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Original Article

The clinical implication of serotype distribution and drug resistance of invasive pneumococcal disease in children: A single center study in southern Taiwan during 2010–2016

Meng-Chien Lee [a], Kuang-Che Kuo [b,*]

[a] Department of Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan
[b] Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taiwan

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Abstract *Background:* The regional study of pediatric invasive pneumococcal disease (IPD) is still limited in Taiwan. The aim of this study is to update the epidemiologic data of pediatric IPD in Taiwan, focusing on the trend of non-13-valent pneumococcal conjugate vaccines (PCV13)-specific serotypes and antimicrobial susceptibility.
Methods: This was a single-center retrospective study by chart reviewing and recruited patients aged <18 years who were reported having IPD between January 2010 and December 2016. Clinical manifestations, serotypes of pneumococcus and antimicrobial susceptibility were compared and analyzed.
Results: A total of 46 patients were enrolled in this study. Serotype 19 A was the most common serotype (32.6%) in pediatric IPD and significantly correlated with empyema. Non-PCV13-specific serotypes such as serotype 15, 15B, 15C and 22 were reported during this period. There was no mortality or significant morbidity associated with these emerging strains. Using the meningitis breakpoint of minimum inhibitory concentration (MIC), although it showed no significant linear trend of the prevalence of ceftriaxone non-susceptible pneumococcus (CNSP) ($p = 0.392$), the prevalence of CNSP increased from 50% (11 over 22) before 2013 to 83% (20 over 24) after 2013 with statistical significance ($p = 0.027$).
Conclusion: The increase in the prevalence of CNSP using meningitis breakpoint was observed since 2013. For treating pneumococcal meningitis, empirical therapy with vancomycin and ceftriaxone is warranted. Although the non-PCV13-specific serotypes reported in our study caused no morbidity and mortality, further monitoring and surveillance are still recommended.

* Corresponding author. Department of Pediatrics, Chang Gung Memorial Hospital, No.123, DAPI Rd. Niaosong Dist., Kaohsiung City, 83301, Taiwan. Fax: +886 7 7338009.
E-mail address: light@cgmh.org.tw (K.-C. Kuo).

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Introduction

Streptococcus pneumoniae remains the leading causative pathogen of pediatric pneumonia, meningitis, and bacteremia worldwide, resulting in substantial morbidity and mortality among children.[1] It reportedly causes 14.5 million episodes of serious infection and approximately 826,000 deaths annually in children aged <5 years worldwide.[2]

Invasive pneumococcal disease (IPD) is defined as an infection that is confirmed by the isolation of *S. pneumoniae* from normally sterile sites such as the blood, cerebrospinal fluid, and pleural space.[3] Reductions in the incidence of vaccine-preventable diseases were observed after pneumococcal conjugate vaccines (PCVs) were introduced.[4] The increase in the emergence of serotype 19A has been an issue worldwide since 7-valent PCV (PCV7) was introduced. Serotype 19A has highly invasive potential and a higher proportion of antibiotic non-susceptibility.[5] The emergence of serotype 19A has successfully reduced since the introduction of 13-valent PCV (PCV13), but the rates of non-PCV13-specific serotypes have increased.[6]

The antimicrobial susceptibility of pneumococcus has been a great concern worldwide. A research of Taiwan medical center from 2000 to 2005 reported increase in the rate of ceftriaxone non-susceptibility from 4.2% in 2000–2004 to 11.5% in 2005.[7] Also, a recent research of children aged <2 years reported 85.7% of non-susceptibility to ceftriaxone according to the meningitis criteria, and 72.7% according to the non-meningitis criteria.[8]

A regional epidemiologic study is crucial to the clinical practice of local physicians. By reviewing the literature, the regional study of IPD remains limited in Taiwan and is mostly focused on the adult population. The aim of this study is to update the epidemiologic data of pediatric IPD in Taiwan, focusing on the trend of non-PCV13-specific serotypes, and the antibiotic resistance.

Methods

Patient collection

This was a single-center retrospective study that was conducted at Kaohsiung Chang Gung Memorial Hospital (KCGMH) in Taiwan between January 2010 and December 2016. The institutional review board of the Chang Gung Medical Foundation approved all medical information, and all patients' and physicians' records were anonymized and de-identified before analysis. Since October 2007, IPD has been listed as a notifiable disease in Taiwan.[9] According to the Communicable Disease Control Act of Taiwan, IPD cases must be reported to the Taiwan Centers for Disease Control (Taiwan CDC) within 7 days since the disease was diagnosed. In this study, we enrolled all patients aged <18 years and defined as IPD using the reporting system of KCGMH. Both hospitalized and non-hospitalized patients were included.

