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# Emergence of antibiotic-resistant non-vaccine serotype pneumococci in nasopharyngeal carriage in children after the use of extended-valency pneumococcal conjugate vaccines in Korea

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ABSTRACT

*Background:* This study was performed to assess the serotype distribution and antibiotic nonsusceptibility of pneumococcal carriage isolates from children in Korea following the introduction of extended-valency pneumococcal conjugate vaccines (PCVs).
*Methods:* From April to June 2014, nasopharyngeal swabs were collected from children who were attending daycare centers in Korea. The collection was conducted in accordance with the World Health Organization Pneumococcal Carriage Working Group standards. Isolates were identified based on colony morphology, the presence of alpha-hemolysis, and inhibition by optochin test. Serotype was determined by Quellung reaction and sequencing analysis (for serogroup 6). The E-test was performed to determine antibiotic susceptibility.
*Results:* A total of 267 pneumococcal isolates were collected from 734 children. Non-PCV13 serotypes accounted for 88.3% and 23A (12.6%), 15B (10.4%), and 15C (9.5%) were most common. Younger age was associated with higher carriage (65.6% vs. 31.2%, $P < 0.001$), while completion of PCV vaccination was associated with lower carriage caused by PCV13 serotypes (7.4% vs. 20.8%, $P = 0.007$). Overall, nonsusceptibility rates were 86.0% to penicillin and 90.5% to erythromycin, with a multidrug resistance rate of 81.5%. Among penicillin-nonsusceptible isolates, those caused by PCV13 serotypes were 11% and non-PCV13 serotypes were 89%. Frequent non-PCV13 serotypes (23A, 15B, and 15C) were all nonsusceptible to both penicillin and erythromycin except one.
*Conclusion:* High rates of carriage caused by non-PCV13 serotypes such as 23A, 15B, and 15C that show nonsusceptibilities to penicillin and erythromycin were noted following the introduction of extended-valency PCVs in Korea.

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## 1. Introduction

*Streptococcus pneumoniae* is a major cause of childhood morbidity and mortality worldwide [1]. The diseases caused by pneumococci range from mild infections such as otitis media to invasive infections such as bacteremia, meningitis, and complicated pneumonia. Pneumococcus frequently colonizes in the nasopharynx of children. Because pneumococcal carriage is a major factor in the occurrence of invasive diseases and in transmission to the community, it is important to assess the epidemiology and microbiologic characteristics of pneumococci carried in children [2].

Pneumococcus consists of more than 90 different serotypes distinguishable by the polysaccharide capsule. The disease burden caused by each of these serotypes has varied over time, primarily due to the introduction of conjugate vaccines. The use of 7-valent

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pneumococcal conjugate vaccine (PCV7, Prevnar®, Wyeth Pharmaceuticals) in the early 2000s in the United States has led to the reduction of invasive pneumococcal diseases (IPD) and carriage due to the serotypes that are included in PCV7, while replacement in carriage and IPD by non-PCV7 serotypes has been reported [3]. The introduction of extended-valency conjugate vaccines, namely 10-valent PCV (PCV10, Synflorix®, GlaxoSmithKline) and 13-valent PCV (PCV13, Prevnar13®, Pfizer) in 2010 or later, has shown to have further impact on the epidemiology of IPD and carriage profiles [4–6].

In Korea, PCV7 was introduced in 2003 as an optional vaccine, and was replaced by PCV10 and PCV13 in 2010 [7]. PCV10 and PCV13 had been used as optional vaccines with vaccination coverage of 60% in 2012, and since May 2014 both PCVs have been included in the national immunization program [8,9]. This study sought to describe the serotype distribution and antibiotic susceptibility of pneumococcal carriage isolates from the children who attend daycare centers four years after the introduction of extended-valency PCVs in Korea.

## 2. Materials and methods

### 2.1. Survey and sample collection

Nasopharyngeal swabs and household surveys were conducted at eight daycare centers located in the four major cities in Korea; Seoul, Seongnam, Busan, and Daejeon, from April to June 2014. The criteria for inclusion were healthy children aged between 6 and 71 months, and attending daycare centers at the time of the study. Written consent was obtained from parents or legal guardians. The parents or legal guardians were asked to respond to the survey using a pre-structured questionnaire to collect demographic information including age, sex, presence of siblings, and vaccination history. Presence of cough, rhinorrhea, or sore throat was defined as respiratory symptoms. The vaccination history included the number of vaccinations and type of vaccines (PCV7, PCV10, PCV13). One or two doses of vaccination was defined as incomplete vaccination; and three or more doses of vaccination was defined as complete vaccination.

