

Antibiotic resistance profiles and multidrug resistance patterns of *Streptococcus pneumoniae* in pediatrics

A multicenter retrospective study in mainland China

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Abstract

Emergent resistance to antibiotics among *Streptococcus pneumoniae* isolates is a severe problem worldwide. Antibiotic resistance profiles for *S pneumoniae* isolates identified from pediatric patients in mainland China remains to be established.

The clinical features, antimicrobial resistance, and multidrug resistance patterns of *S pneumoniae* were retrospectively analyzed at 10 children's hospitals in mainland China in 2016.

Among the collected 6132 *S pneumoniae* isolates, pneumococcal diseases mainly occurred in children younger than 5 years old (85.1%). The resistance rate of *S pneumoniae* to clindamycin, erythromycin, tetracycline, and trimethoprim/sulfamethoxazole was 95.8%, 95.2%, 93.6%, and 66.7%, respectively. The resistance rates of *S pneumoniae* to penicillin were 86.9% and 1.4% in non-meningitis and meningitis isolates, while the proportions of ceftriaxone resistance were 8.2% and 18.1%, respectively. Pneumococcal conjugate vaccine was administered to only 4.1% of patients. Penicillin and ceftriaxone resistance, underlying diseases, antibiotic resistant risk factors, and poor prognosis appeared more frequently in invasive pneumococcal diseases. The incidence of multidrug resistance (MDR) was 46.1% in patients with invasive pneumococcal disease which was more than in patients with non-invasive pneumococcal disease (18.3%). Patients with invasive pneumococcal disease usually have several MDR coexistence.

S pneumoniae isolates showed high resistance to common antibiotics in mainland China. Penicillin and ceftriaxone resistance rate of invasive streptococcal pneumonia patients were significantly higher than that of non-invasive *S pneumoniae* patients. Alarming, 46.1% of invasive clinical isolates were multidrug resistant, so it is important to continued monitor the resistance of *S pneumoniae* when protein conjugate vaccine (PCV13) is coming in mainland China.

Abbreviations: CLI = clindamycin, CLSI = Clinical and Laboratory Standards Institute, CRO = ceftriaxome, ERY = erythromycin, FEP = cefepime; IPD = invasive pneumococcal disease, ISPED = infectious Diseases Surveillance of Pediatrics, MDR = multidrug resistance, MIC = minimum inhibitory concentration, PCV13 = protein conjugate vaccine 13, PEN = penicillin, SXT = sulfamethoxazole/trimethoprim, TCY = tetracycline.

Keywords: antibiotic resistance, children, invasive pneumococcal disease, multidrug resistance, *Streptococcus pneumoniae*

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1. Introduction

Streptococcus pneumoniae (*S pneumoniae*) is a common pathogen for community acquired infection in children. It usually causes pneumonia, meningitis, septicemia, and otitis media, as well as sinusitis and bronchitis,^[1] resulting in considerable mortality. *S pneumoniae* is ranked as number two pathogen (5.2%) for community-acquired pneumonia in children younger than 5 years old,^[2] and the number three pathogen (11.1%) in the recent data obtained from the Infectious Diseases Surveillance of Pediatrics (ISPED).^[3] This represents a serious health threat to young children. Furthermore, it was reported that >14 million episodes of severe pneumococcal diseases occurred worldwide, and approximately 1.6 million patients die of pneumococcal infection, annually.^[4] The most vulnerable population was children younger than 5 years old, and most of the mortalities occurred in developing countries.^[5] An effective antibiotic therapy, which is often empirical, is required to manage *S pneumoniae* infection, which can rapidly deteriorate.^[6] Empirical antibiotics selection includes β -lactams, macrolides, and fluoroquinolones. However, the increase in resistance frequency to each of these agents, especially multidrug resistance (MDR), causes treatment failure or generates significant barriers to the effective treatment of pneumococcal infections.^[4,7-9]

Data obtained from multicenter based studies of antibiotic resistance in Europe and United States have guided the selection of antibiotics for empirical treatment and reduced the induction of resistance in clinical practice.^[10-14] However, such multicenter studies remain scarce in China, and only cross-sectional studies have been individually conducted in Beijing, Shanghai, Guangzhou, Taiwan, and Suzhou metropolitan areas.^[15-17] Furthermore, the data obtained from these studies may not reflect present antibiotic resistant patterns in children, and there is a lack of representation for all regions in China.

