Immunogenicity and safety of pneumococcal 7-valent conjugate vaccine (diphtheria CRM$_{197}$ protein conjugate; Prevenar$^{TM}$) in Korean infants: Differences that are found in Asian children

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Abstract

This study was conducted to determine the immunogenicity and safety of a 7-valent CRM197 protein conjugated pneumococcal vaccine (PCV7) in Korean infants immunized at 2, 4 and 6 months. A total of 202 infants were enrolled and 146 and 141 infants were, respectively, included in post-2nd dose and post-3rd dose immunogenicity evaluations conducted on a per protocol basis. After two and three PCV7 vaccinations, 63.0–98.0 and 97.2–100% of infants achieved an antibody level of $\geq 0.35$ μg/mL, respectively, with a lowest against serotype 6B. No vaccination-related serious adverse reactions were observed. Thus, PCV7 appears safe and highly immunogenic in Korean infants, and adopting two doses for a primary series could be a feasible option for facilitating vaccine coverage rate.

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1. Introduction

Pneumococcal infection is an important cause of mortality and morbidity in infants and children worldwide. After the conjugate Haemophilus influenzae type b (Hib) vaccines were licensed in 1990, more than 98% of Hib disease was eliminated in the US [1]. As a result, pneumococcus has become the most common cause of bacterial meningitis and primary bacteremia in young children. In addition, there has been a rapid emergence of drug-resistance among pneumococci responsible for invasive infections worldwide. Moreover, the increasing antimicrobial resistance of Streptococcus pneumoniae has been more remarkable among isolates from children <5 years old [2–4].

A pneumococcal 7-valent CRM$_{197}$ protein conjugate vaccine (PCV7) containing seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23), the most prevalent serotypes among young children in North America, has been licensed in many countries for the vaccination of infants and young children. PCV7 covers more than 80% strains responsible for invasive disease in children in the US [5], and the above-mentioned seven serotypes are responsible for 65–80% of invasive pneumococcal disease in Europe [6–8]. In Korea, 57–63%
(79–80%, when cross-reactive serotypes are included) of the isolates responsible for invasive infections in children are included in the current 7-valent pneumococcal conjugate vaccine [9,10].

Several studies conducted in developed countries like Western Europe and North America have demonstrated that PCV7 elicits high concentrations of antibodies against most vaccine serotypes [7,11–16]. The vaccination schedule for PCV7 involves a three-dose primary series over 6 months followed by a fourth dose in the second year and has been recommended by the US and some European health national authorities.

However, it has been demonstrated that responsiveness to polysaccharide vaccines and protein conjugate vaccines of H. influenzae type b are ethnically dependent [17,18]. It has also been suggested that the good response shown by Korean infants to Hib conjugate vaccine and the reduced number of doses involved indicate its potential appropriateness as a primary series in Korean children [19]. Possible differences could exist in different parts of the world with respect to the immunogenicities of pneumococcal conjugate vaccines. The current 7-valent pneumococcal conjugate vaccine is expensive and prospective 9-, 11- or 13-valent vaccines are likely to be more expensive. Thus, reducing the number of PCV injections would lower costs, facilitate PCV vaccine coverage and allow PCV to be added to national vaccination programs in less wealthy countries. Actually, vaccination programs for infants in Sweden, Denmark, Norway, Italy, and Finland are based on primary vaccinations at 3 and 5 months and a third dose at 12 months (i.e., the 2 + 1 schedule) [12].

The primary objective of this study was to determine the safety and immunogenicity of three-dose PCV7 as a primary series in Korean young infants, and the secondary objective was to determine the immunogenicity caused by two doses of this vaccine to examine the feasibility of adopting two doses as a primary series. PVC7 was administered at 2, 4 and 6 months of age, and antibody titers against the seven serotypes included in the vaccine were evaluated on a per protocol analysis at 5 months (after two doses) and at 7 months. The safety of the PVC7 was analyzed on an intention to treat basis.

