Special Article

Implication of Pneumococcal Conjugate Vaccines to Public Health: Thailand Perspective

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The pneumococcal conjugate vaccines (PCVs) have demonstrated good safety profile and efficacy against invasive pneumococcal diseases (IPD) caused by the serotypes included in the vaccines. The PCV also benefit to the unvaccinated children and adults from herd immunity. With the widespread use of the vaccine, emerging of non vaccine serotypes has been documented. The IPD burden in Thailand was found to be lower than that found in the western countries but the data in high risk population has been lacking. The PCV has been available in Thailand since 2006 as an optional vaccine, out of National Vaccine Program, with the uptake of less than 5% in children under 5 years of age. The serotypes distribution in Thailand has not changed significantly. In the year 2000-2005, compared with year 2006-2009, the most common serotypes in children < 5 years have been similar; comprising of 6B, 23F, 14, and 19F, however 19A has become more prevalence (6.2%) in the years 2006-2009. With the new breakpoint of penicillin susceptibility for non-meningeal strains, most penumococcal isolates in Thailand were susceptible to penicillin. To project the benefit for widespread use of PCV in Thailand, the cost benefit analyses including the different types of PCV, the various dosing schedule, the benefit from herd immunity and the disadvantage of serotype replacement are needed.

Keywords: *Pneumococcal Conjugate Vaccines, Impact, Thailand*

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Streptococcal pneumoniae (S. pneumoniae) has been a leading cause of morbidity and mortality among children particularly in developing countries. World Health Organisation (WHO)[1] estimated that around 10.6 million children less than 5 years worldwide acquired pneumococcal infection each year. The estimated annual death from pneumococcal diseases was 1.6 million, including 0.7-1 million in children aged < 5 years, of which mostly live in developing countries. The highest incidence was among children < 2 years and adults > 65 years of age. Although majority of pneumococcal infections were not severe, such as otitis media and sinusitis, they caused a significant morbidity and health care expenses. The more severe invasive forms such as pneumonia, bacteremia, sepsis and meningitis, may occur in any settings causing high mortality. The main risk factors for invasive pneumococcal diseases (IPD) include congenital or acquired immunodeficiency (*e.g.*; human immunodeficiency virus infection), absent or deficient splenic function, and cochlear implantation. The emerging problem of drug resistance worldwide has lead to concern of treatment failure. The pneumococcal vaccination is the vital strategy to prevent disease and development of drug resistance.

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Pneumococcal Vaccines

Current pneumococcal vaccines are based on the use of the bacterial capsular polysaccharides (PS) that induce type-specific antibodies which fix and activate complement and promote bacterial opsonization and phagocytosis[2]. The PS has been found to be the primary factor of virulence. Based on PS antigen, there are around 90 serotypes (40 serogroups). Some serotypes were more often to cause invasive disease than others.

The two types of currently licensed vaccines are the purified PS vaccine (PPV), and the conjugate vaccines (PCV) obtained by chemical conjugation of the capsular PS to protein carriers. PPV induce non-T cell response without memory T cells and boosting

effects. The carrier protein in PCV overcomes the PS limited antigenic property. The PCV are more immunogenic and can induce T cell dependent immune response in young children less than 2 years of age. The studies showed that PCV elicited prime-boost immunity and prevent nasopharyngeal colonization. The PCV elicit higher antibody levels than the PPV[3]. The current PCV contain serotypes causing most of IPD in children younger than 5 years. The serotypes included in PCV are; 7-valent: serotypes 4, 6B, 9V, 14, 18C, 19F, and 23 F; 10-valent: PCV7 plus serotype 1, 5, and 7F; and 13-valent: PCV7 plus serotype 1, 3, 5, 7F, 6A, and 19A. It should be noted that serotype 6A is closely related to serotype 6B, of which the immunity was found to be cross protected[4].

