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Original Article

Invasive pneumococcal pneumonia caused by 13-valent pneumococcal conjugate vaccine types in children with different schedules

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KEYWORDS
13-Valent conjugate pneumococcal vaccine;

Abstract *Background:* In Taiwan, the age group with the greatest incidence of invasive pneumococcal disease is 2–5 years of age, which is different from other countries. This study was conducted to identify risk factors and different 13-valent pneumococcal conjugate vaccine (PCV13) schedules associated with vaccine-type invasive pneumococcal pneumonia (IPP) despite prior vaccination.

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Invasive pneumococcal pneumonia;
Vaccine schedule

Methods: A case–control study was conducted prospectively between August 2012 and December 2015 at five participating medical centers. The study enrolled children <15 years of age who were admitted to one of the five medical centers for CAP. Blood samples and acute-phase serum specimens were collected and *Streptococcus pneumoniae* was identified by using a real-time polymerase-chain-reaction (RT-PCR) assay targeting the *lytA* gene.

Results: A total of 25 children diagnosed with vaccine-type IPP and 124 controls were enrolled. Vaccine-type IPP occurred in 6 (28.6%), 14 (24.1%), and 5 (7.1%) children receiving vaccines on a not-age-appropriate schedule (n = 21), primary infant schedule (n = 58), and toddler catch-up schedule (n = 70) ($P = 0.008$), respectively. Of 25 children, the mean age at disease onset was 36 ± 11 months; serotype 19A was responsible for 84% (21/25).

Conclusion: After adjustment for confounding factors, the risk of vaccine-type IPP was significantly higher among children receiving vaccines on a not-age-appropriate schedule, or on a primary infant schedule, compared with children receiving vaccines on a toddler catch-up schedule. Duration of vaccine immunity should be investigated to direct strategies for maintaining individual and population immunity against pneumococcal disease.

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Introduction

Streptococcus pneumoniae is recognized as a major pathogen responsible for pneumonia, accounting for 20–60% of cases of community-acquired pneumonia (CAP).[1,2] Fortunately, since the implementation of pneumococcal conjugate vaccine (PCV), there has been a marked decrease in invasive pneumococcal disease (IPD) and all-cause pneumonia.[3] In addition to preventing pneumococcal pneumonia, PCV also has been shown to reduce virus-associated pneumonia, an observation that suggests that pneumococcal infection plays a crucial role in the development of pneumonia associated with viruses.[4] By preventing the acquisition and carriage of vaccine serotypes in the nasopharynx, PCV impedes a key step in the pathogenesis of pneumococcal disease, and reduces the transmission of vaccine serotypes to unvaccinated children and elderly people. In clinical practice in the United States, the 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar-13, Pfizer, New York, NY, USA) has been reported to decrease hospital admissions for all-cause pneumonia by 21% in children <2 years of age and by 17% in children 2–4 years of age, and to decrease empyema by 50% in children <2 years of age and by 46% in children 2–4 years of age.[5] In France, PCV13 also decreased cases of radiography-confirmed CAP by 16%, cases with pleural effusion by 53%, and cases of pneumococcal CAP by 63% among children between pre- and post-PCV13 periods.[6] In general, PCV has shown significant efficacy in the prevention of pneumonia.

In Taiwan, the epidemiology of *S. pneumoniae* disease among children differs from that in other countries.[7] In Taiwan, children 2–5 years of age have the highest rate of pneumococcal carriage and incidence of IPD and bacteremic pneumonia/empyema[7,8]; in contrast, these conditions peak in children <2 years of age and then decrease with age in Israel and the United States.[9,10] *S. pneumoniae* causes about 40% of CAP cases in Taiwanese children.[11] Children with pneumococcal pneumonia usually develop necrotizing pneumonia, lung abscess, and empyema, which are accompanied by a complicated clinical course; such patients need to be kept in the intensive care unit for respiratory distress, chest tube insertion, or postoperative care.[12] Furthermore, most children with pneumococcal pneumonia have culture-negative disease.[13]