2. Subjects and methods

2.1. Vaccinees

Healthy 2-month-old (42–100 days) Korean infants attending the Seoul National University Children’s Hospital or Ewha Womans University Hospital, both of which are located in Seoul, or attending Pusan National University Hospital were considered for inclusion. The presence of any of the following precluded enrollment: hypersensitivity to any vaccine component (including diphtheria toxoid); infants with thrombocytopenia or any coagulation disorder contraindicating intramuscular injection; known or suspected immunological function impairment; children with a history of anaphylactic reaction; or a history of a previous invasive pneumococcal infection. The following conditions were viewed as temporary or self-limiting and affected subject was included once these conditions had resolved: a current febrile illness (rectal temperature ≥ 38 °C) or another acute illness; or administration of gamma globulin during the previous 3 months.

2.2. Vaccines and vaccination

PCV7 is composed of polysaccharides of serotypes 4, 6B, 9V, 14, 19F, 23F; and oligosaccharides of serotype 18C. Each serotype in PCV7 (Prevenar™; Wyeth Lederle Vaccines S.A., Louvain-la-Neuve, Belgium) is independently coupled to CRM197 (a nontoxic mutant of diptheria toxin) by reductive amination. This pneumococcal vaccine is formulated at 2 μg of serotypes 4, 9V, 14, 18C, 19F, and 23F; and at 4 μg of serotype 6B, and contains approximately 20 μg of CRM197 per dose.

On days of vaccination for all doses, a brief medical assessment was conducted to verify that the child concerned was in good health and met the inclusion/exclusion criteria. Children were immunized at approximately 2, 4, and 6 months of age and received a 0.5 mL intramuscular injection of PCV7 and of DTaP (Diphtheria–tetanus–acellular pertussis) in different legs at each session. Some children were also administered other vaccines (i.e., Hib, inactivated poliovirus, Hepatitis B, influenza, or others) simultaneously or with a minimum of a 2-week interval. When vaccines were administered simultaneously, separate syringes and separate sites were used; injections into the same extremity were separated by at least 1 in. The customary age for the first dose is 2 months of age, but the first dose can be given from 6 weeks. Subsequent doses were administered at dosing intervals of 8 weeks (range: 6–11 weeks). Vaccines were stored refrigerated at 2–8 °C.

2.3. Safety surveillance

At first vaccinations, parents were given a digital thermometer and a diary card containing a list of adverse events and their grades, and instructions for recording concomitant medications, the use of antipyretic agents, axillary temperatures, and details of local and systemic reactions/symptoms that might occur during the 72 h following each vaccination. Diary cards served as memory aids for parents or guardians that allowed them to answer questions asked during telephone interviews conducted by study personnel. On first immunization days (day 0) each child was observed at the study site for a period of 15 min after vaccination to detect any immediate local and/or systemic reactions. Local reactions at injection sites, such as, redness, induration, and tenderness, and systemic events (changes in appetite, activity level, irritability, and sleep patterns) that occurred over 0–3 days were documented by investigators. Serious adverse events that occurred during the course of the study and during the 30 days period after each injection were recorded.
2.4. Serology

Blood for antibody assays was drawn pre-1st dose (age 2 months), post-2nd dose (age 5 months; 1 month after 2nd vaccination), and post-3rd dose (age 7 months; 1 month after 3rd vaccination). Serum was stored in a deep freezer at −70 °C. Serologic assays were performed in the Applied Immunology Microbiology, Wyeth, Pearl River, NY 10965, USA. Standard enzyme-linked immunosorbent assays (ELISA) were used to quantify serum immunoglobulin G (IgG) levels to each of the seven serotypes in PCV7. Antibodies to C-polysaccharide were blocked by preincubation with pneumococcal absorbent prepared by Wyeth-Lederle. ELISA units were converted to μg/mL of IgG using 89SF standard reference serum.

2.5. Statistical analyses

Serum antibody titers were analyzed using logarithms of the antibody concentrations of all subjects that met the per-protocol requirements. Geometric mean concentrations (GMCs) of antibody and two-sided 95% confidence intervals were determined for antibodies to each pneumococcal serotype pre-vaccination, and post-doses 2 and 3. Fold rise of post-2nd and -3rd dose antibody concentrations compared to pre-concentration were calculated, respectively. If either pre- or post-dose two or three concentrations were missing then the subject concerned was excluded from the calculation. Proportions of subjects achieving defined levels of 0.2, 0.35, 0.50, or 1.0 μg/mL were reported for “Post-dose 2” and “Post-dose 3” blood samples. Two-sided 95% confidence intervals were also calculated. Reverse cumulative distribution plots were used to display percentages of children that achieved different antibody concentrations to each of the seven pneumococcal serotypes.