This study was part of ISPED, which is an ongoing national multicenter surveillance program that commenced in 2016 to monitor pediatric antibiotic resistance in mainland China. The national surveillance of *S pneumoniae* resistance in children was organized by the Children's Hospital of Zhejiang University School of Medicine. We report the latest *S pneumoniae* resistance data collected from ISPED, which consists of 10 children's hospitals. It is the first to present an overview of resistance profiles of *S pneumoniae* in children/teenagers <18 years old in 2016 in mainland China. This also included the epidemiological data of pneumococcal diseases nationwide.

2. Materials and methods

2.1. Participant centers and study populations

The present study comprised of 10 hospitals in 8 regions (Shanghai, Hangzhou, Wenzhou, Shenzhen, Jinan, Xi'an, Kaifeng, and Chongqing): Children's Hospital of Fudan University, Children's Hospital of Chongqing Medical University, Shanghai Children's Medical Center of Shanghai Jiaotong University School of Medicine, Children's Hospital of Shanghai Jiaotong University School of Medicine, the 2nd Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, The Children's Hospital of Zhejiang University School of Medicine, Qilu Children's Hospital of Shandong University Jinan, Kaifeng Children's Hospital, Shenzhen Children's Hospital, and Xi'an Children Hospital. All isolates were collected from patients who were under 18 years old. Only a

single isolate was included from each patient. Duplicate isolates and bacterial colonization in cultured plates without clinical evidence of infection were excluded from the study.

2.2. Study design and participants

All patients were retrospectively enrolled from 10 hospitals. A standardized Case Report Form was used for the collection and analysis of demographic and clinical information, including clinical outcomes. In addition, the type and time of specimen collection, admission and discharge diagnosis, recent use of antibiotics, underlying diseases, complications, vaccination history, and outcomes of illness were also collected from the medical records. Pediatricians from each participating hospital were responsible for the analysis of microbiology laboratory findings. Then, the identified positive pneumococcal isolates were tracked using the medical file number of the patient's medical charts where the clinical manifestations were noted. Each center was independent in the isolation and identification of *S pneumoniae*, the performance of antibiotic resistance testing, and the collection of clinical information, but the same criteria adopted by all participating hospitals were followed.

The investigators were able to collect the Case Report Forms of the 2241 isolates, and 80 of these covered isolates obtained from invasive infection.

2.3. Specimen collection

A total of 6132 *S pneumoniae* isolates were collected from patients with community-acquired pneumococcal infections in the 10 hospitals. The specimens included sputum, nasal and throat swab, tracheal aspirate, nasopharyngeal aspirate, bronchoalveolar lavage fluid, high vaginal swab, eye swab, ear swab, pus, urine, pleural fluid, ascites, synovial fluid, aseptic humoral, blood, and cerebrospinal fluid. The study protocol was approved by the Ethics Committee of each participant hospital, and an informed consent was obtained from the parent or guardian of each patient. The collected *S pneumoniae* specimens in each hospital were required to be delivered to the clinical microbiological laboratory within 2 hours after collection, according to routine clinical practice. In order to eliminate sample duplication, additional isolates after the first one from the same individual were excluded.

