

Antimicrobial susceptibility among *Streptococcus pneumoniae* and *Haemophilus influenzae* collected globally between 2015 and 2017 as part of the Tigecycline Evaluation and Surveillance Trial (TEST)

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Purpose: In order to understand the prevalence of *Streptococcus pneumoniae* and *Haemophilus influenzae* globally and provide the basis for rational use of antimicrobials in clinical settings, in vitro activity of tigecycline and comparative agents was evaluated against 3929 *S. pneumoniae* and 4043 *H. influenzae* isolates obtained from 150 centers globally between 2015 and 2017 as a part of the Tigecycline Evaluation and Surveillance Trial (TEST).

Methods: Broth microdilution methods were performed to determine the minimum inhibitory concentration (MIC) of the isolates according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI). The CLSI breakpoint was used to determine antimicrobial susceptibilities, except for that of tigecycline, for which the US Food and Drug Administration (FDA) breakpoints were used.

Results: More than 99% of *S. pneumoniae* isolates were susceptible to vancomycin (100%), linezolid (100%), tigecycline (99.9%), and levofloxacin (99.1%). Macrolides (erythromycin, azithromycin, and clarithromycin, 67.1–69.4% susceptibility globally) and penicillin (61.7% in globally) were the drugs with more resistance to *S. pneumoniae*. Penicillin-intermediate and -resistant isolates were found in 24.8% and 13.6% of *S. pneumoniae* isolates. *H. influenzae* was highly susceptible (>98.7%) to all antibiotics tested except for ampicillin, for which susceptibility was 76.1%. The number of drugs with the lowest susceptibility calculated in Asia were far more than other regions, with 61.5% (8 in 13 drugs) in *S. pneumoniae* and 70.0% (7 in 10 drugs) in *H. influenzae*, respectively.

Conclusions: Vancomycin, linezolid, tigecycline, and levofloxacin can be used as the first choice in the empirical therapy of infection disease caused by *S. pneumoniae*. But macrolides and penicillin should be used prudently in treatment of the infection caused by *S. pneumoniae*, as well as ampicillin treat the infection caused by *H. influenzae*. Asia was the region with the most severe resistance in *S. pneumoniae* and *H. influenzae*.

Keywords: *Streptococcus pneumoniae*, *Haemophilus influenzae*, antimicrobial susceptibility, tigecycline

Introduction

Streptococcus pneumoniae and *Haemophilus influenzae* are among the major cause of respiratory tract infections, including community-acquired pneumonia (CAP) and acute episodes of chronic obstructive pulmonary disease (COPD), which account for significant mortality.^{1,2,3,4} In Germany, the incidence of CAP was 0.97% and mortality was 12.9%.² Lower respiratory infections were the leading cause of death among children younger

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than 5 years old, accounting for mortality of 11.8%.³ Both pathogens also caused sepsis, meningitis, otitis media, and osteoarthritis.^{5,6,7}

In many countries, antimicrobial therapeutic choices for respiratory tract infections are usually empirical because the limited availability and delay of laboratory identification and antibiotic susceptibility testing result. With the increasing prevalence of resistant organism, the importance of surveillance studies is widely shown.

The Tigecycline Evaluation and Surveillance Trial (TEST) is a global surveillance study focused on monitoring antimicrobial resistance worldwide, which has continued for several years and made a great contribution to the prevalence of bacterial resistance, providing important evidence for empirical therapeutic use of antimicrobial agents in different infectious diseases. This report summarizes data of *S. pneumoniae* and *H. influenzae*, the most common pathogens in respiratory tract infections, from TEST between 2015 and 2017. The resistance difference in diverse regions of two bacteria has been compared and the principles of antibiotic use in related diseases has been established.

Materials and methods

Isolate collection

Each participating center was required to contribute at least 135 gram-negative and 65 gram-positive organisms in every study year. Fifteen *S. pneumoniae* and 15 *H. influenzae* were included in that total. All isolates had to be collected from patients with infection and the probable causative organism identified using specific laboratory criteria. Only one isolate per patient was accepted. Banked, stored, or duplicate isolates were not accepted.⁸ All strains were isolated from routine hospital laboratory procedure. They were not specifically obtained for this research.

International Health Management Associates (IHMA, Schaumburg, USA), the reference laboratory, was responsible for the coordination of organism collection, transport, confirmation of identity, storage, and management of the database. Between 10% and 15% of isolates were tested randomly each year by IHMA to verify isolate identity and minimum inhibitory concentration (MIC).

Antimicrobial susceptibility testing

MIC testing was implemented in all centers using broth microdilution methods⁹ and MicroScan®panels (Dade MicroscanInc, West Sacramento, CA, USA). For

S. pneumoniae, the panel included the following antimicrobial agents: amoxicillin-clavulanate, ampicillin, azithromycin, ceftriaxone, clarithromycin, clindamycin, erythromycin, levofloxacin, linezolid, meropenem, minocycline, penicillin, piperacillin-tazobactam, tigecycline, and vancomycin. The panel for *H. influenzae* testing included amikacin, amoxicillin-clavulanate, ampicillin, cefepime, ceftriaxone, levofloxacin, meropenem, minocycline, piperacillin-tazobactam, and tigecycline.