2.6. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the institutional review boards at each of the three centers concerned. Informed written consent was obtained from all parents or legal guardians following a detailed explanation of schedules and contents of the study.

3. Results

3.1. Vaccinees

A total of 202 infants were enrolled of mean age 66.02 ± 10.11 days (range: 46–106 days) and 48.5% (98/202) were boys. One hundred and eighty seven (92.6%) and 177 (87.6%) of 1st dose recipients were given 2nd and 3rd doses of PCV7, respectively. A total of 566 shots of PCV7 were administered during the study period and all were included in the safety evaluation. Thirty-one cases were withdrawn during the study for the following reasons: adverse experiences (n = 1), lost to follow-up (n = 8), parent request (n = 13), and others (n = 9). After excluding cases of protocol violation, a total of 146 and 141 infants were included in post-2nd and -3rd dose immunogenicity evaluations by per protocol analysis, respectively.

3.2. Safety

The safety evaluation was conducted on all 202 enrolled infants; of these only one shot was given to 15 infants (7.4%), two shots to 11 (5.5%), and three shots to 176 (87.1%). Thirty-seven adverse events requiring admission or clinic visit were reported among 22 recipients, and 30 events of these were determined not to be related to the vaccine. Of the remaining seven adverse events, three adverse events (URI, strabismus, and gastroenteritis) were probably not related and four events (pyrexia [n = 2], rash, erythema) were possibly related to the vaccine. The incidence of any solicited local reaction (erythema, induration, and/or tenderness combined) at injection sites was 8.8–23.8% (Table 1). Local reactions did not increase in frequency or severity with repeated vaccine doses, and no local reactions severe enough to require medical attention occurred. The most frequent solicited systemic symptoms and signs after vaccine administration were: irritability (30.2–54.4%), difficulty falling asleep (22.7–24.9%), anorexia (11.8–17.6%), diarrhea (4.1–6.2%), vomiting (1.2–6.2%), and fever of more than 38 °C (2.9–6.1%) (Table 1). Only three recipients experienced high fever of more than 39 °C on day 0 or day 1 after 2nd dose of PCV7, which were resolved without any specific treatments. Rates of febrile responses (>38 °C) were 5.2, 6.1, and 2.9% after 1st, 2nd, and 3rd doses, respectively. Fevers occurred during the 48 h after the 1st dose and usually resolved with 3 days with/without antipyretics. Eleven serious adverse events were reported, but all were considered vaccine unrelated. One infant was withdrawn from the study because of experience of serious adverse event which was not related to the vaccine (urinary tract infection), which resolved without any adverse consequences.

3.3. Immunogenicity

GMCs of antibody levels before vaccination and those achieved by pneumococcal vaccine recipients to each of the seven pneumococcal serotypes contained in PCV7 after the 2nd and 3rd doses are shown in Table 2. A substantial immunologic response to pneumococcal polysaccharides was elicited to all seven pneumococcal serotypes by PCV7. Pre-vaccination GMCs to each serotype ranged from 0.05 to 0.52 μg/mL, with highest value against serotype 1, and the lowest against serotype 4. After the 2nd vaccine dose, GMCs to all seven serotypes were ≥0.35 μg/mL (the serological correlate of protection suggested by WHO) and GMCs of
Systemic reactions

Local reactions

Adverse reactions (%) 1st dose (n treatments.

<table>
<thead>
<tr>
<th></th>
<th>1st dose (n = 193)</th>
<th>2nd dose (n = 181)</th>
<th>3rd dose (n = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>Tenderness</td>
<td>21.2</td>
<td>10.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Erythema</td>
<td>17.2</td>
<td>11.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Swelling</td>
<td>9.3</td>
<td>10.5</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Systemic reactions

Mild fever (≥38.1°C)

Diarrhea

Facial skin change

Vomiting

Rash

>1.0 µg/mL were obtained to all serotypes except serotype 6B; GMC for serotype 6B was 0.58 µg/mL. The 3rd vaccination induced a further rise in GMCs for five serotypes (6B, 7V, 14, 18C and 23F), and almost no change for serotype 4. After the 3rd doses, GMCs ranged from 3.16 to 14.24 µg/mL, with the highest mean value against serotype 14, and lowest against serotype 18C. The kinetics of antibody responses to pneumococcal capsular polysaccharides were serotype specific. Depending on serotype, children vaccinated with PCV7 showed a 3.4–114.6-fold rise in GMCs after 2nd doses and 15.5–114.6-fold rise from pre-vaccination to after the 3rd dose.