During the daycare center visit, five pre-trained pediatricians collected nasopharyngeal swab samples, which were subsequently transported and stored according to standard procedures recommended by the World Health Organization (WHO) Pneumococcal Carriage Working Group [10]. In brief, a calcium alginate swab was passed through a single anterior nostril to reach the nasopharynx and was rotated 180° or remained soaked for five seconds before removal. The swabs were stored in STGG (skim milk, tryptone, glucose, glycerin) media, then were transported to Seoul National University Hospital to be processed within four hours from collection. Samples were plated on trypticase soy agar containing 5% sheep blood with gentamicin and were incubated overnight at 37 °C in 5% $CO_2$. *S. pneumoniae* was identified based on colony morphology, the presence of alpha-hemolysis, and inhibition by optochin test. Serotype was determined by Quellung reaction using antisera (Statens Serum Institute, Copenhagen, Denmark). The serogroup 6 were further serotyped by PCRs and subsequent sequencing analysis of $wciN_{\beta}$ and $wciP_{6B}$ genes, as previously described [11].

The E-test (bioMérieux, Inc. Durham, NC, USA) was performed for typeable isolates to test the antibiotic susceptibilities for penicillin, cefotaxime, chloramphenicol, tetracycline, clindamycin, erythromycin, trimethoprim-sulfamethoxazole, and levofloxacin. Antibiotic-nonsusceptibility breakpoints were used based on the 2014 Clinical and Laboratory Standards Institute breakpoints [12]. Minimal inhibition concentrations for penicillin ($\geqslant$0.12 μg/mL) and cefotaxime ($\geqslant$1.0 μg/mL) on parenteral meningitis breakpoints were used. Penicillin breakpoint parenteral non-meningitis ($\geqslant$2.0 μg/mL) was also used. Multidrug resistance (MDR) was defined as nonsusceptibility to $\geqslant$3 antibiotic classes [13].

### 2.2. Definition and analysis

Isolates that did not react with all pooled antisera and omnisera were classified as non-typeable, meaning that these strains were unencapsulated. Typeable isolates were then classified as PCV13 serotypes or non-PCV13 serotypes. PCV13 serotypes referred to serotypes that include the seven serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F), the additional three serotypes in both PCV10 and PCV13 (1, 5, 7F), and PCV13-specific serotypes (3, 6A, 19A).

The differences in serotype proportion and antibiotic nonsusceptibility rates were tested using the chi-square test. In addition, antibiotic nonsusceptibility rates and the proportion of children carrying individual serotypes were calculated according to their vaccination status. The independent risk of carrying a PCV13 serotype isolate was assessed using logistic regression, adjusting for surveyed variables. Statistical analysis was conducted using SPSS ver. 19.0 (SPSS, Chicago, IL, USA). The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1402-075-557).

## 3. Results

Of the 1082 children who attended daycare centers, 734 (67.8%) agreed to participate in this study (Table 1). Of those, 5.3% were aged between 12 and 23 months, 55.2% were between 24 and 59 months, and 38.4% were between 60 and 71 months (median age, 53 months). Fifty-one percent were male, 63.2% had one sibling, and 32.9% had respiratory symptoms within seven days. Of the 664 children with vaccination records, 106 (16.0%) did not receive any dose of PCVs, 6.8% had received an incomplete series

**Table 1**
Characteristics of the study subjects, pneumococcal carriage from 734 children attending daycare centers in Korea, 2014.

| Variables | N | (%) |
|---|---|---|
| Age group (months) | | |
| 6–11 | 8 | (1.1) |
| 12–23 | 39 | (5.3) |
| 24–59 | 405 | (55.2) |
| 60–71 | 282 | (38.4) |
| Gender | | |
| Female | 358 | (48.8) |
| Male | 376 | (51.2) |
| Siblings[a] | | |
| None | 141 | (21.0) |
| 1 | 425 | (63.2) |
| 2 | 97 | (14.4) |
| $\geqslant$3 | 9 | (1.3) |
| Respiratory symptoms within 7 days[a] | | |
| Yes | 220 | (32.9) |
| No | 448 | (67.1) |
| PCV vaccination history[a,†] | | |
| None | 106 | (16.0) |
| Incomplete | 45 | (6.8) |
| Complete | 513 | (77.3) |
| PCV unknown | 53 | (8.0) |
| PCV7 | 151 | (22.7) |
| PCV10 | 64 | (9.6) |
| PCV13 | 245 | (36.9) |

† Abbreviation: PCV, pneumococcal conjugate vaccine.
[a] Total number of sum is not 734 because not all participants answered to the questionnaires.

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