

Immunogenicity of *Haemophilus influenzae* Type b Conjugate Vaccines in Korean Infants: A Meta-analysis

A meta-analysis was performed on the immunogenicity of *Haemophilus influenzae* type b (Hib) conjugate vaccines after 2 (2 and 4 months) and 3 doses (2, 4, and 6 months) in Korean infants. A database search of MEDLINE, KoreaMed, and Korean Medical Database was done. The primary outcome measure was the proportion of infants with anti-polyribosylribitol phosphate (PRP) concentrations $\geq 1.0 \mu\text{g/mL}$. Eight studies including eleven trials were retrieved. One trial reported on the diphtheria toxoid conjugate vaccine (PRP-D) and 2 trials each on the mutant diphtheria toxin (PRP-CRM) and *Neisseria meningitidis* outer-membrane protein (PRP-OMP) conjugate vaccine. Heterogeneity in study designs between trials on PRP-CRM was noted and one trial reported on a monovalent and another on a combination PRP-OMP vaccine. Thus, a meta-analysis was conducted only on the tetanus toxoid conjugate vaccine (PRP-T). After a primary series of 2 doses and 3 doses, 80.6% (95% confidence interval [CI]; 76.0-85.1%) and 95.7% (95% CI; 94.0-98.0%) of infants achieved an antibody level $\geq 1.0 \mu\text{g/mL}$, respectively. The immunogenic response to the PRP-T vaccine was acceptable after a primary series of 3 doses and also 2 doses. A reduced number of doses as a primary series could be carefully considered in Korean infants.

Key Words : *Haemophilus influenzae* type b; Vaccines; Immunity; Meta-analysis

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INTRODUCTION

Haemophilus influenzae type b (Hib) was an important cause of bacterial meningitis and other serious invasive diseases among children aged <5 yr before the introduction of the Hib conjugate vaccines (1). A dramatic decrease in Hib disease burden was noted in countries that introduced the Hib conjugate vaccine into routine immunization schedules (2).

Four basic different types of conjugate vaccines have been licensed for use in infants against Hib diseases. These vaccines differ in the carrier proteins, structure and length of the capsular polysaccharide molecule, polyribosylribitol phosphate (PRP) and the method of conjugating the carrier protein to the polysaccharide. The first conjugate produced was the diphtheria toxoid conjugate (PRP-D), followed by mutant diphtheria toxin conjugate (PRP-CRM), meningococcal outer membrane protein conjugate (PRP-OMP) and tetanus toxoid conjugate (PRP-T). Hib conjugate vaccines have been shown to be highly efficacious against invasive Hib disease and safe in clinical trials (3-5).

Vaccine efficacy of Hib vaccines are assessed in correlation with the level of production of specific anti-PRP IgG (6). An anti-PRP level $\geq 1.0 \mu\text{g/mL}$ is considered predictive for long-term protection from invasive disease in a vaccinated population (7). Based on this, the WHO recommendations on evaluating the efficacy of Hib conjugate vaccines have been released, e.g. effective vaccines induce $\geq 1.0 \mu\text{g/mL}$ of anti-PRP antibody in 70% or more of infants 1 month after completion of the primary immunization series (8).

With the known safety and proven effectiveness of the Hib conjugate vaccines, WHO recommends it to be included in all routine infant immunization programs, regardless lack of local surveillance data (9). By the end of the year 2005, Hib vaccines were included in the routine infant immunization program in 101 out of 192 WHO member countries (10). However, it is not yet introduced into the national immunization program in Korea. To make important decisions on the policy for Hib vaccination, a nationwide study on the epidemiologic status in relation to the disease burden of invasive Hib diseases as well as cost-effectiveness study is urgent. Also, the

appropriate schedule should be determined.

The Hib vaccination schedule differs between countries in number of doses and periods of vaccination. At present, the current recommendations for the vaccination schedule for Hib vaccine in Korea is that the primary series be given at 2, 4 and 6 months of age for the PRP-T and PRP-CRM vaccine and at 2 and 4 months of age for the PRP-OMP vaccine, with a following booster dose at 12-15 months of age for all three types of vaccines. Although all countries give a booster dose of the Hib vaccine, some countries recommend 2 doses as a primary series, whereas other countries recommend 3 doses before 12 months of age.

