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SUPPLEMENT ARTICLE

Antimicrobial Susceptibility of *Streptococcus pneumoniae* from North America, Europe, Latin America, and the Asia-Pacific Region: Results From 20 Years of the SENTRY Antimicrobial Surveillance Program (1997–2016)

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Background. The SENTRY Antimicrobial Surveillance Program monitors the frequency of occurrence and antimicrobial susceptibility of organisms from various infection types worldwide. In this investigation, we evaluated the antimicrobial susceptibility of *Streptococcus pneumoniae* isolates collected worldwide over 20 years (1997–2016).

Methods. A total of 65 993 isolates were consecutively collected (1 per infection episode) from North America (NA; n = 34 626; 2 nations), Europe (EUR; n = 19 123; 23 nations), the Asia-Pacific region (APAC; n = 7111; 10 nations), and Latin America (LATAM; n = 5133; 7 nations) and tested for susceptibility using reference broth microdilution methods. Resistant subgroups included multidrug-resistant (MDR; nonsusceptible to ≥3 classes of agents) and extensively drug-resistant (XDR; nonsusceptible to ≥5 classes).

Results. The isolates were collected primarily from respiratory tract infections (77.3%), and 25.4% were from pediatric patients. Penicillin susceptibility (≤0.06 mg/L) rates varied from 70.7% in EUR to 52.4% in APAC for all years combined. In NA, there was a slight improvement in susceptibility for the first few years of the program, from 66.5% in 1997–1998 to 69.4% in 1999–2000, followed by a decline until 2011–2012 (57.0%). Similar declines in penicillin susceptibility rates were observed in all regions, with the lowest rates of 67.3% in EUR (2011–2012), 41.6% in the APAC region (2007–2008), and 48.2% in LATAM (2013–2014). These declines were followed by improved susceptibility rates in all regions in later program years, with susceptibility rates of 55.6% to 71.8% in 2015–2016 (65.8% overall). Susceptibility rates to ceftriaxone, erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole followed a similar pattern, with a decrease in the first 12–14 years and a continued increase in the last 6–8 years of the program. MDR and XDR frequencies were highest in APAC (49.8% and 17.3% overall, respectively) and lowest in LATAM (10.8% and 1.9% overall, respectively). The most active agents for MDR/XDR isolates were ceftaroline (99.7%/99.1% susceptible), tigecycline (96.8%/95.9% susceptible), linezolid (100.0%/100.0% susceptible), and vancomycin (100.0%/100.0% susceptible).

Conclusions. *S. pneumoniae* susceptibility to many antibiotics increased in all regions in the last few years, and these increases may be related to PCV13 immunization, which was introduced in 2010.

Keywords. pneumococcal conjugate vaccine; PCV13; *S. pneumoniae*; surveillance.

Streptococcus pneumoniae is the most common pathogen implicated in community-acquired bacterial pneumonia (CABP) and represents an important cause of meningitis, bacteremia, acute otitis media, and sinusitis [1]. Pneumococcal infections are more prevalent in young children and the elderly, with multidrug-resistant (MDR) and extensively drug-resistant (XDR) *S. pneumoniae* presenting challenges for existing antimicrobial agents [2, 3].

Seroprevalence studies conducted in the United States following the introduction of pneumococcal conjugate vaccine (PCV) 7 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 [4, 5]. Moreover, significant declines in penicillin-resistant and MDR *S. pneumoniae* have been attributed to the more recent introduction of PCV13, which has efficacy against serotype 19A; however, proportional increases in replacement serotypes that are penicillin-resistant and/or MDR (eg, 35B, 23A, and 15A) have moderated the decline in pneumococcal resistance rates [6–8].

The SENTRY Antimicrobial Surveillance Program has monitored the frequency of occurrence and antimicrobial susceptibility of organisms from various infection types worldwide since 1997. In the present investigation, we evaluated the antimicrobial susceptibility of *S. pneumoniae* isolates collected worldwide over 20 years.

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METHODS

Organism Collection

From 1997 to 2016, the SENTRY Program collected more than 750 000 clinical isolates from more than 400 sites. In this investigation, we evaluated a total of 65 993 *S. pneumoniae* isolates that were consecutively collected (1 per infection episode) by 372 participating medical centers from North America (NA; 34 626 isolates from 234 medical centers in the United States and Canada), Europe (EUR; 19 123 isolates from 63 medical centers in 23 nations), the Asia-Pacific region (APAC; 7111 isolates from 48 medical centers in 10 nations), and Latin America (LATAM; 5133 isolates from 18 medical centers in 7 nations). Only isolates deemed clinically relevant by the submitting laboratory were included in the survey. A list of nations participating in the SENTRY Program is displayed in Table 1. China and India participated in the SENTRY Program for only a few years, and data from these 2 nations were not included in the analysis. China data (n = 1466) were excluded from the data analysis because this country participated in the program for only a few years and showed very high rates of resistance that would introduce bias in the trend analyses across the APAC region. India was excluded because it provided only 5 *S. pneumoniae* isolates during the years it participated in the program.

