Original Article

Prevalence and Antimicrobial Susceptibility of *Streptococcus pneumoniae* Isolated from Hospital in Thailand between 2016 and 2020

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Objective: To determine prevalence and antimicrobial susceptibility of *Streptococcus pneumoniae* at Taksin Hospital.

Materials and Methods: A retrospective descriptive study was conducted between January 2016 and December 2020. The bacterial susceptibility of isolates to clindamycin, erythromycin, trimethoprim-sulfamethoxazole, levofloxacin, and vancomycin were evaluated by the disk diffusion method. Bacterial susceptibility to penicillin and cefotaxime were evaluated for minimal inhibitory concentration (MIC) by a strip test (E-test).

Results: One hundred and nineteen patients were included, 65.55% male, and the age ranged from three months to 98 years. The median age of patients was 60 years with an interquartile range of 43 to 78 years. Unduplicated pneumococci from different patients were isolated from sputum (70.59%), blood (18.49%), and pus from ears and sinuses (5.04%). *S. pneumoniae* was demonstrated to be 100% susceptible to vancomycin and levofloxacin but less susceptible to clindamycin, erythromycin, and trimethoprim-sulfamethoxazole by disk diffusion method. Pneumococci exhibited total multiple drug resistance (MDR) at 31.94%. The predominant MDR pattern was clindamycin + erythromycin + trimethoprim-sulfamethoxazole (31.10%). The MIC range, MIC_{50}, and MIC_{90} of penicillin was 0.008 to 3.0, 0.25, and 2.0, and for cefotaxime, it was 0.008 to 1.0, 0.25, and 1.0 µg/mL, respectively. From an extra study to determine serotypes, *S. pneumoniae* isolated from blood or CSF (n=25) were randomly picked between 2007 and 2021 from Thai IBIS and Taksin Hospital. The three most common serotypes were 19F (20%), 6B (16%), and 6A (12%).

Conclusion: These results suggest the importance of monitoring the prevalence of pneumococci. The antibiogram of susceptibility helps provide guidelines for clinician to consider empirical treatment. An antibiogram is an overall profile of antimicrobial susceptibility testing results of pneumococci to a battery of antimicrobial drugs. Antibiograms are often used by clinicians to assess local susceptibility rates, as an aid in selecting empiric antibiotic therapy, and in monitoring resistance trends over time within an institution. Antibiograms can also be used to compare susceptibility rates across institutions and track resistance trends.

Keywords: *Streptococcus pneumoniae*; Pneumococci; Drug resistance

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Streptococcus pneumoniae is an important pathogen in humans and poses a serious threat to public health as it causes various illnesses and deaths each year globally[1,2]. It can cause a wide range of disease in children and adults, especially community-acquired pneumonia, invasive pneumococcal disease (IPD), meningitis, sinusitis, otitis media, bronchitis, and conjunctivitis[1,3]. Community-acquired pneumonia is the most common type of pneumococcal disease with 900,000 cases and 400,000 hospitalizations per year in the United States[4]. IPD refers to pneumococci that have already invaded normally sterile sites such as blood, cerebrospinal fluid, pericardial fluid, joint fluid, or pleural fluid. The U.S. Centers for Disease Control and Prevention has estimated the incidence of IPD to be 10.6/100,000 per year and noted it occurs more frequently in adults than children with bacteremia present in 20% of all cases[4]. For Latin America and the Caribbean, pneumococcal diseases cause 12,000 to 18,000 deaths with 4,000 from meningitis and 1,229

