Surveillance of invasive *Streptococcus pneumoniae* in Taiwan, 2002–2003

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A total of 522 *Streptococcus pneumoniae* invasive isolates from diverse sources were collected from January 2002 to December 2003 in Taiwan in order to understand the serotype distribution of invasive isolates in Taiwan. The most frequently isolated serotypes of *S. pneumoniae* were types 14 (18.4%), 23F (15.1%), 3 (13.8%), 19F (13.4%), 6B (8.2%), 9V (3.6%) and 4 (2.5%). The majority of cases were either under 5 years of age (24.1%) or older than 65 years (36.6%). Serotype distribution in adults aged over 14 years and children aged under 2 years was similar, except for that of type 3, which was more prevalent in adults. Penicillin-non-susceptible strains accounted for 67.7% of all strains and were the predominant strains of serotypes 23F, 19F, 6B and 14. Most strains were susceptible to cephem drug, 85.7% of isolates were susceptible to cefotaxime and 92.9% were susceptible to ceftriaxone. A total of 72.6% (379/522) of the isolates were resistant to at least two antibiotics. The 23-valent vaccine in the current commercial market would cover 87.2% of the serotypes and 100% of the penicillin-non-susceptible serotypes of *S. pneumoniae* in Taiwan. The coverage of 7- and 11-valent protein conjugate vaccines of the serotypes in children under 2 years of age would be 78.8 and 86.5%, respectively. These results will help to assess the adequacy of the vaccine formulations marketed in Taiwan.

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INTRODUCTION

Streptococcus pneumoniae is the most common cause of community-acquired pneumonia. Infection of *S. pneumoniae* can cause invasive diseases such as bacteraemia, sepsis and meningitis and respiratory diseases such as pneumonia, otitis media and sinusitis, especially in children and the elderly. An increasing number of strains resistant to antimicrobial agents and now endemic in many countries reflects an uncontrolled use of antibiotics (Schito & Felmingham, 2005; Song *et al.*, 2004). The same tendency is paralleled in Taiwan (Chen *et al.*, 2003; Chiou *et al.*, 1998; Hsueh *et al.*, 1996, 2003; Lo *et al.*, 2003; Shi *et al.*, 1998; Siu *et al.*, 2002), where choosing appropriate antibiotics has become a therapeutic challenge. Interest in the prevention of pneumococcal infections by vaccination has been revived (Whitney *et al.*, 2000, 2003). Since 1983, a 23-valent vaccine covering 23 serotypes of *S. pneumoniae* has been commercially available and is recommended for people over 65 years of age and for immunocompromised individuals. For children under 2 years, a 7-valent protein conjugate vaccine is on the market (Baltimore, 1992; Robbins & Schneerson, 1990). The 23-valent and the 7-valent conjugate vaccines against pneumococcal infection were introduced in Taiwan in 1998 and 2005, respectively. As there are discrepancies in the frequency of distribution among different countries and some serotypes may possess distinct antibiotic-resistance or

epidemiological properties (Hausdorff *et al.*, 2005), it is of great interest to continue to monitor the distribution of *S. pneumoniae* serotypes and antibiotic resistance in Taiwan. The surveillance of serotype distribution will help to establish local epidemiological profiles and is important for assessment of the potential applicability of vaccine formulations.

METHODS

Specimens or isolates of *S. pneumoniae* were obtained from normally sterile sites and reported by the hospitals that voluntarily participate in the reporting system. The age, sex and clinical presentation of each patient were reported. The symptoms included pneumonia, meningitis, bacteraemia, sepsis, arthritis, osteomyelitis, endocarditis, pericarditis and peritonitis. The 28 hospitals ranked at the level of medical centre or regional hospitals from different geographic regions of Taiwan that participated in the study were estimated to provide in-patient service to approximately 27% of Taiwan's population.

A total of 522 bacterial strains collected from cases conforming to the case definition of invasive pneumococcal disease were cultured on blood agar plates. These *S. pneumoniae* isolates were grown on trypticase soy agar plates (BBL; Becton Dickinson Microbiology Systems) with 3–5% sheep blood and incubated at 37 °C in 5% CO₂ overnight. Alpha-haemolytic colonies exhibiting sufficient morphological characteristics of *S. pneumoniae* were isolated. Identification of

these isolates as *S. pneumoniae* was confirmed using Gram staining, the optochin growth inhibition test (Difco Laboratories) and bile solubility testing.