Efficacy and effectiveness of PCV

Randomised trials have demonstrated the good efficacy of the vaccines[5-8]. When infants were fully vaccinated with PCV7 at 2, 4, 6 and 12-15 months of age, vaccine efficacy (VE) was more than 95% against IPD caused by vaccine serotype (VT-IPD)[5]. The PCV has demonstrated higher antibody level in infants, young children, the elderly and immunodeficient persons than the PPV[9]. The efficacy against pneumonia and otitis media was less due to various other causative pathogens. The Cochrane database 2009 revealed that pooled vaccine efficacy (VE) for VT-IPD in children less than 2 years of age was 80% (95% CI, 58%-90%, $p < 0.00001$); for IPD caused by any serotypes was 58% (95% CI, 29%-75%, $p = 0.001$); for WHO defined chest X-ray confirmed pneumonia was 27% (95% CI, 15%-36%, $p < 0.0001$); for clinical pneumonia was 6% (95% CI, 2%-9%, $p = 0.0006$); and for all cause mortality was 11% (95% CI, -1%-21%, $p = 0.08$). The analysis in HIV-infected children also revealed the similar findings[10]. The VE for for otitis media is marginal and differed among types of vaccine, 6% (95% CI, -4% to 16%), 17% (95% CI -2% to 33%), and 34% (95% CI 21% to 44%) relative risk reduction of AOM associated with 7-valent PCV, 9-valent PCV, and 11-valent PCV, respectively[11].

The population based surveillance data from the US (1998-1999 and 2004-2005) after PCV immunization in year 2000 revealed vaccine effectiveness of 77% against IPD in children under 5[12]. The effectiveness of 64% and 54% against PCV7 serotypes meningitis cases were demonstrated in children < 2 and adult > 65 years of age respectively ($p < 0.001$ for both groups)[13], while only 32.1% ($p = 0.08$) reduction in PCV 7 related-serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 23A, and 23B) was observed. However, 60.5% increase in non PCV7 (19A, 22F, and 35B) serotype ($p < 0.001$) was found[13]. The serotype replacement has found be real and could impact the effectiveness of the vaccine after widespread use and deserves further discussion. This emphasizes the need for monitoring of serotype replacement.

Apart from direct protection of the vaccine in the immunized persons, vaccines also induce indirect protection for unimmunized persons, so call herd protection or community immunity[14]. This effect was from reduction of nasopharyn-geal colonization and result in decreased community transmission. Several surveillance studies have confirmed this benefit[15-18].

Impact of pneumococcal conjugate vaccine (PCV)

PCV-7 has been recommended in the US for routine immunization for all children < 24 months of age since 2000. The vaccine serotype coverage was 86% of invasive strains in the preimmunization era. After the implementation of PCV-7, there was a 77% reduction in IPD among children aged less than 5 years and a 39% decrease in hospitalized pneumonia among children aged less than 2 years[12,19]. In 2006, the GAVI Alliance (the Global Alliance for Vaccines and Immunizations), an organization that aligns public and private resources to create global access to vaccines, have created funding through 2015 for PCV introduction in the 72 countries with the lowest gross national income per capita (< $1,000 per capita) in 2003[20]. As of August 2008, PCV7 had been licensed around 90 of 193 WHO member states, 26 out of 193 (13%) countries offered PCV7 to all children as part of national immunization programs or had PCV7 in widespread use (*i.e.*, with estimated national coverage of > 50%); none of these countries was of low-income or lower-middle income[20]. Some countries have provided the vaccine only to certain high-risk groups. As more than 97% of childhood pneumonia occur in low-income countries, the vaccine would have greatest impact in such settings[21].

WHO position paper in 2007[1] suggested that PCV should be prioritized in 1) countries where mortality rate among children under 5 years of age is > 50 deaths /1,000 live births or > 50,000 deaths annually, 2) countries with high HIV prevalence (*i.e.* > 1%). Furthermore, if more than 10% of deaths among children under 5 years of age were attributed to pneumonia, an indicator of high childhood mortality from pneumococcal disease, PCV should also be considered. The decision to introduce the PCV into national routine immunization program need to based on the burden of diseases in

children < 5 years of age, the vaccine serotype coverage and the cost-effectiveness of the vaccine.