The medical centers followed the SENTRY Program protocols and collected a predetermined number of consecutive isolates per infection type (only 1 per infection episode) during a specific time of the year to reduce seasonality or other epidemiological concerns related to specific pathogens [9–11]. If more than 1 isolate was collected from the same infection episode, only the first isolate collected during the time period defined in the protocol was included in the program. The major collection objectives addressed the most common types of infection, including bloodstream infections, community-acquired respiratory tract infections (fastidious pathogens only), pneumonias in hospitalized patients, skin and skin structure infections, urinary tract infections, and intra-abdominal infections. Although the total contribution of clinical isolates per objective has varied over the years, these major collection objectives remain today. Objectives related to other infection types or organism groups have also been introduced throughout the life of the SENTRY Program, and for all objectives, organisms were consecutively collected and only 1 organism per infection episode was included in the program.

All *S. pneumoniae* isolates collected from any infection type were included in this investigation. The isolates were from respiratory tract infections (RTIs; 77.3%), bloodstream infections (17.0%), and other infection types (5.7%). Among isolates from RTIs, 56.4% were from the upper respiratory tract, 38.2% were from the lower respiratory tract, and the specific infection site was not defined in 5.4% of isolates. Isolates from cerebrospinal fluid represented less than 1.0% of the collection. Overall, 25.4% of isolates were from children (≤17 years old), and 67.7% were from adults; age was not reported for 6.9% of the isolates.

MDR status was determined based on nonsusceptibility to ≥3 classes represented by the following antimicrobial agents: penicillin (minimum inhibitory concentration [MIC], ≥4 mg/L),

Table 1. Nations Surveyed and Number of Isolates Per Country Collected by the SENTRY Program (1997–2016)

No. of Isolates per Region/Country			
Asia-Pacific (7111)	Europe (19 123)	Latin America (5133)	North America (34 626)
Australia (2856)	Austria (42)	Argentina (1144)	Canada (2541)
Hong Kong (378)	Belarus (50)	Brazil (1714)	United States (32 085)
Japan (1260)	Belgium (680)	Chile (1635)	
Malaysia (169)	Czech Republic (125)	Colombia (86)	
New Zealand (688)	France (3533)	Mexico (430)	
Philippines (62)	Germany (1724)	Uruguay (26)	
Singapore (280)	Greece (510)	Venezuela (98)	
South Korea (648)	Hungary (128)		
Taiwan (585)	Ireland (900)		
Thailand (185)	Israel (740)		
	Italy (15 440)		
	The Netherlands (32)		
	Poland (1011)		
	Portugal (140)		
	Romania (19)		
	Russia (803)		
	Slovenia (89)		
	Spain (1979)		
	Sweden (1703)		
	Switzerland (619)		
	Turkey (1084)		
	United Kingdom (1431)		
	Ukraine (137)		

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 (TMP-SMX; MIC, ≥1 mg/L). XDR status was determined based on nonsusceptibility to ≥5 classes, as described by Golden et al. [3].

Susceptibility Testing

Isolates were tested for susceptibility by the broth microdilution method using cation-adjusted Mueller-Hinton broth supplemented with 2.5% to 5% lysed horse blood. Susceptibility testing was performed at a central reference laboratory (JMI Laboratories, North Liberty, IA) according to Clinical and Laboratory Standards Institute (CLSI) methods [12, 13]. Validated MIC panels were manufactured at JMI Laboratories (2015–2016) or by Thermo Fisher Scientific (1997–2014; Cleveland, OH), and susceptibility rates were stratified by 2-year periods. Quality control strain *S. pneumoniae* American Type Culture Collection 49619 was tested concurrently with clinical isolates.

RESULTS

Biennial penicillin susceptibility (at ≤0.06 mg/L) trend rates stratified by geographic region are shown in Figure 1. In NA, there was a slight improvement in the first few years of the program, from 66.5% in 1997–1998 to 69.4% in 1999–2000, followed by a decline until 2011–2012 (57.0%). Similar declines in penicillin susceptibility rates were observed in EUR (from 72.6% in 2003–2004 to 67.3% in 2011–2012), the APAC region (from 67.6% in 1997–1998 to 41.6% 2007–2008), and LATAM (from 74.7% in 2001–2002 to 48.2% 2013–2014). These declines were followed by improved susceptibility rates in all regions in the last years of this investigation, with global susceptibility rates of 55.2% to 71.6% in 2015–2016 (65.8% overall).

When CLSI parenteral nonmeningitis breakpoints for penicillin were applied (≤2 mg/L), susceptibility rates decreased to a low of 85.1% in 2009–2010 in NA, 93.5% in 2011–2012 in EUR, 78.7% in 2005–2006 in APAC, and 86.6% in 2013–2014 in LATAM, and then increased in all regions until 2015–2016 to 96.6%, 95.5%, 89.6%, and 94.8% in NA, EUR, APAC, and LATAM, respectively (data not shown). Moreover, susceptibility to erythromycin decreased in NA from 84.9% in 1997–1998 to 55.3% in 2011–2012 and then remained around 55.0%–56.0% until 2015–2016 (Figure 2). A decrease in erythromycin susceptibility was observed in EUR and APAC until 2007–2008 and in LATAM until 2013–2014, and then increased in all these regions until 2015–2016 (Figure 2).