Quality control was performed using *S. pneumoniae* ATCC49619, *H. influenzae* ATCC49247, and *H. influenzae* ATCC49766 each testing day.

Antimicrobial resistance determination

Breakpoints of the Clinical and Laboratory Standards Institute (CLSI)¹⁰ were used to determine the susceptibility of antimicrobial agents, with the exception of tigecycline, for which the US Food and Drug Administration (FDA) breakpoints were used.¹¹ The penicillin oral breakpoints (susceptible ≤ 0.06 mg/L, intermediate 0.125-1, resistant ≥ 2 mg/L) were used for *S. pneumoniae* according to a previous study.⁸ β -lactamase produced by *H. influenzae* was detected using the preferred local methodology at each center.

Statistical analysis

SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. A comparison of susceptibility rates was conducted using Pearson chi-squared test or continuity-adjusted chi-squared test.

Results

From 2015 to 2017, a total of 3,929 *S. pneumoniae* and 4,043 *H. influenzae* isolates were obtained from 150 centers in 47 countries (Table 1). Europe was the main contributor with 62.2% (2442/3929) in *S. pneumoniae* and 62.6% (2529/4043) in *H. influenzae*, followed by North America (19.7% and 18.4%, respectively), Asia (7.8% and 11.6%, respectively), and Latin America (6.2% and 3.8%, respectively). The Middle East and Africa only contributed 69–92 isolates from 6 centers of 5 countries (Table 1).

From all patients, the proportion of subjects of 61–80 years of age was 33.0% and 31.5% in *S. pneumoniae* and *H. influenzae*, respectively, following by 0–20 and 41–60 year-old patients with the proportion of 21.2–28.0%. Sputum and blood were the main specimen source in *S. pneumoniae*, with proportions of 27.7% and 27.5%, respectively. But in *H. influenzae*, sputum (42.0%) was the

Table 1 Number of isolates (centers) contributing *S. pneumoniae* or *H. influenzae* between 2015 and 2017

Region ^a	<i>S. pneumoniae</i>				<i>H. influenzae</i>			
	2015	2016	2017	Total	2015	2016	2017	Total
Africa	25 (2)	22 (2)	22 (2)	69 (3)	25 (2)	26 (2)	21 (2)	72 (3)
Asia	86 (8)	119 (10)	103 (9)	308 (13)	167 (17)	201 (16)	101 (8)	469 (24)
Europe	795 (70)	860 (72)	788 (73)	2,443 (91)	776 (65)	920 (71)	833 (69)	2,529 (87)
Latin America	85 (13)	89 (12)	71 (12)	245 (14)	52 (8)	58 (7)	45 (6)	155 (8)
Middle East	34 (3)	32 (3)	26 (2)	92 (3)	29 (2)	31 (3)	15 (2)	75 (3)
North America	325 (26)	254 (18)	193 (14)	772 (26)	298 (24)	259 (18)	186 (15)	743 (25)
Global	1,350 (122)	1,376 (117)	1,203 (112)	3,929 (150)	1,347 (118)	1,495 (117)	1,201 (102)	4,043 (150)

Notes: ^aAfrica, Morocco, South Africa; Asia, China, Hong Kong, India, Japan, South Korea, Malaysia, Pakistan, Philippines, Singapore, Taiwan, Thailand, Vietnam; Europe, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Serbia, Spain, Switzerland, UK; Latin America, Argentina, Brazil, Chile, Colombia, Mexico, Panama, Venezuela; Middle East, Jordan, Kuwait, Saudi Arabia; North America, Canada, United States.

major source followed by trachea/lung (27.2%) samples including specimens from trachea, bronchials or lungs, such as bronchoalveolar lavage fluid (BALF) and bronchial brush. There were 3.3% *S. pneumoniae* and 0.5% *H. influenzae* isolated from cerebrospinal fluid (Table 2).

S. pneumoniae

More than 99% isolates of *S. pneumoniae* were susceptible to vancomycin (100%), linezolid (100%), tigecycline (99.9%), and levofloxacin (99.1%) (Table 3). Four tigecycline nonsusceptibility isolates, MIC 0.25–2 µg/mL, from Asia, Canada, and Florida, USA. There are 36 levofloxacin

nonsusceptible *S. pneumoniae* isolates (11 intermediate, 25 resistance) from diverse regions. Nineteen isolates (52.8%) from ≥61 -year-old patients, 15 isolates (41.7%) from 30 to 60-year-olds and 2 isolates (5.6%) from patients <18 years.

