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National surveillance of antimicrobial susceptibilities to dalbavancin, telavancin, tedizolid, eravacycline, omadacycline and other comparator antibiotics and serotype distribution of invasive *Streptococcus pneumoniae* isolates in adults: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) programme in 2017–2020

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ABSTRACT

Objectives: The aim of this study was to investigate the trends in serotypes and in vitro antimicrobial susceptibility of *Streptococcus pneumoniae* causing adult invasive pneumococcal disease (IPD) to dalbavancin, telavancin, tedizolid, eravacycline, omadacycline and other comparator antibiotics from 2017–2020 following implementation of the 13-valent pneumococcal conjugate vaccine (PCV-13) and during the COVID-19 (coronavirus disease 2019) pandemic.

Methods: During the study period, 237 *S. pneumoniae* isolates were collected from non-duplicate patients, covering 15.0% of IPD cases in Taiwan. Antimicrobial susceptibility testing was performed using a Sensititre® system. A latex agglutination method (ImmuLex™ Pneumotest Kit) was used to determine serotypes.

Results: Susceptibility rates were high for vancomycin (100%), teicoplanin (100%) and linezolid (100%), followed by ceftaroline (non-meningitis) (98.3%), moxifloxacin (94.9%) and quinupristin/dalfopristin (89.9%). MIC₅₀ and MIC₉₀ values of dalbavancin, telavancin, tedizolid, eravacycline and omadacycline were generally low. Non-vaccine serotype 23A was the leading cause of IPD across the adult age range. Isolates of serotype 15B were slightly fewer than those of PCV-13 serotypes in patients aged ≥65 years. The overall case fatality rate was 15.2% (36/237) but was especially high for non-PCV-13 serotype 15B (21.4%; 3/14). Vaccine coverage was 44.7% for PCV-13 and 49.4% for the 23-valent pneumococcal polysaccharide vaccine (PPSV-23), but was 57% for both PCV-13 and PPSV-23.

Conclusion: The incidence of IPD was stationary after PCV-13 introduction and only dramatically decreased in the COVID-19 pandemic in 2020. The MIC₅₀ and MIC₉₀ values of dalbavancin, telavancin, tedizolid, eravacycline, omadacycline were generally low for *S. pneumoniae* causing adult IPD.

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1. Introduction

Streptococcus pneumoniae is a common pathogen that causes a variety of infections from ear and sinus infections to pneumonia. Invasive pneumococcal disease (IPD) is defined as the isolation of *S. pneumoniae* from normally sterile sites (e.g. joints, blood and brain) [1]. IPD is an invasive form of *S. pneumoniae* infection with a high case fatality rate (CFR), ranging from 11.5–30.8% in adults [2–4]. In countries following the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) targeting children, the overall and PCV-7 serotype rate of IPD declined across all ages and was not limited to children [5–7]. The 13-valent pneumococcal conjugate vaccine (PCV-13) provides similar protection for most vaccine serotypes [8]. The vaccine effectiveness of the six additional serotypes of PCV-13 is lower than that of the other serotypes included in the PCV-7 vaccine (73–73.7% vs. 90–92%) [9,10]. Non-vaccine and some vaccine-covered serotypes have replaced wild-type serotypes in the post-vaccine era [11]. The incidence of non-typeable pneumococci has also increased [12]. Other factors are also thought to have had an impact on serotype differences between regions or countries [13,14].

The history of pneumococcal vaccination in the market and the implementation of public vaccination programmes in Taiwan are illustrated in Fig. 1. Currently, PCV-13 has been implemented in children under 5 years of age. According to the latest reports from the National Immunization Information System of Taiwan, the uptake rate of the second dose of PCV-13 was 98% in 2017–2019 in people born after 2016. The 23-valent pneumococcal polysaccharide vaccine (PPSV-23) has been generally funded for one dose for people aged ≥75 years. In major cities, PCV-13 and PPSV-23 were funded for one dose for people aged ≥65 years.

The prevalence of pneumococcal resistance to penicillin, macrolides, third-generation cephalosporins and trimethoprim/sulfamethoxazole is quite high in Taiwan [15,16]. This might be associated with the spread of serotype-specific clones, such as levofloxacin-non-susceptible serotype 11A-ST3642 and meropenem-non-susceptible serotype 15A-ST63, 23A-ST166 and 15B/C-ST83 clones [17–19]. In addition, more patients with chronic

illness might be exposed to more antibiotics and cause more antibiotic resistance [20]. Pneumococcal conjugate vaccine introduction also has an impact on antibiotic resistance [21]. During the global pandemic of COVID-19 (coronavirus disease 2019), serotypes and antibiotic-resistant *S. pneumoniae* might be influenced by wearing respirators or prescribing antibiotics for empirical use or co-infection [22,23].

The Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) national surveillance programme has monitored trends in the antimicrobial susceptibility of clinically important pathogens collected from hospitals throughout Taiwan since 2001 [24]. In this study, a nationwide survey spanning a 4-year period from 2017–2020 following implementation of the PCV-13 vaccine and the COVID-19 pandemic was conducted to investigate the trends in serotypes and in vitro susceptibility of *S. pneumoniae* to a selection of common and new-generation antimicrobial agents, including dalbavancin, telavancin, tedizolid, eravacycline and omadacycline.