Resistance rates to most antimicrobials were generally similar in NA, EUR, and LATAM in the last 2 years of the investigation (2015–2016) (Table 2). 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 (nonmeningitis breakpoints) (Table 2).

Among 1466 isolates collected from China in 1998, 1999, 2006, and 2009–2013 that were not included in the data analysis, overall susceptibility rates were 47.9%/67.8% for penicillin at ≤0.06/≤2 mg/L, 53.5%/67.5% for ceftriaxone at ≤0.5/≤1 mg/L, 9.2% for erythromycin, and 25.4% for TMP-SMX (data not shown).

When comparing isolates from pediatric patients with those from adult patients, we observed that susceptibility rates were lower among isolates from pediatric patients for some antimicrobials, including azithromycin (57.6% vs 64.0%), ceftriaxone (85.8% vs 87.3% [≤0.5 mg/L; meningitis breakpoint]), penicillin (62.0% vs 66.4% [≤0.06 mg/L; meningitis breakpoint]), and TMP-SMX (69.9% vs 72.3%) (Table 2). Figure 3 displays penicillin susceptibility (at ≤0.06 mg/L) rates per country in the 2015–2016 period.

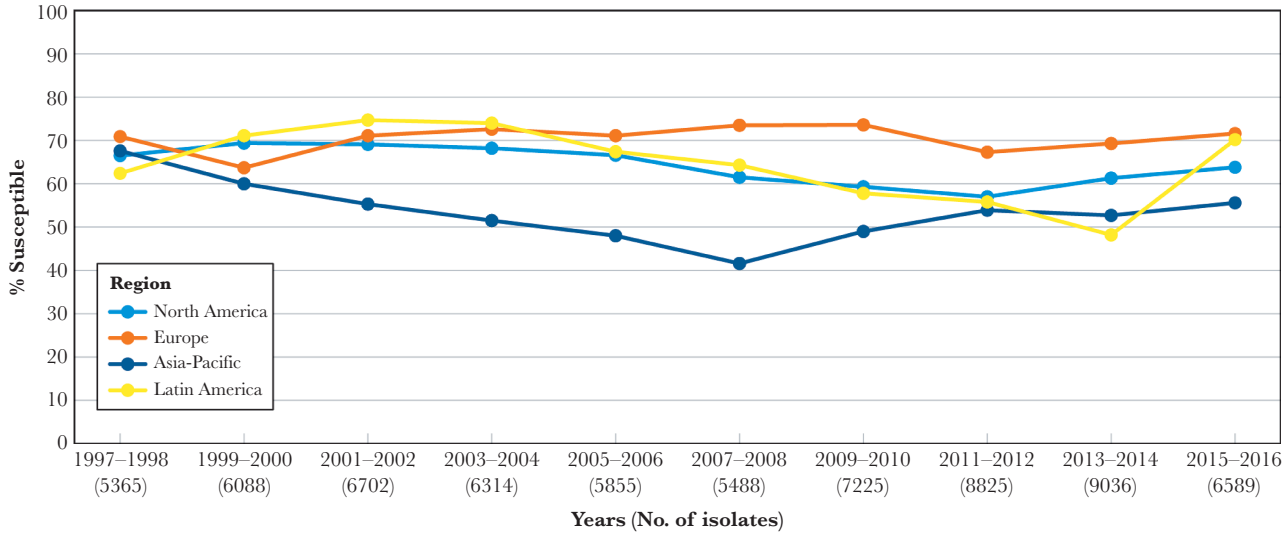

Figure 1. Biennial variation of penicillin susceptibility (minimum inhibitory concentration, ≤0.06 mg/L) stratified by geographic region.

