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Pneumococcal disease and use of pneumococcal vaccines in Taiwan

The use of pneumococcal vaccine plays an important role for prevention of invasive pneumococcal disease (IPD). However, introducing the pneumococcal vaccine into the national immunization program (NIP) is complex and costly. The strategy of progressively integrating the pneumococcal conjugate vaccine (PCV) into the NIP in Taiwan provides valuable experience for policy makers. The 7-valent PCV (PCV7) was first available in Taiwan in late 2005. PCV7 was first provided free to children with underlying diseases, those in vulnerable socioeconomic status, and those with inadequate health care resources. The catch-up immunization program with the 13-valent PCV was launched in 2013 and the national pneumococcal immunization program was implemented in 2015. Children aged 2-5 years had the highest incidence of IPD among pediatric population in Taiwan. Although the incidence of IPD caused by PCV7 serotypes has declined, the overall incidence of IPD remained high in the context of PCV7 use in the private sector. A surge of IPD caused by serotype 19A occurred, accounting for 53.6% of IPD cases among children aged ≤ 5 years in 2011-2012. After the implementation of the national pneumococcal immunization program, serogroup 15 has become the leading serogroup for IPD in children. Continued surveillance is necessary to monitor the serotype epidemiology in Taiwan.

Keywords: Pneumococcal vaccines, Serotype 19A, Invasive pneumococcal disease, Immunization program, Serotype replacement

Introduction

Pneumococcal infection has posed significant threat for health in the world. It is one of the leading causes of human meningitis, pneumonia, and bacteremia, leading to 14.5 million episodes of serious pneumococcal disease and claiming more than 500,000 lives of children under 5 years of age annually [1,2].

Immunization against pneumococci plays a pivotal role for prevention of invasive pneumococcal disease (IPD). Currently, one 23-valent pneumococcus polysaccharide vaccine (PPV23), which is indicated for adults and children aged ≥ 2 years, and 3 pneumococcal conjugate vaccines (PCVs) are available [3-5]. The 3 PCV formulas include 7-valent (PCV7), 10-valent (PCV10), and 13-valent (PCV13). All 3 formulas of PCV were recommended by the manufacturers using a 4-dose schedule, which included receiving three doses of PCV at intervals of approximately 2 months, with the first dose at age < 6 months, followed by a fourth dose at age 12-15 months (3+1 schedule) [6,7]. In ad-

dition to the 3+1 schedule, the World Health Organization (WHO) also endorses an alternative which consists of 2 primary doses given 2 months apart, starting at 2 months of age, followed by a booster at least 6 months after the second dose (2+1 schedule) [8]. The 3 formulas of PCVs have been licensed in European Union using the 2+1 schedule and some of the European countries, as well as countries located outside Europe, have integrated PCV into the national immunization program using the 2+1 schedule [9-11].

WHO has recommended that surveillance of pneumococcal infection should be conducted beginning at least 2 years prior to PCV introduction and continued for at least 5 years post PCV immunization program [12]. The results of high quality surveillance are essential for policymaking and PCV impact evaluation. As of 2012, 86 states have added PCV in their national immunization program, covering 31% of the birth cohort in the world [4]. The incidence of IPD has reduced among children aged <5 years in the states that included the PCV in their immunization program. Reduction in vaccine-type IPD incidence was also evident in individuals older than the target age stratum [12]. Vaccine-type IPD was even reported to be eradicated among vaccine-eligible young children and was nearly eradicated among all other age groups in some areas [13]. In addition to the incidence of vaccine-type IPD, meningitis caused by pneumococcus, the most serious form of IPD, and antibiotic-resistant IPD also decreased after the introduction of PCV [14,15].

In Taiwan, PCV7 was first introduced in late 2005 and nowadays all the 3 formulas of PCVs have been licensed and are available [16-18]. Taiwan applies a step-by-step strategy to introduce PCV into the national immunization program. Starting with risk groups and catch-up program, PCV13 has been included in the national immunization program since January 2015. The strategy would provide valuable experience for policy makers in developing countries. The epidemiology of IPD in the context of partial coverage of PCV showed some unique characteristics. Here we review the literatures to describe the PCV usage and epidemiology of IPD in Taiwan.