PCV13 has been available in the private market since 2011 in Taiwan, and a national catch-up program providing one dose of PCV13 to children 24–60 months of age was launched in 2013, followed by providing 2 doses to children 12–23 months of age in 2014 and a 2 + 1 national infant immunization program in 2015. According to the information from the National Immunization Information System, the proportion of children 2–5 years of age in 2013, 1–2 years in 2014, and <1 year of age in 2015 immunized with the national program of PCV13 was 64.2%, 76%, and 93.5%, respectively (provided by Taiwan CDC). Based on the surveillance data from Taiwan CDC, the incidence of IPD in children 2–5 years of age has decreased by 50%, from 22.8/100,000 in 2011–2012 to 11.9/100,000 in 2013[14]; the incidence of IPD in children <5 years of age decreased by 70%, from 20.8/100,000 in 2011 to 6.2/100,000 in 2015. Nevertheless, clinically, a tiny fraction of children developed invasive pneumococcal pneumonia despite receiving PCV13. In this study, we aimed to identify risk factors and PCV13 schedules that were associated with breakthrough vaccine-type pneumococcal pneumonia in children.

Materials and methods

Study design

A case–control study was conducted prospectively between August 2012 and December 2015 at five participating medical centers. Northern sites included National Taiwan

University Hospital (NTUH), Linkou Chang Gung Memorial Hospital (CGMH), and Mackay Memorial Hospital (MMH). National Cheng-Kung University Hospital (NCKUH) and Kaohsiung Chang Gung Memorial Hospital (KCGMH) were included as southern sites. All five medical centers belong to the Taiwan Pediatric Infectious Disease Alliance (TPIDA), a study group funded by the National Health Research Institutes, Taiwan. The study was approved by the local ethics committee.

The study enrolled children <15 years of age who were admitted to one of the five medical centers for CAP (Fig. 1). CAP was defined as acute lung parenchymal change, radiographic confirmation of a pulmonary infiltrate, and positive respiratory symptoms and signs. Children with a history of recent hospitalization (<14 days prior to the current episode), severe underlying disease, immunosuppression, or recurrent pneumococcal infection were excluded.[11] Invasive pneumococcal pneumonia (IPP) is defined as *S. pneumoniae* identified in the blood or pleural effusion specimen of a patient, using a single-target (*lytA*) quantitative real-time PCR assay or culture method (Fig. 1). Cases were children diagnosed with IPP and receiving at least ≥one dose of PCV13 (Fig. 1). Controls were randomly selected from hospitalized children admitted to the same hospital with prior ≥one dose of PCV13, but without any respiratory symptoms and without a diagnosis of respiratory tract infection (based on clinical symptoms). Exclusion criteria for control enrollment were past history of diagnosis of pneumonia or any suspected or proven pneumococcal disease. Once consent was obtained, the following data were collected: child's medical history, laboratory investigations (for cases), and household characteristics. Vaccination history, and PCV13 status from records of vaccination schedules were obtained by parent/guardian interview. Vaccine doses received at least 14 days before enrollment were considered valid.

An age-appropriate PCV schedule was defined as a PCV vaccination history, which the number of valid doses received was at least equal to the number recommended by the Taiwan Advisory Committee on Immunization Practice and the Taiwan CDC according to the age when IPD onset for cases or the reference date for controls.[15,16]

Specimen and data collection

For cases, blood samples and acute-phase serum specimens were collected from each enrolled child as soon as possible after presentation. Blood samples were sent for bacterial culture at each site and processed according to standard techniques.[17] If pleural fluid was obtained within 7 days of admission, the specimen was sent for culture at the respective site; in addition, an aliquot was submitted (at CGMH) for testing for *S. pneumoniae* by using a real-time polymerase-chain-reaction (RT-PCR) assay targeting the *S. pneumoniae lytA* gene.[18,19] All of the *S. pneumoniae*-positive cases were serotyped using primer/probe sets specific for serotypes 1, 3, 4, 5, 6A/B, 7F, 9V, 14, 18C, 19A/F, and 23F.[19] PCV13 vaccine failure was defined as infection by one of the PCV13 serotypes.