In the context of Thailand, the mortality rate among children under 5 years of age has decreased gradually from 12 per 1,000 live births in year 2003 to 10 per 1,000 live births in year 2007[22]. The estimate number of people living with HIV/AIDS in year 2009, was around half a million[23] (with the population number of 63 million) resulting in the HIV prevalence of less than 1%. Thailand does not meet the WHO PCV introduction criteria. At present, PCV7 is not included in the Thailand's Expanded Program on Immunization (EPI) but recommended as optional vaccine by self pay. The vaccines have been available since 2006 and used mostly in private sector with relatively high price (4,000 baht or 125 USD per dose) compared to other childhood vaccines.

Situations concerning the use of PCV in Thailand

There have been studies providing information involving the use of PCV in Thailand that should be considered by stake-holders as following.

Burden of the disease and serotype distribution in Thailand before the introduction of PCV

During 1980-1990, pneumococcal meningitis was the second most common cause of meningitis in children in Thailand[24]. However, during 1987-1997, after the introduction of *Haemophilus influenzae* type b vaccine in Thailand, pneumococcal meningitis became the most common cause of meningitis[25]. Although it is the first rank pathogen, the number of cases has not been high. A study, using rapid assessment tool, has revealed that the incidence of pneumococcal meningitis in Thailand was around 1.0-2.2/100,000 children under 5[26]. In May 2005-June 2007, blood culture from children under 5 years of age with suspected pneumonia and sepsis were conducted in 2 provinces in northeastern Thailand. The incidence of pneumococcal bacteremia, which included the antigen detection in culture negative samples, was 10.6-28.9 per 100,000 children under 5[27]. If the antigenemia was not counted, the incidence was reduced to 7.5-14 per 100,000 children under 5. Recently, the PnuemoNet study conducted in Bangkok revealed the incidence of IPD in children presented with fever of unknown source, pneumonia, or clinical sepsis, of 11.53 per 100,000 children 28 days- < 24 months of age, and 1.37 per 100,000 children 24 to < 60 months of age (personal communication with Chulathida Chomchai, MD).

A study during 2002-2004 in children younger than 5 years in rural Thailand revealed that the serotypes of 55% of nasopharyngeal carriage and 62% of invasive isolates were covered by PCV7[28]. Another study conducted in 2000-2005 in children younger than 5 years mainly from central Thailand found that of the 115 isolates from sterile sites, 73.9%, 77.4%, 77.4%, 87.8% were in serotypes included in PCV7, PCV9, PCV11 and PCV13, respectively[29]. The most common serotypes were 6B (27.8%), 23F (20%), 14 (10.4%), 19F (9.6%)[29]. The study in 2 provinces in northeastern Thailand during May 2005-June 2007 revealed slightly different serotype distribution; 14 (26%), 6B (21%), 19F (16%), 23F (6%), with slightly higher serotype coverage: 79%, 84%, and 95% by PCV7, PCV10 and PCV13, respectively[27].

The expected impact of the PCV

The information on serotype distribution can lead to expected effectiveness of the routine vaccination. For example, 86% of invasive isolates in the US before the vaccine era was covered by the PCV-7 and led to the 77% reduction of IPD when the vaccine was routinely used[12]. A recent report from Norway revealed the effectiveness of 74% of PCV7 using 2 + 1 schedule with the serotype coverage before vaccine introduction of 73%[30]. The expected effectiveness of PCV7 in Thailand would be around 70%, and of PCV13 would be at least 80%. As more than 89% and 95% of the penicillin non-susceptible and all of the cefotaxime non-susceptible isolates were covered by PCV7 and PCV13, respectively, the expected effectiveness on reduction of non-susceptible pneumococcal diseases in Thailand would be greatly.