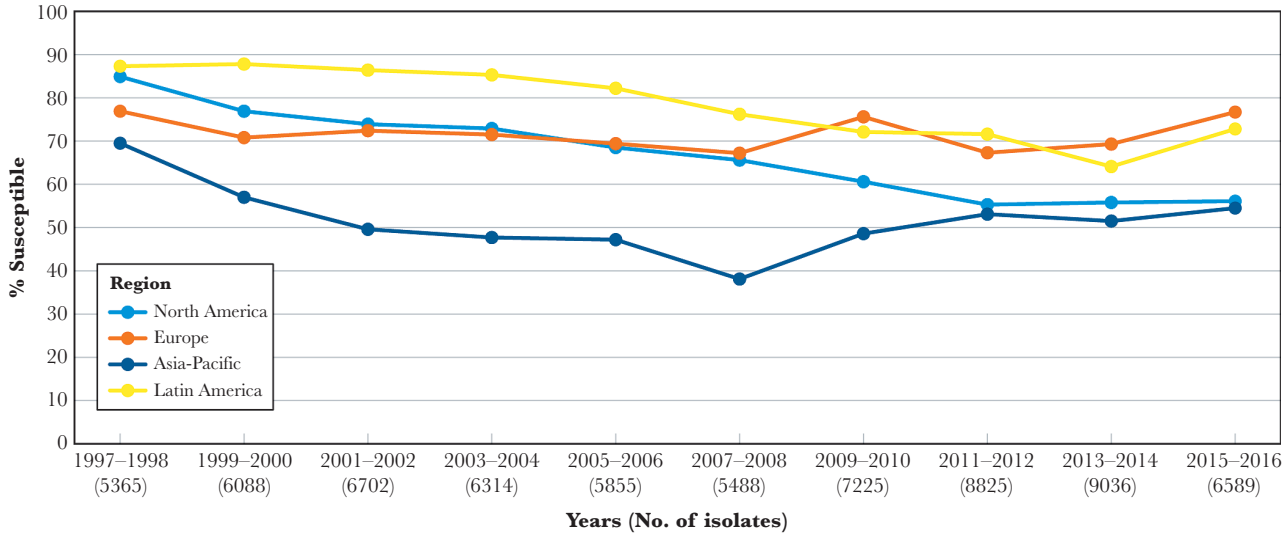

Figure 2. Biennial variation of erythromycin susceptibility (minimum inhibitory concentration, ≤2 mg/L) stratified by geographic region.

MDR and XDR isolate frequencies varied broadly among the geographic regions evaluated. MDR rates were highest in the APAC region, with an overall rate of 41.2% (varying from 23.7% in 1997–1998 to 53.3% in 2007–2008), and lowest in LATAM, with an overall rate of 10.0% (varying from a low of 5.3% in 2003–2004 to 28.7% in 2013–2014) (Figure 4). In NA, MDR rates increased from 8.9% in 1997–1998 to 24.0% in 2009–2010 and then decreased to 17.3% in 2015–2016. Similarly, in EUR, the MDR rates increased from 16.6% in 1997–1998 to 24.1% in 2007–2008 and decreased from 25.4% in 2011–2012 to 19.1% in 2015–2016 (Figure 4). Of note, in the last 2 years of the investigation (2015–2016), the MDR rates were similar in NA, EUR, and LATAM (17.3%–20.9%) but much higher in the APAC region (39.2%) (Table 3 and Figure 4).

In NA, susceptibility rates to penicillin (≤0.06 mg/L), clindamycin, tetracycline, TMP-SMX, and erythromycin exhibited a decreasing trend until 2011–2012, but then increased until 2015–2016. In contrast, susceptibility rates for ceftriaxone (≤1 mg/L) increased slightly from 1999–2000 (96.0%; not tested in 1997–1998) to 2003–2004 (98.1%), and then decreased until 2009–2010 (89.0%), and then increased again to 97.7% in 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%/99.1% susceptible), tigecycline (96.8%/96.0% susceptible), and levofloxacin (96.6%/93.7% susceptible) (Table 3). Amoxicillin-clavulanate, ceftriaxone (at ≤1 mg/L), and penicillin (at ≤2 mg/L) exhibited only moderate activity against MDR isolates (68.5%, 73.5%, and 67.4% susceptible, respectively) and very limited activity against XDR isolates (18.8%, 27.4%, and 10.3% susceptible, respectively), whereas all other compounds tested showed limited activity against MDR and XDR isolates (Table 3). Moreover, susceptibility rates of MDR isolates to amoxicillin-clavulanate, ceftriaxone (at ≤1 mg/L), and penicillin (at ≤2 mg/L) were highest in EUR (82.2–82.6%), followed by LATAM (69.6%–74.5%), APAC (64.3%–72.6%), and NA (56.6%–69.5%) (Table 3).

Ceftaroline was introduced to the SENTRY Program in 2008, and only 23 of 30 333 isolates tested (0.08%) were categorized as nonsusceptible (MIC, >0.5 mg/L) to this newer cephalosporin. The majority of ceftaroline-nonsusceptible isolates were from the APAC region (n = 15; 65.2%), mainly from South Korea (n = 14; 60.9%). Seven isolates (30.4%) were from EUR (Ireland [3], Poland [1], Russia [1], and Spain [2]), and only 1 was from NA.

DISCUSSION

The SENTRY Program has provided contemporary and longitudinal information on the antimicrobial susceptibility patterns of *S. pneumoniae* and other organisms collected worldwide since 1997 [9]. As seen in the present analysis, this program has collected and tested more than 65 000 *S. pneumoniae* isolates from 372 medical centers in 42 nations over 20 years. One of the most striking findings of this investigation was the improvement of *S. pneumoniae* antimicrobial susceptibility rates observed in the last few years of the investigation in all geographic regions evaluated. This improvement is potentially related to widespread immunization with PCV13 since its introduction in 2010 [14].