Statistical analysis

All PCV13-vaccinated children were classified into three groups: 1) children who received 2 doses at 12−23 months of age, or children who received one dose at ≥2 years of age (toddler catch up schedule), 2) children who received 2 or 3 doses at <12 months of age and one booster dose after one year of age (primary infant 2 + 1/3 + 1 schedule), and 3) not age-appropriate schedule according to their PCV13 vaccination records.[15,16] Binary variables were compared using the χ^2 test, and continuous variables were compared by 1-way analysis of variance. Multivariate logistic regression analysis was performed to determine the independent risk factors for vaccine-type infection. Variables associated with vaccination failure at *P* values ≤0.2 in univariate

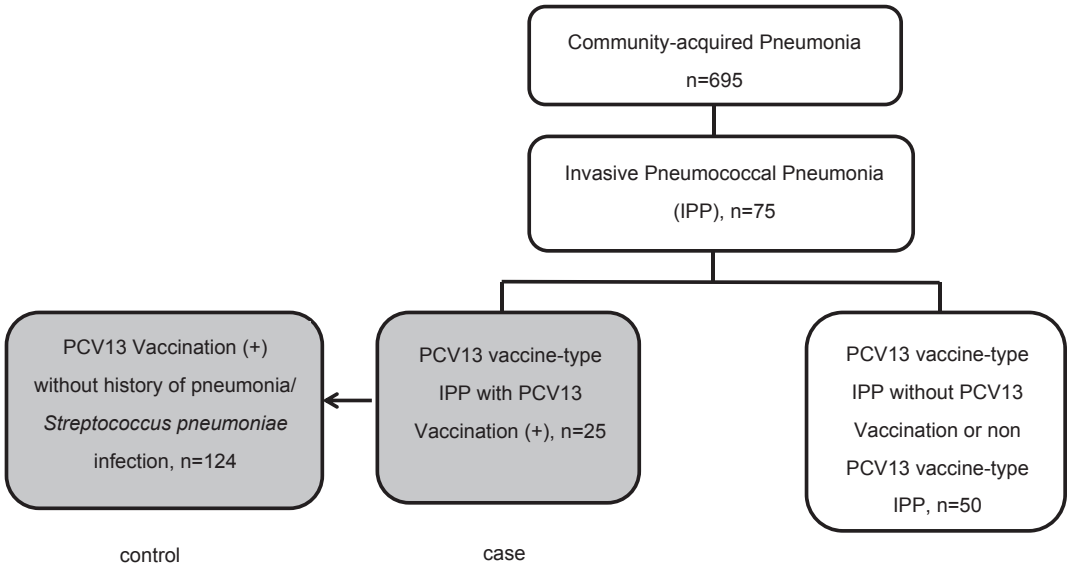

Figure 1. Flowchart of patients enrolled in the study. The study group is highlighted in gray.

analyses were included in the multivariate model. Data were analyzed with SPSS for Windows, version 16.0 (SPSS, Chicago, IL). All *P* values are 2-sided, and a *P* value of <0.05 was considered statistically significant.

Results

Demographic data of enrolled children

During the study period, 25 vaccinated children were diagnosed with vaccine-type invasive pneumococcal pneumonia, and 124 vaccinated controls were enrolled. These 149 children who had received at least one dose of PCV13 were divided into three groups based on their PCV13 vaccination history: 1) those receiving vaccines on a toddler catch-up schedule (n = 70), 2) those on a primary infant 2 + 1/3 + 1 schedule (n = 58), and 3) those on a not-age-appropriate schedule (n = 21).