Clinical data collection

The clinical data of all enrolled cases were recorded by retrospective chart review including their demographic details, diagnosis, laboratory results, clinical manifestations, outcome, susceptibility to antibiotics, and pneumococcal serotypes. Bacterial identification and antibiotics susceptibility testing were conducted by the microbial laboratory of KCGMH. Blood cultures were managed with the BACTEC 9240 system (Becton and Dickinson, USA). Isolates were identified using the API (Analytical Profile Index) system. Minimum inhibitory concentrations (MICs) of penicillin and ceftriaxone were analyzed by E-test. The interpretation was categorized according to the Clinical and Laboratory Standards Institute (CLSI) guidelines for breakpoints from 2009 and updated every year.[10] Since 2008, CLSI had set up two different criteria for interpretation of antibiotic susceptibility by separating them into meningitis and non-meningitis groups. The breakpoints of the two groups were showed as following, penicillin: non-meningitis (susceptible: MIC $\leq$ 2 μg/ml, intermediate: MIC = 4 μg/ml, resistant: MIC $\geq$ 8 μg/ml), meningitis (susceptible: MIC $\leq$ 0.06 μg/ml, resistant: MIC $\geq$ 0.12 μg/ml); ceftriaxone/cefotaxime: non-meningitis (susceptible: MIC $\leq$ 1 μg/ml, intermediate: MIC = 2 μg/ml, resistant: MIC $\geq$ 4 μg/ml), meningitis (susceptible: MIC $\leq$ 0.5 μg/ml, intermediate: MIC = 1 μg/ml, resistant: MIC $\geq$ 2 μg/ml). In this study, pathogens considered as intermediate or resistant strains according to the MIC levels of the CLSI guidelines were categorized as resistant or highly resistant strains, respectively. Either of these strains was regarded as non-susceptible to certain antibiotics. The serotyping of the *S. pneumoniae* was based on the results obtained by Taiwan CDC which was performed by the Quellung test. The isolate which was not able to be serotyped was reported as unknown serotype. All of the unknown-serotype isolates were considered as the non-19A group in this study. The existence of thrombocytosis and thrombocytopenia were determined by each blood sampling during the episode of IPD. Thrombocytosis was defined as platelet count ≧450,000/μL, and thrombocytopenia was defined as platelet count <100,000/μL based on the results reported by the KCGMH laboratory. Bandemia was defined as the existence of band neutrophil in the differentiation study of white blood cell and was reported in percentage.

Statistical analysis

Statistical analyses were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). The chi-square test and Fisher's exact test were used to compare the categorical variables. Continuous variables were compared using Mann–Whitney *U* test and the results were presented as median and range in the table. About the assessment of risk factors of mortality and intensive care unit (ICU) transfer, factors with *p* value of <0.5 in Mann–Whitney *U* test were further underwent binary logistic regression. The correlation between risk factors were also tested by Spearman correlation. A *p* value of <0.05 was considered as statistical significant.

Results

Demography and outcome of IPD

A total of 46 patients were enrolled in this study. The demographic data were listed in Table 1. IPD was most common at ages between 2 and 5 years. Ten cases were reported in January and February respectively, which were the winter months in Taiwan and the most common months in this study. Of 46 cases, only two were considered fatal due to pneumococcal disease. One case was mainly complicated with empyema (serotype 19A) and another one was complicated with meningitis (serotype 19F). The annually accumulated data of different serotypes of *S. pneumoniae* during the period are shown in Fig. 1A. The number and percentage of serotype 19A had increased since 2010 with the peak in 2013 and had declined since then (Fig. 1B).

Table 1 Demographic data of including patients.

	Case number (%)
Sex	
Male	31 (67.4)
Female	15 (32.6)
Age of IPD onset (year)	
<1	4 (8.7)
1 to <2	4 (8.7)
2 to <5	24 (52.2)
>5	14 (30.4)
PCV vaccination status	
PCV 7 or PCV 10	9 (19.6)
PCV 13	12 (26.1)
Unknown	25 (54.3)
Serotype	
19A	15 (32.6)
Non-19A	27 (58.7)
Unknown	4 (8.7)
Number of breakthrough infection	
PCV 7 or PCV 10[a]	6 (66.7)
PCV 13[b]	7 (58.3)
IPD category	
Meningitis	4 (8.7)
Empyema	9 (19.6)
Bacteremia	40 (87.0)

[a] Serotype 14: 2 cases, serotype 19F: 2 cases, serotype 23F: 2 cases.
[b] Serotype 19A: 5 cases, serotype 6A: 1 case, serotype 6B: 1 case.