Amoxicillin-clavulanate susceptibility were above 92% in most regions except for Africa and Asia, which showed 82.6% and 88.0%, respectively. Ceftriaxone susceptibility was observed in 97.8% of isolates globally and more than 96.7% of isolates in many regions other than Africa (92.8%) and Asia (91.6%). Meropenem susceptibility was below 60.9% in Africa, Asia, and the Middle East, but above 81.6% in Europe, North America, and Latin America (Table 3).

Minocycline susceptibility was 74.5% globally, over 79.2% in Europe and North America, but only 30.8% in Asia (Table 3).

With the exception of Latin America, for which susceptibility of azithromycin (33.1%) was lower than that of clarithromycin (66.8%) and erythromycin (66.4%), similar susceptibility was observed in three macrolides (azithromycin, clarithromycin, and erythromycin) in each region. But differences were observed between regions. The isolates with the most susceptibility were obtained in Europe (78.5–78.7%), followed by Latin America (66.4–66.8%, except for azithromycin), and North America (61.2–61.6%). The susceptibility of lincosamide clindamycin (45.9–85.2%) was 4.9–37.3% higher than that of erythromycin (31.4–78.6%) in each region and globally (Table 3).

The susceptibility of penicillin (61.7%) to *S. pneumoniae* globally was the lowest one in all antibiotics in the TEST panel. Africa, Asia, and the Middle East were the sources of isolates with 43.5%, 29.9%, and 20.7% susceptibility, respectively, which were lower than those in Europe (67.6%), North America (65.2%) and Latin America (52.2%).

Table 2 Age distribution and specimen source for culture of *S. pneumoniae* and *H. influenzae* isolates between 2015 and 2017

	<i>S. pneumoniae</i> (n= 3,929)		<i>H. influenzae</i> (n= 4,043)	
	N	%	N	%
Patient age				
0–20 years	861	21.9	1,130	28.0
21–40 years	406	10.3	463	11.5
41–60 years	962	24.5	858	21.2
61–80 years	1,297	33.0	1,273	31.5
≥81 years	370	9.4	304	7.5
Unknown	33	0.8	15	0.4
Specimen source ^a				
Sputum	1,089	27.7	1,698	42.0
Blood	1,080	27.5	170	4.3
Trachea/lungs ^a	731	18.6	1,098	27.2
Nose/sinuses ^b	190	4.8	194	4.9
Cerebrospinal fluid	130	3.3	20	0.5
Other	709	18.1	863	21.4

Notes: ^aTrachea/lungs includes specimens from trachea, bronchials or lungs, such as bronchoalveolar lavage fluid (BALF) and bronchial brush. ^bNose/sinuses includes specimens from nose and sinuses.

Table 3 Antimicrobial susceptibility (MIC₉₀, mg/L, and % susceptibility) among *S. pneumoniae*, PISP, and PRSP isolates in various regions and global between 2015 and 2017 from TEST study

	Africa		Asia		Europe		Latin America		Middle East		North America		Global	
	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s
<i>S. pneumoniae</i>	N=69		N=308		N=2443		N=245		N=92		N=772		N=3,929	
Amoxicillin-clavulanate	4	82.6	4	88.0	1	95.7	2	92.7	2	93.5	1	96.5	2	94.8
Ampicillin ^a	4		8		2		2		4		2		2	
Azithromycin	128	50.7	128	32.0	128	78.5	512	33.1	128	35.2	64	61.2	128	67.1
Ceftriaxone	1	92.8	1	91.6	0.5	98.4	1	96.7	1	98.9	0.5	98.8	1	97.8
Clarithromycin	128	50.7	128	31.7	128	78.7	128	66.8	128	36.3	128	61.6	128	69.4
Clindamycin	128	69.6	128	45.9	128	83.5	128	80.1	128	71.4	128	85.2	128	80.1
Erythromycin	128	50.7	128	31.4	128	78.6	128	66.4	128	34.1	32	61.3	128	69.2
Levofloxacin	1	98.6	1	97.1	1	99.4	1	98.8	1	98.9	1	99.2	1	99.1
Linezolid	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0
Meropenem	1	60.9	1	59.7	0.5	86.4	0.5	81.6	1	55.4	1	84.2	1	82.4
Minocycline	8	68.1	16	30.8	4	79.2	8	70.6	8	52.2	4	81.6	8	74.5
Penicillin	4	43.5	4	29.9	2	67.6	2	52.2	2	20.7	2	65.2	2	61.7
Piperacillin/tazobactam ^a	4		4		2		2		4		2		2	
Tigecycline	0.03	100.0	0.03	99.4	0.03	100.0	0.03	100.0	0.03	100.0	0.03	99.7	0.03	99.9
Vancomycin	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0
PISP	N=13 (18.8%, 13/69)		N=115 (37.3%, 115/308)		N=529 (21.7%, 529/2443)		N=85 (34.7%, 85/245)		N=51 (55.4%, 51/92)		N=180 (23.3%, 180/772)		N=973 (24.8%, 973/3929)	
Amoxicillin-clavulanate	0.25	100.0	1	100.0	1	98.9	1	100.0	1	100.0	1	100.0	1	99.4
Azithromycin	16	53.9	128	24.6	128	63.0	512	31.8	128	28.0	64	44.0	128	50.4
Ceftriaxone	0.25	100.0	0.5	98.3	0.5	98.9	0.5	97.7	0.5	100.0	0.5	100.0	0.5	99.0
Clarithromycin	8	53.9	128	23.6	128	63.2	128	46.4	128	30.0	128	44.6	128	51.9
Clindamycin	0.06	92.3	128	40.0	128	69.5	128	69.1	128	74.0	128	70.3	128	66.7
Erythromycin	8	53.9	128	24.6	128	63.2	128	46.4	128	26.0	128	44.0	128	51.7
Levofloxacin	1	100.0	2	95.7	1	99.1	1	98.8	1	100.0	1	99.4	1	98.8
Linezolid	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0
Meropenem	0.25	92.3	0.5	77.4	0.5	84.5	0.5	83.5	0.5	62.8	0.5	80.6	0.5	81.8