The objective of this study was to evaluate the immunogenicity of a primary series of Hib conjugate vaccines in Korean infants through a meta-analysis. We will therefore determine whether the immunologic responses are acceptable after 3 doses (given at 2, 4, and 6 months of age) and also after 2 doses (given at 2 and 4 months of age) of the Hib conjugate vaccine.

MATERIALS AND METHODS

Literature search

MEDLINE, KoreaMed, and the Korean Medical Database were searched for all studies of Hib conjugate vaccine in Korean children. The search included terms in the title or key words, applying the terms '*Haemophilus influenzae* type b', 'Hib', 'vaccination OR vaccine' and 'immunogenicity'. Also,

a manual search of studies was done on studies referenced in publications identified through the initial search and experts on Hib vaccine in Korea were contacted for unpublished data or ongoing studies.

Selection criteria

We included all clinical trials that reported immunogenicity results following a primary series (immunization at 2, 4, and 6 months of age) of Hib conjugate vaccine in healthy Korean infants. The primary outcome measure was the seroconversion rate after Hib conjugate vaccine. Seroconversion rate was defined as the proportion of infants achieving $\geq 1 \mu\text{g/mL}$ of anti-PRP antibody 4-12 weeks after vaccination. The seroconversion rate after 2 doses and the one after 3 doses of the Hib conjugate vaccine injected according to the recommended schedule or designed trial protocol were evaluated. Studies reporting natural anti-PRP antibody levels or antibody persistence after Hib vaccine were excluded.

Data extraction

Data from each of the studies were extracted independently into a data extraction form by two investigators. Any disagreements were resolved by discussion. Major extraction variables in the form included the years of the publication and the study conduction, type of conjugate vaccine, vaccination schedule, age of enrollment, duration of follow up, method of evaluation of immunogenicity and results of immunogenic responses.

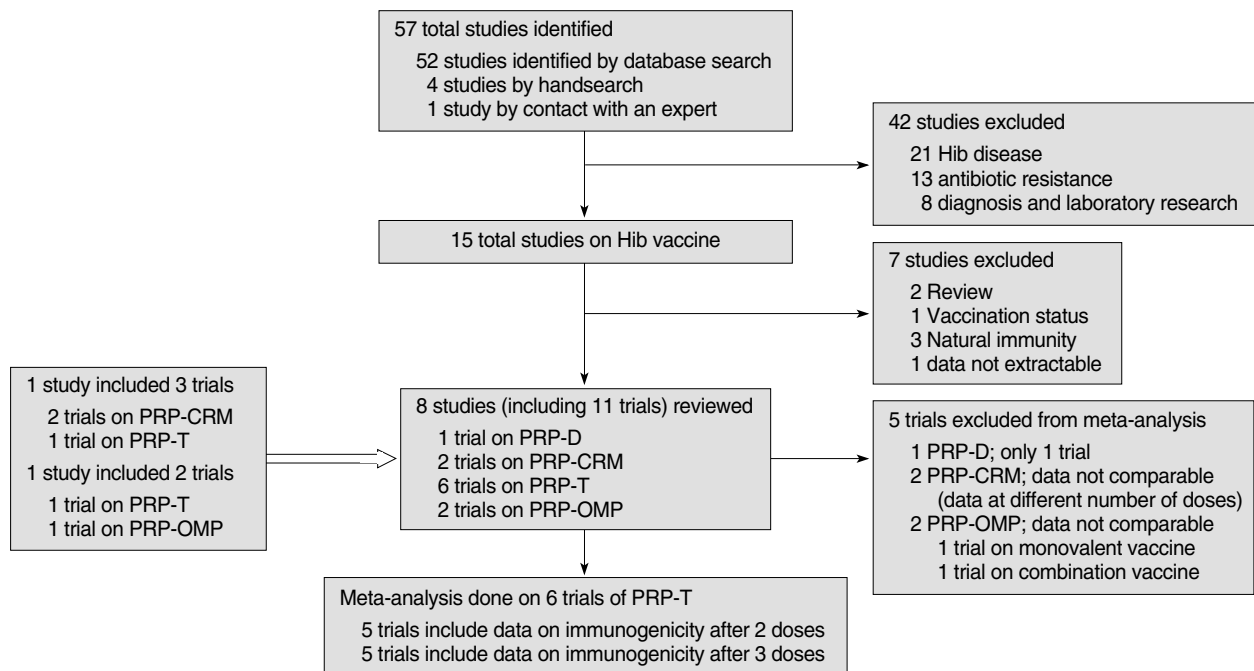


Fig. 1. QUOROM flow diagram.