Bacteremia was the most common presentation of IPD, accounting for 87% (40/46) of IPD cases. Sixteen patients with pneumococcal bacteremia were not associated with pneumonia, empyema, meningitis, or other form of IPD. Among 6 of them, the portal of entry was considered acute otitis media (n = 2), acute tonsillitis (n = 2), mastoiditis (n = 1) and cellulitis of the abdominal wall (n = 1). The rest of the 10 patients were not associated with other source of infection. Serotypes 19A (n = 4) and 19F (n = 4) were the most common serotypes in these 16 isolated cases of pneumococcal bacteremia.

Four patients had pneumococcal meningitis and the median age was 4.46 years old. Two cases of serotype 14, one of serotype 19F, and one of serotype 6A were identified. All patients with meningitis were accompanied with *S. pneumoniae* bacteremia. Of the 26 patients who were diagnosed with pneumonia, 9 were complicated with empyema. All of the patients with empyema underwent interventional drainage including laparoscopic thoracotomy or thoracostomy tube insertion or both.

Some of the laboratory markers may act as a predictor of the outcome of IPD patients (Table 2). Higher levels of serum C-reactive protein (CRP) might be a predictor of mortality. Patients with a higher percentage of bandemia, lower hemoglobin levels, and higher serum CRP levels might have a higher probability of future ICU transfer. However, in multivariate logistic regression models, none of the markers showed in Table 2 was significantly correlated to mortality. On the other hand, CRP acted as an independent factor predicting the risk of future ICU transfer (Odd ratio: 1.021, confidence intervals: 1.007 to 1.035; $p < 0.05$). Owing to the statistical significance in Spearman correlation between CRP, bandemia, hemoglobin, and days of fever before first dose of antibiotic ($p < 0.05$), the significance of factors other than CRP in predicting the outcome still could not be excluded.

Clinical characteristics of cases with serotype 19A or serotype non-19A

The emergence of serotype 19 A pneumococcus was a concerning issue over the past decade. The clinical features of IPD patients with serotype 19A were compared with those with serotype non-19A (Table 3). Results showed that there were no significant age- and gender-related differences between the two groups. Empyema was more common among patients with 19A group, with statistical significance. With regard to the outcome, no significant differences in the rate of ICU transfer, mortality, and duration of hospitalization were observed between the two groups.

Emergence and outcome of non-PCV13-specific serotypes

During the study period, there were seven isolates with non-PCV13-specific serotypes: type 15 (2 patients), 15B (2