Use of Pneumococcal Vaccine in Taiwan

Use of PPV23 in Taiwan

PPV23 was licensed in 1998 and was rarely used before 2001 [19]. With the financial support from a non-government organization, PPV23 has been provided to the elderly aged ≥ 75 years since 2007. It was reported that the overall vaccination

rate was less than 1% in Taiwan before 2007. The cumulative coverage rate among people aged ≥ 75 years had reached 12% in 2007 and 41% in 2008 [20]. Chang has studied the benefit of PPV23 immunization among the elderly aged ≥ 75 years and reported that an additive effect of receiving PPV23 and influenza vaccine was associated with a significantly lower all-cause mortality, hospitalization, and a 13% reduction in inpatient expenditures of all diseases when compared with receiving influenza vaccine alone [21].

Use of PCV in Taiwan

PCV7 was licensed in Taiwan in 2002 [16] and has been available primarily at the recipients' expense since October 2005 [20]. Beginning in July 2009, PCV7 was provided free-of-charge by the government to children aged ≤ 5 years with underlying diseases, including those with splenectomy or spleen functional impairment; those with congenital immunodeficiency or human immunodeficiency virus infection; those with cochlear prosthetic devices or electromagnetic hearing devices; those with chronic kidney disease, severe congenital heart disease, chronic pulmonary disease, or diabetes; those with spina bifida or other clinical conditions that result in cerebral spinal fluid leakage, and those with malignancy or who have received organ transplantation (Fig. 1) [22]. In addition to children with underlying diseases, those who were in low socioeconomic status were also provided with government subsidized PCV7 in January 2010. Tsai et al. [23] reported the doses of PCV7 used in Taiwan would have provided complete immunization for 20.7%, 33.6%, 47.9%, and 46.2% of infants born in 2007, 2008, 2009, and 2010 using the 3+1 schedule, respectively. The manufacturer estimated the cumulative coverage rates of PCV7 among children aged <5 years from 2005 through 2008 to be 0.7%, 8.6%, 15.9%, and 25.2%, respectively [20]. According to a questionnaire investigation and medical records review, Hsieh et al. [24] also reported the rates of at least receiving one dose of PCV7 among children aged 2 months to 5 years were 0.2% in 2005, 5.7% in 2006, 17.1% in 2007, 26.9% in 2008, 37.5% in 2009, and 45.5% in 2010.

PCV10 was licensed in 2009 [17]. In addition to being used in private sector since 2010, PCV10 has been provided by the government to those who lived in areas with inadequate health care resources, i.e., those who lived in mountainous area or surrounding islands outside Taiwan, since May 2010. A total of 128,680 and 114,140 doses of PCV10 were imported in 2010 and 2011, which would provide complete immunization for 20.5% and 15.2% of infants born in the corresponding years

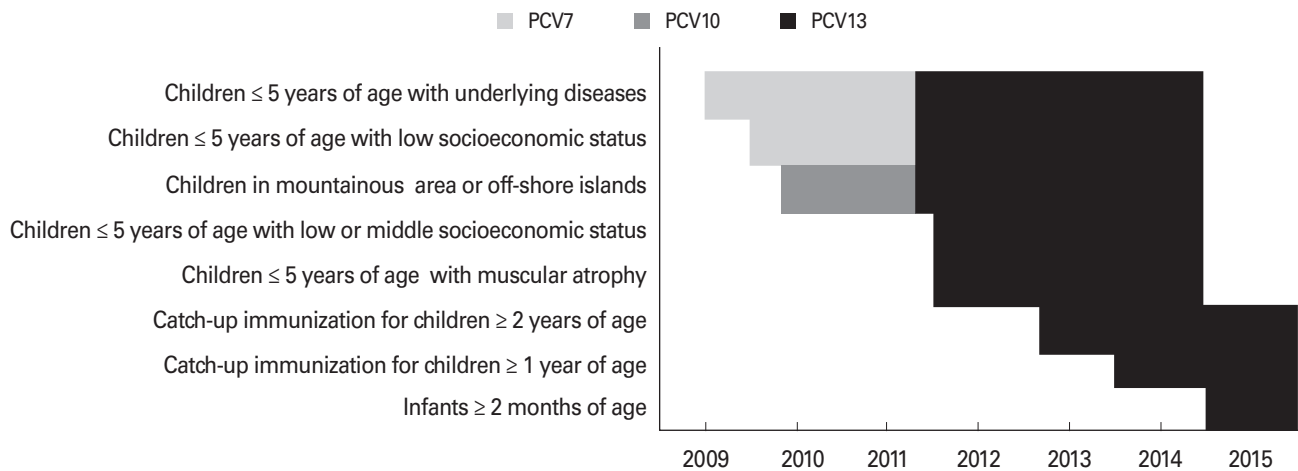


Fig. 1. Strategy of introducing pneumococcal conjugate vaccine into pediatric population in Taiwan.

with the 3+1 schedule, respectively (unpublished data). Use of PCV10 decreased significantly in 2012 and thereafter.