Table 1 shows comparisons of characteristics in these children by different PCV13 schedules. The youngest child was 12-month-old while the eldest child was 79-month-old. Children receiving vaccines on a toddler catch-up schedule were older than children in the other two groups (46 ± 11.2 vs 33.4 ± 12.6 on a primary infant schedule, 31 ± 14.3 on a not-age-appropriate schedule; $P < 0.001$) and had highest day-care attendance rate (70% vs 51.7% in primary infant schedule, 47.6% in not-age-appropriate schedule; $P = 0.05$). The time elapsed between the last dose of PCV13 and enrollment was longest in children following a primary infant schedule (20.1 ± 12. vs 18.1 ± 11.6 in children following a not-age-appropriate schedule and 12.6 ± 8.2 in children following a toddler catch-up schedule group; $P < 0.001$). Children receiving vaccines on a primary infant schedule had the highest breastfeeding rate (91.4% vs 75.7% on a toddler catch-up schedule, 71.4% on a not-age-appropriate schedule; $P = 0.03$). All children received ≥3 doses of DTaP vaccine. Children receiving vaccines on a not-age-appropriate schedule had a higher rate of vaccine-type IPP (28.6%) than did those receiving vaccines on either a primary infant schedule (24.1%) or a toddler catch-up schedule (7.1%) ($P = 0.008$).

Risk factors of vaccine-type IPP after PCV13 vaccination

To evaluate the clinical impact of different PCV13 schedules on vaccine-type IPP, risk factors were analyzed in these vaccinated children. In univariate analysis (Table 2), age, time elapsed between the last dose of PCV13 and enrollment, male sex, chronic disease, exposure to tobacco smoke in the home, day-care attendance, history of breastfeeding, number of siblings, and maternal education were not significantly different between cases and controls. No child with vaccine-type IPP had chronic disease. PCV13 schedules were significantly different between cases and controls ($P = 0.01$).

In multivariate analysis, the PCV13 schedule remained the only independent factor associated with vaccine-types IPP ($P = 0.02$). After adjustment for time elapsed between the last dose of PCV13 and enrollment, the risk of vaccine-type IPP was significantly higher among children receiving vaccines on a primary infant schedule (adjusted odds ratio [aOR], 3.9; 95% confidence interval [CI], 1.2–12) or a not-

Table 1 Demographic characteristics of 149 children by different PCV13 schedules.

Characteristic	PCV13 schedules			
	Toddler catch-up (n = 70)	Primary infant 2 + 1/3 + 1 (n = 58)	Not age-appropriate (n = 21)	*P* value
Age, months	46 ± 11.2	33.4 ± 12.6	31 ± 14.3	<0.001
<2 years old	1 (1.4)	11 (19)	6 (28.6)	<0.001
2–5 years old	65 (92.9)	47 (81)	14 (66.7)	
>5 years old	4 (5.7)	0 (0)	1 (4.8)	
Time elapsed between the last dose of PCV13 and enrollment	12.6 ± 8.2	20.1 ± 12	18.1 ± 11.6	<0.001
Male sex	30 (42.9)	32 (55.2)	11 (52.4)	0.4
Chronic illness[a]	2 (2.9)	3 (5.2)	2 (9.5)	0.4
Exposure to tobacco smoke in the home	33 (47.1)	26 (44.8)	9 (42.9)	0.9
Day-care attendance	49 (70)	30 (51.7)	10 (47.6)	0.05
History of breastfeeding	53 (75.7)	53 (91.4)	15 (71.4)	0.03
Number of children aged under 10 years in household	1.9 ± 0.7	1.6 ± 0.5	1.7 ± 0.6	0.08
Mother education below senior high school	2 (2.9)	0 (0)	1 (1.7)	1.0
Vaccination history				
≥3 doses of *Haemophilus influenzae* type b vaccine	68 (97.1)	58 (100)	21 (100)	0.6
≥3 doses of DTaP vaccine	70 (100)	58 (100)	21 (100)	–
Vaccine-type IPP	5 (7.1)	14 (24.1)	6 (28.6)	0.008

Data are n (%), mean ± standard deviation.

[a] Chronic illness included hearing impairment, epilepsy, anemia, asthma, facial palsy, spinal bifida and hypospadias.

Table 2 Univariate and multivariate analyses of risk factors associated with vaccine-type pneumococcal pneumonia in 149 vaccinated children.

