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Antimicrobial Susceptibility of Streptococcus pneumoniae from North America, Europe, Asia, and Latin America: Results from 20 Years of the SÉNTRY Antimicrobial Surveillance Program (1997–2016) HS Sader¹, RK Flamm¹, J Le², G Denys³, RN Jones¹, RE Mendes¹

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Introduction

- Streptococcus pneumoniae is the most common pathogen implicated in communityacquired bacterial pneumonia (CABP), and multidrug-resistant (MDR) and extensively drugresistant (XDR) S. pneumoniae represent challenges for existing antibacterial agents
- Seroprevalence studies in the United States conducted following the introduction of pneumococcal conjugate vaccines (PCV7) found that serotypes 19A and 35B were the most prevalent serotypes recovered from infected patients; these 2 serotypes were shown to comprise the majority of *S. pneumoniae* isolates with decreased susceptibility to penicillin, ceftriaxone, and other agents used to treat CABP
- Significant declines in penicillin-resistant and MDR S. pneumoniae have been attributed to the efficacy of PCV13 against serotype 19A; however, proportional increases in replacement serotypes that are penicillin-resistant and/or MDR (eg, 35B, 23A, and 15A) have prevented a more substantial decline in pneumococcal resistance rates
- The SENTRY Program has monitored the frequency of occurrence and antimicrobial susceptibility of organisms from various infection types worldwide since 1997
- We evaluated the antimicrobial susceptibility of *S. pneumoniae* isolates collected worldwide over 20 years

Materials and Methods

Organism collection

- A total of 67,487 S. pneumoniae isolates were consecutively collected (1 per patient) by 399 participating medical centers from North America (34,645 isolates from 243 medical centers in the Unites States and Canada), Europe (19,123 isolates from 63 medical centers in 23 nations), the Asia-Pacific region (APAC; 8,586 isolates from 75 medical centers in 12 nations), and Latin America (5,133 isolates from 18 medical centers in 7 nations; Figure 1)
- Only isolates deemed clinically relevant by the submitting laboratory were included (1 isolate per patient infectious episode)
- The S. pneumoniae isolates were from respiratory tract infections (77.7%), bloodstream infections (16.7%), and other infection types (5.7%)
- Overall, 25.3% of isolates were from children (≤17 years old) and 67.7% from adults; the age was not reported in 7.0% of the isolates
- MDR status was determined based on nonsusceptibility to ≥3 classes of the following antimicrobial agents: penicillin (MIC, ≥4 mg/L), ceftriaxone (MIC, ≥2 mg/L), erythromycin (MIC, ≥ 0.5 mg/L), clindamycin (MIC, ≥ 0.5 mg/L), levofloxacin (MIC, ≥ 4 mg/L), tetracycline (MIC, ≥ 2 mg/L), and trimethoprim-sulfamethoxazole (MIC, ≥ 1 mg/L); and XDR status was determined based on nonsusceptibility to ≥ 5 classes as described by Golden et al (2015)

Susceptibility testing

- Broth microdilution tests were conducted at the central reference laboratory according to CLSI methods to determine the antimicrobial susceptibility
- Validated MIC panels were manufactured at JMI Laboratories (2015–2016) or by ThermoFisher Scientific (1997–2014; Cleveland, Ohio, USA)
- S. pneumoniae isolates were tested in cation-adjusted Mueller-Hinton broth supplemented with 2.5% to 5% lysed horse blood according to CLSI document M07
- Susceptibility rates were stratified by 2-year periods
- Quality control strain S. pneumoniae ATCC 49619 was tested concurrently with clinical isolates
- Susceptibility determinations and quality assurance of MIC results were based on CLSI guidelines

Results

 Penicillin susceptibility (at ≤2 mg/L) rates decreased from 1997–1998 (96.1%-97.9%; 96.7% overall) until 2009-2010 in North America (85.1%) and APAC (75.9%), 2011–2012 in Europe (93.5%), and 2013–2014 in Latin America (86.6%) and then increased in all regions until 2015–2016 to 96.6%, 95.5%, 89.6%, and 94.8% in North America, Europe, APAC, and Latin America, respectively (data not shown); penicillin susceptibility at ≤0.06 mg/L showed similar overtime variations (Figure 2)



