Pneumococcal Vaccines

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Streptococcus pneumoniae is the leading bacterial pathogen of infectious diseases in children and adolescents. The 23-valent pneumococcal polysaccharide vaccine could prevent invasive pneumococcal infection with broader serotype coverage but still has some limitations. On the other hand, 7-valent pneumococcal conjugate vaccine has been shown to decrease cases of nasopharyngeal acquired *S. pneumoniae* vaccine serotypes and proved herd immunity. The safety and efficacy against vaccine serotype pneumococcal diseases have been documented. However, the potential risk of increasing non-vaccine serotype pneumococcal diseases should be considered. This article reviews the current status of pneumococcal disease and pneumococcal vaccines. We also review the current situation of pneumococcal infections and vaccines in Taiwan. Surveillance of disease burden and clinical isolates should be continued. *(Chang Gung Med J 2005;28:765-72)*

Key words: pneumococcal polysaccharide vaccine, pneumococcal conjugate vaccine, invasive pneumococcal diseases, acute otitis media, penicillin-nonsusceptible *Streptococcus pneumoniae*.

Streptococcus pneumoniae is a Gram-positive, facultative bacterium, which is commonly encapsulated. The capsule is a major virulence factor. By 1940, 80 serotypes, defined by different capsular polysaccharides, had been described, and the number has now risen to over 90.

S. pneumoniae is the leading bacterial pathogen of non-invasive and invasive diseases in children and adolescents, including acute otitis media (AOM), sinusitis, pneumonia, occult bacteremia, sepsis, meningitis and, sometimes, rapid fatal diseases. Pneumococcal vaccines may potentially prevent these diseases and deaths.

The tetravalent vaccine derived from a capsular polysaccharide was first used in 1945 but not widely so because of the advent of penicillin. Unfortunately, many patients died or suffered from severe sequelae despite antibiotic treatment, and multidrug-resistant pneumococcal strains were also emerging.[1] Vaccine development was rejuvenated in the late 1960s. By 1977, a 14-valent-polysaccharide pneumococcal vaccine was licensed in the United States, supplanted in 1983 by the current 23-valent formulations. This vaccine provides wide serotype coverage at low cost but is not efficacious in young children. More recently, pneumococcal conjugate vaccines have been developed. In 2000, the pneumococcal conjugate vaccine was licensed in the United States.[2] This article reviews the current status of pneumococcal disease and pneumococcal vaccines. We also review the current situation of pneumococcal infections and vaccines in Taiwan.

23-valent pneumococcal polysaccharide vaccines (PPV23)

The currently used PPV23 contain 23 capsular polysaccharide antigen serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) that are responsible for about 90% of invasive pneumococcal infec-

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Received: Aug. 15, 2005; Accepted: Sep. 10, 2005
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tions.[3,4,5] A study based upon the Center for Disease Control's (CDS's) pneumococcal surveillance system showed that the overall efficacy of preventing invasive infection caused by serotypes included in the vaccine was 57% in adults. Efficacy did not decline with increasing interval after vaccination: five to eight years after vaccination it was 71%, and nine years or more after vaccination it was 80%.[6] Another retrospective study in the elderly (≧ 65 years old) revealed significantly reduced risk of pneumococcal bacteremia but no benefit for pneumonia.[7] PPVs could also reduce mortality due to severe acute lower respiratory tract infections[8,9] and showed 62% protective effectiveness against invasive vaccine serotype diseases in children.[10]

Unfortunately, the vaccine is not effective in children younger than two years of age. In infants and young children, the responses of all 23 serotypes may not be consistent[11,12,13] and the antibody titer decreases rapidly within a few months.[14] Revaccination does not engender an anamnestic response.[11] Older children and young adults may have a better response to primary vaccination and revaccination.[15]

PPVs did not reduce the overall nasopharyngeal carriage of *S. pneumoniae* among children due to replacement of non-vaccine serotypes carriage.[16,17] However, it does decrease the incidence of AOM in children[18] but the efficacy persists for only six months and revaccination gives no further benefit.[19]

The adverse effects from PPV23 include local effects (erythema, swelling, tenderness at injection site) in about one third of the vaccine recipients but they seldom persist for more than 48 hours. Systemic reactions (fever, myalgia) are rare and revaccination does not increase side effects.[20]

The main recommendations for use of PPV in children include those aged ≧ 2 years at higher risk of pneumococcal infection. (Tables 1, 2)

7-valent pneumococcal conjugate vaccine (PCV7)

PCV7 includes seven purified capsular polysaccharides of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, 23F and serologically cross-reactive serotypes) that are coupled to a carrier protein. Conjugation of a nonpneumococcal protein to polysaccharides can elicit T cell-dependent memory response that promotes B-cell proliferation, affinity maturation and immunological memory in early life,[21,22] although the number of serotypes is limited.