Risk factor	Case	Control	Univariate analysis		Multivariate analysis	
			Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age, months	36 ± 11	39.7 ± 14.3	0.98 (0.95–1.01)	0.22	–	–
<2 years old	2 (8)	16 (12.9)	–	–	–	–
2–5 years old	23 (92)	103 (83.1)	–	–	–	–
>5 years old	0 (0)	5 (4.0)	–	–	–	–
Time elapsed between last dose of PCV13 and enrollment	19 ± 11.2	15.8 ± 10.7	1.03 (0.99–1.07)	0.17	1.01 (0.97–1.05)	0.7
Male sex	12 (48)	61 (49.2)	1.05 (0.4–2.5)	0.9	–	–
Chronic disease	0 (0)	7 (5.6)	–	–		
Exposure to tobacco smoke in the home	14 (56)	54 (43.5)	1.7 (0.7–3.9)	0.26	–	–
Day-care attendance	16 (64)	73 (58.9)	1.2 (0.5–3.01)	0.6	–	–
History of breastfeeding	19 (76)	102 (82.3)	0.7 (0.3–1.9)	0.5	–	–
Number of children aged under 10 years in household	1.7 ± 0.6	1.8 ± 0.7	0.8 (0.4–1.6)	0.5	–	–
Mother education below senior high school	1 (4)	2 (1.6)	0.4 (0.04–4.6)	0.5	–	–
Vaccination history						
≥3 doses of *Haemophilus influenzae* type b vaccine	25 (100)	122 (98.4)	–	–	–	–
≥3 doses of DTaP vaccine	25 (100)	124 (100)	–	–	–	–
PCV13 schedules						
Toddler catch-up	5 (20)	65 (52.4)	Reference		Reference	
Primary infant 2 + 1/3 + 1	14 (56)	44 (35.5)	4.1 (1.4–12.3)	0.01	3.9 (1.2–12)	0.02
Not age-appropriate	6 (24)	15 (12.1)	5.2 (1.4–19.3)	0.01	4.9 (1.3–18.7)	0.02

age-appropriate schedule (aOR, 4.9; 95% CI, 1.3–18.7), than among children receiving vaccines on a toddler catch-up schedule.

Clinical and microbiological findings in 25 cases with vaccine-type IPP

Of 25 children with vaccine-type IPP despite PCV13 vaccination, cultures were positive in the blood (n = 6) and pleural fluid (n = 4) sampled; RT-PCR findings were positive in the blood (n = 5) and pleural fluid (n = 10). Forty-eight percent occurred in boys (n = 12). The mean age at disease onset was 36 ± 11 months (Table 2). The youngest was 15 months of age, and the oldest was 58 months of age. The mean age at disease onset was similar in all three groups (*P* = 0.6) (Table 3). The mean time elapsed between the last dose of PCV13 and disease onset was longest in a primary infant schedule (23.7 ± 11 vs 9.7 ± 8.2 in a toddler catch-up schedule, 15.9 ± 8.9 in not-age-appropriate schedule; *P* = 0.03). None of these 25 vaccinated children exhibited detectable immunologic abnormalities when assessed by abdominal ultrasound examination, whole-blood cell counts with smears, and determinations of immunoglobulin and complement levels.

During follow-up, there was no clinical suspicion of a possible immunodeficiency among these patients. All vaccinated children were infected by serotype 19A (n = 21, 84%), 3 (n = 3, 13%) or 19F (n = 1, 4%). Sixty-four percent of vaccinated children (n = 16) experienced complications with empyema/necrotizing pneumonia. Among children on a primary infant schedule, those experiencing vaccine failure caused by serotype 19A, as well as those experiencing vaccine failure caused by serotype 3 had received a 3 + 1 series before disease onset. The only child experiencing vaccine failure caused by serotype 19F had received a primary infant 2 + 1 series. Of children immunized on a toddler catch-up schedule, four had received one dose at ≥24 months of age, and one had received 2 doses at 12–23 months of age. Of six children immunized on a not-age-appropriate schedule, half of them had received one dose at ≤12 months of age, two of them had received three doses before 12 months of age without booster, and one had received one dose at 22 months of age.