Table 1. Antimicrobial susceptibility and frequency of multidrugresistant (MDR) and extensively drug-resistant isolates (XDR) among Streptococcus pneumoniae isolates collected in 2015–2016 stratified by geographic region

Antimiorphial agent	MIC	MIC	% susceptible per CLSI ^a (no. tested)					
Antimicropial agent	(mg/Ľ)	(mg/L)	NA	EUR	APAC	LATAM	All regions	
All isolates			(3,640)	(2,111)	(647)	(191)	(6,589)	
Amoxicillin-clavulanate	≤0.03	2	94.9	94.1	87.8	93.7	94.0	
Azithromycin	0.06	>4	56.1	76.6	54.6	72.8	63.0	
Ceftaroline	≤0.008	0.12	100.0 ^b	>99.9 ^b	99.2 ^b	100.0 ^b	99.9 ^b	
Ceftriaxone	0.03	1	88.2°	87.6 ^c	77.8 ^c	90.6 ^c	87.1°	
			97.7 ^b	96.4 ^b	89.5 ^b	95.8 ^b	96.5 ^b	
Clindamycin	≤0.25	>1	85.8	83.3	65.3	84.3	83.0	
Erythromycin	0.03	>2	56.0	76.7	54.2	72.8	63.0	
Levofloxacin	1	1	99.1	98.2	97.1	100.0	98.6	
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0	
Meropenem	0.015	0.5	82.5	86.7	70.8	88.3	83.1	
Penicillin	≤0.06	2	63.8 ^d	71.6 ^d	54.9 ^d	70.2 ^d	65.6 ^d	
			96.6 ^e	95.5 ^e	89.6 ^e	94.8 ^e	95.5 ^e	
Tetracycline	≤0.25	>4	80.5	78.2	56.0	70.0	77.1	
Tigecycline	0.03	0.06	99.5 ^f	99.5 ^f	98.6 ^f	99.5 ^f	99.4 ^f	
TMP-SMX	≤0.5	>4	73.7	72.1	63.1	64.4	71.9	
Vancomycin	0.25	0.25	100.0	100.0	100.0	100.0	100.0	
Pediatric patients			(990)	(365)	(138)	(63)	(1,556)	
Amoxicilin-clavulanate	≤0.03	2	94.8	94.0	83.6	88.9	93.4	
Azithromycin	0.06	>4	53.9	72.9	42.0	61.9	57.6	
Ceftriaxone	0.03	1	87.1°	86.8°	73.9°	84.1°	85.8°	
			97.8 ^b	95.1 ^b	85.8 ^b	90.5 ^b	95.8 ^b	
Clindamycin	≤0.25	>1	87.8	79.2	51.5	79.4	82.3	
Penicillin	≤0.06	2	61.4 ^d	69.9 ^d	47.1 ^d	57.1 ^d	62.0 ^d	
			96.4 ^e	96.2 ^e	83.3 ^e	90.5 ^e	94.9 ^e	
Tetracycline	≤0.25	>4	82.4	75.1	44.2	68.3	76.7	
TMP-ŚMX	≤0.5	>4	70.8	73.7	60.1	55.6	69.9	
Adult patients			(2,439)	(1,513)	(469)	(126)	(4,547)	
Amoxicillin-clavulanate	≤0.03	2	`94.9 ´	93.6	88.6	96.0	93.8	
Azithromycin	0.06	>4	57.1	76.1	57.5	77.8	64.0	
Ceftriaxone	0.03	1	88.8°	86.9°	78.3°	93.7°	87.3°	
			97.7 ^b	96.6 ^b	90.4 ^b	98.4 ^b	96.6 ^b	
Clindamycin	≤0.25	>1	85.2	83.2	68.1	86.5	82.8	
Penicillin	≤0.06	2	64.9 ^d	70.7 ^d	57.1 ^d	76.2 ^d	66.4 ^d	
			96.7 ^e	94.8 ^e	91.3 ^e	96.8 ^e	95.5 ^e	
Tetracycline	≤0.25	>4	80.0	77.5	58.2	72.0	76.7	
TMP-SMX	≤0.5	>4	74.8	70.7	64.8	68.3	72.3	
Frequency of resistance	phenotyp	es (%: all	ages cor	nbined)				
MDR		(,	17.4	19.1	39.4	20.9	22.2	
XDR			3.5	4.0	10.8	4.2	4.4	