The seven serotypes were recovered from 22-84% of recent pediatric isolates.[23,24,25] PCV7 could potentially prevent 85% of invasive pneumococcal disease and 65% of AOM in children younger than six years of age in the United States.[26] The antibody titers usually rise 5- to 10-fold after a primary immunization series, and decline during subsequent months.[27] Fortunately, they can rapidly increase again after a booster dose of either PCV or PPV early in the second year of life.

Several studies showed that primary immunization with PCV following by PCV or PPV boosting could reduce vaccine-serotype carriage rates by about 50%.[28,29,30] However, there was no significant difference in overall carriage rate due to the compensatory rise in non-vaccine serotypes. The efficacy of PCV7 against AOM had similar results.[31,32,33]

In contrast, PCVs could reduce clinical and radiological pneumonia in children with or without

Table 1. Children at High Risk of Invasive Pneumococcal Infection*

High risk (invasive pneumococcal disease attack rate 150/100 000 cases per year)
1. Sickle cell disease, congenital or acquired asplenia, or splenic dysfunction
2. Human immunodeficiency virus infection
Presumed high risk (attack rate not calculated)
1. Congenital immune deficiency
2. Chronic cardiac disease
3. Chronic pulmonary disease (including asthma treated with high-dose oral corticosteroid therapy)
4. Cerebrospinal fluid leaks
5. Chronic renal insufficiency, including nephrotic syndrome
6. Diseases associated with immunosuppressive therapy, radiation therapy and solid organ transplantation
7. Diabetes mellitus

* From Committee on Infectious Diseases, American Academy of Pediatrics, Pediatrics 2000;106:362-6

Table 2. Recommendations for Pneumococcal Immunization with PCV7 or 23PS Vaccine for Children at High Risk of Pneumococcal Disease*

Age	Previous Doses	Recommendations
Up to 23 mo	None	PCV per schedule for healthy children
24-59 mo	4 doses of PCV7	1 dose of 23PS vaccine at 24 mo, at least 6-8 wk after last dose of PCV7 1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine
24-59 mo	1-3 doses of PCV7	1 dose of PCV7 1 dose of 23PS vaccine, 6-8 wk after the last dose of PCV7 1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine
24-59 mo	1 dose of 23PS	2 doses of PCV7, 6-8 wk apart, beginning at least 6-8 wk after last dose of 23PS vaccine 1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine
24-59 mo	None	2 doses of PCV7 6-8 wk apart 1 dose of 23PS vaccine, 6-8 wk after the last dose of PCV7 1 dose of 23PS vaccine, 3-5 y after the first dose of 23PS vaccine

* From Committee on Infectious Diseases, American Academy of Pediatrics, Pediatrics 2000;106:362-6; PCV7: 7-valent pneumococcal conjugate vaccine; 23PS: 23-valent pneumococcal polysaccharide vaccines

HIV.[34,35] Post-licensure evaluation of the effectiveness of PCV7 showed invasive pneumococcal disease was reduced by 58-69%, including 63-78% for vaccine and 50% for vaccine-related serotypes diseases.[36,37,38] Indirect effects on the reduction of invasive vaccine-related pneumococcal diseases in non-immunized adults were also proven, especially among those 20-40 years of age and > = 60 years of age.[38,39] Furthermore, antibiotic-resistant pneumococcal isolates declined after routine PCV7 immunization.[36,37,39,40] Two factors are thought to be responsible: PCV7 decreases infection by vaccine serotypes that are antibiotic-resistant, and the vaccinees received less antibiotic treatment which reduced selective pressure producing resistant strains.

The most common adverse events are local reactions and fever.[41,42] Serious events such as seizures, anaphylactic reactions, serum sickness and thrombocytopenia, are rare.

After licensure, PCV7 was recommended for routine use in infancy in the US by the Advisory Committee on Immunization Practices. It recommended that all children aged ≦ 23 months should be vaccinated with PCV7 using the schedule shown in Table 2. Vaccination is also offered to older children with underlying diseases.