Discussion

The study found that the rate of PCV13 vaccine-type IPP was significantly higher in children receiving vaccines on a not-age-appropriate schedule or primary infant 2 + 1/3 + 1 schedule compared with those receiving vaccines on a toddler schedule, including 2 doses at 12–23 months and one dose at ≥24 months. Serotype 19A was responsible for 84% of these cases.

In the 7-valent pneumococcal conjugate vaccine (PCV7) era, serotypes 6B and 19F were predominately responsible for vaccine failure because of reduced immunogenicity.[20–23] Serotype 6B was more likely to infect children who had received only one or two PCV7 doses, and serotype 19F more frequently infected children who had received 3 or 4 PCV7 doses.[20] Changes in polysaccharide composition and the manufacturing process of PCV13 ameliorates these problems, whereas serotypes 19A and 3

Table 3 Description of 25 cases of vaccine-type pneumococcal pneumonia despite PCV13 vaccination.

	Toddler catch-up (n = 5)	Primary infant 2 + 1/3 + 1 (n = 14)	Not age-appropriate (n = 6)	*P* value
Age	36.1 ± 8.2	37.6 ± 10.9	31.9 ± 13.7	0.6
<2 years old	0 (0)	1 (7.1)	1 (14.3)	0.7
2–5 years old	5 (100)	13 (92.9)	6 (85.7)	
>5 years old	0 (0)	0 (0)	0 (0)	
Male sex	1 (20)	9 (64.3)	2 (33.3)	0.2
Time elapsed between the last dose of PCV13 and disease onset	9.7 ± 8.2	23.7 ± 11	15.9 ± 8.9	0.03
Serotype				
19A	5 (100)	10 (71.4)	6 (100)	0.3
3	0 (0)	3 (21.4)	0 (0)	0.4
19F	0 (0)	1 (7.1)	0 (0)	1.0
CRP (mean) mg/L	93.3	140.5	209.7	0.3
ICU admission	3 (60)	13 (92.9)	4 (66.7)	0.2
Chest tube/pigtail drainage	3 (60)	11 (78.6)	3 (50)	0.4
VATS	0 (0)	2 (14.3)	2 (33.3)	0.5
empyema/necrotizing pneumonia	2 (40)	11 (78.6)	3 (50)	0.2

have been reported to cause the majority of PCV13-serotype-related invasive pneumococcal infection among children vaccinated with PCV13.[23–25] In the USA, PCV13 was highly effective against invasive pneumococcal disease among children with routine 3 + 1 and catch-up schedules, providing 86% effectiveness against PCV13 serotypes, 85.6% and 79.5% effectiveness against serotypes 19A and 3, respectively.[26] In England, Wales, and Northern Ireland, PCV13 effectiveness with routine 2 + 1 schedule for all PCV13 serotypes was 75%, was 67% for serotype 19A, and showed no significant effectiveness for serotype 3.[27] In children immunized in the USA with at least one dose of PCV13, PCV13-serotype-related invasive pneumococcal infection (caused mostly by serotype 19A) usually occurred in the first 6 months of life or in children with underlying diseases including branchial cleft cyst, cochlear malformation, short gut, and hydronephrosis.[25] In contrast, in Spain, 65.6% (21/32) of children with pneumococcal disease who had received at least one dose of PCV13 were infected by serotype 3.

Serotype 19A has emerged as the predominant type in Taiwan since 2010, and has contributed to an overall increase in IPD in Taiwanese children under 5 years of age with a low 7-valent pneumococcal conjugate (PCV7) vaccination rate.[28] In clinical terms, serotype 19A strains are highly associated with necrotizing pneumonia, empyema, and the development of bronchopleural fistula.[12] Serotype 19A is well adapted with high fitness to the nasopharyngeal niche, enabling transmission to others. This serotype also exhibits high invasive potential and is capable of causing extensive and destructive lung disease, reflecting increased bacterial loads.[18] The overwhelming and severe disease burden of serotype 19A in Taiwan is the main reason that serotype 19A remained dominant after immunization.[14,29,30]