The serotype of each pneumococcal isolate was determined by the Quellung reaction with antisera produced by the Statens Serum Institut (Copenhagen, Denmark).

Antibiotic susceptibility tests were performed using VITEK 2 susceptibility tests (bioMérieux) and resistance was defined according to the National Committee for Clinical Laboratory Standards criteria. For these tests, *S. pneumoniae* was grown for 18–24 h in trypticase soy agar containing 5% defibrinated sheep blood (BBL) in 5% CO₂. Bacterial cells were suspended in 0.45% saline, adjusted to the turbidity of a 0.5 McFarland standard and loaded in the AST-GP62 test cards for the VITEK 2 test. The test cards were inserted into the prototype VITEK 2 incubator reader, which gave an interpretation of the test results.

To analyse the differences in serotypes between age groups or in antimicrobial susceptibility, a χ^2 test with Yate's correction or Fisher's exact test was performed. EPI INFO (version 6.0) was used to calculate the odds ratios (OR) and 95% confidence limits. Statistical significance was defined as a value of $P < 0.05$.

RESULTS

A total of 522 isolates of invasive *S. pneumoniae* together with the basic information from patients were collected during a 2-year surveillance period from January 2002 to December 2003. Isolates were obtained from 28 hospitals ranked at the level of medical centre or regional hospitals from different geographic regions of Taiwan: north (13), middle (10), south (3) and east (2). The major specimen types collected were blood (482 cases, 92.3%), cerebrospinal fluid (16 cases, 3.1%), pleural effusion (15 cases, 2.9%), ascites (four cases, 0.8%) and sputum (five cases, 1.0%).

The age distribution of the 522 invasive *S. pneumoniae* cases was as follows: under 2 years, 52 cases; 3–5 years, 74 cases; 6–14 years, 21 cases; 15–44 years, 69 cases; 45–64 years, 96 cases; 65 years and over, 191 cases; and unknown, 19 cases.

The serotype distribution analysis demonstrated that 26 serotypes were identified within the 522 cases of *S. pneumoniae*, with the most common serotypes in decreasing order

of frequency being: 14 (96 cases), 23F (79 cases), 3 (72 cases), 19F (70 cases), 6B (43 cases), 9V (19 cases), 4 (13 cases) and 11 (10 cases) (Fig. 1 and Table 1).

For people aged 65 years and over, the most frequent serotypes were: 14 (17.3%), 3 (16.8%), 19F (16.2%), 23F (13.1%), 6B (6.3%) and 9V (3.1%), and in this group, a higher crude mortality rate was also observed. For infants under 2 years of age, the most frequent serotypes were 14 (28.8%), 23F (17.3%), 6B (13.5%), 19F (11.5%) and 3 (7.7%). Serotype distribution in adults aged over 14 years and in children aged less than 2 years was similar except for that of type 3, which was 17.4 and 7.7%, respectively. Type 3 was significantly more prevalent in adults over 14 years. Type 14 was significantly more prevalent in children under 14 years. The clinical outcomes after infection also varied and were mainly pneumonia (42.3%), bacteraemia (21.5%), sepsis (15.7%) and meningitis (3.5%). The crude mortality rate was 14.4% from our results, with types 6B and 3 being the most frequent serotype (13.3 and 20.0%, respectively) in mortality cases.

Among the serotypes of *S. pneumoniae* isolates from the 522 cases, the coverage rate of the 23-valent polysaccharide vaccine was 87.2% and that of the 7-valent conjugate vaccine was 63.0%. The coverage rates varied among different age groups. The coverage rate of the 7-valent vaccine in children under 2 years old was 78.8% (41/52) and in people over 3 years old was 61.2% (276/451). In children under 14 years, the coverage rate of the 23-valent vaccine was 87.1% (128/147) and of the 7-valent conjugate vaccine was 76.2% (112/147). In adults older than 14 years, the coverage rate of the 23-valent vaccine was 87.6% (312/356) and of the 7-valent conjugate vaccine was 57.6% (205/356). For children under 2 years old, the coverage rate of the 23-valent vaccine was as high as 88.5% (46/52); however, the protection of the 23-valent polysaccharide vaccine is not sufficient because of its inability to induce a T-cell-dependent immune response and the 7-valent conjugate vaccine has to be used instead, with a coverage rate of 78.8% as above.