(Continued)

Table 3 (Continued).

	Africa		Asia		Europe		Latin America		Middle East		North America		Global	
	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s
Minocycline	4	84.6	16	20.0	8	65.4	16	60.0	4	56.9	16	64.4	8	59.2
Tigecycline	0.03	100.0	0.03	98.3	0.03	100.0	0.03	100.0	0.03	100.0	0.03	100.0	0.03	99.8
Vancomycin	0.25	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.5	100.0
PRSP	N=26 (37.7%, 26/69)		N=101 (32.8%, 101/308)		N=263 (10.8%, 263/2,443)		N=32 (13.1%, 32/245)		N=22 (23.9%, 22/92)		N=89 (11.5%, 89/772)		N=533 (13.6%, 533/3,929)	
Amoxicillin-clavulanate	8	53.9	8	63.4	8	62.7	8	43.8	4	72.7	8	69.7	8	62.9
Azithromycin	128	7.7	128	5.9	128	39.7	512	6.3	128	18.2	128	14.6	128	24.6
Ceftriaxone	4	80.8	2	76.2	2	87.3	2	81.3	1	95.5	2	89.9	2	85.4
Clarithromycin	128	7.7	128	5.9	128	39.7	128	19.4	128	18.2	128	14.6	128	25.4
Clindamycin	128	23.1	128	23.8	128	53.4	128	35.5	128	50.0	128	61.8	128	46.5
Erythromycin	128	7.7	128	4.0	128	39.7	128	19.4	128	18.2	128	14.6	128	25.1
Levofloxacin	1	96.2	2	97.0	1	97.3	1	96.9	1	100.0	1	98.9	1	97.6
Linezolid	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0	1	100.0
Meropenem	2	0.0	1	3.0	2	4.9	2	3.1	1	0.0	2	2.3	2	3.6
Minocycline	16	30.8	8	7.9	8	51.3	8	28.1	8	36.4	8	56.2	8	40.9
Tigecycline	0.03	100.0	0.03	100.0	0.03	100.0	0.03	100.0	0.03	100.0	0.03	100.0	0.03	100.0
Vancomycin	0.25	100.0	0.5	100.0	0.5	100.0	0.5	100.0	0.25	100.0	0.5	100.0	0.5	100.0

Notes: ^aNo breakpoints available.

Abbreviations: PRSP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; MIC₉₀, MIC required to inhibit 90% of isolates; %s, percentage of isolates that are susceptible; TEST, Tigecycline Evaluation and Surveillance Trial.

In total, 973 (24.7%) and 533 (13.6%) isolates of *S. pneumoniae* showed intermediate and resistance to penicillin—penicillin-intermediate *S. pneumoniae* (PISP) and penicillin-resistant *S. pneumoniae* (PRSP), respectively. The susceptibility of macrolides, β -lactams, clindamycin and minocycline were strongly influenced by penicillin nonsusceptibility among *S. pneumoniae*. The susceptibility of PISP isolates to macrolides, minocycline, clindamycin and meropenem lower than PSSP (penicillin-susceptible *S. pneumoniae*) isolates with the decrease of susceptibility of 32.9–34.4%, 28.9%, 26.3% and 18.2% respectability. Susceptibility was reduced by 96.4% in meropenem, about 60% in macrolides among PRSP. Statistical analysis showed significant difference in all drugs between PSSP and PISP or between PISP and PRSP although only 0.6% and 1% reduction in Amoxclav and ceftriaxone compared PSSP to PISP ($P=0.003$, $P<0.0001$ respectively) (Figure 1).

Susceptibility of eight drugs (61.5%, 8/13) in Asia, two drugs (15.4%, 2/13) in the Middle East, and one drug (7.8%,1/13) in Africa were the lowest sensitive drugs in six regions in 13 antibiotics with breakpoint.