In the US, rate of IPD caused by penicillin and erythromycin non-susceptible strain declined around 80% in children < 2 years of age, the uptake of vaccine at that time was around 73%[31]. There also was a report from Portuguese where PCV7 was recommended on voluntary basis for children < 2 years or those at high risks for IPD that the decreased in penicillin non-susceptibility has been observed. This reduction was also observed in adults, while the vaccine uptake was 43%[32].

The effectiveness on reduction of non-susceptible invasive isolates could be over-estimated using the former penicillin breakpoint compared to the newly recommended breakpoint by The Clinical and Laboratory Standards Institute (Table 1)[33]. In Thailand, using the new breakpoint has increased the rate of penicillin susceptibility from 26% to 94% (Fig. 1)[34].

Reduction of serotype coverage following

widespread use of PCV7 have been reported. The emergence of non-vaccine serotype has been of concern. After the routine use of PCV7 in the US, the serotype 19A increased from 2% to 35%[31]. In the first 3 years after introduction of routine PCV7, overall IPD significantly in Alaska Native children younger than 2 years decreased 67% (from 403/100,000 in 1995-2000 to 134/1,000,000 in 2001-2003). However, between 2001-2003 and 2004-2006, an 82% increase in IPD to 245/100,000 was observed and the rate caused by non-vaccine serotypes increased 140% compared with the pre-vaccine period, of which serotype 19A was accounted for 28.3%[35]. The impact of serotype replacement was found to reduce the efficacy of vaccine greatly in Spain and France[36,37]. However, in the US, PCV7 resulted in sustained reduction of the IPD, although the proportion of the IPD from non-vaccine serotypes was increased[38]. Moreover, there appeared to be natural dynamic changes of serotype distributions without vaccine pressure effect, probably due to multifactorial factors[39], that integrated into the appearing serotype replacement.

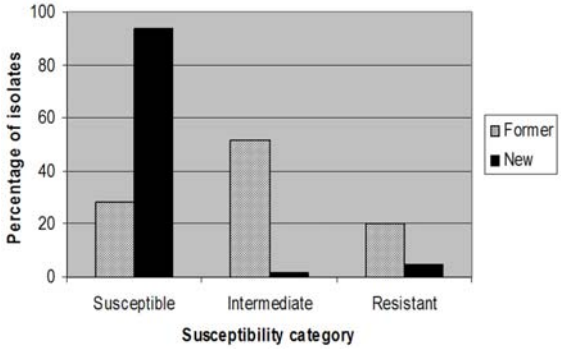

Fig. 1 Penicillin susceptibility of *S. pneumoniae* isolated from sterile sites in children < 5 years old using former and new CLSI criteria, Thailand, 2006-2009[34].
(Former criteria: susceptible, intermediate, and resistant MIC for penicillin were ≤ 0.06, 0.12-1, and ≥ 2 μg/ml, respectively, for all pneumococcal isolates, regardless of clinical syndrome or route of penicillin administration. New criteria: susceptible and resistant MIC are ≤ 0.06 and ≥ 0.12 μg/ml, respectively, for meningitis with intravenous penicillin; and susceptible, intermediate and resistant MIC are ≤ 2, 4, and ≥ 8 μg/ml, respectively, for nonmeningitis with intravenous penicillin. The non-meningitis criteria was used for *S. pneumoniae* isolated from blood, and meningitis criteria was used for CSF).