S. pneumoniae infection and vaccination in Taiwan

Asymptomatic nasopharyngeal carriage rates of pneumococci in Taiwanese children are 19.9-22.3%[43,44,45] and this can lead to development of diseases or spread of the pathogens. The isolation rate was higher in children aged between two and five years, and most common serotypes were 23F, 6B, 19F, 14.[43,44] Pneumococci was also responsible for 21.8% of persistent otitis media with middle ear effusion in Taiwanese children.[46] The overall incidence of invasive pneumococcal infection in Taiwan is still unknown. Several studies have reported that the rate of pneumococcal meningitis in children and adults is approximately 19%-33%.[47,48,49,50] Mortality from invasive diseases varied from 4.5% to 42.6%[51,52,53,54,55,56] and severe sequelae occurred in 24.7% of surviving patients.[52]

Further, a trend of increasing penicillin-nonsusceptible *S. pneumoniae* (PNSSP) has been noted: 27.35% in 1993, 37.5% in 1994, 55.5% in 1995, 77.5% in 1996, 66% in 1997 and 87.1% in 1998.[57] The prevalence of PNSSP clinical isolates in 1999-2002 was 40% to 80%.[58] All PNSSP were resistant to multiple antibiotics[59,60] and approximately 60% were also resistant to extended-spectrum cephalosporins and carbapenems.[59] Spread of the Taiwan clone (19F) and the Spanish clone (23F) could be one of the major reasons for the rapid increase in antimicrobial resistance among *S. pneumoniae* isolates in Asia.[61] However, no significant difference was found in the mortality rates of patients with PSSP and patients with PNSSP infections.[53,62]

About PPV23

In the 1980s, studies on the types of pneumococcal isolates in Asian populations showed that the number of types in the 23-valent pneumococcal vaccine were fewer in Asia than the number observed in the U.S.: the proportion of types was 62.9% in Taiwan and 87.9-92.8% in the U.S.[63] However, recent studies in Taiwan have shown that 92.5-100% of the clinical isolates were included in PPV23.[59,64] (See also work by Huang YC, as yet unpublished.) The serotypes 23F, 6B, 14, 19F, 3 and 9 accounted for 77.5-85% of all clinical isolates.[59] (See also work by Huang YC, as yet unpublished.) Furthermore, the most prevalent serotypes encountered in invasive diseases in adults in Taiwan were 3, 14, 23; and 23, 14, 6, 19, 3 in children.[54,56] About 85.7-100% of them were included in the serotypes represented in the PPV23.[54,55,56] Most common serotypes resistant to penicillin (6B, 9V, 14, 19F, 23F) were all covered by PPV23.[54] A 2-year prospective observational cohort study among HIV-1-infected patients showed vaccination with PPV23 and receipt of highly active antiretroviral therapy (HAART) were associated with reduced risks of pneumococcal disease.[65] Vaccination did not increase the risks of all cause community-acquired pneumonia, HIV progression and mortality. Another study by Lai JC (unpublished data) attempted to evaluate the antibody responses to the seven serotypes (4, 6B, 7F, 9V, 14, 18C, 19F, 23F) of PPV23 in elderly patients with chronic obstructive pulmonary disease (COPD). More than 80% of the patients had increased IgG titer 6-weeks after immunization, even patients > 75 years old. The more the antibody titer increased, the less acute exacerbation of COPD occurred. Antibody titers decreased one year later. No obvious adverse events occurred among these vaccinees, except for fever (5.1%) and local heat, erythema or pain (12.1%).

In Taiwan, PPV23 has been available since April 1999. Experts at a consensus meeting in 2003 and 2004 suggested that the primary targets for immunization are the elderly (≧ 65 years of age) and high-risk patients (those with chronic lung disease, chronic obstructive pulmonary disease, chronic cardiovascular disease and diabetes mellitus). They also suggested immunization with PPV23 and flu vaccine in the flu season for people over 65 years of age. Since April 2005, PPV23 vaccinations have been publicly funded in Taipei city for patient ≥ 65 years of age with serious diseases and those living in nursing homes.

About PCV7

The most common nasal carriage serotypes of *S. pneumoniae* in Asian children were 6 (21.5%), 23 (16.5%) and 19 (15.7%).[43] Furthermore, a study in northern Taiwan showed the most common carriage serotypes were 23F (22%), 6B (18.9%), 19F (18.9%) and 14 (8.4%) that were included in PCV7 and also composed 70.6% of all penicillin-resistant *S. pneumoniae isolates.*[44] Epidemiology of invasive pneumococcal infection in Taiwan showed that the most prevalent serotype was 23, followed by 6, 14, 19 and 3.[54] PCV7 would cover 92% of the serotypes among young children and 70% among older children and adults. Furthermore, 100% PNSSP isolates in invasive disease were included in PPV23.