Fig. 1. Serotype distribution of invasive *S. pneumoniae* disease in Taiwan in samples collected from January 2002 to December 2003. rvt, Other vaccine-related types; uvt, other vaccine-unrelated types.

Table 1. Serotype distribution of invasive isolates according to age group and symptom

	No. of isolates of each serotype (%)							No. of isolates with vaccine-covered serotypes (%)			
	All	14	23F	19F	6B	3	9V	Other	23-Valent*	7-Valent†	11-Valent‡
0-2 years	52 (10.0)	15 (28.8)§	9 (17.3)	6 (11.5)	7 (13.5)	4 (7.7)§	3 (5.8)	8 (15.4)	46 (88.5)	41 (78.8)¶	45 (86.5)
3-14 years	95 (18.2)	24 (25.3)§	17 (17.9)	12 (12.6)	13 (13.7)	5 (5.2)§	3 (3.2)	21 (22.1)	82 (86.3)	71 (74.7)¶	76 (80.0)
15-64 years	165 (31.6)	23 (13.9)	20 (12.1)	20 (12.1)	11 (6.7)	30 (18.2)	5 (3.0)	56 (34.0)	143 (86.7)	90 (54.5)	125 (75.8)
>65 years	191 (36.6)	33 (17.3)	25 (13.1)	31 (16.2)	12 (6.3)	32 (16.8)	6 (3.1)	52 (27.2)	169 (88.5)	115 (60.2)	152 (79.6)
Age unknown	19 (3.6)	1 (5.3)	8 (42.1)	1 (5.3)	0 (0.0)	1 (5.3)	2 (10.5)	6 (31.6)	15 (78.9)	12 (63.2)	13 (68.4)
Death	75 (14.4)	9 (12.0)	8 (10.7)	9 (12.0)	10 (13.3)	15 (20.0)	1 (1.3)	23 (30.7)	69 (92.0)	42 (56.0)	57 (76.0)
Total	522 (100)	96 (18.4)	79 (15.1)	70 (13.4)	43 (8.2)	72 (13.8)	19 (3.7)	143 (27.4)	455 (87.2)	329 (63.0)	411 (78.7)

*23-Valent polysaccharide vaccine (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F).

†7-Valent pneumococcal conjugate vaccine (serotypes 4, 9V, 14, 19F, 23F, 18C and 6B).

‡11-Valent pneumococcal conjugate vaccine (serotypes 4, 9V, 14, 19F, 23F, 18C, 6B, 1, 5, 3 and 7F).

§Significant differences between 0–14 years group and other (OR = 2.23, $P = 0.0004$ for serotype 14; OR = 0.30, $P = 0.0009$ for serotype 3).

¶Significant differences between age group and other in 7-valent vaccine (OR = 2.52, $P = 0.01$ for 0–2 years group; OR = 2.14, $P = 0.02$ for 3–14 years group).

As shown in Table 2, the isolates showed high levels of drug resistance to tetracycline (84.7 %, 442), erythromycin (78.4 %, 409), trimethoprim/sulfamethoxazole (52.3 %, 274) and penicillin (51.3 %, 268). The penicillin-non-susceptible strains accounted for 67.8 % of all strains. However, the isolates were found to exhibit high susceptibility to ceftriaxone (92.9 %, 485), ofloxacin (87.0 %, 454), cefotaxime (85.8 %, 448) and chloramphenicol (72.0 %, 376). No vancomycin-resistant isolates were detected. Significantly more isolates from children under 14 years showed high resistance to penicillin than isolates from adults above 14 years (67.4 and 44.4 %, respectively).

Table 3 summarizes the predominant serotypes of *S. pneumoniae* resistant to penicillin. Among the seven major serotypes, 23F showed the highest rate (96.2 %) of penicillin resistance, followed by serotypes 19F (77.1 %), 6B (72.1 %), 9V (68.4 %), 14 (59.4 %), 4 (23.1 %) and 3 (4.2 %). Three of the serotype 3 strains were found to be penicillin-resistant.

The antibiotic-resistance patterns of the isolates to penicillin, cefotaxime, chloramphenicol and erythromycin in relation to the vaccine and non-vaccine serotypes are summarized in Table 4. Of the invasive isolates, 27.6 % (144/522) were resistant to three or four kinds of antimicrobials and 45.0 % (235/522) were dual resistant. The proportion of serotype 23F strains exhibiting resistance to three or more antibiotics was significantly high (62.1 % for four antibiotics and 25.2 % for three antibiotics, respectively). Serotype 6B also demonstrated a high proportion of triple resistance. Among serotype 3 strains, resistance to two or three antibiotics was quite frequent (68.1 %, 49/72), but no strain exhibited multiple resistance to all four antibiotics. The 7-, 11- and 23-valent vaccines can cover over 80 % of the multiple-drug-resistant strains.