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from sepsis, and 327,000 cases of pneumonia per year in children below five[5]. Patterns of pneumococcal antimicrobial susceptibility may vary by countries, geographical locations, age of patients, and sites of infection. Until the late 1970s, all pneumococci were susceptible to commonly used antimicrobial agents[6]. Since then, pneumococcal drug resistance has been a major public health problem worldwide[7]. In recent years, a high incidence of pneumococcal infection in both children and adults in Thailand have been reported. It poses a serious threat to public health[8-10]. The widespread use of antimicrobial agents also facilitates changes in the pattern of drug resistance. In Malaysia, pneumococci have become resistant to erythromycin (42%), tetracycline (37%), and trimethoprim-sulfamethoxazole (24%)[11]. In southern Vietnam, 25 pneumococcal isolates from meningitis cases showed 100% resistance to penicillin, erythromycin, clindamycin, and tetracycline, as well as 92%, 48%, and 20% resistance to trimethoprim-sulfamethoxazole, ceftriaxone, and chloramphenicol, respectively[12]. In Ethiopia, 57 pneumococcal isolates demonstrated 100% resistance to penicillin, as well as 59.6%, 17.5%, 38.6%, 17.5%, and 24.6% resistance to erythromycin, clindamycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole, respectively. Multidrug resistance (MDR) or resistance to three or more classes of drugs, has been found in 33.3% of pneumococci, with the most common MDR pattern having co-resistance to penicillin, erythromycin, clindamycin, and tetracycline[13]. The SENTRY Antimicrobial Surveillance Program has monitored antimicrobial susceptibility of different human pathogens from various clinical specimens worldwide, including pneumococci between 1997 and 2016. A total of 65,993 pneumococcal isolated from North America, Europe, Asia-Pacific, and Latin America were tested. The results demonstrated that MDR was highest in Asia-Pacific with 49.8% overall, and lowest in Latin America with 10.8% overall[10]. In a Canadian report, MDR decreased from 8.5% in 2011 to 5.6% in 2015[14].

The aim of the present study was to evaluate the prevalence and rate of drug resistance of pneumococci isolated from patients at Taksin Hospital, a public tertiary care hospital with 500 beds in central Bangkok operated by the Bangkok Metropolitan Administration. The present study determined patterns of antibiogram profiles to provide guidance on the treatment of pneumococcal diseases for clinicians.

Materials and Methods

Bacterial isolates and identification procedure

One hundred nineteen isolates were collected from patients admitted at Taksin Hospital between January 2016 and December 2020. Only one isolate from each patient was collected to prevent duplicate of the bacterial strain. Pneumococccci were isolated from various specimens and identified based on colony morphology and confirmed by optochin and bile solubility tests[3]. If the specimen was sputum and contained more than 25 polymorphonucler cells and less than 25 squamous epithelial cells per low-power field at a 10×10 microscope magnification, it was accepted for culture[3]. All isolates were kept in a brain heart infusion broth, plus 20% glycerol (V/V) at –80°C until use[3,15].

Ethics approval

The present study was conducted after ethical approval from the Human Research Committee of Siam University was obtained with reference codes SIAMPY-IRB 2020/011.

Antimicrobial susceptibility testing

The bacterial susceptibility of the isolates to clindamycin (2 µg), erythromycin (15 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), levofloxacin (5 µg), and vancomycin (30 µg) were evaluated by the disk diffusion method as provided by the Clinical Laboratory Standards Institute (CLSI)[16]. The medium was Mueller Hinton agar, supplemented with 5% sheep blood. The inoculum was prepared by the pneumococcal colony suspension method in which colonies from an overnight culture of 18 to 20 hours on sheep blood agar plates were used. The turbidity of inoculum was adjusted to the 0.5 McFarland standard. The inoculated MH agar was incubated at 35°C in 5% CO_2 for 20 to 24 hours. *S. pneumoniae* ATCC 49619 was used as a control strain. The criteria for interpretation as susceptible, intermediate, and resistant was carried out according to the CLSI's recommendation[16]. An isolate was assigned as MDR if it was resistant to three or more classes of drugs[17].

Bacterial susceptibility of isolates to penicillin and cefotaxime were evaluated for minimal inhibitory concentration (MIC) by a strip test (E-test, BioMerieux, Durham, NC, USA) in which a strip was placed on the surface of Mueller Hinton agar, supplemented with 5% sheep blood according to the manufacturer's guidelines. *S. pneumoniae* ATCC 49619 was also used as a control strain. The MIC of penicillin and cefotaxime was interpreted