It is well documented that routine immunization with PCVs is associated with significant declines in invasive pneumococcal infection occurrences and antimicrobial resistance rates [5, 14–20]. The introduction of PCV7 immunization in the early 2000s led to a significant reduction in the incidence of *S. pneumoniae* invasive infections and resistance rates in the United States and EUR, followed by an increase in the incidence of infections caused by non-PCV7 serotypes [16, 19]. A large

Table 2. Antimicrobial Susceptibility and Frequency of Multidrug-Resistant and Extensively Drug-Resistant Isolates Among *Streptococcus pneumoniae* Isolates Collected in 2015–2016, Stratified by Geographic Region and Patient Age Group

			% Susceptible per CLSI,[a] No. Tested				
Antimicrobial Agent	MIC_{50}, mg/L	MIC_{90}, mg/L	NA	EUR	APAC	LATAM	All Regions
All isolates			(3621)	(2111)	(643)	(191)	(6566)
Amoxicillin-clavulanate	≤0.03	2	94.9	94.1	87.7	93.7	93.9
Azithromycin	0.06	>4	56.2	76.6	55.0	72.8	63.1
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[c] 97.7[b]	87.6[c] 96.4[b]	77.7[c] 89.5[b]	90.6[c] 95.8[b]	87.1[c] 96.5[b]
Clindamycin	≤0.25	>1	86.0	83.3	65.4	84.3	83.1
Erythromycin	0.03	>2	56.1	76.7	54.5	72.8	63.1
Levofloxacin	1	1	99.1	98.2	97.0	100.0	98.6
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Meropenem	0.015	0.5	82.7	86.7	70.8	88.3	83.2
Penicillin	≤0.06	2	64.1[d] 96.6[e]	71.6[d] 95.5[e]	55.2[d] 89.6[e]	70.2[d] 94.8[e]	65.8[d] 95.5[e]
Tetracycline	≤0.25	>4	80.7	78.2	56.1	70.0	77.2
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)	(1556)
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
Ceftaroline	≤0.008	0.12	100.0[b]	100.0[b]	100.0[b]	100.0[b]	100.0[b]
Ceftriaxone	0.03	1	87.1[c] 97.8[b]	86.8[c] 95.1[b]	73.9[c] 85.8[b]	84.1[c] 90.5[b]	85.8[c] 95.8[b]
Clindamycin	≤0.25	>1	87.8	79.2	51.5	79.4	82.3
Levofloxacin	1	1	99.6	99.2	100.0	100.0	99.6
Penicillin	≤0.06	2	61.4[d] 96.4[e]	69.9[d] 96.2[e]	47.1[d] 83.3[e]	57.1[d] 90.5[e]	62.0[d] 94.9[e]
Tetracycline	≤0.25	>4	82.4	75.1	44.2	68.3	76.7
TMP-SMX	≤0.5	>4	70.8	73.7	60.1	55.6	69.9
Adult patients			(2439)	(1514)	(469)	(126)	(4548)
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
Ceftaroline	≤0.008	0.12	100.0[b]	99.9[b]	98.9[b]	100.0[b]	99.9[b]
Ceftriaxone	0.03	1	88.8[c] 97.7[b]	86.9[c] 96.6[b]	78.3[c] 90.4[b]	93.7[c] 98.4[b]	87.3[c] 96.6[b]
Clindamycin	≤0.25	>1	85.2	83.2	68.1	86.5	82.8
Levofloxacin	1	1	99.0	98.3	96.2	100.0	98.5
Penicillin	≤0.06	2	64.9[d] 96.7[e]	70.7[d] 94.8[e]	57.1[d] 91.3[e]	76.2[d] 96.8[e]	66.4[d] 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 phenotypes (all ages combined), %							
MDR			17.3	19.1	39.2	20.9	20.1
XDR			3.5	4.0	10.9	4.2	4.4

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; MIC, minimum inhibitory concentration; MDR, multidrug-resistant; NA, North America; TMP-SMX, trimethoprim-sulfamethoxazole; XDR, extensively drug-resistant.

[a]Criteria as published by CLSI 2018.

[b]Using nonmeningitis breakpoints.

[c]Using meningitis breakpoints.

[d]Using oral breakpoints.

[e]Using parenteral, nonmeningitis breakpoints.

[f]Food and Drug Administration breakpoints (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm).

multisite population-based study performed by the Centers for Disease Control and Prevention [14] has documented that between 2004 and 2010 the incidence of invasive pneumococcal infections caused by PCV13/non-PCV7 serotypes increased progressively among both children and adults. This increase resulted in high resistance rates to penicillin and other antimicrobial agents during the same time period, as higher rates of antimicrobial resistance are found in PCV13/non-PCV7 serotypes [5]. However, rapid reductions in the incidence of infections caused by PCV13/non-PCV7 serotypes among children younger than 5 years old were observed in the United States after PCV13 immunization was introduced. This decline later became evident among adults and continued in the following years [14, 16].