DISCUSSION

S. pneumoniae can cause invasive infections with high morbidity and mortality in all ages, including symptoms of pneumonia, bacteraemia and meningitis. Risk groups for serious invasive pneumococcal infections are children (<2 years), the elderly (>65 years) and immunocompromised individuals (Schreiber & Jacobs, 1995). The emerging resistance to penicillin and other commonly used antibiotics has revived interest in the prevention of pneumococcal disease by vaccination (Bogaert *et al.*, 2004). Continuing surveillance of serotype distribution and antibiotic resistance of clinical isolates is importance for vaccine evaluation.

According to our surveillance data on 28 hospitals, people over 65 years of age and young children under 2 years old were the major high-risk groups for *S. pneumoniae* infection. This age distribution is similar to that of other countries (Luey & Kam, 1996).

Twenty-six different invasive *S. pneumoniae* serotypes were identified in Taiwan in this study. The most frequently

Table 2. Susceptibility of isolates from patients aged less than or older than 14 years in Taiwan, 2002–2003, to nine antimicrobial agents

Antibiotic	No. of isolates (%)								
	All age groups			Under 14 years of age			Older than 14 years of age		
	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant
Penicillin	168 (32.2)	86 (16.5)	268 (51.3)	24 (16.3)	24 (16.3)	99 (67.4)*	140 (39.3)	58 (16.3)	158 (44.4)*
Cefotaxime	448 (85.8)	67 (12.9)	7 (1.3)	114 (77.6)	30 (20.4)	3 (2.0)	319 (89.6)	33 (9.3)	4 (1.1)
Ceftriaxone	485 (92.9)	33 (6.3)	4 (0.8)	133 (90.5)	13 (8.8)	1 (0.7)	334 (93.8)	19 (5.4)	3 (0.8)
Chloramphenicol	376 (72.0)	0	146 (28.0)	106 (72.1)	0	41 (27.9)	257 (72.2)	0	99 (27.8)
Erythromycin	82 (15.7)	31 (5.9)	409 (78.4)	9 (6.1)	9 (6.1)	129 (87.8)*	69 (19.4)	20 (5.6)	267 (75.0)*
Ofloxacin	454 (87.0)	60 (11.5)	8 (1.5)	136 (92.5)	9 (6.1)	2 (1.4)	303 (85.1)	48 (13.5)	5 (1.4)
Tetracycline	58 (11.1)	22 (4.2)	442 (84.7)	15 (10.2)	8 (5.4)	124 (84.4)	41 (11.5)	14 (3.9)	301 (84.6)
TMP/SMX†	158 (30.3)	91 (17.4)	273 (52.3)	28 (19.1)	24 (16.3)	95 (64.6)*	124 (34.8)	66 (18.6)	166 (46.6)*
Vancomycin	522 (100)	0	0	147 (100)	0	0	356 (100)	0	0

*Significant differences between two age groups in resistance (OR=2.51, $P=0.00001$ for penicillin; OR=2.42, $P=0.0017$ for erythromycin; OR=2.01, $P=0.0007$ for trimethoprim/sulfamethoxazole).

†TMP/SMX, trimethoprim/sulfamethoxazole.

isolated serotypes of *S. pneumoniae* were 14, 23F, 3, 19F, 6B and 9V, in decreasing order of frequency. Serotype distribution in age groups above and below 14 years was similar, with only slight differences in rank order, in particular for type 3, which was more prevalent in adults aged over 14 years. However, the overall frequency of isolation of serotype 3 was higher than in other countries (Denham & Clarke, 2005; Reinert *et al.*, 2005), except in Japan and Italy (Kasahara *et al.*, 2005; Marchese *et al.*, 2005). More isolates from children younger than 14 years old were resistant to penicillin than from adults over 14 years and this was statistically significant. After further analysis, the