A atimic rebial exect	MIC ₅₀	MIC	% susceptible per CLSI ^a (no. tested)					
Antimicropial agent	(mg/Ľ)	(mg/Ľ)	NA	EUR	APAC	LATAM	All regions	
All isolates			(3,640)	(2,111)	(647)	(191)	(6,589)	
Amoxicillin-clavulanate	≤0.03	2	94.9	94.1	87.8	93.7	94.0	
Azithromycin	0.06	>4	56.1	76.6	54.6	72.8	63.0	
Ceftaroline	≤0.008	0.12	100.0 ^b	>99.9 ^b	99.2 ^b	100.0 ^b	99.9 ^b	
Ceftriaxone	0.03	1	88.2°	87.6 ^c	77.8 °	90.6°	87.1°	
			97.7 ^b	96.4 ^b	89.5 ^b	95.8 ^b	96.5 ^b	
Clindamycin	≤0.25	>1	85.8	83.3	65.3	84.3	83.0	
Erythromycin	0.03	>2	56.0	76.7	54.2	72.8	63.0	
Levofloxacin	1	1	99.1	98.2	97.1	100.0	98.6	
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0	
Meropenem	0.015	0.5	82.5	86.7	70.8	88.3	83.1	
Penicillin	≤0.06	2	63.8 ^d	71.6 ^d	54.9 ^d	70.2 ^d	65.6 ^d	
			96.6 ^e	95.5 ^e	89.6 ^e	94.8 ^e	95.5 ^e	
Tetracycline	≤0.25	>4	80.5	78.2	56.0	70.0	77.1	
Tigecycline	0.03	0.06	99.5 ^f	99.5 ^f	98.6 ^f	99.5 ^f	99.4 ^f	
TMP-SMX	≤0.5	>4	73.7	72.1	63.1	64.4	71.9	
Vancomycin	0.25	0.25	100.0	100.0	100.0	100.0	100.0	
Pediatric patients			(990)	(365)	(138)	(63)	(1,556)	
Amoxicillin-clavulanate	≤0.03	2	94.8	94.0	83.6	88.9	`93.4 ´	
Azithromycin	0.06	>4	53.9	72.9	42.0	61.9	57.6	
Ceftriaxone	0.03	1	87.1°	86.8°	73.9 ^c	84.1°	85.8°	
			97.8 ^b	95.1 ^b	85.8 ^b	90.5 ^b	95.8 ^b	
Clindamycin	≤0.25	>1	87.8	79.2	51.5	79.4	82.3	
Penicillin	≤0.06	2	61.4 ^d	69.9 ^d	47.1 ^d	57.1 ^d	62.0 ^d	
			96.4 ^e	96.2 ^e	83.3 ^e	90.5 ^e	94.9 ^e	
Tetracycline	≤0.25	>4	82.4	75.1	44.2	68.3	76.7	
TMP-ŠMX	≤0.5	>4	70.8	73.7	60.1	55.6	69.9	
Adult patients			(2,439)	(1,513)	(469)	(126)	(4,547)	
Amoxicillin-clavulanate	≤0.03	2	`94.9´	93.6	88.6	96.0	93.8	
Azithromycin	0.06	>4	57.1	76.1	57.5	77.8	64.0	
Ceftriaxone	0.03	1	88.8°	86.9°	78.3 ^c	93.7°	87.3°	
			97.7 ^b	96.6 ^b	90.4 ^b	98.4 ^b	96.6 ^b	
Clindamycin	≤0.25	>1	85.2	83.2	68.1	86.5	82.8	
Penicillin	≤0.06	2	64.9 ^d	70.7 ^d	57.1 ^d	76.2 ^d	66.4 ^d	
			96.7 ^e	94.8 ^e	91.3 ^e	96.8 ^e	95.5 ^e	
Tetracycline	≤0.25	>4	80.0	77.5	58.2	72.0	76.7	
TMP-ŚMX	≤0.5	>4	74.8	70.7	64.8	68.3	72.3	
Frequency of resistance	phenotyp	es (%; all	ages cor	nbined)				
MDR	. 71	(, , , , , , , , , , , , , , , , , , ,	17.4	19.1 [′]	39.4	20.9	22.2	
XDR			3.5	4.0	10.8	4.2	4.4	