as susceptible, intermediate, and resistant according to CLSI's recommendation[16]. The new criteria for penicillin was used by clinicians to consider whether the route of penicillin administration was parenteral or oral and whether pneumococcal meningitis was present in a patient. According to the former criteria, pneumococcal isolates from patients with different diseases and received either oral or parenteral penicillin administration, would be interpreted as susceptible, intermediate, and resistant when MICs were 0.06 or less, 0.12 to 1, and 2 or more µg/mL, respectively[18]. Meanwhile for the new criteria[16], there were three categories. The first category was isolate from meningitis patient with parenteral penicillin treatment as susceptible and resistant if MICs was 0.06 or less and 0.12 or more µg/mL, respectively. The second category was isolate from non-meningitis patient with parenteral penicillin treatment as susceptible, intermediate, and resistant if MICs were 2 or less, 4, and 8 or more µg/mL, respectively. The third category was isolate from non-meningitis patient with oral penicillin treatment as susceptible, intermediate, and resistant if MICs were 0.06 or less, 0.12 to 1, and 2 or more µg/mL, respectively[16].

For cefotaxime, which is available in injection form only, the new criteria consider whether a patient has meningitis or not. There were two categories. The first category was isolate from patient with meningitis as susceptible, intermediate, and resistant if MICs were 0.5 or less, 1, and 2 or more µg/mL, respectively. The second category was isolate from non-meningitis patient as susceptible, intermediate, and resistant if MICs were 1 or less, 2, and 4 or more µg/mL, respectively[16,19].

Serotype determination

The authors conducted a small study concerning serotypes of *S. pneumoniae*. Therefore, the authors performed an extra study to determine serotypes. *S. pneumoniae* isolated from blood or CSF (n=25) were randomly picked between 2007 and 2021. There were 24 patients aged 5 years or younger from the Invasive Bacterial Infection Surveillance of Thailand, National Institute of Health (Thai IBIS), and one patient aged 68 years from Taksin Hospital. Capsular serotypes of 25 randomly selected pneumococcal isolates from 25 IPD cases were confirmed with a well-established sequential multiplex of polymerase chain reaction (PCR) as described by Pai et al[20] and by using specific primers and PCR condition as previously described[20]. There were two types of pneumococcal vaccines available in Thailand, the 13-serotypes and the 23-serotypes vaccines. Therefore, the isolates that were not one of the 13-serotypes and 23-serotypes were labeled as non-vaccine serotype.

Table 1. Prevalence of *S. pneumoniae* according to patient age groups and specimens (n=119)

	No. of patients (%)
Age (year)	
≤5	6 (5.04)
6 to 10	4 (3.36)
11 to 20	3 (2.52)
21 to 30	6 (5.04)
31 to 40	7 (5.88)
41 to 50	10 (8.40)
51 to 60	23 (19.33)
61 to 70	13 (10.92)
71 to 80	27 (22.70)
81 to 90	17 (14.29)
≥90	3 (2.52)
Specimens	
Sputum	84 (70.59)
Blood	22 (18.49)
Pus from ears and sinuses	6 (5.04)
Urine	2 (1.68)
Throat swab	2 (1.68)
Pus from eye	1 (0.84)
Pericardial fluid	1 (0.84)
Bronchial wash	1 (0.84)

Data analysis

Data were entered and analyzed with IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA) for descriptive analyses. Categorical variables i.e., ages of patients, sources of clinical specimens and pneumococcal serotypes were expressed as frequency and percentages. The ages of patients were also expressed as range and median (interquartile range, IQR).

Results

In the present study, there were 28, 35, 14, 25, and 17 isolates in 2016, 2017, 2018, 2019, and 2020, respectively. Seventy-eight patients (65.55%) were male and 41 (34.45%) were female. The male to female gender ratio was 1.9 to 1. The age ranged from three months to 98 years old. The median age of patients was 60 years with an IQR of 43 to 78 years. Pneumococci came (69.76%) from patients aged over 50 years (Table 1). The sources of clinical specimens

are also shown in Table 1. The three most common clinical specimens were sputum (70.59%), blood (18.49%), and pus (5.04%). *S. pneumoniae* isolated from quantitative urine culture ranged 10^4 to 10^5 or more CFU/mL.