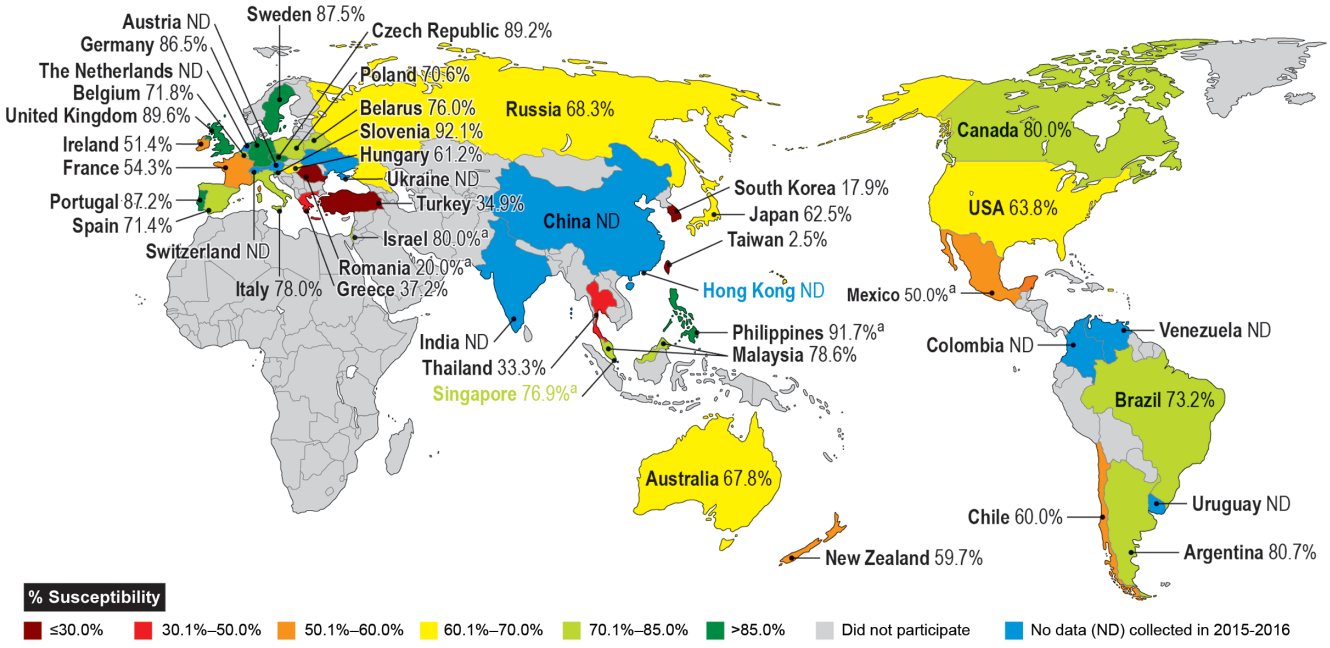

Figure 3. Penicillin susceptibility at ≤0.06 mg/L in the 2015–2016 period according to country of isolation. [a]Small sample size, <20 isolates tested in 2015–2016.

The effect of PCV immunization on the distribution of serotypes causing invasive infections has been documented in other nations, but its effect on *S. pneumoniae* antimicrobial susceptibility may vary from country to country [14, 19–22]. Although making a direct correlation between the improvement in antimicrobial susceptibility observed in the last few years of the investigation and PCV immunization is difficult, the data presented here strongly suggest that PCV13 immunization has resulted in improving *S. pneumoniae* susceptibility to several antimicrobials worldwide.

Another interesting finding was the variable susceptibility rates among the geographic regions. In general, susceptibility rates were highest in EUR and LATAM compared with NA and lowest in the APAC region when data from countries within each region were combined; however, it is important to note that susceptibility rates may vary significantly among EUR, LATAM, and APAC countries. Regional differences in *S. pneumoniae* susceptibility rates are probably due to a combination of multiple factors, including clonal epidemiology of this organism in the region, antimicrobial usage, and PCV immunization practices, among others [19, 23–25]. Moreover, decreased susceptibility to erythromycin in the early years of the program in all geographic regions (until 2007–2008 to 2011–2012, depending on the