discrepancy of penicillin resistance was found to be due to the different prevalence rates of serotype 3 isolates between these two age groups (6.1% in the group ≤ 14 years old, 17.4% in the group > 14 years old), because the penicillin-non-susceptibility rate is low in serotype 3 isolates. Mortality among patients ≥ 65 years old was higher than in the other age groups. The mortality rate of serotype 3 and 6B in the elderly (> 65 years) was 20 and 50%, respectively. Among the most prevalent serotypes, the crude mortality rates of serotype 6B and 3 were 13.3 and 20.0%, respectively; both rates were about twice those of serotypes 14, 23F and 19F (12.0, 10.7 and 12.0%, respectively). In this study, 93.0 and 2.3% of serotype 6B strains were isolated from blood and cerebrospinal fluid, respectively. Higher association with invasive disease has been reported for serotype 6B (Hanage *et al.*, 2005). Whether the higher mortality can be attributed to the higher invasiveness of serotypes 3 and 6B or to stronger antibiotic resistance of serotype 6B deserves further investigation.

Table 3. Susceptibility to penicillin of different serotypes of invasive *S. pneumoniae* in Taiwan

Serotype	No. of isolates	Penicillin susceptibility (%)		
		Sensitive	Intermediate	Resistant
14	96	10 (10.4)	29 (30.2)	57 (59.4)
23F	79	1 (1.3)	2 (2.5)	76 (96.2)*
3	72	53 (73.6)	16 (22.2)	3 (4.2)*
19F	70	6 (8.6)	10 (14.3)	54 (77.1)*
6B	43	5 (11.6)	7 (16.3)	31 (72.1)*
9V	19	3 (15.8)	3 (15.8)	13 (68.4)
4	13	9 (69.2)	1 (7.7)	3 (23.1)
11	10	9 (90.0)	0	1 (10.0)
Others	120	72 (60.0)	18 (15.0)	30 (25.0)

*Significant differences in penicillin resistance (OR=36.23, $P=0.0000001$ for serotype 23F; OR=4.13, $P=0.0000001$ for serotype 19F; OR=2.67, $P=0.005$ for serotype 6B; and OR=0.03, $P=0.00000001$ for serotype 3).

The coverage of the 23-valent polysaccharide vaccine and 7-valent conjugate pneumococcal vaccine for all age groups was 87.2% (455/522) and 63.0% (329/522), respectively. For the elderly aged 65 years and over, the coverage of the 23-valent polysaccharide vaccine was 88.5% (169/191). In children under 2 years of age, the coverage rate of the 23-valent vaccine was as high as 88.5% (46/52); however, the protection from the 23-valent vaccine is not sufficient and the 7-valent conjugate vaccine has to be used instead. For infants under 2 years old, the coverage of the 7- and 11-valent conjugate pneumococcal vaccines was 78.8% (41/52) and 86.5% (45/52), respectively. The vaccination rate of pneumococcal vaccine in Taiwan has been quite low; whether this can explain the high prevalence of vaccine-covered serotypes deserves further study.

Table 4. Serotype distribution of invasive isolates according to antibiotic-resistance patterns

Resistance pattern*	No. of isolates (%)						No. of isolates with vaccine covered serotype (%)				
	All	14	23F	19F	6B	3	9V	Other	23-Valent	7-Valent	11-Valent
4	29 (5.6)	3 (10.4)	18 (62.1) [†]	1 (3.4)	1 (3.4)	0 (0) [‡]	0 (0)	6 (20.7)	27 (93.1)	23 (79.3)	23 (79.3)
3	115 (22.0)	29 (25.2)	29 (25.2) [†]	12 (10.4)	24 (20.9)	12 (10.4)	0 (0)	9 (7.9)	110 (95.7)	95 (82.6) [§]	107 (93.0)
2	235 (45.0)	53 (22.6)	31 (13.2)	52 (22.1)	12 (5.1)	37 (15.7)	14 (6.0)	36 (15.3)	216 (91.9)	166 (70.6)	203 (86.4)
1	84 (16.1)	11 (13.1)	1 (1.2)	4 (4.8)	4 (4.8)	10 (11.8)	4 (4.8)	50 (59.5)	58 (69.0)	34 (40.5)	44 (52.4)
0	59 (11.3)	0 (0)	0 (0)	1 (1.7)	2 (3.4)	13 (22.0)	1 (1.7)	42 (71.2)	44 (74.6)	11 (18.6)	27 (45.8)
Total	522	96 (18.4)	79 (15.1)	70 (13.4)	43 (8.2)	72 (13.8)	19 (3.7)	143 (27.4)	455 (87.2)	329 (63.0)	404 (77.4)

*Resistance patterns: 1, PEN, CHL or ERY; 2, PEN-CT, PEN-CHL, PEN-ERY or CHL-ERY; 3, PEN-CT-CHL, PEN-CT-ERY or PEN-CHL-ERY; and 4, PEN-CT-CHL-ERY (PEN, penicillin; CT, cefotaxime; CHL, chloramphenicol; ERY, erythromycin).