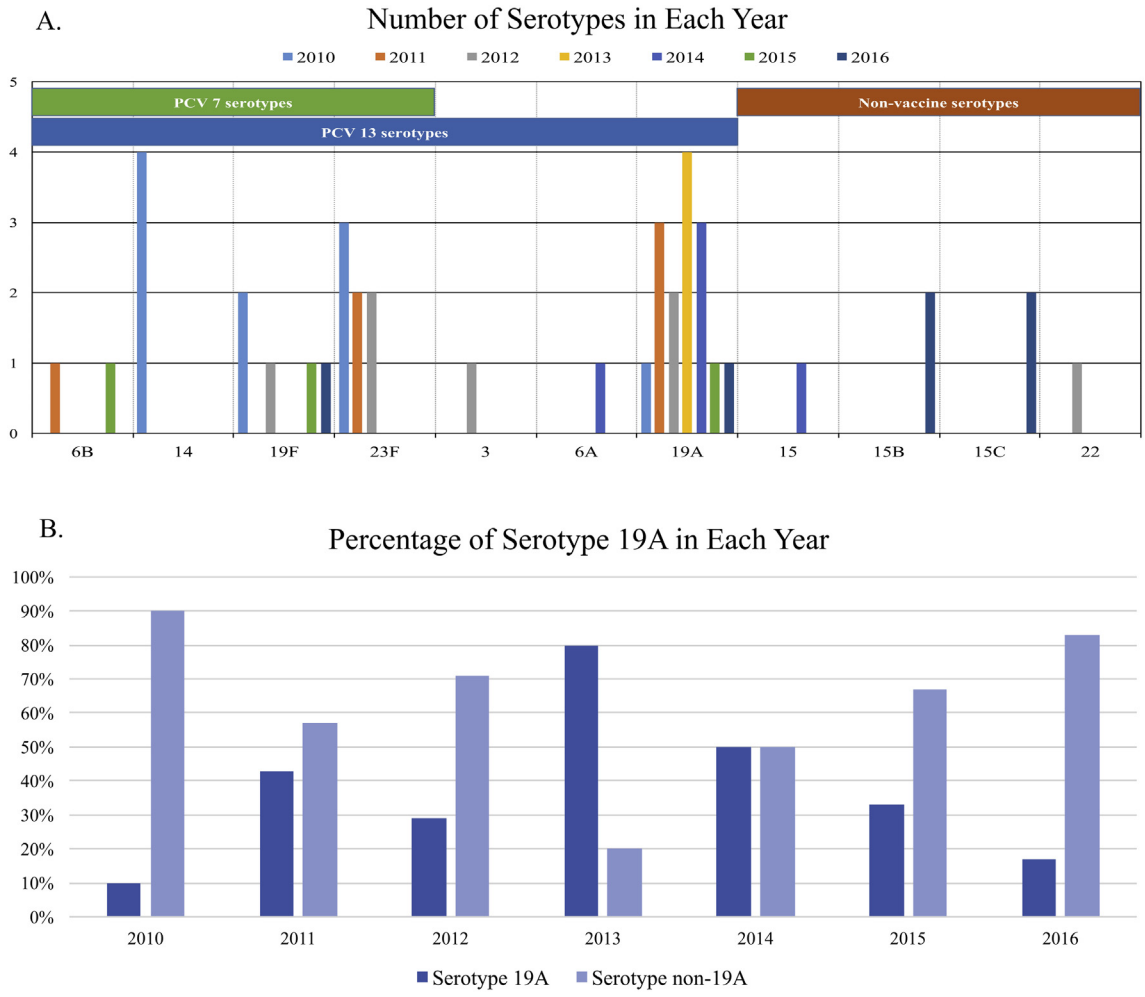

Figure 1. (A) The accumulated number of different serotypes in each year. (B) The trend of the prevalence of serotype 19A.

Table 2 Predictors of outcome in pediatric invasive pneumococcal disease.

	Survival			ICU transfer		
	Yes (n = 44)	No (n = 2)	*p*-value	Yes (n = 12)	No (n = 34)	*p*-value
Age (year)	4.3 (13.1)	4.7 (0.6)	0.483	4.3 (9.5)	4.3 (13.1)	0.717
WBC (count/μL)	18,400 (33,700)	23,850 (15,900)	0.419	18,850 (32,000)	18,400 (31,300)	0.540
Bandemia (%)	0.8 (18)	4.5 (9.0)	0.644	2.0 (17.5)	0.0 (9.0)	0.002*
Hb (g/dL)	11.7 (12.2)	10.6 (3.2)	0.483	10.7 (8.9)	12.2 (6.9)	0.001*
CRP (mg/L)	131.1 (454)	346.2 (41)	0.032*	276.1 (242)	59.8 (366)	0.000*
fever before the first dose of antibiotics (days)	2.0 (10.0)	3.5 (3.0)	0.459	5.5 (10.0)	1.5 (8.0)	0.004*

All variants are presented as median (range); WBC: white blood cell; CRP: C-reactive protein; ICU: intensive care unit; Hb: Hemoglobin.
*statistically significant ($p < 0.05$).

patients), 15C (2 patients), and 22 (1 patients). Of these 7 patients, all of them were diagnosed with pneumococcal bacteremia and 4 of them were accompanied with pneumonia. None of the patients was fatal and needed ICU care.

The median length of hospital stay of patients infected with non-PCV13-specific serotypes was 9 days, while that of patients infected with vaccine-specific serotypes (39 patients) was 15 days. Non-PCV13-specific strain was firstly

Table 3 Comparison of invasive pneumococcal disease patients between serotype 19A and non-19A.

	Serotype 19A (n = 15)	Non-serotype 19A (n = 31)	*p*-value
Age (year)	3.5 ± 2.0	4.3 ± 2.6	0.251
Sex			
Male	8 (53.3)	25 (80.6)	0.082
Disease			
Bacteremia[a]	4 (26.7)	12 (38.7)	0.520
Pneumonia[b]	4 (26.7)	13 (41.9)	0.352
Empyema	7 (46.7)	2 (6.5)	0.003*
Meningitis	0 (0)	4 (12.9)	0.288
Lab			
WBC (count/μL)	19,600 ± 2112	25,419 ± 7696	0.607
Bandemia (%)	3.8 ± 1.2	1.5 ± 0.5	0.040*
Myelocyte (%)	0.6 ± 0.3	0.5 ± 0.2	0.650
Thrombocytosis (Platelet count >450,000/μL)	11 (73.3)	11 (35.5)	0.027*
Thrombocytopenia (Platelet count <100,000/μL)	1 (6.7)	7 (22.6)	0.243
C-reactive protein (mg/L)	214.1 ± 35.5	121.1 ± 21.8	0.025*
Outcome			
ICU transfer	6 (40.0)	6 (19.4)	0.165
Mortality	1 (6.7)	1 (3.2)	1.000
Hospital stay (day)	15.9 ± 1.8	19.9 ± 3.5	0.321