PCV13 was licensed in 2010 and was available in Taiwan in 2011 [18]. In place of PCV7 and PCV10, PCV13 was provided to those with underlying diseases, those with low socioeconomic status, and those who lived in areas with inadequate health care resources in October 2011 [22]. The government provided PCV13 to those with middle socioeconomic status and those with muscular atrophy in January 2012.

Although including the PCV into the vaccine program has been recommended by the WHO for years, the complex logistic task and huge financial burden of integrating 3 or 4 PCV doses into the existing vaccine programs remained a significant concern in most countries [8,25]. In contrast to the high IPD incidence in infants and young children less than 2 years of age in most countries, the epidemiology was characterized by the high incidence for children aged 2-5 years in Taiwan [26-28]. To mitigate the disease burden of IPD among the age group, the catch-up program among children 2-5 years of age was chosen to be the initial strategy of integrating PCV to the national immunization program [27]. An universal PCV13 catch-up program was launched in March 2013, providing one dose of PCV13 immunization to children aged 2-5 years. Wei et al. [27] reported a total of 2,027,160 doses of PCV13 were imported in 2011-2013, which would provide complete immunization for 85.9% of infants born during the respective period using the 3+1 schedule. According to the immunization records, the proportion of children aged 2-5 years immunized with PCV13 increased from 31.9% in February 2013 to 64.2% in December 2013 [27]. The catch-up program showed good results among the age group and thus was extended to chil-

dren aged 1-2 years in January 2014, providing 2 doses, divided by 8 weeks, of PCV13 to children 1-2 years of age [27].

Integration of PCV13 into the national immunization program in Taiwan

PCV13 was introduced to the national immunization program using the 2+1 schedule in January 2015, providing healthy infants with 2 primary doses given 2 months apart, starting at 2 months of age, followed by a booster dose at 12-15 months. The children with abovementioned underlying diseases are immunized with the PCV13 using the 3+1 schedule.

Before the implementation of the national PCV immunization program, the question of whether to provide both PCV13 and PCV10 or universal PCV13 was considered. The pros and cons of providing both PCV10 and PCV13 to the national pneumococcal immunization program were evaluated. Compared with PCV7, the added serotypes in PCV10, i.e., serotype 1, 5, and 7, were rarely recovered in the nasopharyngeal colonization as well as clinical isolates in Taiwan [26,29]. The fact that PCV10 does not include 19A, the most prevalent serotype for pediatric IPD in Taiwan, curtails the fitness of using PCV10 in this area. However, Poolman reported that the polysaccharide-protein conjugate 19F in PCV10 induces a considerable level of cross-opsonophagocytic antibodies against serotype 19A [30]. Limited reports also support a significant effectiveness of PCV10 against serotype 19A IPD [31]. PCV10 provides additional protection against acute otitis media caused by nontypable *Hemophilus influenzae*, which accounts for 22.9% of acute otitis media cases in Taiwan [32,33]. After thorough literature review and much discussion, Taiwan Advisory Committee on Immunization Practices (ACIP) decided to use the

PCV13 as the pneumococcal vaccine used in the national immunization program.

Surveillance of IPD and PCV Administration

The surveillance of pneumococcal infection was first carried out as part of antimicrobial susceptibility surveillance at hospital level in Taiwan. The major networks of antimicrobial susceptibility surveillance include the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program, which was coordinated by Taiwan National Health Research Institutes, and the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, which was coordinated by an university hospital [34-36]. These surveillance networks reported primarily the clinical manifestation and antimicrobial susceptibility of invasive or non-invasive pneumococcal infection. In addition to the collaborative networks, the epidemiology of the antimicrobial susceptibility, clinical presentation and serotypes distribution of pneumococcal infection were also reported by some international networks, multicenter surveillance, or uni-center surveillance [37-39].