- Criteria as published by CLSI [2018 Using non-meningitis breakpoints
- ^c Using meningitis breakpoints. Using oral breakpoints.
- Using parenteral, non-meningitis breakpoints ^f Breakpoints from FDA Package Insert. ⁹ TMP-SMX, trimethoprim-sulfamethoxazole

- breakpoints; Table 1)

NA, North America; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America

Figure 2. Biennial variation of penicillin susceptibility (MIC, ≤0.06 mg/L) stratified by geographic region



Figure 3. Biennial variation of erythromycin susceptibility (MIC, ≤2 mg/L) stratified by geographic region



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 Susceptibility to erythromycin decreased in North America from 84.9% in 1997–1998 to 55.3% in 2011–2012 and then remained around 55.0%-56.0% until 2015–2016 (Figure 3)

 A decrease in erythromycin susceptibility was observed in Europe until 2007–2008, in the APAC region until 2005– 2006, and in Latin America until 2013–2014 and then increased in all these regions until 2015–2016 (Figure 3)

 Resistance rates to most antimicrobials were generally similar in North America, Europe, and Latin America in the last 2 years of the investigation (2015–2016; Table 1)

 Amoxicillin-clavulanate, penicillin, and ceftriaxone were active against 94.0%, 95.5%, and 96.5% of isolates collected in 2015–2016 from all regions combined (non-meningitis

Susceptibility rates for azithromycin, ceftriaxone, penicillin, and trimethoprim-sulfamethoxazole were generally lower among isolates from pediatric compared to adult patients (Table 1)

 MDR and XDR frequencies were highest in APAC and generally lowest in Latin America (Figure 4)

MDR rates increased from 8.9% in 1997–1998 to 24.0% in 2009–2010 in North America and then decreased to 17.4% in 2015–2016; MDR rate increases in the initial years of the program with subsequent rate decreases were also noted in other geographic regions (Figure 4)

Figure 4. Biennial frequency of multidrug-resistant isolates stratified by geographic region



- In the last 2 years of the investigation (2015–2016), MDR and XDR rates were similar in North America, Europe, and Latin America (Table 1 and Figure 4)
- In North America, susceptibility rates to ceftriaxone (at $\leq 1 \text{ mg/L}$), clindamycin, tetracycline, trimethoprim-sulfamethoxazole, and penicillin (at ≤0.06 mg/L) exhibited a decreasing trend until 2011–2012 and then increased until 2015–2016 (Figure 5)
- The most active agents for MDR/XDR isolates were linezolid (100.0%/100.0% susceptible), vancomycin (100.0%/100.0% susceptible), ceftaroline (99.7%/99.2% susceptible), and tigecycline (97.1%/96.5% susceptible; Table 2)
- Some trending analysis may have limitations due to inconsistent participation of certain countries, especially in the Asia-Pacific and eastern European regions

Table 2. Antimicrobial susceptibility of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Streptococcus pneumoniae for all years combined and stratified by geographic region

