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SUPPLEMENT ARTICLE

Geographic and Temporal Patterns of Antimicrobial Resistance in *Pseudomonas aeruginosa* Over 20 Years From the SENTRY Antimicrobial Surveillance Program, 1997–2016

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Background. The SENTRY Antimicrobial Surveillance Program was established in 1997 and encompasses over 750 000 bacterial isolates from ≥400 medical centers worldwide. Among the pathogens tested, *Pseudomonas aeruginosa* remains a common cause of multidrug-resistant (MDR) bloodstream infections and pneumonia in hospitalized patients. In the present study, we reviewed geographic and temporal trends in resistant phenotypes of *P. aeruginosa* over 20 years of the SENTRY Program.

Methods. From 1997 to 2016, 52 022 clinically significant consecutive isolates were submitted from ≥200 medical centers representing the Asia-Pacific region, Europe, Latin America, and North America. Only 1 isolate per patient per infection episode was submitted. Isolates were identified by standard algorithms and/or matrix-assisted laser desorption ionization-time of flight mass spectrometry. Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) methods and interpreted using CLSI and European Committee on Antimicrobial Susceptibility Testing 2018 criteria at JMI Laboratories.

Results. The most common infection from which *P. aeruginosa* was isolated was pneumonia in hospitalized patients (44.6%) followed by bloodstream infection (27.9%), with pneumonia having a slightly higher rate of MDR (27.7%) than bloodstream infections (23.7%). The region with the highest percentage of MDR phenotypes was Latin America (41.1%), followed by Europe (28.4%). The MDR rates were highest in 2005–2008 and have decreased in the most recent period. Colistin was the most active drug tested (99.4% susceptible), followed by amikacin (90.5% susceptible).

Conclusions. Over the 20 years of SENTRY Program surveillance, the rate of MDR *P. aeruginosa* infections has decreased, particularly in Latin America. Whether the trend of decreasing resistance in *P. aeruginosa* is maintained will be documented in future SENTRY Program and other surveillance reports.

Keywords. antimicrobial; multidrug resistance; *Pseudomonas aeruginosa*; surveillance; susceptibility.

The SENTRY Antimicrobial Surveillance Program was established in 1997 and encompasses over 750 000 bacterial isolates from more than 400 medical centers worldwide.

Among the pathogens tested in the SENTRY Program, *Pseudomonas aeruginosa* remains a common cause of multidrug-resistant ([MDR] nonsusceptible [NS] to at least 1 antimicrobial in 3 or more drug classes) bloodstream infections and pneumonia in hospitalized patients. Zilberberg et al [1] found that MDR *P. aeruginosa* was much more common in bloodstream infections (14.7%) and pneumonia (22.0%) than carbapenem-resistant *Enterobacteriaceae* from bloodstream infections (1.1%) and pneumonia (1.6%), which makes treatment of serious *P. aeruginosa* infections more challenging. Furthermore, delaying appropriate antimicrobial therapy has been associated with increased morbidity and mortality [2]. Patients with MDR *P. aeruginosa* have a higher 30-day mortality than patients with non-MDR *P. aeruginosa* [3].

Frequently, MDR *P. aeruginosa* isolates are resistant to carbapenems and other β-lactams, which is mediated through multiple mechanisms, including acquisition of metallo-β-lactamases, increased chromosomal AmpC production, extended spectrum β-lactamases, increased efflux, or changes in membrane permeability [4, 5]. In the present study, we reviewed geographic and temporal trends in resistant phenotypes of *P. aeruginosa* over the 20 years of the SENTRY Antimicrobial Surveillance Program.

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METHODS

During the period from 1997 to 2016, 52 022 clinically significant *P. aeruginosa* isolates were submitted for testing in the SENTRY Program from ≥400 medical centers representing the Asia-Pacific (excluding China and India), European (including Turkey and Israel), Latin American, and North American regions.