2. Patients and methods

2.1. Study setting and bacterial isolates

All isolates of *S. pneumoniae* were collected from clinical specimens from normally sterile sites of adult patients (age ≥20 years) with IPD who were treated at 18 participating hospitals located in different regions of Taiwan, comprising 9 in Northern Taiwan, 5 in Central Taiwan, 3 in Southern Taiwan and 1 in Eastern Taiwan from January 2017 through December 2020. Duplicate isolates from the same patient were excluded, and the selection priority was as follows: blood, cerebrospinal fluid (CSF), pleural fluid, peritoneal fluid and joint fluid. Identification of isolates was confirmed by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Biotyper; Bruker Daltonics, Billerica, MA, USA) along with optochin susceptibility and bile solubility tests by the central laboratory at National Taiwan University Hospital.

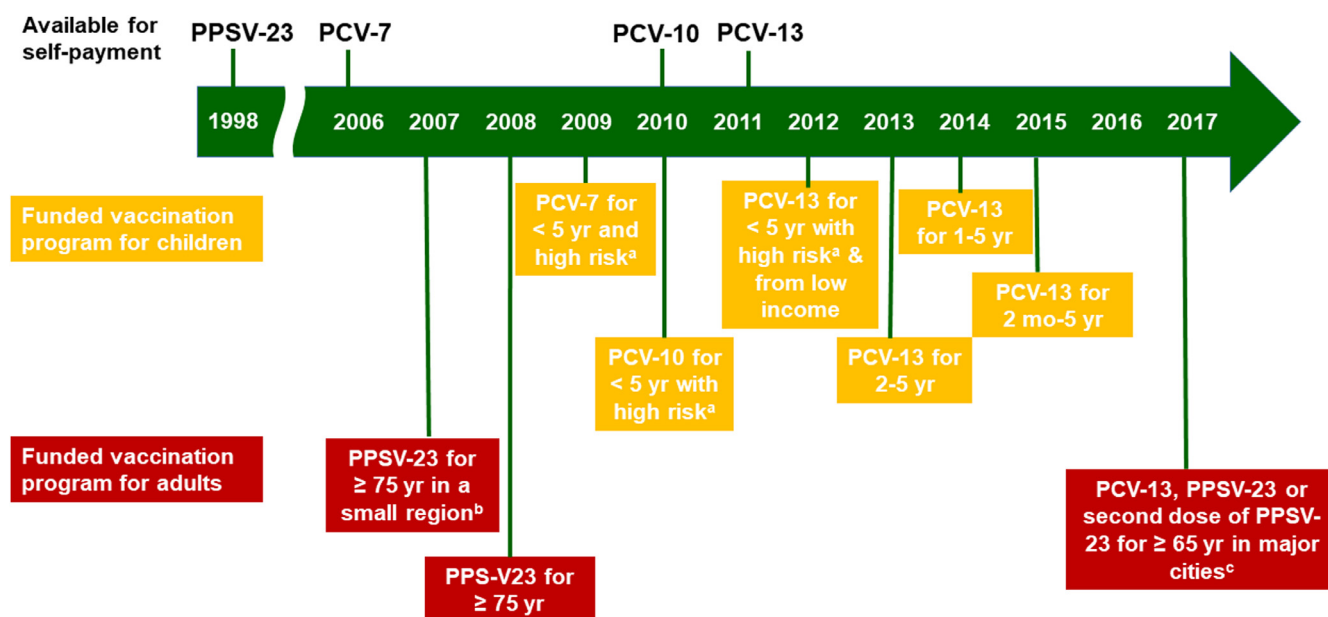


Fig. 1. Timelines of the introduction of various pneumococcal vaccines (PCVs) and funded vaccination programmes for children and elderly adults in Taiwan. ^a Indicates persons with immunocompromising conditions, cerebrospinal fluid leakage or cochlear implant. ^b Includes Yunlin and Chiayi counties and Chiayi city of Taiwan. ^c Includes Taipei and Taoyuan cities of Taiwan. PPSV, pneumococcal polysaccharide vaccine.

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed on *S. pneumoniae* isolates using a Sensititre® system (TREK Diagnostic Systems, East Grinstead, UK) according to the manufacturer's instructions. Antimicrobial agents included in the custom-made Gram-positive (GP) panel consisted of oxacillin, cefazolin, ceftaroline, moxifloxacin, dalbavancin, telavancin, teicoplanin, vancomycin, daptomycin, eravacycline, omadacycline, tigecycline, linezolid, tedizolid, mupirocin and quinupristin/dalfopristin. Clinical isolates and reference strains were grown under atmospheric conditions at 37°C in cation-adjusted Mueller–Hinton broth with lysed horse blood (CAMHBT+LHB; TREK Diagnostic Systems). Three to five colonies of *S. pneumoniae* were transferred from an overnight sheep blood agar plate and were incubated in a 5% CO₂ atmosphere into 5 mL of CAMHBT+LHB and adjusted to a 0.5 McFarland standard. A suspension of 100 μL was transferred into 11 mL of CAMHBT+LHB to achieve an inoculum of 5 × 10⁵ CFU/mL. Following incubation, minimum inhibitory concentrations (MICs) were read using the Sensititre manual viewer with reference to the antimicrobial breakpoint tables from the Clinical and Laboratory Standards Institute (CLSI) [25], the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [26] or the literature [27]. *Streptococcus pneumoniae* ATCC 49619 was used as quality control strain for susceptibility tests in each test run.