Antimicrobial susceptibility testing

For disk diffusion testing (Table 2), pneumococci were susceptible to clindamycin, erythromycin, trimethoprim-sulfamethoxazole at a range of 43.70% to 60.50%. They demonstrated susceptibility (100%) to levofloxacin and vancomycin. From antibiogram profiles (Table 3), pneumococci exhibited total MDR phenotypes (31.94%). This percentage of MDR came from 31.10% plus 0.84%, which equals to 31.94%. The predominant pattern was clindamycin resistance plus erythromycin resistance plus trimethoprim-sulfamethoxazole resistance (31.10%).

The result of determination of the MIC in µg/mL of pneumococci by the E-test method is shown in Table 4. The present study showed the penicillin MIC range, MIC_{50}, and MIC_{90} value were 0.008 to 3.00, 0.25, and 2.0 µg/mL, respectively. Cefotaxime MIC range, MIC_{50}, and MIC_{90} value were 0.008 to 1.00, 0.25, and 1.0 µg/mL, respectively. The authors were interested in learning the various susceptibility rates that were interpreted as susceptible according to the new criteria (CLSI, 2019)[16]. The penicillin susceptibility rates of pneumococci were 98.85% according to the non-meningitis criteria, 28.74% according to the meningitis criteria, and 28.74% according to non-sterile site criteria. Likewise, 100% and 72.73% of pneumococci were susceptible to cefotaxime using the non-meningitis and meningitis criteria, respectively (Table 5).

Serotype determination

There were 24 non-duplicate isolates from Thai IBIS and one isolate from Taksin Hospital from normally sterile sites with 20 from blood and five from cerebrospinal fluid. The three most common serotypes, accounting for 48% of all isolates were 19F (20%), 6B (16%), and 6A (12%) (Table 6). The PCV13 and PV23 serotype coverage rates was 72% and 80%, respectively. The serotypes found in PCV13 were type 3, 6A, 6B, 14, 19F, and 23. The serotypes found in PV23 were also found in PCV13, plus serotypes 8 and 10. The 13-PCV and 23-PPV coverage rates was 72% (18/25) and 80% (20/25), respectively. The 13-PCV coverage of 72% means that vaccine can prevent 72% of people from getting IPD. The non-vaccine serotypes were found in 20%

Table 2. Antimicrobial susceptibility of *S. pneumoniae* by the disk diffusion method (n=119)

Antimicrobial agents	No. of isolates (%)		
	Susceptible	Intermediate	Resistant
Clindamycin	72 (60.50)	3 (2.52)	44 (36.98)
Erythromycin	53 (44.54)	2 (1.68)	64 (53.78)
SXT*	52 (43.70)	3 (2.52)	64 (53.78)
Levofloxacin	119 (100)	-	-
Vancomycin	119 (100)	-	-

SXT=trimethoprim/sulfamethoxazole

Table 3. Antibiogram profiles of *S. pneumoniae* (n=119)

Antimicrobial agents#			Number resistant (%)
CL	ER	SXT	37 (31.10)
CL*	ER	SXT	1 (0.84)
CL	ER		6 (5.04)
CL*	ER*		1 (0.84)
CL			1 (0.84)
CL*			1 (0.84)
ER	SXT		14 (11.76)
ER	SXT*		2 (1.68)
ER			4 (3.36)
ER*			1 (0.84)
SXT			12 (10.09)
SXT*			1 (0.84)

CL=clindamycin; ER=erythromycin; SXT=trimethoprim/sulfamethoxazole

Multidrug resistance: ≥3 classes of drugs, * Intermediate resistance

Table 4. Minimal inhibitory concentration (MIC) in µg/mL of *S. pneumoniae* by E-test

Antimicrobial agents	MIC range	MIC_{50}	MIC_{90}
Penicillin	0.008 to 3.0	0.25	2.0
Cefotaxime	0.008 to 1.0	0.25	1.0

MIC_{50}, MIC_{90} are required to inhibit the growth of 50% and 90% of pneumococci, respectively

Table 5. Antimicrobial susceptibility by using MICs of penicillin and cefotaxime

Antimicrobial agents	% Susceptible	% Intermediate	% Resistant
Penicillin parenteral (nonmeningitis)	98.85	1.15	-
Penicillin parenteral (meningitis)	28.74	-	71.26
Penicillin (oral penicillin V)	28.74	60.92	10.34
Cefotaxime (nonmeningitis)	100	-	-
Cefotaxime (meningitis)	72.73	27.27	-