Participating centers submitted bacterial clinical isolates (1 isolate per patient per infection episode) that were consecutively collected by infection type according to a common protocol. The common SENTRY Program protocol established the number of isolates for the target infection types and the time period each year during which the isolates should be collected. Each institution contributed a specified number of isolates per year with approximately 50 isolates per target infection type. Infection types included bloodstream infection (BSI), pneumonia in hospitalized patients, skin and skin structure infection (SSSI), intra-abdominal infection, and urinary tract infection. Isolates were identified by the submitting laboratory's standard algorithms and/or matrix-assisted laser desorption ionization-time of flight mass spectrometry and confirmed at JMI Laboratories (North Liberty, IA).

Susceptibility (S) testing was performed at JMI Laboratories by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method and interpreted using CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018 criteria [6, 7] The antimicrobials tested included amikacin, cefepime, ceftazidime, ciprofloxacin, colistin (tested 2006–2016), meropenem, piperacillin-tazobactam, and tobramycin. Gentamicin, imipenem, and levofloxacin were also tested for resistant phenotype determination.

Resistant phenotypes analyzed using EUCAST criteria were as follows: MDR (NS to at least 1 antimicrobial in ≥3 drug classes), extensively drug-resistant ([XDR] NS to at least 1 agent in all but ≤2 drug classes), and pan drug-resistant (PDR), according to Magiorakos et al [8]. Ceftazidime-NS and meropenem-NS were determined according to EUCAST interpretive criteria.

RESULTS

Infection Types

The most common infection type from which *P. aeruginosa* was isolated was pneumonia in hospitalized patients (44.6%, n = 23 227) followed by BSI (27.9%, n = 14 539) and SSSI (19.1%, n = 9952) as shown in Table 1. The number of isolates from each of the 4 regions by infection type is shown in Figure 1. *Pseudomonas aeruginosa* was most frequently isolated from pneumonia in all 4 regions.

Antimicrobial Susceptibility

Pneumonia had a higher rate of isolates with MDR and XDR (27.7% and 19.0%, respectively) than BSIs (23.7% and 17.4%, respectively) as shown in Table 1. Multidrug-resistant rates over time are shown in Table 2, ranging from a high of 27.5% in 2005–2008 to a low of 21.8% in 2013–2016. Extensively drug-resistant rates also peaked in 2005–2008 at 20.2%. Pan drug-resistant isolates were rare throughout the study period. First identified in 2005–2008, PDR isolates totaled 0.1% and remained at 0.1% in the 2009–2012 and 2013–2016 time frames (Table 2). The frequency of ceftazidime-NS isolates was highest (25.1%) in the 2005–2008 period and has decreased to 19.2% most recently (Table 2). The rate of meropenem-NS isolates was highest (27.3%) in 2009–2012 and decreased to 22.7% in 2013–2016 (Table 2).

Activities of specific antimicrobials with CLSI and EUCAST clinical breakpoints are shown in Table 3 for all isolates and MDR and XDR phenotypes. Colistin (added to testing in 2006) was the most active agent overall (99.4%/99.4%S [CLSI/EUCAST]) and against isolates with MDR (98.9%/98.9%S [CLSI/EUCAST]) and XDR (98.7%/98.7%S [CLSI/EUCAST] phenotypes (Table 3). Amikacin was the second most active agent, inhibiting 90.5%/86.0% (CLSI/EUCAST) of all isolates, 65.0%/52.7% (CLSI/EUCAST) of MDR, and 55.9%/42.6% (CLSI/EUCAST) of XDR isolates. Tobramycin was slightly less active than amikacin and inhibited 84.6%/84.6% (CLSI/EUCAST) of all isolates, 45.7%/45.7% (CLSI/EUCAST) of MDR, and 34.2%/34.2% (CLSI/EUCAST) of XDR isolates.