2.4. Identification of bacterial isolates and tests of antibiotic susceptibility

Bacteria were identified by automatic bacterial identification system (VITEK Compact, France) or Optochin Discs (OXOID, UK) at each surveillance center. Twelve antibiotics susceptibility of *S pneumoniae* were tested by Kirby-Bauer method in Children's Hospital of Fudan University, Shanghai Children's Medical Center of Shanghai Jiaotong University School of Medicine, Children's Hospital of Shanghai Jiaotong University School of Medicine and Qilu Children's Hospital of Shandong University, while automatic bacterial drug sensitivity analysis system (VITEK Compact, France) were used in 6 other hospitals according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (2015). When the minimum inhibitory concentration (MIC) of penicillin was ≥ 2 , another E-Test method was used for supplementary experiments. The American Type Culture Collection (ATCC) 49,619 strain of *S pneumoniae* was

used as controls during the susceptibility test. MDR *S pneumoniae* isolates were assigned when the isolates were resistant to ≥ 3 classes of antimicrobial agents. Invasive *S pneumoniae* isolates were reserved and stored at -80°C in 40% sterilized glycerin bouillon until further analysis.

2.5. Statistical analysis

WHONET software (version 5.6) (WHO collaborating Center, Boston, Massachusetts) and SPSS 19.0 (IBM Corporation, Armonk, New York) were used for statistical analysis. Statistical comparisons were conducted using chi-squared or Fisher exact tests. Two-tailed *P*-values $<.05$ were considered statistically significant.

2.6. Ethics approval and consent to participate

The study design was approved from ethical committee rules of Children's Hospital of Zhejiang University School of Medicine, Zhejiang, China (2018-IRB-008). The patient and (or) parental written informed consent was waived due to the anonymized data.

3. Results

3.1. Sample sources of *S pneumoniae* isolates

A total of 6132 *S pneumoniae* isolates were identified from specimens obtained from patients who were under 18 years old in the 10 children's hospitals in 2016. Most specimens were sputum samples ($n=5531$, 90.1%), while the other specimens obtained by tracheal aspirate, bronchoalveolar lavage, or nasopharyngeal aspirate ($n=307$, 5.0%), through blood or other body fluids (135 blood samples, 25 cerebrospinal fluids, 2 pleural effusions, 1 catheter, 1 serum, and 1 aseptic humoral) and from other sources (pus, middle ear effusion, eye secretions, or urine).

When *S pneumoniae* was identified in body fluids enclosed by normal anatomy, invasive infection was suggested. The majority of invasive *S pneumoniae* isolates (137, 83.0%) were identified in

children under 5 years old, among which were more than half of them (87, 52.7%) were younger than 2 years old.

3.2. Demographical and clinical highlights

The male-to-female ratio among the total *S pneumoniae* positive patients was 1.37:1.00 (3547 vs 2585), and 5028 (90.5%) of them were inpatients. The median age for patients with invasive and non-invasive pneumococcal diseases was 3.8 and 3.9 years old, respectively. Eighteen patients with invasive *S pneumoniae* infection were not initially admitted to these hospitals until later.

In mainland China, the heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in September 2008, and the vaccine has not been widely used in most parts of China. In this study, 4.1% of the patients were vaccinated against *S pneumoniae*, of which only 2 were vaccinated against the 13-valent conjugate vaccines (PCV13) vaccine, while the rest were vaccinated with PCV7 vaccines. As of now, the PCV13 vaccine has not been listed in mainland China.

Patients with invasive pneumococcal diseases appeared more frequently underlying diseases, antibiotic resistance risk factors, and poor prognosis when compared with patients who had non-invasive pneumococcal diseases. As shown in Table 1, the underlying diseases included pulmonary disease, cardiovascular disease, immunocompromised status/autoimmune disease, and diabetes mellitus. As expected, the prognosis of invasive pneumococcal diseases was poor than non-invasive pneumococcal diseases. Further analyses revealed significantly higher frequencies of previous hospitalization or intensive care unit hospitalization, and tertiary antibiotic usage (carbapenems and macrolides) in the prior 3 months up to the enrollment of invasive pneumococcal patients, compared with non-invasive pneumococcal patients (Table 1).

The percentage of patients with invasive pneumococcal disease (IPD), who received penicillin treatment in the prior 3 months, was significantly lower than that in patients with non-invasive pneumococcal disease (non-IPD). Furthermore, Table 1 revealed

Table 1
Demographics and clinical characteristics of the enrolled patients.