[a] Bacteremia without pneumonia or meningitis.
[b] Bacteremic pneumonia without empyema.
WBC: white blood cell; ICU: intensive care unit.
*Statistically significant ($p < 0.05$).

reported in 2012, and an increasing number of cases have been reported since then, with a peak of 4 cases in 2016 (Fig. 1A).

Antibiotic susceptibility of pneumococcus

In this study, all isolates of pneumococcus were susceptible to vancomycin and levofloxacin. The susceptibility of penicillin and ceftriaxone to non-meningitis IPD and meningitis IPD were analyzed from 2010 to 2016 under CLSI non-meningitis and meningitis breakpoints, respectively (Fig. 2).

Using the non-meningitis breakpoint, the percentage of penicillin non-susceptibility seemed to decrease since 2013, from 100% in 2013 to 70% in 2016. The accumulated number of pneumococcus with high resistance to penicillin was two before 2013 and one after 2013. The overall ceftriaxone non-susceptible rate of pneumococcus was 19.6%. Although ceftriaxone non-susceptible pneumococcus (CNSP) was consecutively reported since 2013, the rate of ceftriaxone non-susceptibility after 2013 did not show any significant difference with the rate before 2013 ($p = 0.247$).

Using the meningitis breakpoint, the rate of penicillin non-susceptibility was persistently high in each year during the period of study. Overall, the prevalence of penicillin non-susceptible pneumococcus (PNSP) was 93.5% and that of CNSP was 73.9%. There showed no significant trend of the prevalence of CNSP ($p = 0.392$). However, the prevalence of CNSP had increased from 50% (11/22) before 2013 to 83% (20/24) after 2013, with a statistical significance ($p = 0.027$). Moreover, 17.4% of pneumococcus were highly resistant to ceftriaxone. Although pneumococcus with high resistance to ceftriaxone had been consecutively reported since 2013, the prevalence showed no statistical difference before and after 2013 ($p = 0.247$).

The comparison of the antibiotic resistance among the 19A group, non-19A group, and non-PCV13-specific group is shown in Fig. 3. Using the non-meningitis breakpoint, the serotype 19A showed significantly higher rates of antibiotics resistance to penicillin than the serotype non-19A ($p = 0.009$). The antibiotic susceptibility rate of non-PCV13-specific serotypes seemed to be similar with that of the entire non-19A group in both non-meningitis and meningitis criteria by post hoc comparison (Fig. 3).

Discussion

The highlight of this study is to contribute to the local epidemiologic database of serotypes distribution and drug resistance of pediatric IPD in Southern Taiwan.

PCV7, PCV10, and PCV13 were licensed in Taiwan in 2005, 2010, and 2011, respectively. Taiwan CDC first introduced a public-funded PCV program, targeting a minority of children younger than 5 years old, who was at high risk of certain medical conditions or born into families of low or middle income, between July 2009 and February 2013. A national catch-up PCV13 program was then launched in March 2013, targeting children aged 2–5 years and expanded to cover children aged 1–5 years in 2014. PCV13 was not introduced as the routine immunization for infants until January 2015.[11]

Since the introduction of PCV13, the emerging trend of non-PCV13-specific strains has been monitored worldwide. The serotypes 15, 15B, 15C, and 22 had been continually reported since 2012 and peaked in 2016, as reported in our

study. Fortunately, there was no significant morbidity or mortality associated with these emerging non-PCV13-specific strains. Moreover, these strains had an even shorter length of hospital stay than vaccine-specific group. The antibiotic susceptibility characteristics of these serotypes were similar to those of other non-19A strains in using both non-meningitis and meningitis breakpoints. Although the non-PCV13-specific strains in this report might seem to be harmless, continuing surveillance is still necessary due to small number of cases of this research.