Because penicillin and ceftriaxone were not included in the GP Sensititre® panel, susceptibility testing of the isolates ($n = 126$; 2018–2019) to these two agents was conducted using the VITEK®2 automatic susceptibility system (bioMérieux, Marcy-l'Étoile, France).

2.3. Serotyping

A latex agglutination method (ImmuLex™ Pneumotest Kit; SSI Diagnostica, Hillerød, Denmark) was used to determine serotypes according to the manufacturer's instructions. Pneumococcal isolates were cultured for 24 h in Todd Hewitt broth (SSI Diagnostica) and then 10 μL of the isolate culture was mixed with specific antisera to observe agglutination reactions. All results were confirmed

using the Quellung reaction with traditional pneumococcal antisera (SSI Diagnostica) in the capsular reaction.

2.4. Statistical analysis

The χ^2 test for trend (Cochran–Armitage test for trend) was used to detect an increasing or decreasing trend in the proportion of a given serotype among all IPD isolates in the years examined. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Bacterial isolates

A total of 237 non-duplicate *S. pneumoniae* isolates were collected from major teaching hospitals throughout Taiwan during the 4-year study period. The numbers of isolates obtained in each year were 81 in 2017, 71 in 2018, 55 in 2019 and 30 in 2020, representing 17.9%, 15.5%, 12.4% and 13.2% of cases each year, respectively. The collected isolates represented 16.8% (122/727) of cases in Northern Taiwan, 18.7% (59/315) in Central Taiwan, 8.2% (39/473) in Southern Taiwan and 24.3% (17/70) in Eastern Taiwan. Of these isolates, blood was the major source ($n = 219$; 92.4%), followed by pleural effusion ($n = 7$; 3.0%), ascites ($n = 6$; 2.5%) and CSF ($n = 5$; 2.1%). The number of isolates stratified by age are shown in Fig. 2.

3.2. Antimicrobial susceptibility

The MIC distributions of the 16 antimicrobial agents against the 237 *S. pneumoniae* isolates are shown in Table 1. CLSI-approved MIC interpretive breakpoints were applied to ceftaroline (non-meningitis), moxifloxacin, vancomycin, linezolid and quinupristin/dalfopristin. For teicoplanin, EUCAST-approved MIC interpretive breakpoints were used. The susceptibility rates were high for the six antimicrobial agents, especially vancomycin (100%), teicoplanin (100%) and linezolid (100%), followed by ceftaroline (98.3%), moxifloxacin (94.9%) and quinupristin/dalfopristin (89.9%).

(A) Patients stratified by age

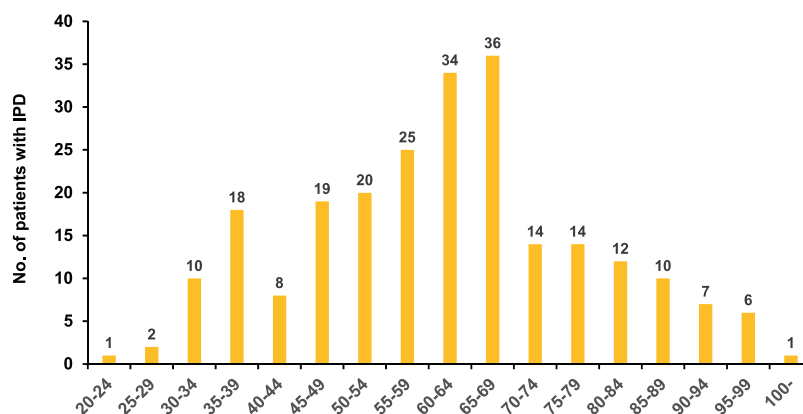


Fig. 2. Distribution of 237 *Streptococcus pneumoniae* isolates associated with invasive pneumococcal diseases (IPD) by age.

Table 1

Distribution of minimum inhibitory concentrations (MICs) of 16 antimicrobial agents against 237 *Streptococcus pneumoniae* isolates collected from hospitals throughout Taiwan during 2017–2020

Antimicrobial agent	MIC (mg/L)			No. (%) of isolates		
	Range	MIC ₅₀	MIC ₉₀	S	I	R
Oxacillin	≤0.03 to >64	16	32	NA ^a	NA	NA
Cefazolin	0.12 to >128	8	32	NA	NA	NA
Ceftaroline (non-meningitis)	≤0.03–2	0.12	0.5	233 (98.3)	NA	NA
Moxifloxacin	0.06–8	0.25	0.25	225 (94.9)	1 (0.4)	11 (4.6)
Teicoplanin	≤0.03–1	0.06	0.06	237 (100)	NA	NA
Vancomycin	0.25–1	0.5	0.5	237 (100)	NA	NA
Dalbavancin	≤0.03–0.12	≤0.03	≤0.03	NA	NA	NA
Telavancin	≤0.03–0.25	≤0.03	≤0.03	NA	NA	NA
Daptomycin	0.06–0.5	0.25	0.25	NA	NA	NA
Tigecycline	≤0.03–2	0.06	0.25	NA	NA	NA
Eravacycline	≤0.03–0.06	≤0.03	≤0.03	NA	NA	NA
Omadacycline	≤0.03–1	0.06	0.12	NA	NA	NA
Linezolid	0.5–2	1	1	237 (100)	NA	NA
Tedizolid	0.12–0.5	0.25	0.25	NA	NA	NA
Mupirocin	0.12–16	0.5	4	NA	NA	NA
Quinupristin/dalfopristin	0.12–2	1	2	213 (89.9)	24 (10.1)	0

MIC_{50/90}, MIC required to inhibit the growth of 50% and 90% of organisms, respectively; S, susceptible; I, intermediate; R, resistant.