	MIC ₅₀	MIC	% susceptible per CLSI ^a (no. tested)					
Antimicrobial agent	(mg/Ľ)	(mg/Ľ)	NA	EUR	APAC	LATAM	All regions	
MDR isolates			(6,163)	(4,168)	(4,273)	(553)	(15,157)	
Amoxicillin-clavulanate	≤2	>4	` 56.7 ´	82.4	70.1	74.5	68.2	
Azithromycin	>4	>4	4.5	3.1	0.7	7.3	3.1	
Ceftaroline	0.12	0.25	>99.9 ^b	99.6 ^b	99.2 ^b	100.0 ^b	99.7 ^b	
Ceftriaxone	1	2	43.3°	49.3°	37.5°	46.2 ^c	43.4 °	
			69.6 ^b	82.6 ^b	67.2 ^b	72.7 ^b	72.6 ^b	
Clindamycin	>1	>1	27.2	16.7	19.2	37.5	22.4	
Erythromycin	>2	>2	1.8	2.3	0.7	5.3	1.7	
Imipenem	≤0.5	1	43.8	53.6	42.9	42.2	46.2	
Levofloxacin	1	1	97.1	96.5	96.1	99.1	96.7	
Linezolid	0.5	1	100.0	100.0	100.0	100.0	100.0	
Meropenem	0.5	1	44.5	52.4	43.6	41.7	45.9	
Penicillin	2	4	8.9 ^d	25.1 ^d	23.7 ^d	20.1 ^d	17.9 ^d	
			58.8 ^e	82.2 ^e	64.1 ^e	69.6 ^e	67.1 ^e	
Tetracycline	>4	>4	9.6	10.6	2.4	18.6	8.2	
Tigecycline	≤0.12	≤0.12	97.2 ^f	94.9 ^f	99.1 ^f	96.1 ^f	97.1 ^f	
TMP-SMX ^g	>4	>4	18.4	34.6	24.5	19.0	24.6	
Vancomycin	≤1	≤1	100.0	100.0	100.0	100.0	100.0	
XDR isolates			(2,202)	(659)	(1,488)	(95)	(4,444)	
Amoxicillin-clavulanate	>4	>4	8.1	35.2	27.3	14.7	18.7	
Azithromycin	>4	>4	0.6	0.2	0.1	2.3	0.4	
Ceftaroline	0.25	0.5	100.0 ^b	98.4 ^b	97.9 ^b	100.0 ^b	99.2 ^b	
Ceftriaxone	2	>2	2.6 ^c	5.7°	1.6 ^c	0.0 ^c	2.7 ^c	
			32.2 ^b	23.4 ^b	17.7 ^b	26.6 ^b	25.9 ^b	
Clindamycin	>1	>1	6.0	10.8	8.8	14.9	7.8	
Erythromycin	>2	>2	0.0	0.0	0.1	0.0	0.1	
Levofloxacin	1	1	96.7	90.8	91.2	98.9	94.0	
Linezolid	0.5	1	100.0	100.0	100.0	100.0	100.0	
Meropenem	1	1	1.6	0.8	2.2	1.2	2.7	
Penicillin	4	>4	0.2 ^d	3.0 ^d	0.4 ^d	0.0 ^d	0.7 ^d	
			5.4 ^e	22.2 ^e	13.0 ^e	5.3 ^e	10.4 ^e	
Tetracycline	>4	>4	2.0	4.3	0.9	6.3	2.1	
Tigecycline	≤0.12	≤0.12	95.4 ^f	94.7 ^f	98.9 ^f	98.9 ^f	96.5 ^f	
TMP-SMX ^g	>4	>4	0.4	3.3	1.7	0.0	1.2	
Vancomycin	≤1	≤1	100.0	100.0	100.0	100.0	100.0	

Criteria as published by CLSI [2018 ^b Using non-meningitis breakpoint

[°] Using meningitis breakpoints Using oral breakpoints.

Using parenteral, non-meningitis breakpoi ^f Breakpoints from FDA Package Insert.

^g TMP-SMX, trimethoprim-sulfamethoxazole

NA, North America; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America



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Conclusions

- Resistance rates to most antimicrobial agents tested against S. pneumoniae were generally higher in the APAC region compared to North America, Europe, and Latin America
- S. pneumoniae susceptibility to many antibiotics increased in all regions in the last few years, and these increases may be related to the anti-pneumococcal vaccine PVC-13 introduction since 2010
- Ceftaroline, linezolid, tigecycline, and vancomycin remain very active (>99% susceptibility) against S. pneumoniae, including MDR and XDR isolates

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Figure 5. Biennial variation of susceptibility rates to key antimicrobial agents in North America



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