Variables	Total ^a (n=6132)	Invasive (n=165)	Non-invasive (n=5967)	<i>P</i>
Age, y	4.0 \pm 7.0	3.8 \pm 3.0	3.9 \pm 7.0	.87
Female/Male	2585/3547	77/88	2507/3460	.21
Outpatient/inpatient	525/5607	18/147	507/5460	.62
Underlying diseases, ^b n (%)				
Pulmonary disease	1029 (46.1)	8 (10.2)	1021 (47.4)	.01*
Cardiovascular disease	52 (2.32)	20 (25.6)	32 (1.5)	.00*
Renal disorder	13 (0.58)	1 (1.3)	12 (0.56)	.37
Immunocompromised status/Autoimmune disease	17 (0.76)	7 (8.9)	10 (0.46)	.00*
Diabetes mellitus	12 (0.53)	5 (6.4)	7 (0.32)	.00*
Antibiotic resistance risk factors in the recent 3 months, n (%)				
Hospital admission	171 (7.7)	15 (20.2)	156 (7.2)	.00*
Intensive care unit admission	430 (8.5)	33 (21.6)	397 (8.1)	.00*
Penicillin	536 (24.1)	7 (9.5)	529 (24.6)	.00*
Cephalosporins	1175 (52.8)	38 (51.4)	1137 (52.8)	.81
Carbapenems	53 (2.4)	5 (6.8)	48 (2.2)	.03*
Macrolides	91 (4.1)	9 (12.2)	82 (3.8)	.00*
Clinical outcome				
Non-cured, n (%)	289 (14.8)	29 (58.0)	251 (13.3)	.01*

^a Six thousand one hundred thirty two *S pneumoniae* isolates collected from different specimen sources in 10 hospitals.

^b Two thousand two hundred forty one case report forms collected from 6 hospitals.

* Significant difference between invasive and non-invasive groups with $P<.05$.