In northern Japan, an increasing trend of non-PCV13-specific serotypes 6C, 15A, and 23A were reported in children, which carry a macrolide resistance gene *erm* (B).[12] In the United States, a significant increase in the prevalence of the non-PCV13-specific serotypes 11A (4.0–6.4%), 15B (2.0–3.5%), 15C (1.5–2.7%), and 35B (4.0–9.1%) was reported from 2012 to 2013. In Taiwan, a study by H.-C. Chi et al. reported that a significant increase in the prevalence of serotype 15B from 0.6% to 6.7% ($p < 0.01$) and serotype 15A from 0 to 4.4% ($p < 0.01$) was observed among adults since 2015, which might be inferred to the impact of vaccination in children.[13] This result was consistent with our findings regarding the emerging serotypes in Taiwanese children. The dominant serotypes and antimicrobial susceptibilities of pneumococcus that were reported in Taiwan were further summarized in Table 4.[8,14–17]

As to that identified in other studies,[15,18] serotype 19A is the most common strain of *S. pneumoniae* identified in our study. The prevalence of serotype 19A demonstrates an increasing trend before 2013 and declined after then. This change was probably attributed to the vaccination policy in Taiwan. Serotype 19A emerged as the predominant strain of pneumococcal disease globally after the introduction of PCV7 in children, but its prevalence in pneumococcal infections has decreased by replacement of PCV13.[19–22]

Similar to the results of other studies,[23,24] serotype 19A was found to be highly resistant to antibiotics. However, it did not result in worse outcome generally. This might be due to the low mortality rate in our study because KCGMH is one of the medical centers in southern Taiwan that routinely use broad-spectrum antibiotics in patients with severe disease and in those who undergo early surgical drainage of infected spaces. In the univariate analysis, we indicated that IPD with serotype 19A was correlated with empyema, which was consistent to the result reported by C.-Y. Lai et al.[25] By the observation of the other study, the serotype 19A pneumococcus caused more non-meningitis IPD than meningitis.[26,27] None of the meningitis in our study was caused by serotype 19A pneumococcus consistently.

In patients with non-meningitis pneumococcal infections, except for highly penicillin-resistant strains, it is generally accepted that penicillin or other β-lactam remain as first-line medication, provided that adequate dosages are prescribed.[28] In this study, only 3 isolates (6.5%) of pneumococcus showed high resistance to penicillin. Therefore, β-lactam might remain a useful drug for treating non-meningitis IPD with a higher dose and careful monitoring.[28]

CNSP has been a concerning issue in recent years. Ceftriaxone non-susceptibility was reported to be significantly associated with age of <5 years and 13-valent vaccine serotypes and also increased mortality among patients ≥5 years of age with meningitis.[29]In our research, by using

Table 4 The summary of dominant serotypes and antimicrobial susceptibilities reported in Taiwan.

Author	Year of inclusion	Age of cases enrolled	Source of isolates	Dominant serotypes	Non-susceptible rate of penicillin	Non-susceptible rate of ceftriaxone
Lee et al. (Ref. 8)	2011–2013	All ages	All sterile sites	19A,14,6A,23F, 6B and 3	NM: <30% M: >60%	NM: >20% (all cases); age<6, >55%; age>65, 13.3% M:>40% (6A,15B,19A,19F,23F)
Cho et al. (Ref. 14)	2010–2015	Age less than 18	Sterile sites (22.9%) Unsterile sites (77.1%)	19A, 15A, 19F and 15B		
Hsiao et al. (Ref. 15)	2009–2013	Age less than 18	All sterile sites	19A,19F, 14, 6B, 23F and 3	NM: 20% M: 98.1%	NM: 16% M: 16%
Tsai et al. (Ref. 16)	2006–2010	All ages	Sputum (42.6%), blood (29.1%), pus/wounds (25.3%), pleural effusion (1.7%), cerebrospinal fluid (0.8%) and others (0.6%)	19F,23F,14,6B, 19A and 3	NM: 36.8% M: 88.3%	NM: 16.2% M: 54%
Tsai et al. (Ref. 17)	2002–2008	All ages	Sputum (54.7%), pus/wounds (20.4%), others (10.2%), blood (9.2%), throat swab (4.0%), nasal swab (1.2%) and urine (0.3%)		NM: 30.4% M: 75.5%	NM: 19.4% M: 62.9%
This study	2010–2016	Age less than 18	All sterile sites	19A, 23F, 19F, 14, 6B, 15B and 15C	NM: 76.1% M: 93.5%	NM: 19.6% M: 73.9%

NM: non-meningitis; M: meningitis.