Reverse cumulative distribution curves shown in Fig. 1 and the data in Table 3 present percentages of children that achieved certain antibody levels to each vaccine serotype. After 2nd vaccinations, between 78.8 and 100% of children had ≥0.20 µg/mL of post-vaccination antibody titers to all serotypes, 63.0–98.0% achieved ≥0.35 µg/mL, 49.3–98.0% ≥0.50 µg/mL, and 31.5–97.3% ≥1.0 µg/mL, with lowest value against serotype 6B. After 3rd vaccinations, between 97.9 and 100% of children had ≥0.20 µg/mL of post-vaccination antibody titers to all serotypes, 97.9–100% achieved ≥0.35 µg/mL, 97.2–99.3% ≥0.50 µg/mL and 93.6–97.9% ≥1.0 µg/mL.

### 4. Discussion

Children younger than 2 years old do not respond well to polysaccharide vaccines, because polysaccharides are type 2 T-cell-independent antigens which only activate mature B cells and not T cells. Pneumococcal polysaccharides conjugated to protein carriers like a conjugated Hib vaccine, can induce a T-cell-dependent response. Immunologic responses depend on the conjugate proteins present, examples of which include CRM197, OMPC (outer membrane protein complex of the B11 strain of *Neisseria meningitides* serogroup B) and diphtheria toxoid. Relatively poor responses were observed when the carrier protein was OMPC [20,21] or diphtheria toxoid [22], and a better response was obtained when the carrier protein was CRM197 [11,12,21]. Resultantly, a heptavalent PCV7 (Prevenar™) containing CRM197 as a carrier protein has been licensed in many countries and is widely used in the US and some European countries. This study is the first to evaluate the immunogenicity and safety of PCV7 in Korean children.

The safety results obtained during this study indicate that three consecutive doses of PCV7 can be safely administered to Korean children of 2, 4, and 6 months of age. Local reactions to PCV7 were generally mild and no increase in the rate or severity was observed after administering 2nd or 3rd doses. Systemic reactions were common, especially after the first dose. However, because several vaccines were administered simultaneously, it is not possible to attribute systemic reactions to particular vaccine components. Moreover, safety monitoring in this cohort of >200 infants did not reveal any severe adverse events related to vaccination that resulted in hospitalization, or emergency or clinic visits. The local and systemic reactions observed were generally mild and more severe local and systemic reactions were uncommon and self-limited.

Recently, the protective levels of antibodies elicited by CRM197 conjugated vaccines against invasive pneumococcal disease represented concentration aggregated across serotypes, and 0.35 µg/mL has been associated with a clinical efficacy of 93.0% (95% CI, 81.0–98.2%) against invasive disease [23], based on the data from three clinical efficacy trials: one in Northern California [11], one among Navajo Indians [24] and one in Soweto, South Africa [25]. In addition, the ≥0.20 µg/mL level based on an analysis of Northern California Kaiser Permanente efficacy data [11] is another recommended serotype non-specific thresh-
The present study shows that PCV7 is immunogenic when administered as a primary series of three doses. Compared to published data of the US or European infants, Korean infants had higher post-vaccination GMCs (Fig. 2). A Taiwanese study found that post-3rd dose GMCs to all serotypes were higher than those found in European or the US studies [27]. The GMCs after 3rd dose in Korean infants were higher than those of Taiwanese infants for all seven serotypes included in the vaccine. Unfortunately, no information was provided about post-2nd dose GMCs in the Taiwanese study.