Statistical analysis

The seroconversion rate was calculated together with the 95% confidence interval (CI) for each trial and they were pooled across the trials by the inverse variance method (11). A chi-square statistic was calculated to assess statistical heterogeneity across the trials. When the extent was considered to be significantly large (P value of <0.10), a random effects model was also considered (12). According to the WHO Technical Report Series, effective Hib vaccines have been found to induce $\geq 1.0 \mu\text{g/mL}$ anti-PRP antibody in 70% or more of the infants 1 month after the completion of the primary immunization series (8). We assessed whether the lower 95% CI of the pooled seroconversion rate in infants vaccinated would exceed this criterion after a primary series of 2 doses and 3 doses of the Hib conjugate vaccine.

RESULTS

Identification of studies and trials

The process of study inclusion is summarized in Fig. 1 according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines (13). Fifty-seven studies were identified; 52 by electronic database search, four studies by handsearch, and one unpublished study was obtained through contact with an expert on Hib vaccine. Among these studies, fifteen studies relevant to the Hib conjugate vaccine in Korean children were retrieved. Seven out of these studies were excluded: two publications were review articles of the Hib vaccine, one study reported on the policy of Hib vaccines in Korea, three studies focused on natural antibody titers and antibody persistence in children and one study of a PRP-T conjugate

vaccine did not include data for seroconversion. Eight studies were finally included in the review (14-20). Among these eight studies, one study included three different trials and another study reported on two different trials. Thus the identified trials to be reviewed were 11 in total. The characteristics of the included studies are shown in Table 1.

Description of the trials

PRP-D

There was one trial on the immunogenicity of the PRP-D vaccine. The proper regimen for the primary series of the PRP-D vaccine is vaccination at 2, 4, and 6 months of age. The trial reported on the immunologic response after 2 doses and 3 doses of the vaccine. The seroconversion rate after 2 doses and 3 doses of the vaccine reported 26.3% and 57.9%, respectively (Table 2).

PRP-CRM

Two trials on the PRP-CRM vaccine were identified. One trial reported the immunogenic response after a total of three doses (given at age 2, 4, and 6 months) and another trial reported data after 1 dose and 2 doses of a primary series of the PRP-CRM vaccine and before and after a booster dose of the vaccine. Thus, data were not comparable between the two trials. According to the data reported in both trials, the seroconversion rate after the PRP-CRM vaccine showed a low response after 2 doses but with the 3rd dose, the seroconversion rate increased up to 100%. However, there was only one report each after 2 doses and 3 doses of the PRP-CRM vaccine with a limited number of subjects in both trials.

PRP-OMP

There were two trials reporting immunogenicity of the

Table 1. Characteristics of trials included in the analysis

Author (Ref. No.)	Publication	Study period	No. of infants	Vaccine	Age of enrollment	Schedule	Route	Blood sample	Laboratory method
Choi SY (14)	1999	Feb. 1994-July 1995	42	PRP-D	2 mo	2, 4, 6	IM	2, 6, 7, 15, 16 mo	Farr assay
Lee HJ ^[1]	Unpublished	1992	32	PRP-CRM	2 mo	2, 4, 6	IM	2, 7 mo	Farr assay
Lee HJ ^[2]	Unpublished	1992	49	PRP-CRM	2 mo	2, 4, 6	IM	2, 4, 6, 15-23 mo	Farr assay
Lee HJ ^[3]	Unpublished	1992	61	PRP-T	2 mo	2, 4, 6	IM	2, 4, 6, 15-23 mo	Farr assay
Yoo ES (15)	1995	May 1992-July 1993	34	PRP-T	2 mo	2, 4, 6	IM	2, 4, 6, 9 mo	ELISA
Kim JS (16)	1996	NA	40	PRP-T	6-10 wks	2, 4, 6	IM	2, 6, 8 mo	Farr assay
Chung EH (17)	2003	March 2001-April 2002	63	PRP-T	2 mo	2, 4, 6	IM	2, 6, 7 mo	ELISA
Kim KH (18) ^[1]	2008	March 2005-Nov. 2005	59*, 90 [†] , 149	PRP-T	6-12 wks (43-91 days)	2, 4, 6	IM	2, 4*, 6 [†] , 7 mo	ELISA
Kim KH (18) ^[2]	2008	March 2005-Nov. 2005	72	PRP-OMP	6-12 wks (43-91 days)	2, 4	IM	2, 4, 5 mo	ELISA
Yang PS (19)	2002	Dec. 1999-May 2001	120	PRP-T	2 mo	2, 4, 6	IM	7-8, 19-20 mo	Farr assay
Chung EH (20)	2006	Jan. 2004-June 2005	58	PRP-OMP+ Hepatitis B	2 mo (42-84 days)	2, 4	IM	2, 4, 6 mo	ELISA

Number in brackets designate different trials in one publication.

