

Presentation

Global Control of Pneumococcal Infections by Pneumococcal Vaccines

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Abstract: *Streptococcus pneumoniae* is a major worldwide cause of morbidity and mortality. Pneumococcal carriage is considered to be an important source of horizontal spread of this pathogen within the community. Pneumococcal conjugate vaccine (PCV) is capable of inducing serotype-specific antibodies in sera of infants, and has been suggested to reduce nasopharyngeal carriage of vaccine-type pneumococci in children. PCV is generally immunogenic for pediatric patients with invasive pneumococcal disease, with an exception for the infecting serotypes. Based on evidences from the clinical trials of PCV, the health impact of childhood pneumococcal pneumonia appears to be high in developing countries where most of global childhood pneumonia deaths occur. PCV vaccination may prevent hundreds of deaths per 100,000 children vaccinated in developing countries, while PCV vaccination is expected to prevent less than 10 deaths per 100,000 children vaccinated in the developed countries. Therefore, the WHO has proposed a strategy to reduce the incidence of severe pneumonia by 75% in child less than 5 years of age compared to 2010 levels by 2025.

Key words: *Streptococcus pneumoniae*, Bacterial colonization, Invasive pneumococcal disease, Pneumococcal conjugate vaccine, Serotype-specific IgG, Opsonization index, Childhood pneumonia, WHO

PNEUMOCOCCAL DISEASES AND PNEUMOCOCCAL CONJUGATE VACCINE

Streptococcus pneumoniae is a major worldwide cause of morbidity and mortality resulting from pneumonia, bacteremia, and meningitis [1]. An important feature is that pneumococcal diseases will not occur without preceding nasopharyngeal (NP) colonization with homologous strain [2]. Pneumococcal carriage is considered to be an important source of horizontal spread of this pathogen within the community. Crowding in the hospital or day-care center, increases horizontal spread of pneumococcal strains. The rates of NP colonization of *S. pneumoniae* were found to be 20 to 40% in healthy children in Japan [3] and Thailand (Oishi K, et al. unpublished data). In contrast the rate of NP colonization of *S. pneumoniae* was reported to be high (approximately 90%) in Gambia, Africa [4].

Antibodies to pneumococcal capsular polysaccharide (CPS) and complement provide protection against pneumococcal strains with homologous or cross-reactive capsular serotypes [5]. The seven-valent pneumococcal

conjugate vaccine (PCV7) is capable of inducing serotype-specific antibodies in sera of infants, and has been suggested to reduce nasopharyngeal carriage of vaccine-type (VT) pneumococci in toddlers, possibly by preventing acquisition rather than by eradicating pneumococci from the NP [6, 7].

The introduction in 2000 of PCV7 for children in the United States younger than 2 years and children aged 2–4 years in a high-risk category was effective, dramatically reducing the incidence of invasive pneumococcal disease (IPD) [8, 9].

In Japan, PCV7 was licensed in October 2009, the Japanese government began to subsidize it for children less than 5 years of age in November 2010. PCV7 for children under 5 years of age was subsequently included in the routine immunization schedule at public expense in April 2013. According to “Research report on evidence of and measures for improvement of usefulness of vaccination” (Ihara-Kamiya Research Project that started in 2007), incidence of IPD per 100,000 population under the age of five decreased significantly owing to the immunization program. Namely, meningitis decreased from 2.8 in 2008–

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2010 to 0.8 in 2012 (decrease by 71%), and non-meningitis IPD from 22.2 to 10.6 (decrease by 52%) (<http://www.nih.go.jp/niid/ja/iasr-vol34/3343-iasr-397.html>).

Vaccine-induced protective immunity is currently estimated by measuring the concentrations of serotype-specific immunoglobulin G (IgG) using enzyme-linked immunosorbent assay [10] and the opsonization index (OI) using a multiplex opsonophagocytic assay [11]. We recently determined the geometric mean concentration (GMC) of serotype-specific IgG and the geometric mean titers (GMT) of OIs among 17 pediatric patients with IPD using paired sera obtained at the onset of IPD and after PCV doses following the resolution of IPD. The GMCs of serotype-specific IgG for all PCV7 serotypes other than serotype 6B were significantly increased after the last PCV7 dose compared with those at the time of IPD onset (Table 1), as were the GMTs of OIs for all PCV7 serotypes (Table 2). These data suggest that PCV7 is generally immunogenic for pediatric patients with IPD, with an exception for the infecting serotypes [12].