Taiwan Centers for Disease Control (TCDC) has implemented or participated in IPD surveillance projects since 2001 [28, 40,41]. Health care facilities were encouraged to submit the clinical information of IPD cases and pneumococcal isolates to TCDC during the surveillance periods. IPD became one of the reportable diseases in October 2007, with the case definition of isolation of *Streptococcus pneumoniae* from normally sterile sites of individuals with invasive infection. Physicians are required to report the clinical characteristics of IPD cases in a web-based database within 7 days of establishing the clinical diagnosis, including the site of infection, the underlying clinical condition, and the outcome. The pneumococcal isolates should be collected and transferred to TCDC for species and serotype identification [28]. Reporting IPD cases is mandatory and physicians are subject to penalties for neglecting to report IPD cases.

Serotype Epidemiology of IPD in Taiwan

Epidemiology of IPD caused by vaccine serotypes

Reports on the vaccine coverage and leading serotypes of pneumococcal isolates are shown in Table 1. Fung had reported that 41.3%, 45.8%, and 63.3% of 550 clinical pneumococcal isolates were covered by PCV7, PCV13, and PPV23 in 1996-1997, respectively, when the pneumococcal vaccine has

not been licensed in Taiwan [42]. Between 2001, when the PPV23 was introduced to the private sector in Taiwan, and 2005, when the PCV7 was introduced to the private sector in Taiwan, the surveillance reports showed a high coverage for PCV7, PCV13, and PPV23, except for Chen et al.'s report [41] which showed the coverage rate was 63.0% for PCV7 and 87.2% for PPV23 [43-46]. Most of the leading serotypes during this period were covered by the PCV7.

After the introduction of PCV7 in 2005, the pneumococcal infection caused by serotypes covered in PCV7 decreased. Hsieh et al. [28] reported that 58.2% of IPD cases in 2007 were caused by serotypes covered by PCV7. Based on the mandatory reportable disease surveillance database between 2008 and 2012, Chiang et al. [26] showed a consistent decreasing trend in the IPD caused by PCV7 serotypes, from 59.8% in 2008 to 37.2% in 2012. The most significant decrease occurred in children 2-4 years of age, from 65.8% in 2008 to 12.9% in 2012. The trend of decreasing IPD caused by PCV7 serotypes was also present in older age groups, although it was not as significant as that in the young children. The least change in PCV7 serotypes IPD occurred in the age group of 65-74 years, which showed 53.2% in 2008 and 46.7% in 2012.

Unlike the consistent decreasing trend of IPD caused by PCV7 serotypes, the IPD caused by PCV13 serotypes decreased in the first years after introduction of PCV7 in late 2005 and restored in 2008-2013. The discrepancy of trends of IPD caused by PCV7 and PCV13 serotypes was associated with the progressive emergence of IPD caused by the replacement serotypes not in PCV7 but was covered by PCV13, especially serotype 19A. Surveillance reports showed the coverage rate of IPD caused by PPV23 was above 80% after the licensure of PPV23 in 1998 except Hsieh et al.'s study [28], which showed 77.7% of IPD cases were covered by PPV23.

In contrast to the decreasing trend of IPD incidence in countries using the PCV, the IPD incidence remained high in the context of gradual increasing PCV7 immunization rate in Taiwan. Chiang et al. [26] showed the incidence of IPD among all age groups was 3.3 cases per 100,000 person-years in 2008 and 3.2 cases per 100,000 person-years in 2012.

The prevalence of serotype 19A IPD

The epidemiology of IPD in Taiwan was characterized by a surge of serotype 19A IPD. The proportion of IPD caused by serotype 19A among all population increased from 5.5% in 2008 to 25.3% in 2012 [26]. The serotype 19A IPD was most prevalent among children eligible for PCV7 immunization,

Table 1. Vaccine coverage and leading serotypes of pneumococcal isolates in Taiwan