^a NA, not applicable. There are no MIC interpretive criteria recommended by the Clinical and Laboratory Standards Institute 2021 [25] or the European Committee on Antimicrobial Susceptibility Testing 2021 [26].

While there is insufficient evidence of MIC interpretive breakpoints of dalbavancin, telavancin, daptomycin, eravacycline, tigecycline and tedizolid by the latest CLSI and EUCAST guidelines, the MIC₉₀ values (i.e. the MIC required to inhibit the growth of 90% of organisms) of these antimicrobial agents were generally very low (<0.25 mg/L) for *S. pneumoniae*. Generally, the new antimicrobial agents were more potent than the commercially available agents. The MIC₉₀ values (both ≤0.03 mg/L) of dalbavancin and telavancin were ≥16-fold lower than that of vancomycin (0.5 mg/L). The MIC₉₀ values of eravacycline (≤0.03 mg/L) and omadacycline (0.12 mg/L) were 2- to 8-fold lower than that of tigecycline (0.25 mg/L). The in vitro activity of tedizolid was 4-fold higher than that of linezolid with MIC₉₀ values of 0.25 mg/L and 1 mg/L, respectively.

The rates of *S. pneumoniae* isolates ($n = 126$) susceptible, intermediate and resistant to penicillin/ceftriaxone based on non-meningitis MIC interpretive criteria were 86.5% ($n = 109$)/65.1% ($n = 82$), 13.5% ($n = 17$)/22.2% ($n = 28$) and 0% ($n = 0$)/12.7% ($n = 16$), respectively [25]. Based on meningitis interpretive criteria for penicillin/ceftriaxone, the rates of susceptible, intermediate and resistant isolates were 19.8% ($n = 25$)/42.9% ($n = 54$), 22.2% (ceftriaxone, $n = 28$) and 80.2% ($n = 101$)/34.9% ($n = 44$), respectively [25].

3.3. Serotyping

The most common serotypes were non-vaccine serotypes 23A ($n = 35$; 14.8%) and 15A ($n = 31$; 13.1%), followed by vaccine serotypes 3 ($n = 25$; 10.5%), 19A ($n = 24$; 10.1%) and 14 ($n = 19$; 8.0%) (Fig. 3A). The distributions of different serotypes by age group are shown in Fig. 3B–D. The distribution pattern was similar between patients aged ≥65 years and the whole study population, except for serotype 15B. The proportion of serotype 15B isolated was relatively lower than that of PCV-13 serotypes in patients older than 65 years who received more PPSV-23. Serotypes 15A and 23A were the dominant serotypes in Northern and Central Taiwan, the regions with higher population densities in Taiwan (Fig. 4). Seven isolates were classified into group serotype 11ACD but were not further typed owing to their rarity. Two other isolates were non-typeable.

The vaccine coverage was 44.7% ($n = 106$) for PCV-13 and 49.4% ($n = 117$) for PPSV-23, but 57% ($n = 128$) for both PCV-13 and PPSV-23. The proposed coverage rate of the 20-valent pneumococcal conjugate vaccine (PCV-20) in Taiwan was 55.7% ($n = 132$). Isolates identified as serotype 11ACD were classified as uncovered by PCV-20, including serotype 11A. Serotype 15B was not covered by the current PCV-13 but was covered by PPSV-23 and PCV-20. There