The immunogenicity and safety of PCV7 in Taiwanese infants was assessed.[66] After three doses of vaccine, the geometric mean concentration of immunoglobulin G showed a significant rise to all seven serotypes. More than 95% of infants had antibody titer ≧ 0.15 μg/mL of all serotypes, and 93% (23F) to 100% (4 and 19F) of infants achieved an antibody titer ≧1 μg/mL. Mild to moderate local reactions at the injection site were the common side effect (17% to 30%) after vaccination but did not correlate to the number of vaccinations. Fever, restlessness, fussiness and loss of appetite were the most common systemic reactions (22% to 53%). Experts at consensus meetings in 2004 and 2005 suggested universal immunization for all children younger than two years of age, as well as those at high risk from invasive pneumococcal diseases (asplenia, immunodeficiency, cerebrospinal fluid leakage, immunosuppressive therapy and certain chronic diseases) ages 24-59 months. In Taiwan, PCV7 will be available by the end of 2005.

Conclusion

To date, the efficacy and safety of PPV23 has been well documented but the vaccine has some limitations, including insufficient immunogenicity in children younger than two years of age, rapid decline of antibody level and no booster response. On the other hand, PCV7 has been shown effective in preventing nasopharyngeal carriage of vaccine serotype *S. pneumoniae* and proved herd immunity. Safety

and efficacy against serotype invasive pneumococcal diseases and decreasing resistant strains were also demonstrated. However, the potential risk of increasing non-vaccine pneumococcal disease serotypes should be considered. Surveillance of clinical isolates will be continued and vaccines may require reformulation.

In Taiwan, PPV23 is considered for use in the elderly and for high-risk patients. Universal PCV7 immunization for all children < 24 months old and children 24-59 months who are at high risk from invasive pneumococcal disease, is also suggested. Post-licensure evaluation of the effectiveness of the vaccines is important.

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肺炎鏈球菌疫苗

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肺炎鏈球菌是造成成人或兒童侵襲性感染常見的致病原。臨床症狀包括：急性中耳炎、鼻竇炎、肺炎、菌血症、敗血症、腦膜炎等，甚至導致死亡。目前爲止，已發現多達九十種以上之血清型。而肺炎鏈球菌疫苗之接種有可能可以預防疾病之發生或死亡。目前最常使用的是二十三價多醣體疫苗或七價接合型疫苗。二十三價多醣體疫苗可有效降低侵襲性肺炎鏈球菌疾病並提供較廣泛之血清型保護力。但有其侷限之處，尤其是對小於兩歲之孩童無法提供足夠且持久的免疫力。另一方面，七價接合型疫苗則可藉由活化T-淋巴球之免疫反應，而對小於兩歲之孩童提供較佳之免疫力。其在預防中耳炎、對抗侵襲性疾病及減少抗藥性菌株產生之效果及安全性也已經證實。另可有效降低孩童鼻咽部此七種血清型肺炎雙球菌之帶原率並提供群體免疫力。然而，不同血清型之間並沒有免疫交叉保護作用。因此對非疫苗血清型菌株導致之疾病則有增加之潛在危險性。所以對於臨床分離菌株之血清型必須持續監測，以做爲疫苗成份再製造之參考依據。在臺灣，肺炎鏈球菌仍是造成肺炎、腦膜炎或其它侵襲性感染之主要病菌。抗藥性亦是逐年上升。故引進疫苗接種有其必要性及重要性。目前已上市的是二十三價多醣體疫苗。近年臺灣分離之肺炎鏈球菌血清型絕大多數屬於這二十三型。建議接種於老年人及高危險群包括：慢性肺部疾病者、心血管疾病及糖尿病者。而七價接合型疫苗也將於 2005 年年底引進臺灣。考慮全面施打於小於兩歲之孩童及侵襲性肺炎鏈球菌疾病之高危險群，包括無脾臟者、免疫不全者、腦脊髓液滲漏者、接受免疫抑制治療者及其它慢性疾病患者。而後續評估疫苗於臺灣本土接種後之保護效力及肺炎鏈球菌血清型之分布有其必要性。(長庚醫誌 2005;28:765-72)

關鍵字：肺炎鏈球菌多醣體疫苗，肺炎鏈球菌接合型疫苗，侵襲性肺炎鏈球菌疾病，急性中耳炎，抗藥性肺炎鏈球菌。

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受文日期：民國94年8月15日；接受刊載：民國94年9月10日
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