for 19F and 19A after the vaccine, there are distinct differences in function. The ELISA results show a good correlation with the OPA for 19F, however many of the antibodies for 19A did not have detectable function.

With the increase in vaccination of PCV, there have been changes in epidemiology for VRT serotypes. PCV7 includes 6B and was presumed to show cross-reaction for the VRT 6A. In the US, this was observed with a decrease in incidence of IPD for 6B and 6A. However, in the past few years an increase in disease caused by 6A has been noted. Recently, the explanation of this phenomenon has been disclosed. Among serotypes that were classified as 6A, a part of them have been found to have a minor difference in capsule, thus this new serotype has been designated as 6C.

When the immune response to serogroup 6 was studied, it was found that after PCV7, a good immune response is elicited for the VRT 6A, however, PCV7 does not seem to induce immunity for 6C. Although all infants showed functional activity for serotype 6B, 81% of infants showed functional

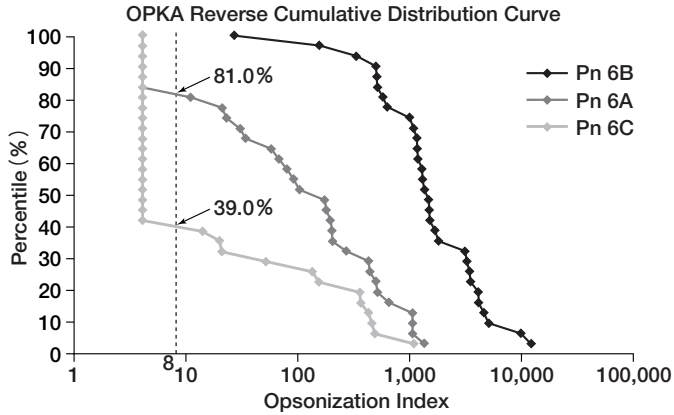


Figure 2 Reverse cumulative distribution curves of opsonic indices generated by PCV7 to serotypes 6B, 6A and 6C

The vertical dotted line represents the opsonic detection limit of 8 for the OPA.

opsonic antibody activity to 6A and only 39% to 6C (Figure 2).

Conclusions

Although Hib vaccine is not included in NIP vaccine in Korea, invasive Hib diseases have decreased prominently in Korea after its introduction. With the increased using of PCV7 and introduction of new PCVs, continuous monitoring on the changes in disease and serotype pattern is warranted since the effectiveness of vaccine depends on many locally variable factors such as the prevalence of vaccine-type organisms and the level of vaccine coverage as well as the vaccine itself.

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