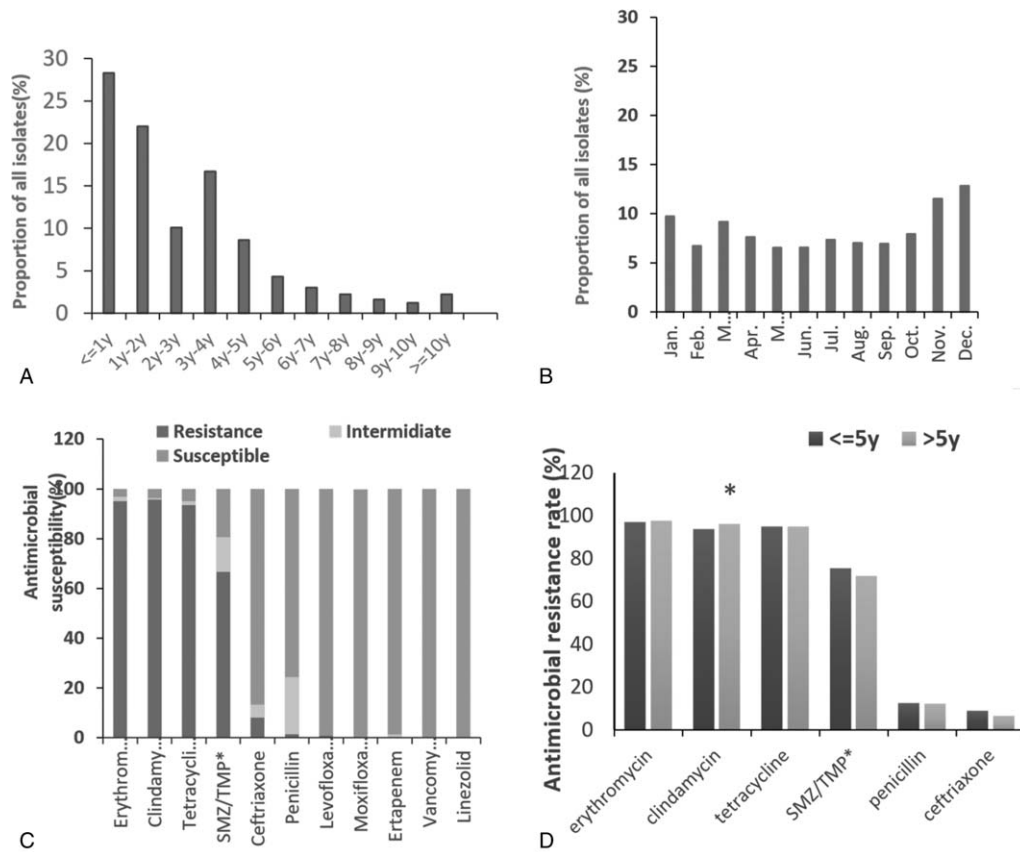


Figure 1. Age and seasonal distribution among clinical specimens. A. Proportion and age distribution of *S pneumoniae* isolates collected from different specimen sources. B. Proportion and seasonal distribution of *S pneumoniae* isolates collected from different specimen sources. C. Antibiotic susceptibility of *S pneumoniae* isolates. D. Comparison of antibiotic resistance between patients ≤ 5 years and patients > 5 years. * $P < .05$. An asterisk indicates a statistically significant difference between time periods ($P < .05$).

no significant difference in the frequency of using cephalosporins in the prior 3 months before hospitalization between the IPD and non-IPD groups.

Pneumococcal diseases occur mainly in children younger than 5 years old (85.1%), and children younger than 2 years old accounted for 50.3% (Fig. 1A). The monthly incidence of pneumococcal diseases was relatively stable, but with 2 peak periods, including March (9.18%) and the winter season of November to January (11.25%, 12.85%, and 9.75%, respectively) (Fig. 1B).

3.3. Antimicrobial resistance among the *S pneumoniae* isolates

According to the CLSI (2015) breakpoints, Penicillin resistance in nonmeningeal and meningeal isolates was 1.4% and 86.9%, respectively (Table 2). All meningeal *S pneumoniae* isolates in the Shenzhen, Wenzhou, Xian, Hangzhou, Chongqing, and Kaifeng regions were completely resistant to penicillin. The highest resistance to penicillin for nonmeningeal isolates was found in Chongqing (2.2%). There was no resistance to penicillin for nonmeningeal *S pneumoniae* isolates in the Jinan, Shenzhen, Wenzhou, Xi'an, Hangzhou, and Kaifeng regions. A summary of antimicrobial agent data for all *S pneumoniae* isolates is presented in Table 2.

The resistance to ceftriaxone was 8.2% and 18.1% among nonmeningeal and meningeal isolates, respectively (Table 2). Antibiotics susceptibilities determined for all clinical isolates are presented in Fig. 1C. The percentage of resistance to clindamycin, erythromycin, tetracycline, and trimethoprim/sulfamethoxazole was 95.8%, 95.2%, 93.6%, and 66.7%, respectively (Table 2). All isolates were susceptible to quinolone, linezolid, and vancomycin.

All antibiotic resistance of *S pneumoniae* isolates except clindamycin were comparable between younger and older than 5 years old groups (Fig. 1D), in which the resistance of isolates obtained from the > 5 years old group (96.1%) were higher than those obtained from the < 5 years old group (93.5%) ($P < .05$, Fig. 1D).

The antibiotic resistance of invasive pneumococcal isolates was also compared with that of non-invasive pneumococcal isolates. Invasive pneumococcal isolates exhibited higher rates of resistance to penicillin and ceftriaxone, compared with non-invasive pneumococcal isolates (Table 3).

For invasive and non-invasive isolates, the resistance to penicillin was 79.5% and 1.3%, respectively ($P = .00$), and the resistance to ceftriaxone was 34.9% and 8.6%, respectively ($P = .00$). These results indicate that there was no significant difference in resistance rates among these *S pneumoniae* isolates to all tested antibiotics, except for penicillin and ceftriaxone, between invasive and non-invasive infections.

Table 2
Susceptibilities to antimicrobial agents by *S pneumoniae* isolates from patients with pneumococcal infections in 10 hospitals.