[†]Significant differences between resistance pattern in 23F (OR = 12.29, $P < 0.0000001$ for pattern 4; OR = 2.55, $P = 0.0005$ for pattern 3).

[‡]Significant differences between resistance pattern in 3 (OR = 0.00, $P = 0.02$ for pattern 4; OR = 2.55, $P = 0.0005$ for pattern 3).

[§]Significant difference between resistance pattern in 7-valent vaccine (OR = 3.45, $P = 0.00001$ for pattern 3).

^{||}Significant differences between resistance pattern in 11-valent vaccine (OR = 4.57, $P = 0.00001$ for pattern 3; OR = 2.85, $P = 0.000003$ for pattern 2).

Between 1999 and 2003, the prevalence rate of penicillin non-susceptibility varied from 38 to 81 % worldwide (Schito & Felmingham, 2005). In a previous report, the prevalence rate (60–84 %) of clinical penicillin-non-susceptible isolates was remarkably high in Taiwan between 1981 and 2000 (Hsueh *et al.*, 2002). Although the policy for the restrictive use of antibiotics began in 2001, the penicillin-resistance rate of *S. pneumoniae* was still high in this study. Analysis of the antimicrobial-resistance results showed that there was a high prevalence of β -lactam- and macrolide-resistant *S. pneumoniae* in Taiwan. Penicillin is still the major antibiotic used to treat infection of invasive *S. pneumoniae*. Our surveillance study of *S. pneumoniae* in Taiwan revealed that only 32.2 % (168/522) of the isolates were susceptible to penicillin, results similar to those of a study conducted in 2000–2001 that also surveyed *S. pneumoniae* resistance in Taiwan (Hsueh *et al.*, 2003). The MIC analysis clearly showed that serotypes 23F, 19F, 6B, 9V and 14 generally were not susceptible to penicillin. Thus, antibiotic selection pressures may have resulted in serotypes 23F, 19F, 6B, 9V and 14 becoming more prevalent (Doern, 2001). For serotype 3, strains resistant to penicillin have rarely been found (Kasahara *et al.*, 2005). In our study, three penicillin-resistant isolates were discovered in serotype 3 pneumococci. All three penicillin-resistant isolates were also resistant to erythromycin and tetracycline. Two of the three penicillin-resistant serotype 3 isolates exhibited an identical PFGE pattern, which was similar to that of other penicillin-resistant and erythromycin-susceptible serotype 3 isolates and belonged to multilocus sequence type ST180. The PFGE pattern of the other penicillin-resistant type 3 isolate was quite distinct and different from that of all other type 3 isolates (data not shown). Macrolide-resistant ST180 of serotype 3 has been reported to be prevalent in many Asian countries such as Hong Kong and Japan (Bozdogan *et al.*, 2004; Kasahara *et al.*, 2005). It is possible that these penicillin-resistant serotype 3 clones have evolved through recombination with other resistant *S. pneumoniae* clones or were introduced into Taiwan very recently. Of the invasive isolates, 88.7 % were resistant to at least one of the four antibiotics (penicillin, cefotaxime, chloramphenicol and erythromycin). Strains of five of the most prevalent serotypes (14, 23F, 19F, 6B, 3) accounted for 74.3 % of strains resistant to these four antibiotics. Of the invasive isolates, 72.6 % were resistant to at least two antibiotics. The proportion of serotype 23F strains exhibiting multiple drug resistance was extremely high (98.7 %). Serotypes 14, 19 and 6B also demonstrated a high proportion of multiple drug resistance. Among serotype 3 strains, resistance to more than two antibiotics other than penicillin was quite high. The 7-, 11- and 23-valent vaccines can cover over 70 % of the multiple-drug-resistant strains.

In conclusion, the current vaccines can cover approximately 80 % of the invasive strains in the target age groups and the multiple-drug-resistant strains. The occurrence or possible introduction of new clones such as the multiple-resistant type 3 strains into Taiwan and the impact of this should be

monitored. Continuous surveillance is important for elaboration of the control and immunization policy of Taiwan.

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