In US and UK studies, serotypes 6B and 23F evoked lowest responses after 2nd doses [12]. However, in the present study, after 2nd doses GMCs to all serotypes were elevated to ≥0.35 μg/mL, the serological criteria recommended by WHO for all serotypes. The antibody concentration of serotype 23F showed a 12-fold increase and achieved a GMC of 1.60 μg/mL after 2nd doses. For serotype 6B, more than a three-fold increase was found after 2nd doses, with a GMC of 0.58 μg/mL (95% CI: 0.47–0.71 μg/mL). A comparison of post-2nd dose GMCs in this study and post-3rd dose GMCs in the US and Europe studies showed no inferiorities to any serotype, except serotype 6B. Moreover, antibody concentrations in the present study increased significantly after 3rd vaccinations, except for serotype 4 and 19F. The GMC for 19F was decreased after 3rd dose, but the titer was higher than any of previous publication. The reason why GMC for 19F decreased after 3rd dose is not known.

Post-licensing follow-up data have shown that PCV7 has had a marked impact on the incidence of invasive pneumococcal disease [28–31] and on the spread of antibiotic-resistant pneumococci, with a serotype-specific efficacy of 97% against invasive disease [11,32]. Additionally, the indirect effect of immunizing young children on adults in the US improves the cost effectiveness of a PCV pediatric program [28,30]. In Korea, PCV7 was introduced at the end of 2003 and given to infants as an optional vaccine in private clinics; as yet PCV7 has not been included in the national immunization program as a mandatory vaccine. The coverage rate of PCV7 in Korea was estimated to have been around 30% in 2006 based on the number of doses distributed and surveillance data regarding the immunization coverage rate. The high price of PCV7 has played a major role in preventing it being adopted in routine vaccination programs. A vaccination schedule based on a three-dose primary series over 6 months and one booster dose during the second year has been recommended in the US and in some European countries. However, post-marketing surveillance reports from the US cautiously suggest that two doses in the primary series are sufficient for protection [29]. In addition, several studies on conjugate pneumococcal vaccines among infants have yielded good immunogenicity results at reduced doses, e.g., a Sweden study with two doses of PCV7 as a primary series.

![Fig. 1. Reverse cumulative distribution curves of antibiotic concentrations generated by PCV7 concurrent with DTaP: (A) after 2nd vaccination and (B) after 3rd vaccination.](image)

![Fig. 2. Serotype-specific GMCs after three doses of pneumococcal conjugate vaccine in infants.](image)
Table 2
Geometric mean concentrations and 95% confidence interval of antibodies to each pneumococcal serotype in subjects receiving primary doses of PCV7 when given with DTaP vaccine

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Pre-vaccination (A)</th>
<th>Post-2nd dose (B)</th>
<th>Rising fold (B/A)</th>
<th>Post-3rd dose (C)</th>
<th>Rising fold (C/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pn 4</td>
<td>0.05 (0.04–0.06)</td>
<td>5.61 (4.85–6.49)</td>
<td>114.57 (89.30–147.00)</td>
<td>5.60 (4.95–6.34)</td>
<td>114.55 (90.09–145.65)</td>
</tr>
<tr>
<td>Pn 6B</td>
<td>0.17 (0.14–0.20)</td>
<td>0.58 (0.47–0.71)</td>
<td>3.41 (2.59–4.48)</td>
<td>5.58 (4.82–6.48)</td>
<td>31.13 (24.25–39.96)</td>
</tr>
<tr>
<td>Pn 9V</td>
<td>0.25 (0.22–0.29)</td>
<td>3.16 (2.78–3.60)</td>
<td>12.54 (10.24–15.37)</td>
<td>3.94 (3.50–4.43)</td>
<td>15.52 (12.84–18.76)</td>
</tr>
<tr>
<td>Pn 14</td>
<td>0.52 (0.41–0.66)</td>
<td>8.87 (7.13–11.03)</td>
<td>17.05 (11.48–25.33)</td>
<td>14.24 (11.92–17.01)</td>
<td>25.09 (17.44–36.10)</td>
</tr>
<tr>
<td>Pn 18C</td>
<td>0.19 (0.16–0.22)</td>
<td>2.19 (1.90–2.53)</td>
<td>11.53 (9.19–14.47)</td>
<td>3.16 (2.73–3.65)</td>
<td>16.68 (13.27–20.98)</td>
</tr>
<tr>
<td>Pn 19F</td>
<td>0.17 (0.14–0.20)</td>
<td>7.67 (6.32–9.32)</td>
<td>46.20 (34.25–62.31)</td>
<td>4.85 (4.12–5.71)</td>
<td>28.55 (21.86–37.30)</td>
</tr>
<tr>
<td>Pn 23F</td>
<td>0.13 (0.11–0.16)</td>
<td>1.60 (1.33–1.92)</td>
<td>12.14 (9.05–16.29)</td>
<td>3.70 (3.13–4.38)</td>
<td>26.21 (20.09–34.19)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, 95% confidence interval.

b Geometric mean ratios of post-dose 2 concentration divided by each pre-concentration were calculated.

c Geometric mean ratios of post-dose 3 concentration divided by each pre-concentration were calculated.