H. influenzae

H. influenzae isolates were highly susceptible (>98.7%) to all antibiotics in the TEST panel except for ampicillin, for which susceptibility ranged from 57.6% in Asia to 86.1% in Africa (Table 4).

In total, 877 (21.7%) β -lactamase-positive *H. influenzae* and 110 (2.7%) BLNAR (β -lactamase negative, ampicillin-

intermediate or resistant) isolates were reported between 2015 and 2017. The highest prevalence of β -lactamase-positive *H. influenzae* was observed in Asia (37.3%) and the North America (28.7%) (Table 4). Susceptibility of β -lactamase-positive *H. influenzae* isolates to antibiotics in the TEST panel were higher than 97%, except for amoxicillin-clavulanate in Asia, which showed 89.1% susceptibility.

Asia was the region with the highest prevalence of BLNAR isolates (8.3%), with 1.1–2.8% prevalence in other regions. Susceptibility was calculated only for isolates from Asia, Europe, and globally because there were inadequate (<10) isolates from other regions. The susceptibility of BLNAR isolates over 93% to all antibiotics except for ampicillin (Table 4).

Susceptibility of seven drugs (70.0%, 7/10) in Asia, one drug (10.0%,1/10) in Africa were the lowest sensitive drugs in six regions in 10 antibiotics with breakpoint.

Discussion

Europe and North America were the two largest contributors of *S. pneumoniae* and *H. influenzae* between 2015 and 2017, representing 81.8% and 80.9% of the total samples, respectively. The data may be could not reflect the truth of Africa and the Middle East because only 69–92 isolates were collected in these regions. We should analysis the results of our study combined with other investigations.

In this research, about one third of isolates in *S. pneumoniae* and *H. influenzae* were sourced from 61–80-year-old patients, followed by 0–20 and 41–60-year-olds, very similar to the investigation of Tian et al.¹² About one half of *S. pneumoniae* from lower respiratory

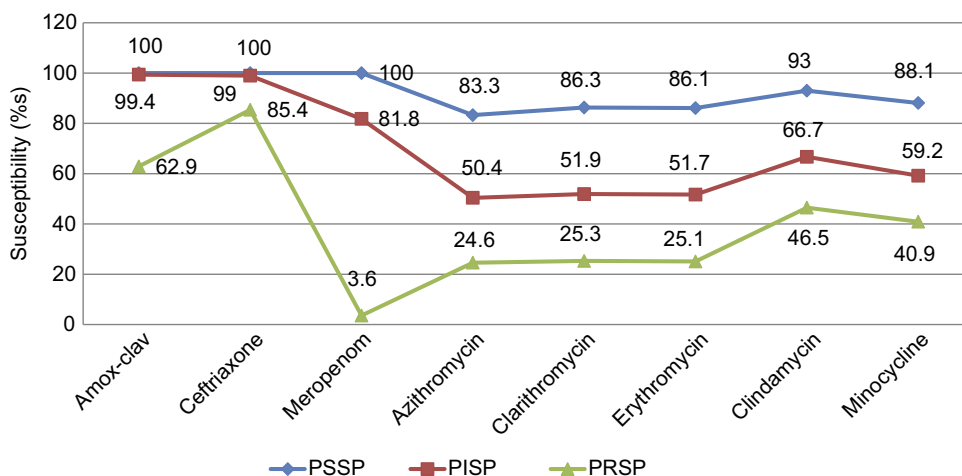


Figure 1 The susceptibility of β -lactams, macrolides and minocycline to PSSP, PISP and PRSP (%) globally between 2015 and 2017 from the TEST study. **Abbreviations:** Amox-clav, amoxicillin-clavulanate; PSSP, penicillin-susceptible *S. pneumoniae*; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; TEST, Tigecycline Evaluation and Surveillance Trial.

Table 4 Antimicrobial susceptibility (MIC₉₀, mg/L and % susceptibility) among *H. influenzae*, β -lactamase-positive *H. influenzae*, and BLNAR *H. influenzae* in various regions and global between 2015 and 2017 from TEST study