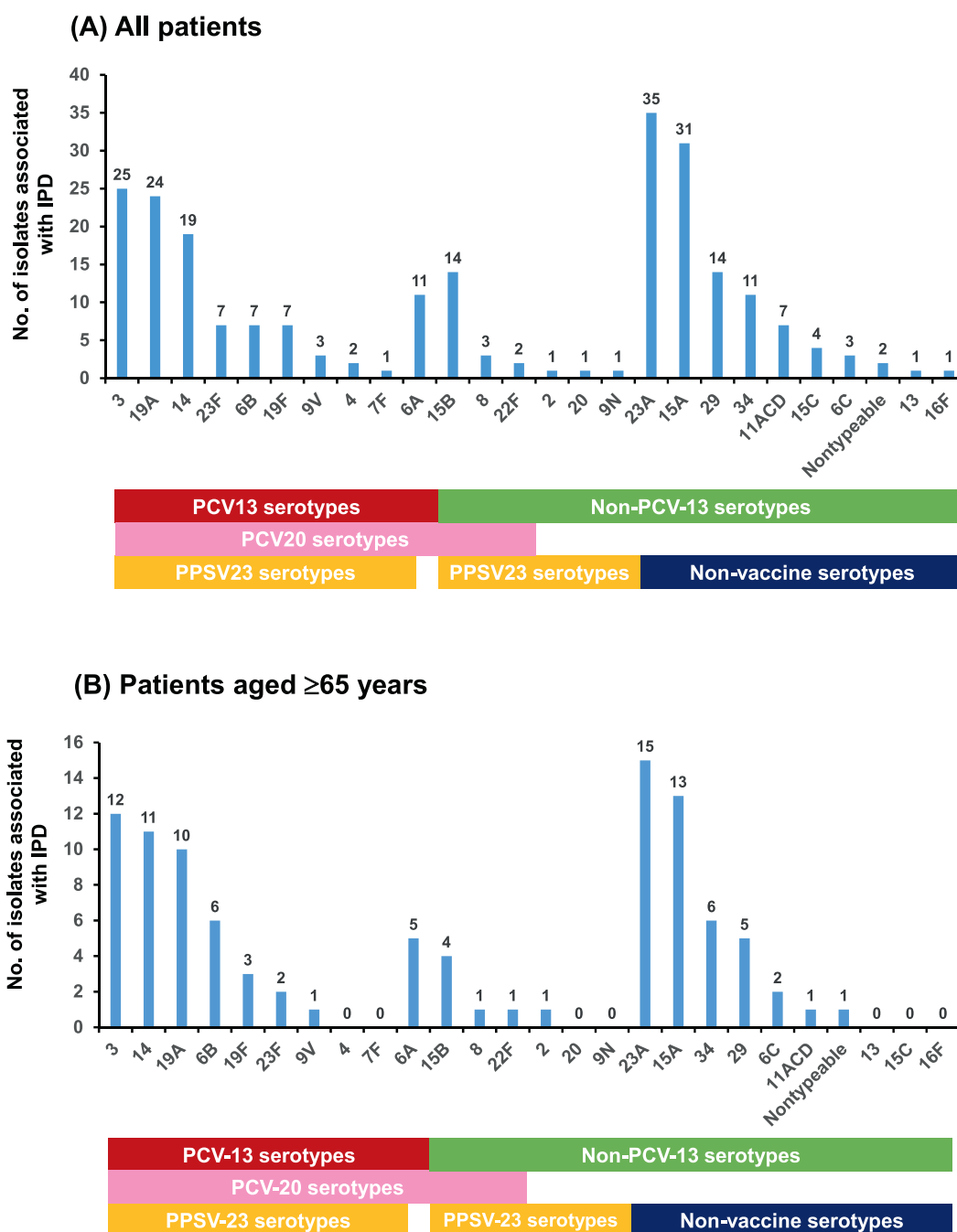


Fig. 3. Number of patients with invasive pneumococcal disease (IPD) from 2017–2020 and association of vaccine coverage by serotype for (A) all patients studied, (B) patients aged ≥65 years, (C) patients aged 50–64 years and (D) patients aged 20–49 years.

was no significant difference in the trend of serotypes or vaccine coverage by year from 2017 to 2019 (Table 2).

The CFR of these patients with IPD was 15.2% (n = 36), with an increase in age as shown by age stratification in Fig. 5A. The CFRs of the top five most common serotypes were 20.0% for serotype 23A, 16.1% for 15A, 16.0% for 3, 20.8% for 19A and 5.3% for 14 (Fig. 5B). Patients infected with serotype 15B had the highest CFR (21.4%; 3/14), although it was the sixth predominant serotype (n = 14; 5.9%) causing IPD.

3.4. Serotypes and antimicrobial resistance

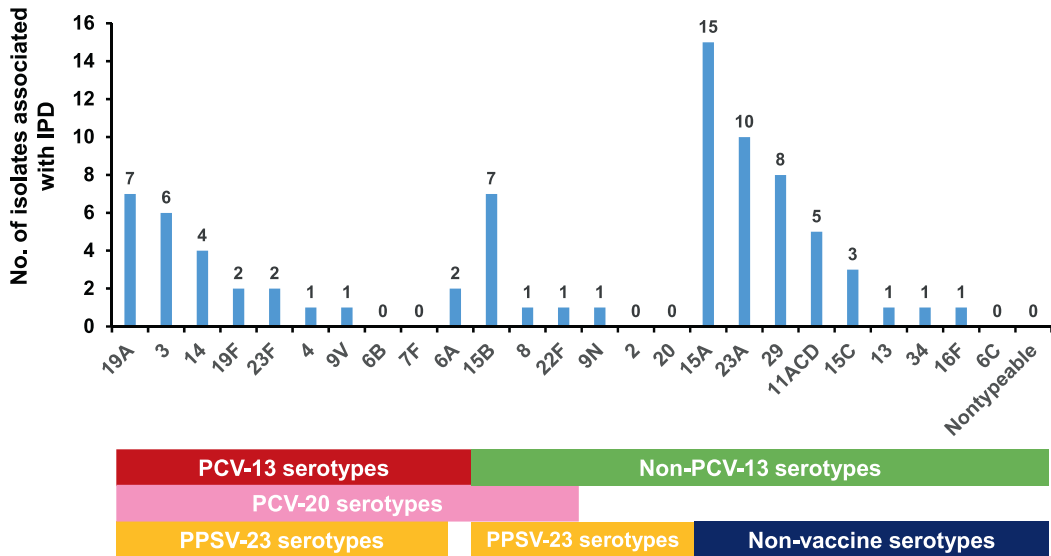
The main serotypes of isolates non-susceptible to ceftazidime (n = 4), moxifloxacin (n = 12) and quinupristin/dalfopristin