*4 months (after 1 dose); [†]6 months (after 2 dose).

mo, months; wks, weeks.

Table 2. Immunogenicity results of trials included in the analysis

Study (Ref. No.)	Vaccine	No. of infants	Antibody levels ($\mu\text{g/mL}$) at age				% of infants with antibody $\geq 1.0 \mu\text{g/mL}$		
			2 mo (pre)	4 mo (after 1 dose)	6 mo (after 2 dose)	7-9 mo (after 3 dose)	4 mo (after 1 dose)	6 mo (after 2 dose)	7-9 mo (after 3 dose)
Choi SY (14)	PRP-D	42	0.07		0.19	1.39		26.3%	57.9%
Lee HJ ^[1]	PRP-CRM	32	0.07			14.9			100%
Lee HJ ^[2]	PRP-CRM	49	0.12	0.13	1.32		2.0%	47.0%	
Lee HJ ^[3]	PRP-T	61	0.10	0.81	5.13		38.0%	84.0%	
Yoo ES (15)	PRP-T	34	0.15	0.64	6.62	22.0	48.7%	82.4%	95.5%
Kim JS (16)	PRP-T	40	0.14		11.5	20.3		85.0%	87.5%
Chung EH (17)	PRP-T	63	0.17		4.14	14.7		77.7%	98.4%
Kim KH (18) ^[1]	PRP-T	59*, 90 [†] , 149	<0.15	0.91*	4.46 [†]	15.0	42.4%*	78.9% [†]	97.3%
Yang PS (19)	PRP-T	120				24.6			98.3%
Kim KH (18) ^[2]	PRP-OMP	72	<0.15	0.98	7.78		52.8%	91.7%	
Chung EH (20)	PRP-OMP+ Hepatitis B	58	<0.15	1.96	10.02		63.2%	96.6%	

Number in brackets designate different trials in one publication.

*4 months (after 1 dose); [†]6 months (after 2 dose).
mo, months.

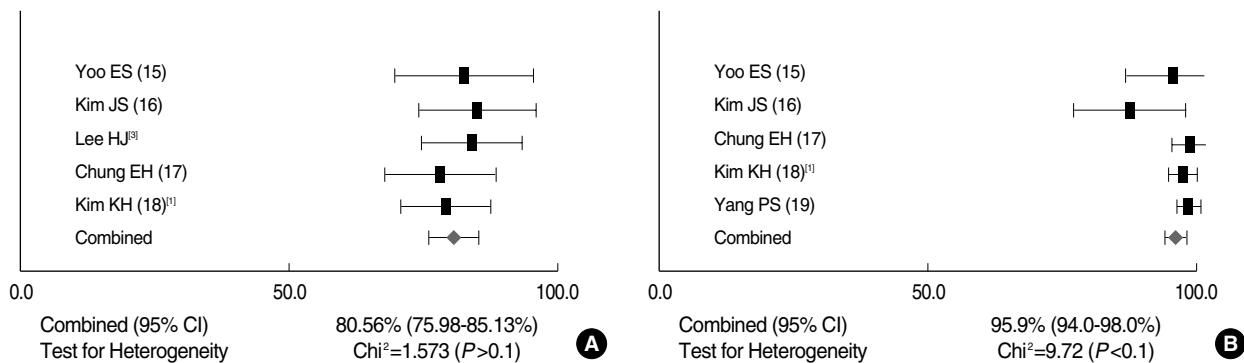


Fig. 2. Forest plot of seroconversion rate and 95% CI of individual trials of the PRP-T conjugate vaccine: (A) after 2 doses, (B) after 3 doses.

PRP-OMP vaccine. However, the vaccines included in the trials were different in character, one reported the immunogenicity of a monovalent PRP-OMP vaccine whereas the other trial reported on a combination vaccine, PRP-OMP+ Hepatitis B. A good immunologic response up to 91.7% and 96.6% after 2 doses was observed in the trial of the monovalent PRP-OMP vaccine and the combination vaccine, respectively.