Table 6. Serotypes of *S. pneumoniae*

Serotypes	No. of patients (%)
3 PCV-13	2 (8)
6A PCV-13	3 (12)
6B PCV-13	4 (16)
8 PPV-23	1 (4)
10 PPV-23	1 (4)
14 PCV-13	2 (8)
15A/F nonvaccine serotype	2 (8)
19F PCV-13	5 (20)
23 PCV-13	2 (8)
Other nonvaccine serotype	3 (12)
Total	25 (100)

PCV-13=13-valent pneumococcal conjugate vaccine; PPV-23=23-valent pneumococcal polysaccharide vaccine

of isolates of which 8% were serotype 15A/F.

Discussion

Most patients in the present study were adults. The study was similar to a report from the U.S. in 2019 that showed that most patients were aged 50 years or older and the range was from younger than 1 year to 85 years or older[20]. The SENTRY Antimicrobial Surveillance Program also reported that 67.7% of 65,993 pneumococcal isolates collected worldwide were from adults, whereas 25.4% were from children[10]. The authors found that males predominated, similar to other reports, although the reason is not clear[13,21,22]. The present study investigation confirms other studies in which pneumococci was mostly isolated from sputum[11]. In the study from Malaysia, the most frequent specimen from which pneumococci isolated was in sputum (40%), followed by blood (38%), eye (15%), pus (4%), and bronchial aspirate (2%)[11].

In the antimicrobial susceptibility test, the authors found that 36.98% of pneumococcal isolates were resistant to clindamycin and 53.78% resistant to erythromycin and trimethoprim-sulfamethoxazole (Table 3). However, the drug resistance percentages were lower than those reported from other countries. Of the 796 pneumococcal isolates from Sao Paulo state in Brazil, 99.6% were resistant to erythromycin and 49.4% resistant to trimethoprim-sulfamethoxazole[23]. In Taiwan, 68.2% were resistant to clindamycin, 86.4% resistant to erythromycin, and 40.9% resistant to trimethoprim-sulfamethoxazole[22]. According to the SENTRY Antimicrobial Surveillance Program, global data of pneumococci susceptibility was obtained from North America, Europe, Latin America, and Asia-Pacific. North America had 34,626 isolates from Canada and USA. Europe had 19,123 isolates from 23 nations that included Austria, Belarus, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, The Netherlands, Poland, Portugal, Romania, Russia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, and Ukraine. Latin America had 5,133 isolates from seven nations that included Argentina, Brazil, Chile, Colombia, Mexico, Uruguay, and Venezuela. Finally, Asia-Pacific had 7,111 isolates from 10 nations that included Australia, Hong Kong, Japan, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, and Thailand. Resistance to erythromycin increased in North America from 15.1% during the year 1997 to 1998 to 44.7% in 2011 to 2012 and then stabilized around 44% to 45% until 2015 to 2016. Likewise, an increase in erythromycin resistance was observed in Europe and Asia-Pacific until 2013 to 2014 with a resistance range of 30% to 50%, and then slightly decreased until 2015 to 2016 with a resistance of 25% to 45%[10].

The present study results showed that MDR was widespread, similar to the other reports from across the world[10,13]. Clindamycin, erythromycin, and trimethoprim-sulfamethoxazole are not effective drugs against pneumococci in vitro. The authors did not find any pneumococci that were resistant to vancomycin in the present study, which supports the idea that vancomycin resistance has not been described in pneumococci[10,12,22,23]. For levofloxacin, a Vietnamese study[12] found pneumococci that were 100% susceptible, which is similar to the present study results, whereas a CDC study found 99.8% susceptibility[21] and a Taiwanese study noted 92.7% susceptibility[22].