(n = 24) were serotype 14 (n = 2; MICs of both 1.0 mg/L), 15A (MICs of 2.0, 4.0 and 4.0 mg/L, respectively) and 19A (n = 6; MICs of all 2 mg/L), respectively (Table 3). Among the 12 isolates non-susceptible to moxifloxacin, 10 exhibited MICs of 4.0 mg/L, 1 (serotype 15A) had a MIC of 2.0 mg/L and one (serotype 14) had an MIC of 8.0 mg/L. One serotype 29 isolate was non-susceptible to ceftazidime, moxifloxacin and quinupristin/dalfopristin.

4. Discussion

This study investigated the trends in serotypes and in vitro susceptibility of *S. pneumoniae* causing adult IPD to new-generation antimicrobial agents using nationwide survey data from 2017–2020, following implementation of the PCV-13 vaccine and the

(C) Patients aged 50-64 years



(D) Patients aged 20-49 years

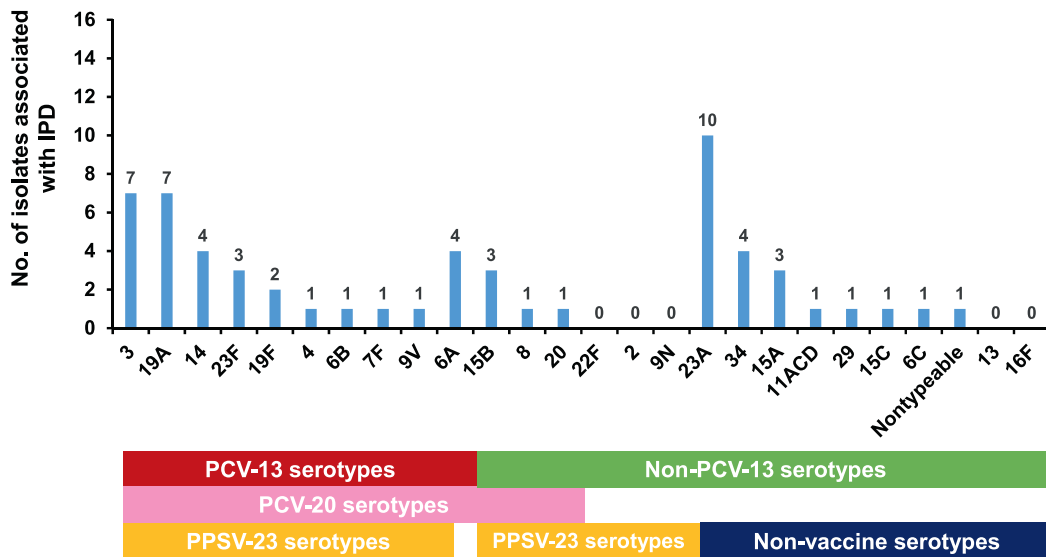


Fig. 3. Continued

COVID-19 pandemic. We found that the MIC₅₀ and MIC₉₀ values of these new-generation antimicrobial agents were generally low for the isolates. Non-vaccine serotype 23A was the leading cause of IPD across the adult age range. There were slightly fewer isolates of serotype 15B than of PCV-13 serotypes in patients aged ≥65 years. The overall CFR was 15.2% (36/237) but was especially high for non-PCV-13 serotype 15B (21.4%; 3/14). Several serotypes, especially 14, 19A and 15A, were non-susceptible to ceftaroline, moxifloxacin and quinupristin/dalfopristin.

A total of 1585 IPD cases were reported to the IPD surveillance system of the Taiwan Centers for Disease Control from 2017–2020. The collection of 237 non-duplicate isolates of *S. pneumoniae* in this study represented 15.0% of the total cases in Taiwan. The incidence of IPD was stationary from 2017–2019 with 453, 459 and 445 cases per year, respectively, but dropped to 228 cases in

2020. Physical measures for COVID-19 mitigate the incidence of other airborne-transmitted infections but also impede exposure of the elderly to vaccines for pneumococcal disease or influenza. The dramatic decrease in the incidence of IPD in 2020 is supposed to be the net effect of face mask use and social distancing [28–30].

The Sensititre susceptibility system is a microbroth method that provides qualitative (susceptible or resistant) and quantitative (MIC) results in one dried-plate format. The MIC₉₀ values were ≤1.0 mg/L for all antibiotics tested, with the exception of oxacillin, ceftaroline, mupirocin and quinupristin/dalfopristin. The MIC₅₀ and MIC₉₀ values of *S. pneumoniae* to ceftaroline were 0.12 mg/L and 0.5 mg/L, respectively. Before ceftaroline was launched in Taiwan in 2019, the MIC₅₀ and MIC₉₀ values of *S. pneumoniae* to ceftaroline were 0.12 mg/L and 0.25 mg/L, respectively [31]. Empirical monotherapy with ceftriaxone for pneumococcal meningitis