The most concerned emerging non-vaccine serotype has been 19A. A prospective surveillance in the US found that serotype 19A accounted for 46% of non-PCV7 serotypes in children in 2007-2008[40]. Increased of this serotype was found in Korea even before PCV7 implementation suggesting that emergence of non-vaccine serotype was not necessarily caused by vaccine use. A study revealed that the expansion of multidrug-resistant ST320 gene was responsible for the increase in serotype 19A before PCV7 use[41]. PCV7 has been available in Thailand since 2006. A follow-up study in central Thailand of the 172 *S. pneumoniae* isolates obtained from sterile sites from January 2006 to February 2009 revealed that PCV-7 and PCV-13 serotype coverage in children younger than 5 years were 70.3% and 81.2%, respectively. PCV-9, PCV-10, PCV-11 had very similar coverage as PCV-7[34]. Serotype 19A was found in 6% of the isolates. In comparison with the coverage in the year 2000-2005 of the same catchment area, the coverage of PCV7 in 2006-2009 was slightly lower. This very small change was probable because the PCV has been used in only about 5% of children under 5 years of age due to its high cost. The

Table 1. The Clinical and Laboratory Standards Institute Definitions of *in vitro* Susceptibility and Nonsusceptibility Nonmeningeal and Meningeal Pneumococcal Isolates , 2008[33]

Drug and Isolate Location	Susceptible (μg/mL)	Nonsusceptible (μg/mL)	
		Intermediate	Resistant
Penicillin (oral)	≤ 0.06	0.12-1.0	≥ 2.0
Penicillin (IV)			
Nonmeningeal(previous breakpoint)	≤ 2.0 (≤ 0.06)	4.0 (0.1-1.0)	≥ 8.0 (≥ 2.0)
Meningeal	≤ 0.06	None	≥ 0.12
Cefotaxime/Ceftriaxone			
Nonmeningeal	≤ 1.0	2.0	≥ 4.0
Meningeal	≤ 0.5	1.0	≥ 2.0

decreased in serotype coverage would make vaccines less efficacious. With the availability of PCV-13, a higher coverage and effectiveness has been expected, but could be decreased over the time with the wide use. It is important to monitor disease burden and serotype coverage of the isolates after the vaccine become available.

Vaccine cost effectiveness

One of the most important factors for policy makers to decide for widely implementation PCV is the result of cost effectiveness and cost benefit. Apart from the medical and indirect costs, the factors needed to be considered are the herd protection (indirect protection), serotype coverage of the PCV, dosing regimens and catch up program to enhance the duration of protection, and the vaccine price. A cost analysis model revealed that non-vaccine serotype replacement could reduce the benefit of the vaccine[42]. Recent papers have included net-indirect vaccine benefit, *i.e.* herd protection minus serotype replacement effect[43], to analyze the cost effectiveness for vaccine implementation[43-45]. A recent study revealed that the PCV10, PCV13 could have better net health benefits than PCV7 through less replacement disease and increased herd protection[46].

The standard regimen includes 3-dose primary series starting at age of 6-8 weeks or later, with interval of approximately 2 months or at least 4 weeks, plus one booster at 12-15 months of age (3 + 1). There have been some countries implemented 2-dose primary series at 2 and 4 months of age plus a booster dose at 12-15 months of age (2 + 1) and reported good effectiveness as expected[30]. The single booster dose given after the age of 12 months is needed to boost the waning immunogenicity and enhance the duration of protection. Recently, the Pediatric Disease Society of Thailand recommended either 3 + 1 or 2 + 1 regimen for Thai children. Duration of protection of the PCV against vaccine types lasted around 2-3 years after primary series.

The PCV7 are now in national immunization program for most developed countries, and recently in 2 African GAVI's eligible countries (Rwanda and Gambia). Currently, PCV is not in Thai National Program of Immunization Program. However, PCV has been recommended by the Pediatric Infectious Diseases Society of Thailand as the optional vaccine for healthy children and recommended for all in children at high risk. The cost analyses for the context of Thailand are needed.