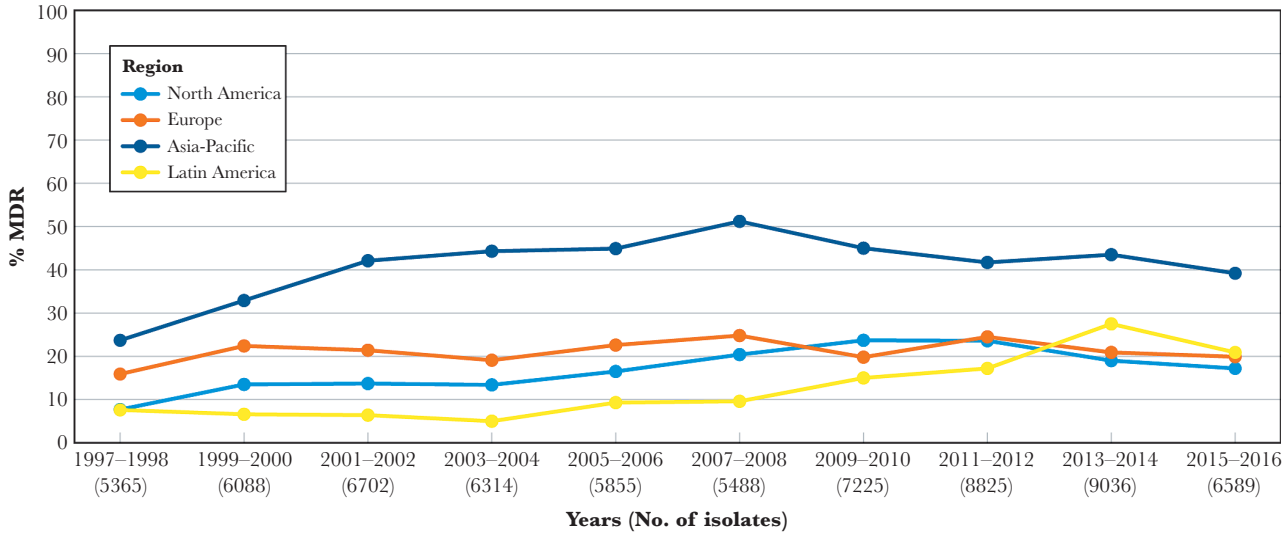

Figure 4. Biennial frequency of multidrug-resistant isolates stratified by geographic region.

Table 3. Antimicrobial Susceptibility of Multidrug-Resistant and Extensively Drug-Resistant *Streptococcus pneumoniae* for All Years Combined and Stratified by Geographic Region

			% Susceptible per CLSI,[a] No. Tested				
Antimicrobial Agent	MIC_{50}, mg/L	MIC_{90}, mg/L	NA	EUR	APAC	LATAM	All Regions
MDR isolates			(6155)	(4168)	(2968)	(553)	(13 844)
Amoxicillin-clavulanate	≤2	>4	56.6	82.4	72.6	74.5	68.5
Azithromycin	>4	>4	4.5	3.1	1.0	7.3	3.4
Ceftaroline	0.12	0.25	>99.9[b]	99.6[b]	98.7[b]	100.0[b]	99.7[b]
Ceftriaxone	1	2	43.3[c] 69.5[b]	49.3[c] 82.6[b]	32.3[c] 68.7[b]	46.2[c] 72.7[b]	42.8[c] 73.5[b]
Clindamycin	>1	>1	27.2	16.7	26.5	37.5	24.3
Erythromycin	>2	>2	1.8	2.3	0.9	5.3	1.9
Imipenem	≤0.5	1	43.8	53.6	38.5	42.2	45.8
Levofloxacin	1	1	97.1	96.5	95.3	99.1	96.6
Linezolid	1	1	100.0	100.0	100.0	100.0	100.0
Meropenem	0.5	1	44.5	52.4	39.5	41.7	45.2
Penicillin	2	4	8.9[d] 58.8[e]	25.1[d] 82.2[e]	15.7[d] 64.3[e]	20.1[d] 69.6[e]	15.7[d] 67.4[e]
Tetracycline	>4	>4	9.6	10.6	2.7	18.6	8.8
Tigecycline	≤0.12	≤0.12	97.2[f]	94.9[f]	98.7[f]	96.1[f]	96.8[f]
TMP-SMX	4	>4	18.3	34.6	27.5	19.0	25.2
Vancomycin	≤1	≤1	100.0	100.0	100.0	100.0	100.0
XDR isolates			(2202)	(659)	(962)	(95)	(3918)
Amoxicillin-clavulanate	>4	>4	8.1	35.2	32.2	14.7	18.8
Azithromycin	>4	>4	0.6	0.2	0.02	2.3	0.4
Ceftaroline	0.25	0.25	100.0[b]	98.4[b]	96.6[b]	100.0[b]	99.1[b]
Ceftriaxone	2	>2	2.6[c] 32.2[b]	5.7[c] 23.4[b]	1.7[c] 19.3[b]	0.0[c] 26.6[b]	2.9[c] 27.4[b]
Clindamycin	>1	>1	6.0	10.8	12.9	14.9	8.7
Erythromycin	>2	>2	0.0	0.0	0.2	0.0	0.1
Levofloxacin	1	1	96.7	90.8	88.2	98.9	93.7
Linezolid	0.5	1	100.0	100.0	100.0	100.0	100.0
Meropenem	1	1	1.6	8.0	2.4	1.2	2.8
Penicillin	4	4	0.2[d] 5.4[e]	3.0[d] 22.2[e]	0.1[d] 13.7[e]	0.0[d] 5.3[e]	0.7[d] 10.3[e]
Tetracycline	>4	>4	2.0	4.3	1.0	6.3	2.3
Tigecycline	≤0.12	≤0.12	95.4[f]	94.7[f]	98.2[f]	98.9[f]	96.0[f]
TMP-SMX	>4	>4	0.4	3.3	1.9	0.0	1.2
Vancomycin	≤1	≤1	100.0	100.0	100.0	100.0	100.0

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; MIC, minimum inhibitory concentration; MDR, multidrug-resistant; NA, North America; TMP-SMX, trimethoprim-sulfamethoxazole; XDR, extensively drug-resistant.