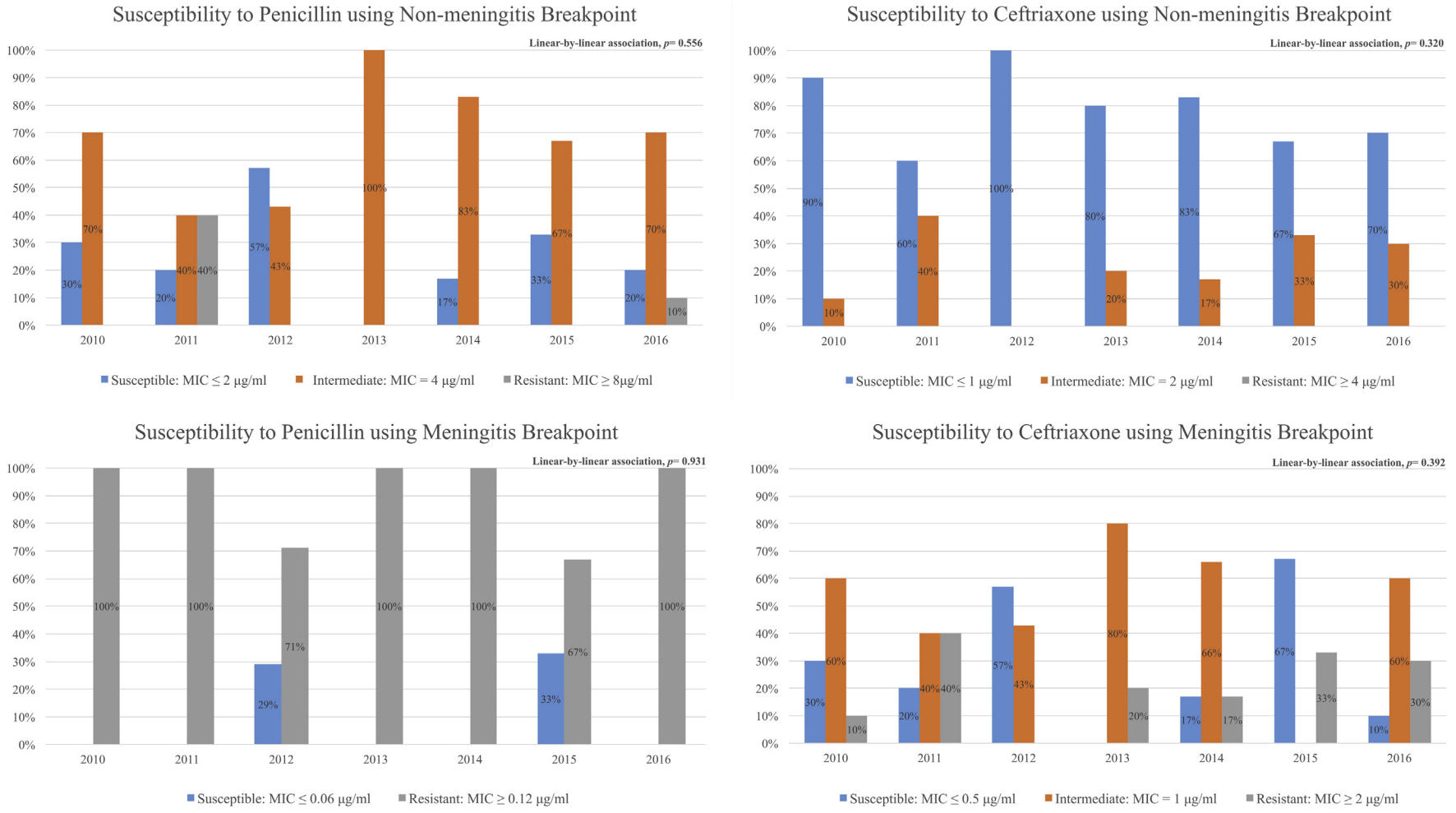

Figure 2. The distribution of susceptibility to penicillin and ceftriaxone in each year under different criteria.MIC: Minimum inhibitory concentration.