Hospital	No. of isolates (invasive*/meningeal isolates)	Resistance to:											
		Penicillin				Ceftriaxone							
		Nonmeningeal isolates		Meningeal isolates		Nonmeningeal isolates		Meningeal isolates					
		P%	R%	P%	R%	P%	R%	P%	R%				
Fu Dan [‡]	231 (20/4)	1.5	1.5	50	0	0	NA [†]	NA					
Medical center [§]	115 (6/1)	NA	NA	NA	NA	NA	NA	NA					
Ji nan	171 (9/4)	2.7	0	50	0	0	100	0					
Shang hai [¶]	655 (11/2)	NA	NA	NA	NA	NA	NA	NA					
Shen zhen [#]	1819 (27/3)	0	0	100	4.7	12.8	0	33.3					
Wen zhou ^{**}	951 (12/1)	0	0	100	5.4	0	0	100					
Xi an ^{††}	241 (25/3)	2.3	0	100	13.4	11.9	0	0					
Hang zhou ^{‡‡}	208 (22/4)	1.1	0	100	4.8	0	75	0					
Chong qing ^{§§}	1738 (32/2)	4.8	2.2	100	NA	NA	NA	NA					
Kai feng	3 (1/1)	100	0	100	NA	NA	NA	NA					
Total	6132 (165/25)	22.9	1.4	86.9	5.2	8.2	38	18.1					

Erythromycin		Clindamycin		Tetracycline		Sulfamethoxazole/Trimethoprim		Moxifloxacin		Ertapenem		Levofloxacin	
P%	R%	P%	R%	P%	R%	P%	R%	P%	R%	P%	R%	P%	R%
3.9	91.3	1.3	92.2	NA	NA	2.6	87.4	0.4	0.4	NA	NA	0	0.9
0	99.1	0.9	94.8	NA	NA	2.6	92.1	0	0.9	NA	NA	0	0.9
1.9	89.6	1.3	86.4	0	100	2.4	77.6	NA	NA	NA	NA	0	1.8
1.4	97.1	0.8	95.7	NA	NA	2.9	78.9	0	0	NA	NA	NA	NA
NA	NA	NA	NA	1.9	92.3	15.6	62.8	0.1	0	1.2	0.1	0	0.1
NA	NA	NA	NA	0.7	95.3	21.7	57.3	0	0	0.5	0.1	0	0
1.4	96.6	0	94.6	4.4	84.4	7.5	88.2	0	0	6.5	1.1	0	0
0	100	12.5	75	0.5	90.9	12.3	65.9	0	0	0	0	0	0
NA	NA	0.1	97.5	2.2	93.7	51.1	0	0.1	0	NA	NA	0	0
NA	NA	0	100	0	100	NA	NA	0	0	0.5	0	0	0
1.8	95.2	0.5	95.8	1.5	93.6	13.9	66.7	0.06	0.04	1.1	0.1	0	0.2

* Invasive strains were isolated from sterile sites such as blood, CSF, pleural fluid, ascites, and joint fluid in patients with pneumococcal infections.

† NA, not available.

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§ Shanghai Children's Medical Center of Shanghai Jiaotong University School of Medicine.

|| Qilu Children's Hospital of Shandong University Jinan.

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‡‡ The Children's Hospital of Zhejiang University School of Medicine.

§§ Children's Hospital of Chongqing Medical University.

||| Kaifeng Children's Hospital.

3.4. Multidrug resistance (MDR) patterns

Approximately 21.4% (1315/6132) of *S pneumoniae* isolates were classified as MDR. The multiple resistance patterns of pneumococcal isolates obtained from the present study are

presented in Table 4. 46.1% (76/165) pneumococcal isolates obtained from invasive infection had MDR, which exhibited >1 MDR pattern. The resistance patterns of SXT-TCY-CRO, ERY-CLI-PEN, and CLI-TCY-PEN were more frequently identified in

Table 3
Percentages of resistance to 7 antimicrobials among *S pneumoniae* isolates obtained from different patient groups.