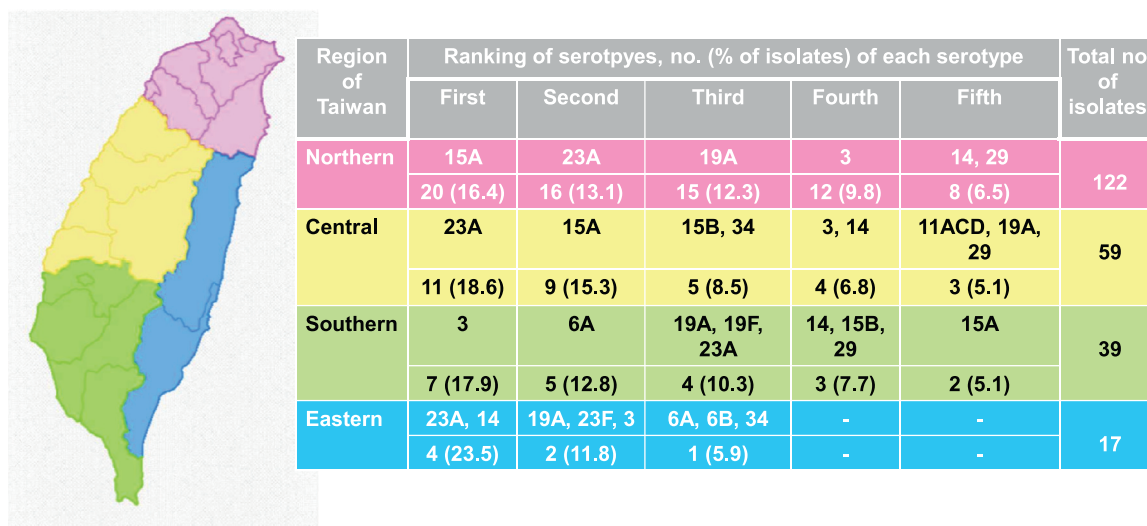


Fig. 4. Distribution of predominant serotypes of *Streptococcus pneumoniae* isolates associated with invasive pneumococcal disease in different regions of Taiwan.

Table 2

Distribution of the main serotypes of 237 *Streptococcus pneumoniae* isolates and coverage rates of pneumococcal vaccines during 2017–2020

Main serotype (no. of isolates) and coverage	% of isolates					P-value
	All	2017	2018	2019	2020	
Serotype						
23A (n = 35)	14.8	12.3	16.9	14.5	16.7	0.26
15A (n = 31)	13.1	9.9	15.5	16.4	10	0.94
3 (n = 25)	10.5	4.9	14.1	14.5	10	0.43
19A (n = 24)	10.1	12.3	4.2	10.9	16.7	0.39
14 (n = 19)	8	6.2	11.3	7.3	6.7	0.81
Others (n = 103)	43.5	54.3	38	36.4	40	0.23
Vaccine coverage						
PCV-13	44.7	46.9	38	45.5	46.7	0.72
PCV-20	55.7	56.8	49.3	58.2	56.7	0.63
PPSV-23	49.4	49.4	45.1	54.5	50	0.52
PCV-13 or PPSV-23	57	58	54.9	58.2	56.7	0.93

PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

Table 3

Distribution of serotypes among *Streptococcus pneumoniae* isolates that were non-susceptible to selected antimicrobial agents

Antimicrobial agents (no. of isolates non-susceptible to the agent)	No. (%) ^a of isolates in each indicated serotype												
	3	6A	9V	11ACD	14	15A	15B	19A	19F	23A	23F	29	NT
Quinupristin/dalfopristin (n = 24)	4 (16.0)	1 (9.1)		1 (14.3)	4 (21.1)	2 (6.5)	1 (7.1)	6 (25)	1 (14.3)	2 (5.7)	1 (14.3)	1 (7.1)	
Moxifloxacin (n = 12)			1 (33.3)		2 (10.5)	3 (9.7)		1 (4.2)		1 (2.9)	2 (28.6)	1 (7.1)	1 (50)
Ceftaroline (based on non-meningitis criteria) (n = 4)					2 (10.5)			1 (4.2)				1 (7.1)	

NT, non-typeable.

^a Percentage of isolates non-susceptible to selected antimicrobial agent in each indicated serotype. Numbers of isolates with different serotypes are shown in Fig. 3A.

may be inadequate [32,33]. If ceftaroline is used for community-acquired pneumonia (CAP), pneumococcal meningitis might also be covered [34]. Eravacycline was the most potent agent with an MIC ranging from ≤ 0.03 mg/L to 0.06 mg/L. The susceptibility rate of omadacycline is 93.2% when applying breakpoints identified by the US Food and Drug Administration (FDA) (MIC, ≤ 0.12 mg/L) for bacterial CAP [27].

The main serotypes were non-vaccine serotypes 23A and 15A, followed by vaccine serotype 3 in adults. The order was the same in those aged ≥ 65 years. There was no significant change in serotypes during the post-PCV-13 era. In general, vaccine coverage was 44.7% for PCV-13 and 49.4% for PPSV-23. The vaccine coverage for both PCV-13 and PPSV-23 was 57%. If there is a protective effect of PPSV-23 following PCV-13, combining these two vaccines

might be beneficial. Otherwise, if PCV-20 is introduced, the proposed coverage is 55.7%. Serotype 15B is not covered by the current PCV-13 on the market, but is covered by PPSV-23 and PCV-20. However, the CFR was high for serotype 15B.