The authors did not collect clinical data of patients. Therefore, all 119 values of penicillin MIC and cefotaxime MIC were used for dividing the authors' pneumococcal isolates into two and three categories. If the authors applied the meningitis criteria only for isolates from the cerebrospinal fluid, it may have led to an underestimation of penicillin and cefotaxime resistance in cases of meningitis from blood. The previous criteria for susceptibility of pneumococci to penicillin indicated only one category with breakpoints of 0.06 or less µg/mL, 0.12 to 1 µg/mL, and 2 or more µg/mL for susceptibility, intermediate susceptibility, and resistance, respectively. The previous criteria were established by CLSI in the 1970s and used until 2007. The new criteria were established by

CLSI in January 2008 and have been followed until now. There are three categories according to the revised breakpoints as shown in Table 6 for meningitis, non-meningitis, and intravenous and oral administration[18,19]. Likewise, the revised cefotaxime MIC breakpoints of 0.5 or less, 1, and 2 or more µg/mL for susceptibility, intermediate susceptibility, and resistance, respectively, has been established by the CLSI for meningeal infections since 1994[23], and 1.0 or less, 2, and 4 or more µg/mL for meningeal infections since 2002[18]. The present study results were in agreement with other studies that the new criteria for penicillin and cefotaxime in meningitis increased the incidence of penicillin- and cefotaxime-resistant pneumococci causing meningitis[8,18,19].

Currently, there are at least 97 immunological different serotypes of pneumococci, each varies in polysaccharide structure of the capsule[25]. Pneumococcal virulence depends on the capsule whose mechanism of action is antiphagocytosis. The 13-valent pneumococcal-diphtheria CRM_{197} protein conjugate vaccine (PCV-13) is composed of the thirteen serotypes that are the most common causes of IPD in the U.S. and often are drug resistant in children, which are 1, 3, 4, 5, 7F, 6A, 6b, 9V, 14, 18C, 19A, 19F, and 23F. PCV-13 is effective against IPD, resulting from serotypes in the vaccine due to a property of serotype specific immunity. PCV-13 is recommended for infants, children and adults 50 years and older. The 23-valent pneumococcal polysaccharide vaccine (PPV-23) is composed of twenty-three serotypes, which are 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. PPV-23 is recommended for adults aged 65 or older. However, PPV-23 has a limitation in that cannot be used in children younger than two years because it has the poor immunogenic property[25]. In the present study, the authors demonstrated high percentages of 13-PCV (72%) and 23-PPV (80%) coverage rates. From serotyping of 25 isolates, 19F was the most common serotype (20%), similar to the Vietnamese study that also found 19F as the most common serotype (32%)[12]. Interestingly, serotype 15A/F, which was the non-vaccine serotype in the present study, was reported after PCV-13 implementation in Turkey[26]. At present, both 13-PCV and 23-PPV are available for use in Thailand. There were limitations to the present study. First, data on a small set of invasive pneumococcal isolates was presented for serotypes. Second, the authors could not collect clinical information concerning pneumococcal vaccination data of the patients.

Conclusion

The results from the present study suggest that penicillin, cefotaxime, levofloxacin, and vancomycin could be effective drugs in the treatment of non-meningitis IPD. For IPD treatment, which is meningitis IPD, cefotaxime, and vancomycin could be effective drugs. From an extra study to determine serotypes, *S. pneumoniae* isolated from blood or CSF (n=25) were randomly picked between 2007 and 2021. The three most common serotypes, accounting for 48% of all isolates were 19F (20%), 6B (16%), and 6A (12%). The present study data should support ongoing studies and increase surveillance of drug resistance, so that, further development of drug resistance is minimized. In addition, antibiogram profiles are needed to avoid ineffective empirical drug treatment.

What is already known on this topic?

S. pneumoniae, which is one of the most common causes of community-acquired pneumonia, can cause IPD, otitis media, and sinusitis. According to the previous studies, drug resistance is the problem worldwide. Therefore, further study of pneumococcal prevalence and drug resistance should be investigated, particularly among Thai patients.

What this study adds?

At Taksin Hospital, unduplicated *S. pneumoniae* from different 119 patients were isolated from sputum (70.59%), blood (18.49%), and pus from ears and sinuses (5.04%). This study demonstrated patterns of antibiogram profiles to provide guidance on the treatment and prevention of pneumococcal diseases for clinicians. *S. pneumoniae* exhibited MDR (31.94%) and the predominant resistance pattern was clindamycin plus erythromycin plus trimethoprim-sulfamethoxazole (31.10%).

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Conflicts of interest

All authors declare no personal or professional conflicts of interest, and no financial support.

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