PRP-T

There were six trials reporting the seroconversion rate after vaccination with the PRP-T vaccine at 2, 4, and 6 months of age. Among these trials, one trial did not evaluate the seroconversion rate after 2 doses and one trial did not have data after 3 doses.

conjugate vaccine. Data from a total of 288 and 394 children were included in the meta-analysis of the seroconversion rate after 2 doses and 3 doses of the PRP-T vaccine, respectively.

The seroconversion rate for the PRP-T vaccine after 2 doses from 5 trials ranged from 78.0% to 85.0%. The pooled seroconversion rate was 80.6% (95% CI; 76.0-85.1%). There was no statistically significant heterogeneity ($P > 0.1$, $\chi^2 = 1.573$). The seroconversion rate for the PRP-T vaccine after 3 doses from 5 trials ranged from 87.5% to 98.4%. The pooled seroconversion rate was 95.9% (95% CI; 93.5-97.5%). There was statistically significant heterogeneity in the outcomes ($P < 0.1$, $\chi^2 = 9.72$) (Fig. 2). To account for the statistical heterogeneity, we also tried a random effects model, of which the pooled estimate 95.4% (95% CI, 92.5-97.6%) showed little difference.

Immunogenicity of Hib conjugate vaccines: a meta-analysis

Six trials reported on the immunogenicity of the PRP-T

DISCUSSION

The results of the meta-analysis on the immunogenicity of

the PRP-T vaccine demonstrate that the PRP-T conjugate vaccines are highly immunogenic in Korean infants. After a primary series of PRP-T conjugate vaccine given at 2, 4, and 6 months of age, 80.6% and 95.9% of the infants had anti-PRP antibody levels $\geq 1.0 \mu\text{g/mL}$ after the second dose and third dose, respectively. According to this study, the lower limit of 95% CI after 2 doses was 76.0%, which is higher than the WHO recommendations for effective Hib conjugate vaccines (8). Thus, infants after 2 doses (given at 2 and 4 months of age) of PRP-T have responses considered acceptable for effectiveness of prevention of disease. Although there was no significant heterogeneity between the results of the trials after 2 doses of the PRP-T vaccine, heterogeneity was noted in the results of trials after 3 doses. This mainly came from one study which showed a seroconversion rate of 87.5%, whereas the other four studies ranged from 95.5% to 98.4%. However, a seroconversion rate of 87.5% is also allowable according to the definition of an effective Hib vaccine and the result of that single study does not affect the conclusion that the vaccine is effective after 3 doses. The small sample size of the study did not have a critical impact on the pooled seroconversion rate.

There was only one trial on the PRP-D. PRP-D is well known for its limited immunogenicity in infants and the report in Korean infants showed data comparable to previous reports in other countries (6). According to the results of the PRP-CRM, it seems that there is a low response after 2 doses and a significant boosting effect after the 3rd dose. However, considering there was only one trial each after 2 doses and 3 doses of the PRP-CRM it is not appropriate to make any conclusions on the response. The PRP-OMP vaccine showed good immunologic responses after 2 doses of both a monovalent PRP-OMP vaccine and a combination vaccine with the Hepatitis B. Further studies related with these vaccines in Korean children are needed.

According to the results of this study, we can carefully consider the possibility adopting of a 2-dose primary schedule. The results of the meta-analysis are acceptable after 2 doses and there is evidence in previous reports supporting a 2-dose primary schedule. According to a report on methods of economization of the Hib vaccine, immunogenicity, longevity of anti-PRP antibody response and immunologic memory of a 2-dose regimen was comparable with a 3-dose regimen (21). In a meta-analysis of vaccine efficacy against invasive Hib disease, the protective efficacy was 82% (odds ratio=0.18, 95% CI; 0.04-0.74) for two doses (5). Vaccines in these studies included PRP-T, PRP-D and PRP-OMP. When excluding the PRP-D trial, which showed no efficacy after the vaccine, the efficacy was 100% and 93% after 2 doses of PRP-T and PRP-OMP, respectively (22, 23). In a review of four different Hib vaccines and vaccination strategies of infants in Scandinavia, the effectiveness of PRP-CRM and PRP-T was excellent regardless of the schedule or number of primary doses. Two doses at various ages before 12 months were adminis-