	Resistance of age groups (%)				Resistance of specimens (%)		
	<=5 yr		>5 yr	P	Invasive	Non-invasive	P
	SXT	2471 (75.3)	173 (71.8)	.24	70 (70)	2887 (77.2)	.09
ERY	1128 (97)	119 (97.5)	.79	60 (95.2)	1187 (97.1)	.43	
CLI	1113 (93.5)	444 (96.1)	.04**	91 (94.8)	2793 (96.3)	.41	
TCY	3986 (94.9)	463 (94.7)	.83	92 (93.9)	4357 (95.1)	.48	
CRO	229 (8.7)	9 (6.3)	.29	15 (34.9)	232 (8.6)	.00*	
PEN	29 (1.2)	6 (2.0)	.23	97 (79.5)	34 (1.3)	.00*	
FEP	682 (95.8)	30 (4.2)	.09	8 (1.1)	34 (1.3)	.47	

CLI=clindamycin; CRO=ceftriaxone; ERY=erythromycin; FEP=cefepime; PEN=penicillin; SXT=sulfamethoxazole/trimethoprim; TCY=tetracycline.

* Significant difference between invasive and non-invasive groups with P<.05.

** Significant difference between <=5 yr and >5 yr groups with P<.05.

Table 4
Multiple drug resistance patterns among *S pneumoniae* isolates.

Resistance patterns	Invasive		Non-invasive		P
	No.	Proportion (%)	No.	Proportion (%)	
SXT+ERY+CLI	28/99	28.3	874/3767	23.2	.24
SXT+TCY+CRO	10/40	25.0	206/3814	5.4	.00*
ERY+CLI+PEN	13/63	20.6	3/1000	0.3	.00*
CLI+TCY+PEN	29/87	23.2	29/2636	1.1	.00*
SXT+CLI+PEN	8/80	10.0	0	NA	NA
SXT+TCY+PEN	31/100	31.0	0	NA	NA
SXT+PEN+CRO	10/90	11.1	0	NA	NA
TCY+PEN+CRO	14/99	14.2	0	NA	NA
SXT+ERY+PEN	6/125	4.8	0	NA	NA
SXT+CLI+PEN	8/125	6.4	0	NA	NA
SXT+TCY+PEN	32/129	24.8	0	NA	NA
SXT+TCY+PEN+CRO	8/125	6.4	0	NA	NA
ERY+CLI+TCY	0	NA	4/500	0.8	-
SXT+ERY+CLI+TCY	0	NA	2/500	0.4	-

CLI = clindamycin; CRO = ceftriaxone; ERY = erythromycin; PEN = penicillin; SXT = trimethoprim/sulfamethoxazole; TCY = tetracycline.

NA = not available.

* Significant difference between invasive and non-invasive groups with $P < .05$.

invasive pneumococcal diseases, compared with non-invasive pneumococcal diseases (25% vs 5.4%, 20.6% vs 0.3%, 23.2% vs 1.1%, $P < .05$). Among the 197 MDR isolates, invasive pneumococcal isolates carried the multiple resistance patterns of SXT-CLI-PEN, SXT-TCY-PEN, SXT-PEN-CRO, TCY-PEN-CRO, SXT-ERY-PEN, SXT-CLI-PEN, SXT-TCY-PEN and SXT-TCY-PEN-CRO, while the patterns of ERY-CLI-TCY and SXT-ERY-CLI-TCY were only detected in non-invasive pneumococcal diseases.

4. Discussion

The present study extricated and analyzed data obtained from the ISPED program that commenced in January 2016. Focus was given on the antibiotic resistance frequency and pattern, MDR and the clinical features of *S pneumoniae* isolates identified among children/teenagers in 10 children's hospitals in 2016, which represent 8 regions in mainland China. The main findings include the following: 85% of *S pneumoniae* infected populations in this cohort were children younger than 5 years old; the overall resistance rate of *S pneumoniae* to clindamycin, erythromycin, tetracycline, and trimethoprim/sulfamethoxazole was 95.8%, 95.2%, 93.6%, and 66.7%, respectively, but these were significantly higher in patients with invasive infection, when compared with patients with non-invasive infection; approximately 21.4% of all isolates were classified as MDR, and 46.1% isolates obtained from patients with invasive infection were MDR; the overall rates of resistance to fluoroquinolones, vancomycin, and linezolid among the *S pneumoniae* isolates remained low. The resistance to levofloxacin and moxifloxacin was only detected in 0.2% and 0.04% of the isolates, respectively.