Table 3
Proportions of infants with ≥0.20, ≥0.35, ≥0.50, and ≥1.0 μg/mL antibodies to the indicated serotype-specific pneumococcal polysaccharides during the course of immunization with PCV7 at 2, 4, and 6 months

<table>
<thead>
<tr>
<th>Serotype</th>
<th>% Infants with ≥0.20 μg/mL</th>
<th>% Infants with ≥0.35 μg/mL</th>
<th>% Infants with ≥0.50 μg/mL</th>
<th>% Infants with ≥1.0 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dose 1</td>
<td>Post-dose 2</td>
<td>Post-dose 3</td>
<td>Pre-dose 1</td>
<td>Post-dose 2</td>
</tr>
<tr>
<td>Pn 4</td>
<td>12.3 (7.0–17.7)</td>
<td>98.0 (95.6–100.25)</td>
<td>100.0 (100.0–100.0)</td>
<td>4.8 (3.8–5.8)</td>
</tr>
<tr>
<td>Pn 6B</td>
<td>45.2 (37.1–53.3)</td>
<td>78.8 (72.1–85.4)</td>
<td>100.0 (100.0–100.0)</td>
<td>23.3 (16.4–30.1)</td>
</tr>
<tr>
<td>Pn 9V</td>
<td>56.2 (48.1–64.4)</td>
<td>98.0 (95.6–100.0)</td>
<td>100.0 (100.0–100.0)</td>
<td>32.2 (24.6–40.0)</td>
</tr>
<tr>
<td>Pn 14</td>
<td>73.3 (66.1–80.5)</td>
<td>99.3 (98.0–100.7)</td>
<td>100.0 (100.0–100.0)</td>
<td>58.9 (50.9–66.9)</td>
</tr>
<tr>
<td>Pn 18C</td>
<td>47.3 (39.2–55.4)</td>
<td>96.6 (93.6–99.5)</td>
<td>98.6 (96.6–100.5)</td>
<td>28.1 (20.8–35.4)</td>
</tr>
<tr>
<td>Pn 19F</td>
<td>43.8 (35.8–51.9)</td>
<td>98.0 (95.6–100.3)</td>
<td>97.9 (95.5–100.3)</td>
<td>23.3 (16.4–30.1)</td>
</tr>
<tr>
<td>Pn 23F</td>
<td>31.5 (24.0–39.0)</td>
<td>95.9 (92.7–99.1)</td>
<td>97.9 (95.5–100.3)</td>
<td>19.2 (12.8–25.6)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, 95% confidence interval.
at age 3 and 5 months [12] and a UK study with two doses of a 9-valent pneumococcal conjugate vaccine at age 2 and 4 months [13]. These findings suggest that two doses of a PCV in early infancy might be adequate for primary immunization. Moreover, reducing the number of PCV injections would reduce costs and facilitate vaccine coverage rate in Korea and other developing countries.

In the present study, sampling after booster doses at age 12–15 months was not executed, and thus the ability of vaccine to prime immunologic memory was not evaluated. However, based on recent present knowledge, the booster vaccination is recommended for all enrolled infants. In addition, functional studies were not performed on antibody avidity or immunologic priming, both of which are important factors of protection against disease. However, ELISA IgG antibody concentrations appear to be the best parameter for evaluating pneumococcal conjugate vaccine, because IgG represents the desired immune response. Moreover, this methodology has been validated in infants, a bridge of IgG antibody concentration to efficacy data has been established, and a cross-laboratory standardization process has been completed [26].

We conclude that when used in a three-dose primary series at 2, 4, and 6 months of age, this PCV7 appears safe and highly immunogenic. Furthermore, adopting two doses of PCV7 as a primary series in Korean infants could be a feasible option for facilitating vaccine coverage rate.

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