tered as a primary series in Denmark, Finland (since 1988), Norway and Sweden compared with 3 doses in Iceland and Finland (1986-1987), and no difference in clinical effectiveness was observed (24). Also, in a comparison of five different vaccination schedules with PRP-T, although there was a significant difference in anti-PRP antibody concentrations between a 2-dose and 3-dose schedule, they concluded that two injections of PRP-T vaccine were immunogenic enough to maintain protection up to 12 to 24 months of age (25). It is not desirable to apply a policy based on data of other countries or different regions, especially considering the possibility of different vaccine responses related to ethnicity and natural boosting. But these data can be valuable sources for reference, particularly considering the local epidemiology of these countries of the Scandinavian region were higher than reports in Korea (26).

There is little doubt as to the need of the booster dose in the Hib conjugate vaccination schedule. An increase of reports on vaccine failures in the UK were seen where the Hib vaccination program did not include a booster dose (27), whereas there is no increase in vaccine failures in countries where routine boosting is done (28). Thus, we can carefully consider the possibility of adopting a 2-dose primary schedule with a booster. Moreover, we have to think of the impact of a 2-dose primary schedule. With the high cost of the vaccine, more children in the Korean population could be able to receive a vaccine compared with a 3-dose primary schedule. The Hib conjugate vaccination rate, up to January 2007 is approximately 65.2% and 54.8% for the primary series and booster dose in Korean children (unpublished data). Although an analysis on the cost benefit of the Hib vaccine in Korea should be done, a 2-dose primary schedule could lower the nationwide health cost related to the vaccine, making it feasible to adopt the Hib conjugate vaccine into the national immunization program.

An important issue on considering the possibility of a 2-dose schedule is that this could be applicable to the PRP-T vaccine, which we evaluated through a meta-analysis and the PRP-OMP vaccine, which is already licensed for 2 doses. To apply this policy to other types of Hib conjugate vaccines and especially combination vaccines, further studies on the immunogenicity are needed.

There are some limitations to this study. The effect of the Hib conjugate vaccine is reviewed based on immunologic results. Among the clinical trials included in the analysis, there were no studies that reported cases of vaccine failure or the effect of the vaccine compared with a placebo or control. However, this limitation can be overcome by the fact that the anti-PRP antibody level is widely used in evaluating vaccine efficacy for the Hib vaccine (7, 27, 29). Also, experimental data supports the use of anti-PRP antibody responses as a surrogate of clinical vaccine efficacy (30). Two characteristics of the anti-PRP antibodies play a major role in protection against diseases; anti-PRP antibodies are opsonic and activate com-

plement-mediated bactericidal activity.

The antibody threshold for protection against invasive Hib diseases was derived from data on the unconjugated PRP polysaccharide vaccine. Since immunological memory and antibody avidity maturation are well known immunologic characteristics of conjugate vaccines, the protective antibody threshold could be an overestimate. Evidence for this is seen in previous efficacy trials of the Hib conjugate vaccine. In Finland, even though only 40% of infants immunized with PRP-D at 3, 4, and 6 months of age developed anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$ measured 1 month after the third dose, vaccine efficacy was 90% (6). In Navajo infants immunized with PRP-OMP at 2 and 4 months, vaccine efficacy was 95%, despite the fact that only 59% developed anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$ (23). When using a threshold that might have the possibility of underestimating protective efficacy, conclusions made based on this threshold can be safe.

A better way to evaluate the efficacy of the Hib vaccine, next to a well designed randomized controlled efficacy trial, would be to directly evaluate the bactericidal activity of the anti-PRP antibodies elicited. There was one trial among those included in the meta-analysis which reported the results of a serum bactericidal assay (18). According to the results, anti-PRP IgG titers correlated well with bactericidal activity for both PRP-T and PRP-OMP vaccines. Also both vaccines showed comparable bactericidal activity after 2 and 3 doses of vaccine in infants. However, because the serum bactericidal assay is difficult and tedious to perform, it is not as widely used in laboratories as the ELISA.

The Hib vaccination schedule varies in countries in association with the disease burden, cost benefit and national policy. With the worldwide data showing that invasive Hib disease has been practically eliminated in many countries, and considering the demonstrated safety of the vaccine, it should be promptly adopted to the national immunization program in Korea. Based on the results of a meta-analysis, we can say that Korean infants show a good response to Hib conjugate vaccines and a reduced number of doses as a primary series could be carefully considered.

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