	Africa		Asia		Europe		Latin America		Middle East		North America		Global	
	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s
<i>H. influenzae</i>	N=72		N=469		N=2,529		N=155		N=75		N=743		N=4,043	
Amikacina	8		8		8		8		8		8		8	
Amoxicillin-clavulanate	1	100.0	4	95.3	1	99.8	2	100.0	2	100.0	2	99.9	2	99.3
Ampicillin	2	86.1	64	57.6	16	80.7	32	81.3	64	73.3	32	70.4	32	76.1
Cefepime	0.5	100.0	2	98.3	0.5	99.5	0.5	100.0	0.5	100.0	0.5	99.6	0.5	99.4
Ceftazidime	1	100.0	1	98.5	1	98.5	1	100.0	1	98.7	1	99.5	1	98.7
Ceftriaxone	0.06	100.0	0.25	100.0	0.06	100.0	0.06	100.0	0.06	100.0	0.06	100.0	0.06	100.0
Levofloxacin	0.015	100.0	0.5	96.8	0.03	99.3	0.015	100.0	0.5	98.7	0.03	100.0	0.03	99.1
Meropenem	0.12	100.0	0.5	99.6	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	99.9
Minocycline	1	98.6	1	98.9	1	99.3	1	100.0	1	100.0	2	98.8	1	99.2
Piperacillin/tazobactam	0.06	100.0	0.06	99.8	0.06	99.8	0.06	100.0	0.06	100.0	0.06	100.0	0.06	99.9
Tigecycline	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0
BL-Pos <i>H. influenzae</i>	N=8 (11.1%, 8/72)		N=175 (37.3%, 175/469)		N=436 (17.2%, 436/2,529)		N=27 (17.4%, 27/155)		N=18 (24.0%, 18/75)		N=213 (28.7%, 213/743)		N=877 (21.7%, 877/4043)	
Amoxicillin-clavulanate			8	89.1	2	99.1	4	100.0	2	100.0	2	99.5	2	97.3
Cefepime			2	97.7	0.5	99.3	0.5	100.0	0.5	100.0	0.5	100.0	0.5	99.2
Ceftazidime			1	98.3	1	98.2	1	100.0	1	100.0	1	100.0	1	98.8
Ceftriaxone			0.25	100.0	0.06	100.0	0.06	100.0	0.12	100.0	0.06	100.0	0.06	100.0
Levofloxacin			0.25	97.1	0.03	100.0	0.015	100.0	0.12	100.0	0.03	100.0	0.03	99.4
Meropenem			0.5	99.4	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	99.9
Minocycline			1	98.3	1	99.1	1	100.0	1	100.0	2	99.1	1	98.9
Piperacillin/tazobactam			0.06	100.0	0.06	100.0	0.06	100.0	0.06	100.0	0.06	100.0	0.06	100.0
Tigecycline			0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0	0.25	100.0
BLNAR	N=2 (2.8%, 2/72)		N=39 (8.3%, 39/469)		N=57 (2.3%, 57/2529)		N=2 (1.3%, 2/155)		N=2 (2.7%, 2/75)		N=8 (1.1%, 8/743)		N=110 (2.7%, 110/4043)	
Amoxicillin-clavulanate			4	97.4	4	100.0							4	99.1
Cefepime			2	94.9	2	93.0							2	94.6
Ceftazidime			1	100.0	2	94.7							2	97.3
Ceftriaxone			0.25	100.0	0.5	100.0							0.25	100.0
Levofloxacin			0.03	97.4	0.12	100.0							0.12	99.1
Meropenem			0.5	100.0	0.5	98.3							0.5	99.1

(Continued)

Table 4 (Continued).

	Africa		Asia		Europe		Latin America		Middle East		North America		Global	
	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s	MIC ₉₀	%s
Minocycline			1	100.0	1	94.7							2	97.3
Piperacillin/tazobactam			0.12	100.0	0.25	100.0							0.25	100.0
Tigecycline			0.25	100.0	0.12	100.0							0.25	100.0

Notes: BL-Pos *H. influenzae* and BLNAR isolates are not detailed here when N<10 in a region (Africa, N=8 in BL-Pos *H. influenzae* and Africa, N=2; Latin America, N=2; Middle East, N=2; North America, N=8 in BLNAR). *No breakpoints available.

Abbreviations: BLNAR includes both β -lactamase negative, ampicillin-resistant, and β -lactamase-negative, ampicillin-intermediate isolates. MIC₉₀, minimum inhibitory concentration required to inhibit 90% of isolates; %s, percentage of isolates that are susceptible; N/A, no data; TEST, Tigecycline Evaluation and Surveillance Trial.

tract (sputum and trachea/lungs), and one quarter from blood indicated the common infection site of *S. pneumoniae*. The familiar relationship of *H. influenzae* with infection of respiratory tract reflected through two thirds of *H. influenzae* sourced from sputum and trachea/lungs. Compared with *H. influenzae*, more infections of the central nervous system were caused by *S. pneumoniae*.

As the most susceptible antibiotics against *S. pneumoniae*, vancomycin, linezolid, tigecycline, and levofloxacin must play an important role in empirical therapy of clinical infection disease caused by *S. pneumoniae*. We should pay attention to four nonsusceptible isolates to tigecycline in our study. There is no report about the resistant mechanism of *S. pneumoniae* collected from clinical disease against tigecycline. Cattoir et al¹³ analysis of five isolates of *Enterococcus faecium* which tigecycline nonsusceptible (three in vitro mutants and two clinical isolates). One amino acid substitution in RpsJ protein(S10 ribosomal protein) caused by four modifications was regarded as the main reason of increasing MIC of tigecycline in *E. faecium*. Lupien et al¹⁴ detected the resistance mutant isolates of *S. pneumoniae* against tigecycline induced in the laboratory. They found the resistance of tigecycline to gram-positive coccus correlated with ribosome constituents, such as ribosomal protein, 16S rRNA and rRNA methyltransferase, different from resistance to gram-negative bacilli mainly related with the efflux. There were 36 *S. pneumoniae* exhibited levofloxacin-nonsusceptible isolates in this study. Research of Schmitz et al¹⁵ verified that levofloxacin-resistant *S. pneumoniae* associated with 1 or 2 point-mutations of quinolone resistance determining regions (QRDRs). In accordance with our results, these resistant isolates sourced from adult total, possibly because quinolone cannot be used in children and the resistant isolates have not been screened.