IMPACT OF CHILDHOOD PNEUMONIA AND PNEUMOCOCCAL CONJUGATE VACCINE WORLDWIDE

Determining the cause of pneumonia in young children is difficult, but nearly all studies undertaken in the developing world have identified *S. pneumoniae* as the most frequent bacterial cause of severe pneumonia [13]. In 2003, the World Health Organization (WHO) estimated that up to 1 million children die each year from pneumococcal disease, primarily pneumococcal pneumonia [14]. Currently, the WHO provisionally estimates that pneumococcal infections are responsible for 1.6 million deaths each year, including approximately 716,000 deaths among children < 5 years of age [15]. Therefore, the health impact of childhood pneumococcal pneumonia appears to be high in developing countries, especially those with high child mortality rates, where > 90% of global childhood pneumonia deaths occur [16].

Several clinical trials of PCV have been conducted in African countries. PCV9 reduced the incidence of IPD caused by vaccine serotype in human immunodeficiency syndrome (HIV)-negative children by 83% and that of radiological pneumonia by 20% [17]. Another study repor-

Table 1. Comparison of serotype-specific IgG concentrations between the time of onset of invasive pneumococcal disease (IPD) and after PCV7 vaccination in 17 children following the resolution of IPD.

serotype	serotype specific IgG concentrations ($\mu\text{g/ml}$)		P-value first vs. second
	at the first blood sampling	at the second blood sampling	
4	0.46 (0.26–0.81)*	4.08 (3.23–5.16)	< 0.01
6B	0.97 (0.58–1.62)	1.47 (0.82–2.65)	0.266
9V	0.34 (0.19–0.61)	3.97 (2.91–5.42)	< 0.01
14	1.76 (0.92–3.36)	6.30 (3.63–10.94)	< 0.01
18C	0.41 (0.22–0.76)	3.63 (2.69–4.91)	< 0.01
19F	1.23 (0.80–1.89)	3.51 (2.48–4.96)	< 0.01
23F	0.69 (0.40–1.21)	2.66 (1.52–4.67)	< 0.01

*Numbers in parentheses, 95% CI

Table 2. Comparison of serotype-specific opsonization index (OI) between the time of onset of invasive pneumococcal disease (IPD) and after PCV7 vaccination in 17 children following the resolution of IPD.

serotype	serotype specific OI (Log_{10} OI)		P-value first vs. second
	at the first blood sampling	at the second blood sampling	
4	0.63 (0.42–0.96)*	3.54 (3.36–3.70)	< 0.01
6B	0.53 (0.36–0.79)	1.64 (0.94–2.60)	< 0.01
9V	0.80 (0.43–1.46)	3.60 (3.34–3.81)	< 0.01
14	0.78 (0.43–1.38)	3.71 (3.54–3.90)	< 0.01
18C	0.93 (0.57–1.51)	3.53 (3.29–3.69)	< 0.01
19F	0.65 (0.41–1.01)	3.13 (2.85–3.38)	< 0.01
23F	0.56 (0.37–0.85)	3.04 (2.21–4.06)	< 0.01

*Numbers in parentheses, 95% CI

ted that PCV9 efficacy was 37% against first episode of radiological pneumonia [18]. Furthermore, PCV9 reduced the incidence of pneumonia-associated with any of respiratory viruses in children by 31% [19]. This finding also suggests that *S. pneumoniae* plays a major role in the development of pneumonia-associated with respiratory viruses, and viruses contribute to the pathogenesis of bacterial pneumonia. These effects of PCV against childhood pneumonia were found in the clinical trials in African countries, but not in developing countries in Asia.

Based on the accumulated evidences, the impact of PCV vaccination on childhood illness and mortality in the developing countries appears to be much greater than that in industrialized countries. PCV vaccination is expected to prevent about 700 deaths per 100,000 children vaccinated in developing countries, such as Gambia, while in the United States, PCV vaccination is expected to prevent 6 deaths per 100,000 children vaccinated [20]. The authors also demonstrated that analysis of expected health impact of the Global Alliance for Vaccines and Immunization (GAVI) eligible countries illustrated the values of accelerated PCV may prevent 3.7 millions child deaths. According to this idea, the WHO has proposed a strategy to reduce mortality from pneumonia in children less than 5 years of age to fewer than 3 per 1000 births and to reduce the incidence of severe pneumonia by 75% in child less than 5 years of age compared to 2010 levels by 2025 [21].

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