[a]Criteria as published by CLSI 2018.

[b]Using nonmeningitis breakpoints.

[c]Using meningitis breakpoints.

[d]Using oral breakpoints.

[e]Using parenteral, nonmeningitis breakpoints.

[f]Food and Drug Administration breakpoints (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm).

region) could be related to increased use of macrolides to treat respiratory infections in the late 1990s and early 2000s [26, 27].

Our results also illustrated that only a few antimicrobials retained reliable activity against MDR and XDR isolates. Besides linezolid and vancomycin, which remain active against 100.0% of *S. pneumoniae* isolates, only ceftaroline, tigecycline, and levofloxacin exhibited good activity against MDR and XDR isolates [6, 7]. Although the third-generation cephalosporin ceftriaxone demonstrated very limited activity against MDR and XDR isolates, the newer cephalosporin ceftaroline was active against 99.7% of MDR and 99.1% of XDR isolates. Ceftaroline resistance was limited to very few countries (60.9% [14/23] of ceftaroline-nonsusceptible isolates were from South Korea). Among orally available drugs, linezolid exhibited complete activity (100.0% susceptibility), and levofloxacin was the second most active antimicrobial against MDR and XDR isolates, with 96.6% and 93.7% susceptibility rates, respectively. All other oral antimicrobials showed limited activity against MDR and XDR isolates, indicating the need for new oral agents to treat *S. pneumoniae* infections.

The limitations of this study should be considered when interpreting these data. During the 20-year period of the SENTRY Program evaluated here, some medical centers, or some countries, did not participate in some years, and that could have introduced bias in the data analysis. Results from India and China were excluded from the analysis to avoid this

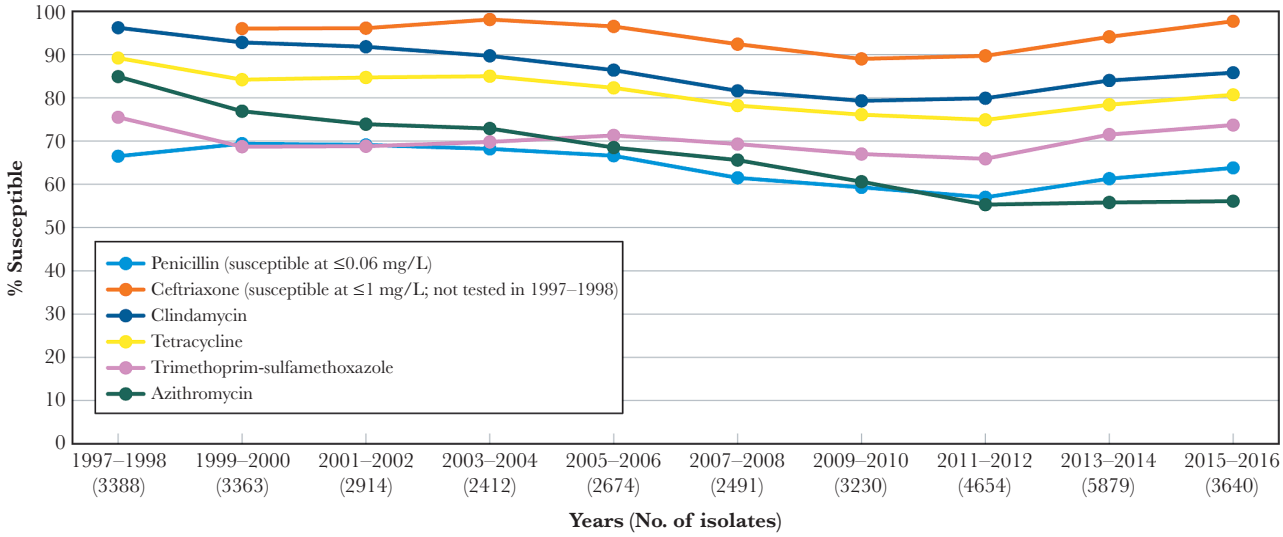

Figure 5. Biennial variation of susceptibility rates to key antimicrobial agents in North America.

type of bias, but some medical centers and/or countries that did not participate during the entire period may have caused slight skewing in the data analysis. Another limitation of the study is the fact that the criteria used to categorize a bacterial isolate as "clinically significant" were not defined in the study protocol and were based on local infectious disease algorithms, which may vary among participating medical centers. Despite the study limitations, the results presented here provide valuable information on antimicrobial susceptibility trends of *S. pneumoniae* infections worldwide from 1997 through 2016. The findings of this investigation highlight the need for continued monitoring of pneumococcal resistance patterns worldwide.

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