Period	Age (yr)	No. of isolates	Vaccine serotype coverage (n, %)				Leading 5 serotypes (n, %)	Notes
			PCV7	PCV10	PCV13	PPV23		
1996-1997	All	550	227 (41.3)	227 (41.3)	252 (45.8)	348 (63.3) ^{a)}	19F: 94 (17.1); 23F: 57 (10.4); 6B: 52 (9.5); 23A: 33 (6.0); 35: 27 (4.9); 39: 27 (4.9)	Clinical isolates from 14 laboratories [42]
1997-2003	≤ 13	860	715 (83.1) ^{b)}	718 (83.5) ^{c)}	804 (93.5) ^{d)}	793 (92.2) ^{a,e)}	23F: 219 (25.5); 19F: 208 (24.2); 6B: 159 (18.5); 14: 111 (12.9); 6A: 52 (6.0)	Nasopharyngeal carrier and clinical (IPD and non-IPD) isolates were included [45]
1998-1999	All	288	(~90)	NA	NA	NA	23: 65 (22.6); 6: 54 (18.8); 14: 51 (17.7); 19: 25 (8.7); 3: 22 (7.6)	IPD cases in the regional hospital and medical centers in Taiwan [43]
1999-2004	≤ 14	286	243 (85.0)	244 (85.3)	263 (92.0)	260 (90.9) ^{a)}	14: 81 (28.3); 23F: 60 (21.0); 6B: 49 (17.1); 19F: 39 (13.6); 3: 14 (4.9)	IPD cases in the regional hospital and medical centers in Taiwan [44]
2002-2003	All	522	329 (63.0)	339 (64.9)	NA	455 (87.2)	14: 96 (18.4); 23F: 79 (15.1); 3: 72 (13.8); 19F: 70 (13.4); 6B: 43 (8.2)	IPD cases in the regional hospital and medical centers in Taiwan [41]
2004-2006	≤ 15	68	57 (83.8)	57 (83.8)	62 (91.2)	62 (91.2) ^{a)}	14: 23 (33.8); 23F: 12 (17.6); 6B: 11 (16.2); 19F: 9 (13.2); 3: 4 (5.9)	IPD cases from 5 hospitals [46]
2006-2010	All	530	372 (70.2)	372 (70.2)	448 (84.5)	466 (87.9)	19F: 127 (24.0); 23F: 98 (18.5); 14: 72 (13.6); 6B: 66 (12.5); 19A: 40 (7.5)	Clinical isolates from 20 hospitals. A maximum of 10 isolates annually for each hospital [23]
2007	All	521	303 (58.2)	306 (58.7)	400 (76.8)	405 (77.7)	14: 110 (21.1); 19F: 63 (12.1); 3: 59 (11.3); 6B: 51 (9.8); 23F: 51 (9.8)	IPD cases from 76 hospitals [28]
2008-2009	All	231	134 (58.0)	134 (58.0)	173 (74.9)	~193 (83.5) ^{a)}	19F: 56 (24.2); 23F: 26 (11.3); 6B: 23 (10.0); 3: 22 (9.5); 14: 20 (8.7)	Isolates of community acquired infection in 3 hospitals [37]
2008-2012	All	3,659	1,817 (49.7)	1,829 (50.0)	2,968 (81.1)	3,096 (84.6)	14: 598 (16.3); 19A: 544 (14.9); 3: 467 (12.8); 23F: 429 (11.7); 19F: 314 (8.6)	IPD cases, population based surveillance data [26]
2008-2013	≤ 5	1,143	468 (40.9)	468 (40.9)	994 (87.0)	1,004 (87.8) ^{a)}	19A: 437 (38.2); 14: 133 (11.6); 23F: 122 (10.7); 19F: 116 (10.1); 6B: 95 (8.3)	IPD cases, population based surveillance data [27]

Values are presented as number (%).

IPD, invasive pneumococcal disease; NA, not available.

^{a)}The immunity caused by the serotype in the 23-valent pneumococcus polysaccharide vaccine (PPV23) is assumed to possess cross protect potential for all the sub-serotype. For example, the immunity against 15B in the PPV23 is protective against serogroup 15.

^{b)}The 7-valent pneumococcal conjugate vaccine (PCV7) coverage rates for nasopharyngeal isolates, those recovered from individuals with non-invasive and invasive pneumococcal diseases were 81.3%, 91.2%, and 93.4%.

^{c)}The 10-valent pneumococcal conjugate vaccine (PCV10) coverage rates for nasopharyngeal isolates, those recovered from individuals with non-invasive and invasive pneumococcal diseases were 81.4%, 91.2%, and 93.4%.

^{d)}The 13-valent pneumococcal conjugate vaccine (PCV13) coverage rates for nasopharyngeal isolates, those recovered from individuals with non-invasive and invasive pneumococcal diseases were 93.3%, 91.2%, and 94.7%.

^{e)}The PPV23 coverage rates for nasopharyngeal isolates, those recovered from individuals with non-invasive and invasive pneumococcal diseases were 91.1%, 100%, and 96.1%.

accounting for 53.6% of IPD cases among children aged ≤5 years in 2011-2012 [27].