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วัคซีนป้องกันโรคติดเชื้อนิวโมคอคคัสชนิดคอนจูเกต ข้อควรพิจารณาสำหรับประเทศไทย

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วัคซีนป้องกันโรคติดเชื้อนิวโมค็อกคัสชนิดคอนจูเกต เป็นวัคซีนที่นำเอาส่วนโพลีแซคคาไรด์แอนติเจนบนแคปซูลของเชื้อนิวโมค็อกคัสมาจับกับโปรตีนพาหะสามารถกระตุ้นการสร้างภูมิคุ้มกันในเด็กอายุน้อยกว่า 2 ปี เป็นวัคซีนที่มีประสิทธิภาพที่ดีและปลอดภัย โดยเฉพาะการป้องกันโรคชนิดรุนแรงที่เกิดจากซีโรไทปที่บรรจุในวัคซีน ในประเทศที่มีการใช้อย่างแพร่หลาย พบว่ามีอุบัติการณ์โรคลดลงในกลุ่มเด็กโตและผู้ใหญ่ที่ไม่ได้รับวัคซีนด้วย ซึ่งเป็นผลจาก herd immunity แต่พบปัญหาคือมีการเพิ่มขึ้นของการติดเชื้อที่เกิดจากซีโรไทป์ที่ไม่ได้บรรจุในวัคซีน โดยเฉพาะ ซีโรไทป์ 19A ซึ่งอาจทำให้ประสิทธิภาพของวัคซีนลดลงในระยะยาว และเน้นให้เห็นความจำเป็นที่ต้องมีการเฝ้าระวังซีโรไทป์อย่างต่อเนื่อง

สำหรับประเทศไทยคาดว่าอุบัติการณ์การติดเชื้อชนิดรุนแรงจากนิวโมค็อกคัสไม่มากเท่าในต่างประเทศ และยังไม่เข้าเกณฑ์ขององค์การอนามัยโลก ในการพิจารณาเข้าในแผนการให้วัคซีนของประเทศ อย่างไรก็ตาม ประเทศไทยยังขาดข้อมูลการติดเชื้อในผู้ป่วยที่อยู่ในกลุ่มเสี่ยง จึงยังไม่สามารถทราบอุบัติการณ์ที่แท้จริงของการติดเชื้อชนิดรุนแรงจากนิวโมค็อกคัส วัคซีนป้องกันโรคติดเชื้อนิวโมค็อกคัสชนิดคอนจูเกตนี้ ได้มีที่ใช้ในประเทศไทยตั้งแต่ พศ. 2549 เป็นวัคซีนเผื่อเลือกราคาสูงยังมีการใช้ค่อนข้างต่ำ โดยมีการใช้วัคซีนน้อยกว่า 5% ในเด็กอายุน้อยกว่า 5 ปี จากการศึกษาการเปลี่ยนแปลงของซีโรไทป์ในประเทศไทยพบว่า ไม่มีการเปลี่ยนแปลงมากนักเมื่อปรียบเทียบช่วงปี พศ. 2543-2548 และช่วงปี พศ. 2549–2552 โดยซีโรไทป์ที่พบบ่อยยังคงเป็น 6B, 23F, 14 และ 19F อย่างไรก็ตามพบว่า 19A มีแนวโน้มเพิ่มขึ้นเล็กน้อยจากการปรับเกณฑ์การพิจารณาเชื้อนิวโมค็อกคัสดื้อยาใหม่ ใน พศ. 2551 โดยเฉพาะ non meningeal site พบว่าส่วนใหญ่ของเชื้อนี้ในประเทศไทยยังคงไวต่อเพนิซิลลิน การประเมินว่าวัคซีนนี้มีความคุ้มค่าหรือไม่นั้นต้องมีการศึกษา cost benefit เพิ่มเติมซึ่งตัวแปรที่ต้องพิจารณา คือชนิดของวัคซีน (ความครอบคลุมของซีโรไทป์) ตารางการฉีดผลพลอยได้จาก herd immunity และผลกระทบจาก การเพิ่มขึ้นของการติดเชื้อที่เกิดจากซีโรไทป์ที่ไม่ได้บรรจุในวัคซีน