A national case–control study of the effectiveness of PCV against IPD (conducted by Taiwan CDC) demonstrated that the effectiveness of an age-appropriate PCV13 schedule against all serotypes was 80%.[16] Against serotype 19A, effectiveness was 89%; however, the study also showed that effectiveness of pneumococcal conjugate vaccine including PCV7, PCV10, and PCV13, declined from 81% within 6 months of the last dose of PCV, and to 19% after 2 years. This observation is believed to have resulted from the emergence of serotype 19A since 2010 in a population in which 57% of children have received PCV7/PCV10.[16] In fact, children receiving vaccines on a 2 + 1/3 + 1 PCV13 schedule in the national study conducted between 2008 and 2013 had just entered the peak age for pneumococcal pneumonia (2–5 years) in Taiwan where PCV13 was introduced in April 2011. The effectiveness of a primary infant schedule of PCV13 is better evaluated when these children have passed their high-risk age, and by more precise methods including PCR, given the lack of sensitivity of culture methods in cases with pneumococcal pneumonia.[13]

Pneumococcal immunization programs are initiated at an early age because pneumococcal disease causes the highest mortality and morbidity rates in early life; however, low effectiveness in infants compared with older children in the catch-up campaign has been observed in *Haemophilus influenzae* type b vaccine.[31] Vaccination in infancy is not effective; in infants, vaccination generally induces an immune response of low magnitude and reduced persistence. Sustained persistence of antibody production is seen when the fourth PCV dose is administered after 12 months of age.[32] In our study, the 2 + 1/3 + 1 dosing schedules already included one dose of PCV13 at age ≥12 months, but still had higher rate of vaccine failure than did the toddler catch-up schedule recommended by the Taiwan Advisory Committee on Immunization Practices (ACIP).[15] The protection provided by conjugate vaccine depends on maintenance of an adequate level of serum antibody against encapsulated bacteria. It is likely that protective antibody levels fall after administration on the 2 + 1/3 + 1 dosing schedule, given that protection is not sustained above a protective threshold through the high-risk period (2–5 years of age) in some individuals, or that the serum

concentration of antibody needed to achieve clinical protection at peak age should be higher for the most prevalent circulating serotype 19A strains.

Recently, Andrew et al. noted that the calculated serotype-specific correlates of protection for serotypes 19A and 3 should be 1.0 and 2.83 μg/mL, much higher than 0.35 μg/mL that was regarded as predictive of protection against IPD in the past.[27] Increasing antibody production after immunization would be another way to improve the vaccine effectiveness.

This study had several limitations. First, this study was a case—control study. We may have selection or observation bias in sample collection. Second, we did not exactly match age/sex in the control group with the case group since age is an important factor to evaluate IPD. In Taiwan, the Taiwan ACIP and the Taiwan CDC implemented a 2 + 1 national infant immunization program since 2015.[15] Primary infant immunization is important for decreasing pneumococcal colonization and increasing herd immunity. Further study is needed to evaluate the effective duration of protective immunity following 2 + 1/3 + 1 immunization against IPP.

In conclusion, the risk of vaccine-type IPP was significantly higher among children receiving vaccines on a not-age-appropriate schedule or on a primary infant schedule, compared with children receiving vaccines on a toddler catch-up schedule, after adjustment for confounding factors. Our observations imply that increased vaccine coverage, continued surveillance, and investigation of the duration of vaccine-induced immunity will be helpful for directing strategies that will maintain individual and population immunity against diseases caused by *S. pneumoniae*.

Author contributions

H.Y.L., Y.C.H., and C.C.L. conceived and designed this study and revised the manuscripts. K.Y.C performed the statistical analysis. H.Y.L., Y.C.H., H.C., L.Y.C., Y.C.H., and L.M.H. collected the samples. H.Y.L. analyzed the data and wrote the paper. All authors reviewed the manuscript.

Conflicts of interest

The authors declare no conflicts of interests.

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