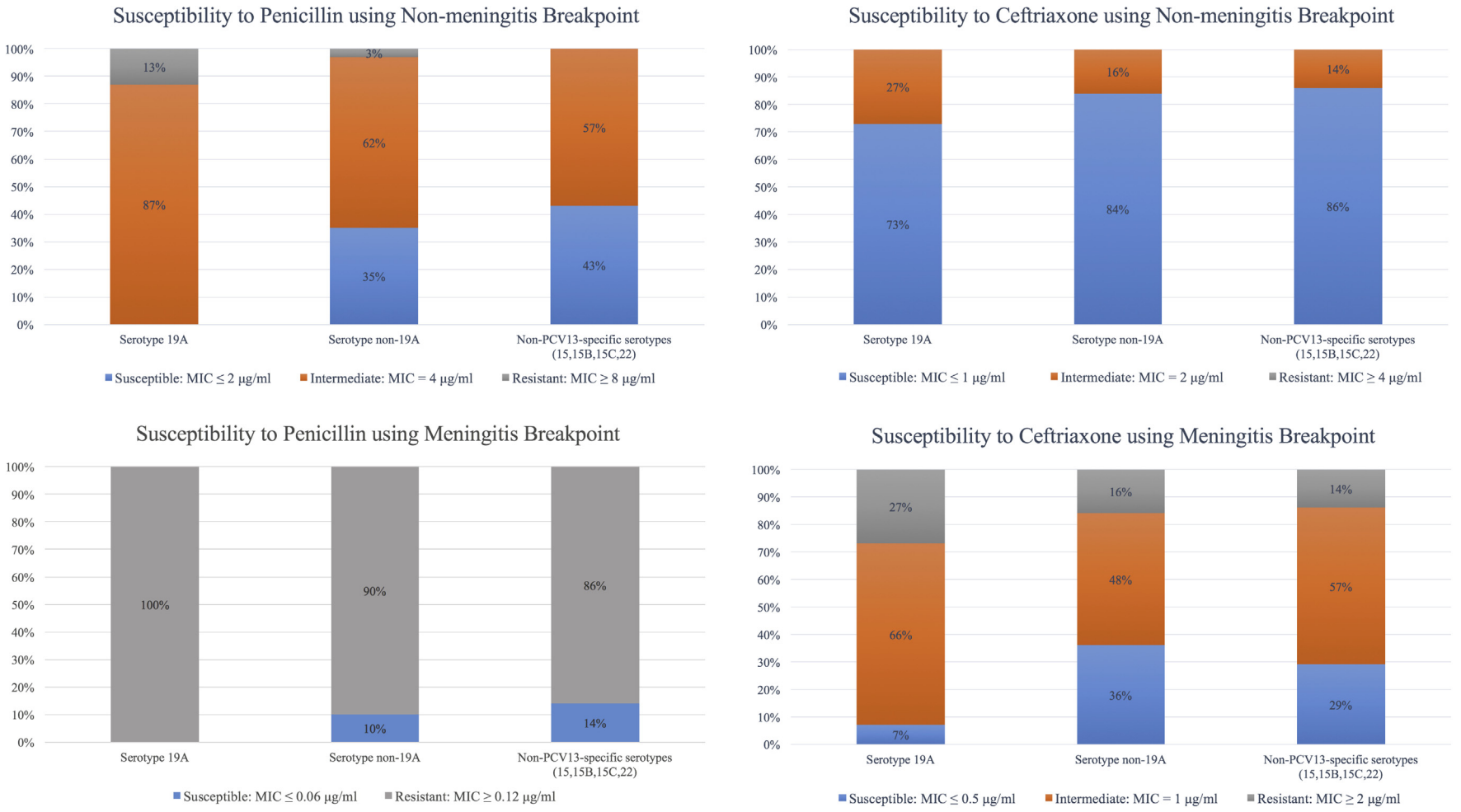

Figure 3. Comparison of antimicrobial susceptibility in different serotype groups under both meningitis and non-meningitis criteria. MIC: Minimum inhibitory concentration.

meningitis breakpoint, although no significant increasing trend was observed in the prevalence of CNSP, the prevalence of CNSP has increased significantly since 2013 and the overall prevalence is as high as 73.9%. Moreover, the susceptibility of vancomycin to pneumococcus in this study is 100%. Therefore, early administration of vancomycin combined with high-dose ceftriaxone (>100 mg/kg/day) might be considered as an empirical therapy for pediatric pneumococcal meningitis.

Although this research has contributed the epidemiologic data of pediatric IPD of the southern Taiwan, there are still some limitations of the study. Firstly, it is a single-centered study. Although KCGMH is the biggest center for children in southern Taiwan, the result might not represent the actual regional epidemiology. Second, because of the time limit, the study was conducted on only small numbers of cases. By increasing the time frame of research, the power of evidence might be strengthened and the epidemiological trend might be more significant.

In conclusion, for pediatric patients with non-meningitis IPD, β-lactam antibiotics might remain the first-line medication via adequate doses. For treating pneumococcal meningitis, early administration of vancomycin combined with high-dose ceftriaxone (>100 mg/kg/day) might be considered due to the increase in prevalence of CNSP since 2013. Although the non-PCV13-specific strains in this study cause no mortality and the characteristics of antimicrobial susceptibility are similar to that of the non-19A group, further monitoring and surveillance are recommended.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2019.04.006.