In the present study, a persistently high resistance rate to macrolide class drugs was noted, which was also reported by a previous investigation.^[18] A number of studies have also revealed that the rates of resistance to macrolide by pneumococci in many cities in China were significantly higher, compared with those in Western countries.^[17,19,20] The high macrolide resistance in children may relate to the inappropriate use of macrolides, which are frequently associated with imprudent practice, in which antibiotics are routinely given to patients without known

pathogens, as well as the spreading of macrolide-resistant strains in China. Thus, it is highly advised not to select macrolides as the first-line drug for treating *S pneumoniae* infections under circumstances of high macrolide resistance in China.

Furthermore, there was a minor increase in penicillin resistance among nonmeningeal isolates (1.4%/0.7%), and there was a nearly 30% increase in meningeal isolates (86.9%/57.5%) and in the intermediate rate of penicillin in nonmeningeal isolates (22.9%/3.9%), when compared with previous Asian Network for Surveillance of Resistant Pathogens (ANSORP) studies in China,^[21] when the revised CLSI breakpoints were used. More than 75% of the nonmeningeal isolates remained susceptible to parenteral penicillin in this cohort, implying that the compounds of penicillin and β -lactamase inhibitors can be selected when the initial treatment fails.

In the present study, the detected ceftriaxone resistance was 8.2% and 18.1% among nonmeningeal and meningeal isolates, respectively, which were higher when compared with the 2008 to 2009 ANSORP study (3.7% and 0.1%, respectively).^[21] The rates of the resistance to β -lactams and cephalosporins also increased.

According to these results, penicillin and β -lactam compounds should be chosen in the treatment of invasive pneumococcal disease (IPD) to reduce possible failure with the random selection of antibiotics. In clinic, monotherapy with ceftriaxone is not recommended for intracranial infection and critical infection with *S pneumoniae* due to the high resistance in IPD (34.9%). Hence, monotherapy with vancomycin or the combination of vancomycin and ceftriaxone should be selected instead. Clindamycin, erythromycin, tetracycline, and trimethoprim/sulfamethoxazole are not the first choice for empirical therapy in *S pneumoniae* infection.

In the present cohort, the overall MDR rate of *S pneumoniae* isolates was 21.4%, which was significantly lower than those published. For instance, in an ANSORP study, the reported overall MDR rate was 59.3%, while the individual rate was 83.3% in China and 75.5% in Vietnam.^[21] However, 46.1% isolates obtained from invasive infections exhibited MDR, which was significantly higher when compared with non-invasive infections. Furthermore, the MDR in invasive infection was

accompanied by >1 drug resistance pattern. This high MDR in invasive infections was consistent with early reports. In 2010, 89.5% of isolates identified from invasive pneumococcal infections in China were MDR,^[19] and approximately 88.0% of these isolates were MDR in a Shanghai based study conducted in 2015.^[22] The empirical treatment of invasive infections often requires a combination of 2 or 3 antibiotics, and longer durations. In addition, concurrent infections justify the additional antibiotics. These circumstances inevitably lead to the induction of high or multidrug resistance among patients with invasive infections. The present data may provide guidance for the selection of antibiotics in the empirical treatment of *S pneumoniae* infections among pediatric patients in mainland China.

This study is the most comprehensive nationwide multicentric study on *S pneumoniae* infection in mainland China to date supported by ISPED. Our study has 2 limitations. First, because of large sample size of *S pneumoniae* and scattered in different hospitals, capsular serotyping was not performed currently. Second, there were 2 different detection methods for antibiotic susceptibility testing in 10 hospitals, which resulted in certain differences in drug sensitivity test results. These deficiencies need to be improved in the future monitoring process in order to obtain more accurate monitoring results.

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