The reason for the prevalence of serotype 19A IPD among children in Taiwan remained undetermined. The fact that the prevalence of serotype 19A IPD was first present in children eligible for PCV7 and then extended to other age groups suggested that the serotype replacement caused by PCV7 contributed to the surge of serotype 19A IPD [26]. Chen et al. [47] had reported a high drug resistance profile of serotype 19A pneumococcus in Taiwan. The multi-locus sequence typing analysis showed ST320 was a major genotype of serotype 19A

and was related to a high drug resistance profile in Taiwan [38,48,49]. It was reported that ST320 had been prevalent before the introduction of PCV7 in Korea, suggesting that the clonal expansion and the unique characteristics of serotype 19A pneumococcus, e.g., high drug resistance profile, played a role for the prevalence of serotype 19A IPD [50].

With the launch of the catch-up immunization program among children aged 2-5 years in 2013, the IPD incidence decreased significantly in the age group, from 22.8 cases per 100,000 person-year in 2011-2012 to 11.9 cases per 100,000 person-year in 2013. The IPD incidence decrease in the age

group was largely associated with that caused by serotype 19A, which decreased from 12.9 cases per 100,000 in 2011-2012 to 6.0 cases per 100,000 person-year in 2013 [27]. After the catch-up program was extended to children aged 1 year in 2014, the IPD incidence among children 1 year of age decreased from 11.4 cases per 100,000 in 2013 to 7.1 cases per 100,000 person-year in 2014. The decrease of incidence was also associated with that caused by serotype 19A, from 5.5 cases per 100,000 person-year in 2013 to 2.5 cases per 100,000 person-year in 2014 (unpublished data).

Serotype 19A has been the most prevalent serotype for IPD among children aged <5 years in 2009-2014 [26,27]. Instead of serotype 19A, serogroup 15 IPD becomes the leading serotype among children of the age group in 2015 [51]. The prevalence of serogroup 15 IPD has raised significant concern because it was not covered by current 3 formulas of PCV. Continued surveillance is necessary to monitor the serotype epidemiology in Taiwan.

Pneumococcal colonization and virulence of serotype-specific pneumococcus

Nasopharyngeal colonization of pneumococcus among children has been surveyed in the past years [24,29,45,52-56]. Having a sibling in a family, history of acute otitis media and household exposure to smoking have been found to be associated with pneumococcal colonization in PCV-unvaccinated children. The number of siblings ≥ 2 in a family, history of upper respiratory tract infection and child-care attendance were found to be associated with pneumococcal colonization in children regardless of vaccination history [24]. Previous reports showed that children who have received PCV immunization are less likely to be colonized with vaccine-type pneumococcus, leading to the decreased probability of developing an IPD episode [24,56]. The high pneumococcal colonization rate among children aged 2-5 years consists with the high IPD incidence among children of this age group.

The discrepancy of serotype distribution among colonized pneumococcal isolates and that of IPD isolates suggests a serotype-specific virulence difference. Hsieh et al. [28] reported serotypes 14, 19A, 3, and 6B possessed high odds of developing IPD, compared with the serotype distribution of nasopharyngeal pneumococcal colonization. One unique pulsed-field gel electrophoresis pattern of serotype 14 was prevalent among IPD patients with complicated pneumonia, suggesting a specific clone is accounted for serotype 14 prevalence [57]. Serotype 3 has been reported to be significantly associ-

ated with hemolytic uremic syndrome in children with IPD [58]. Further study on the serotype specific virulence of pneumococcus will facilitate the IPD control in Taiwan.

Conclusion

Taiwan uses a step-by-step strategy to integrate PCV into the national immunization program. PCV was first provided to children with underlying diseases, those in vulnerable socioeconomic status, and those with inadequate health care resources. The catch-up immunization program was launched in 2013 and the national pneumococcal immunization program with 2+1 schedule was implemented in 2015.

The epidemiology of pneumococcal infection has some unique characteristics. Unlike most countries' surveillance results that IPD peak in infants and young children, Children aged 2-5 years had the highest incidence of IPD among pediatric population in Taiwan. Although the incidence of IPD caused by PCV7 serotypes has declined, the overall incidence of IPD remained high in the context of gradually increasing PCV7 immunization rate. A surge of IPD caused by serotype 19A occurred, accounting for 53.6% of IPD cases among children aged ≤ 5 years in 2011-2012. After the implementation of national pneumococcal immunization program, serogroup 15 became the leading serotype for IPD in children less than 5 years old in 2015.

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