The superactivity of tigecycline against *S. pneumoniae* and *H. influenzae* in the current study have shown consistent results in many recent studies. In China, 881 *S. pneumoniae* isolates obtained from 26 hospitals between 2011 and 2016 showed 100% tigecycline susceptibility.¹⁶ Pfaller et al observed significant tigecycline activity against *S. pneumoniae*, with a mean MIC₉₀ of 0.06 mg/L, from North America, Europe, Latin America, and Asia-Pacific.¹⁷ Data from the SENTRY Antimicrobial Surveillance Program indicated tigecycline MIC₉₀ values against *S. pneumoniae* below 0.06 mg/L in Latin

America,¹⁸ the US,¹⁹ and Asia,²⁰ and a MIC₉₀ value of 0.5 mg/L against *H. influenzae* in the US.¹⁹

Lower susceptibilities of amoxicillin-clavulanate, ceftriaxone, and meropenem were observed in Africa and Asia compared to those in other regions in our study. There is a systematic review²¹ about antimicrobial resistance in Africa collected from 2013–2016 showing 17.4% and 2.2% median resistance to amoxicillin-clavulanate and ceftriaxone, similarly with our investigation (82.6% and 92.8% susceptibility in Africa, respectively). A report from China²² showed resistances of *S. pneumoniae* that were greater than 30% to amoxicillin-clavulanate and ceftriaxone, more serious than our study (88.0% and 91.6% susceptibility in Asia, respectively). By contrast, the susceptibility to these two drugs in Korea²³ and Iran²⁴ were similar to those found in our study. The same resistance trends about amoxicillin-clavulanate and ceftriaxone in diverse study shows the severe drug resistance may be the real status in Africa and Asia.

There are fewer reports about the prevalence of meropenem-resistance *S. pneumoniae*. A study about a Chinese hospital²⁵ showed a 15.4% resistance of meropenem, lower than Asia in this study (40.3% nonsusceptible). Similar to the present investigation, a susceptibility of 84.4% for meropenem against 450 *S. pneumoniae* collected from the US and Europe in 2014 shown by Pfaller et al.²⁶ Meropenem-resistance *S. pneumoniae* 15A-ST63 clone has been found in Japan.²⁷ Miyazaki et al²⁸ found serotype 35B were the most prevalent in Japan with the highest nonsusceptibility of 81.0% in these *S. pneumoniae*. 15A and 35B is not included in the currently used PCV-13 vaccine (pneumococcal conjugate valent) in Japan. The two serotype of *S. pneumoniae* may be the main serotype of infection disease of *S. pneumoniae* in future Japan even in other regions.

The susceptibility of minocycline in 2015–2017 was higher than 2009–2012 TEST study in *S. pneumoniae*⁸ increasing from 51.7–74.5% globally and 20.9–64.8% to 30.8–81.6% in six regions. More observation and analysis should be made in future to determine whether these trends are significant.

The susceptibility of *S. pneumoniae* to macrolides were comparable in 2015–2017 and 2009–2012⁸ except for those from the Middle East, for which susceptibility decreased from 65.9–66.3% in 2009–2012 to 34.1–36.3% in 2015–2017. In the present investigation, the global susceptibility to macrolides was the lowest in all antibiotics tested except for penicillin. The Middle East and Asia

were the regions showing the lowest susceptibility to macrolides.

Similar results have been reported in other research. Grace et al²⁹ summarized results from the Middle East since 2003, which showed a rapid increase in resistance of *S. pneumoniae* against macrolides from below 30% before 2007 to 77% after 2007. The findings of community-acquired respiratory tract infection pathogen surveillance (CARTIP) in the Asia-Pacific region³⁰ and a study of 17 cities in China²² showed that resistance of macrolides was approximately 90%. Results from the Survey of Antibiotic Resistance (SOAR) in 2012–2014 indicated that the nonsusceptibility of macrolides to *S. pneumoniae* was 80% in South Korea and 50% in India, Singapore, and Thailand.³¹ However, meta-analysis data of Iroh Tam et al from South Africa³² and children in Africa³³ showed that susceptibility of erythromycin were 97.6% and 94.0%, which were far more sensitive than the 50.7% found in our study. The number of *S. pneumoniae* isolates from Africa were the least of those obtained from the six regions in our study. To reflect the real situation in Africa, more isolates should be collected. Results consistent with those from our study were found in SENTRY¹⁸ in Latin America, with an observed susceptibility to erythromycin of 65.5%. The results from an investigation of the European Antimicrobial Resistance Surveillance Network (EARS-Net) and Antibiotic Resistance and Prescribing in European Children (ARPEC) showed resistance to macrolides of 15.3% and 33.1%.³⁴ The reports from Latin America and Europe were all similar to our findings (about 66% and 78% susceptibility, respectively).