In children under 5 years of age, more than one-half of the IPD cases were caused by non-PCV-13 serotypes, especially 15B and 15 non-B [11]. PCV-13 vaccine serotype 3, also included in PPSV-23, was not a problem in children but was in the adult population. The relative failure of PCV-13 for serotype 3 might be due to its capsular polysaccharide (CPS) release interfering with antibody-mediated killing and protection by anti-CPS antibodies [35].

IPD is the invasive form of pneumococcal infection and only a small proportion of patients infected with *S. pneumoniae* progress to IPD [36]. Because of the high CFR of IPD, surveillance of isolates

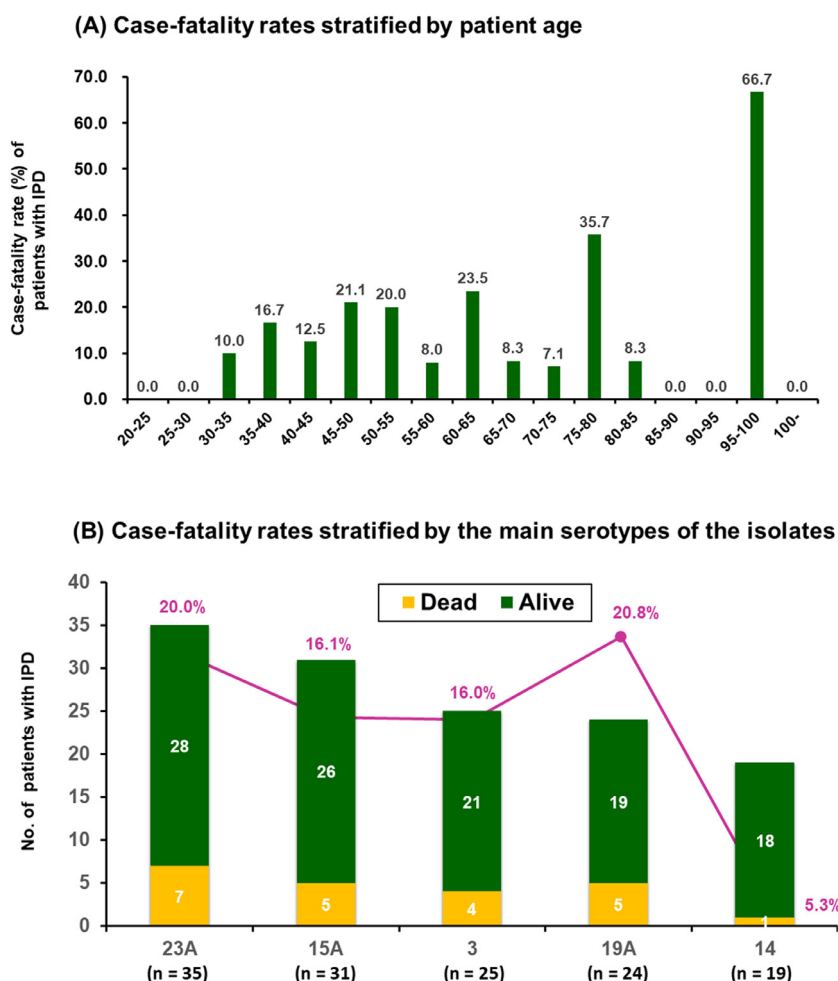


Fig. 5. Case fatality rate of invasive pneumococcal disease (IPD) (A) by age and (B) by main serotypes of *Streptococcus pneumoniae* isolates.

from IPD is conducted in most countries, but not for isolates of *S. pneumoniae* causing only pneumonia that cause higher mortality than IPD. However, *S. pneumoniae* is still the most important bacterial pathogen in CAP. It is reasonable to monitor trends in antibiotic resistance of *S. pneumoniae* causing CAP or other upper airway infections and to evaluate the real-world effects of pneumococcal vaccines against these infections [37].

Our study has several strengths. First, the collection of isolates covered up to 15.0% of IPD cases in Taiwan and was rechecked at the central laboratory. Second, the isolates were collected from Taiwan. Third, due to the low prevalence of COVID-19 in Taiwan, the quality of healthcare was adequate to avoid biasing mortality. There were some limitations of our study, including a lack of reliable vaccination history, antibiotic exposure and co-morbidities among the enrolled patients, and isolates were only from the main teaching hospitals.

In summary, the incidence of IPD was stationary after PCV-13 introduction but dropped in the COVID-19 pandemic in 2020. The MIC₉₀ values of new-generation antimicrobial agents were generally low for *S. pneumoniae*. The main serotypes were non-vaccine serotypes 23A and 15A and vaccine serotype 3 for adults. Multivalent pneumococcal conjugate vaccines (PCV-15 and PCV-20) are being investigated. It is important to continue surveillance of serotypes and MICs of common antimicrobial agents for *S. pneumoniae* with or without co-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and after new vaccine introduction.

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Competing interests

None declared.

Ethical approval

This study was approved by the research ethics committees or institutional review boards of the 18 participating hospitals. The requirement for informed consent from each patient was waived.

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