The susceptibility of clindamycin to *S. pneumoniae* 4.9–37.3% higher than that of erythromycin in each region and globally, indicated that there are a portion of isolates resistant to macrolides meanwhile sensitive to clindamycin. These *S. pneumoniae* may be the M phenotype isolates carrying *mef(E)/mel* efflux pump gene, which is resistance to 14- and 15-membered macrolides but susceptible to lincosamides, and streptogramin B. These isolates display low level resistance (MICs 1–8 µg/mL) to erythromycin usually.³⁵ The most common macrolides resistance mechanism in *S. pneumoniae* is ribosomal methylation coded by *erm(B)* gene which confer resistance to macrolides, lincosamides, and streptogramin B. This phenotype is characterized as the MLS_B.³⁵ From our investigation, The proportion of MLS_B was about 20% in globally which were the major reason lead to the resistance of macrolides against *S. pneumoniae*. The proportion of M phenotype is about 10% globally.

Susceptibility of *S. pneumoniae* to penicillin is very important, only 61.7% in globally. Latin America, Africa, Asia, and the Middle East yielded *S. pneumoniae* isolates with lower susceptibility to penicillin compared with Europe and North America. Similar results have been found in other studies. In Asia, from 17 hospitals of China, the resistance of *S. pneumoniae* to penicillin was 50%,²² similar to that reported from Guangzhou, China.²⁵ The susceptibility of penicillin was just 21.2% in Korea and 49.3%, 63.8%, and 49.0% in India, Singapore, and Thailand, respectively.³¹ The resistance of penicillin to *S. pneumoniae* increased to 40–70% after 2008 in the Middle East,²⁹ and the susceptibility was 68.6% and 78.0% in Africa.^{32,33} These results approximated those data of Asia, the Middle East, and Africa in our study. However, reports from SENTRY in Latin America indicated a susceptibility of 87.2%, which was higher than 51.7% reported in the current study for this region.¹⁸

A significant decrease in susceptibility was observed in PISP and PRSP against three β -lactams, three macrolides, clindamycin, and minocycline (Figure 1), that is to say, the multidrug resistance (MDR) isolates increasing significantly with the resistance of penicillin. MDR was observed in 59.3% of isolates from Asian countries in ANSORP Surveillance, reflecting the severe resistance of *S. pneumoniae*. Clinical therapy of infection due to MDR *S. pneumoniae* is difficult and often ineffective. The misuse and overuse of antimicrobials may be responsible for this rise in MDR isolates.

With the susceptibility of over 98.7% in all antibiotics except for ampicillin in *H. influenzae* manifested that these antimicrobial drugs can be used as the first choice in the empirical treatment of *H. influenzae*. Reports on the susceptibility of *H. influenzae* to ampicillin differ greatly, from 16.7% in Korea³¹ to 52.5–63.3% in Singapore,³¹ Thailand,³¹ and China³⁶ to 91.1% in India.³¹ So, surveillance in different regions, such as diverse countries, provinces, cities even hospitals is necessary for the empirical therapy of infectious disease.

In Asia, except for ampicillin, six drugs were the lowest sensitive drug in all regions in *H. influenzae* from 2015–2017. Highest prevalence of BL-Pos and BLNAR *H. influenzae* appeared in Asia also, 37.3% and 8.3%, respectively, significantly increased compared with the same TEST study of 2004–2012 (27.8% and 3.5%, respectively).⁸ We should pay attention to the relatively severe resistance of *H. influenzae* in Asia. It is extremely

urgent to control the development of the resistance of antimicrobial drugs.

Conclusions

In summary, the high activities determined for vancomycin, linezolid, tigecycline, and levofloxacin against *S. pneumoniae* manifested that these antibiotics can be used as the first choice in the empirical therapy of infection disease caused by *S. pneumoniae*. However, macrolides and penicillin should be used prudently in treatment the infection caused by *S. pneumoniae*, as well as ampicillin to *H. influenzae*.

Asia was the region with the most severe resistance in *S. pneumoniae* and *H. influenzae*, followed by Africa and the Middle East. Insufficient resource of isolates maybe lead to the deviation of resistance in these regions. But the likely trends found by many other surveillance studies indicated that our research has value. With the serious trend toward drug resistance in *S. pneumoniae* and *H. influenzae*, it is imperative to implement rational and normative use of antibacterial agents at full scale and to take practical actions and adopt effective measures to limit the progress of bacterial resistance in all countries.

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Disclosure

Sisi Pan and Ying Yu are employees of Pfizer Investment Co., Ltd. The authors report no other conflicts of interest in this work.

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