Table 1. *Pseudomonas aeruginosa* Isolates (1997–2016) Stratified by Infection Type and Percentage of Isolates With Resistant Phenotypes

Resistant Phenotype[a]	Bloodstream Infection (n = 14 539)	Pneumonia in Hospitalized Patients (n = 23 227)	Skin and Skin Structure Infection (n = 9952)	Intra-abdominal Infection (n = 648)	Urinary Tract Infection (n = 2838)	Other Infection (n = 818)	Total (n = 52 022)
Multidrug resistant	23.7%	27.7%	21.7%	19.3%	23.0%	19.1%	24.9%
Extensively drug resistant	17.4%	19.0%	15.8%	12.7%	16.5%	12.3%	17.6%
Pan drug resistant	0.1%	0.1%	0.0%	0.5%	0.1%	0.0%	0.1%
Ceftazidime nonsusceptible	22.0%	24.7%	20.1%	19.1%	18.4%	17.2%	22.5%
Meropenem nonsusceptible	22.3%	27.1%	20.6%	21.9%	19.2%	18.1%	23.9%

[a]Criteria as published by European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018.

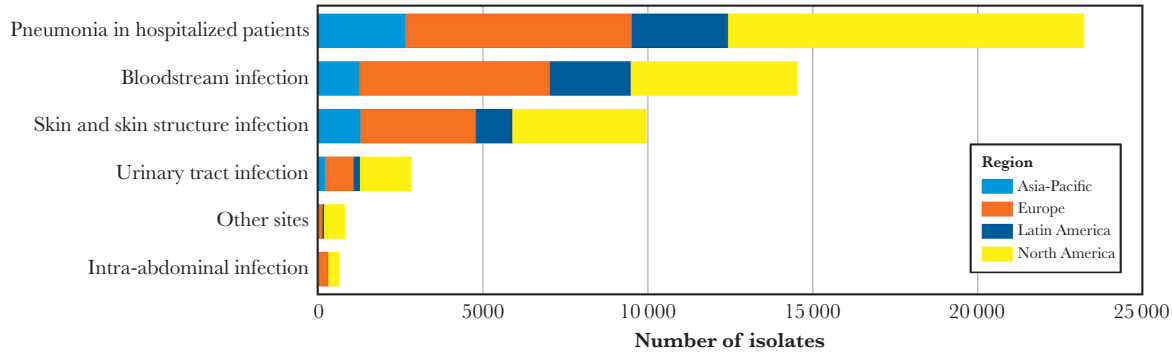

Figure 1. Distribution of *Pseudomonas aeruginosa* isolates by infection type and region.

Other commonly used antipseudomonal β-lactams (cefepime, ceftazidime, meropenem, and piperacillin-tazobactam) had susceptibilities for all isolates ranging from 73.2% to 79.3% and 13.8% to 27.5% for MDR and 5.5% to 17.6% for XDR (CLSI and EUCAST; Table 3). Ciprofloxacin had overall 73.0%S with CLSI breakpoints and 67.8%S with the lower EUCAST breakpoints, only 24.6%/17.1%S for MDR, and 13.6/7.8%S for XDR (CLSI/EUCAST). Aztreonam was the least active antimicrobial tested with overall susceptibility of 64.7%/4.6%, and only 15.6%/1.1%S for MDR and 12.0/0.5%S for XDR (CLSI/EUCAST; Table 3).

Geographic Resistance Trends

Isolates with the MDR phenotype were most frequently isolated in Latin America with 41.1%, followed by Europe with 28.4%, North America with 18.9%, and Asia-Pacific with 18.8% (Figure 2).

Table 4 shows the percentage susceptibility of the antimicrobials by 4-year period for all regions and for each individual region. Susceptibilities for North American and European isolates were relatively stable with variations within 10% between each period. The largest shift in susceptibility for North American isolates was the decrease in meropenem susceptibility from 85.2% in 1997–2000 to 79.0% in 2005–2008, with susceptibility increasing to 81.8% in 2013–2016. European isolates showed a similar shift for meropenem, from a high of 76.5% in 1997–2000 and a low of 68.9% in 2009–2012 with a return to 70.6% in 2013–2016.

The largest variations were seen in Latin America, with amikacin susceptibility increasing from 70.2% in 2001–2004 to 86.8% in 2013–2016. β-lactam susceptibilities also varied greatly with meropenem susceptibility dropping from a high of 70.8% in 1997–2000 to a low of 56.2% in 2009–2012. Meropenem susceptibility rose to 67.7% in 2013–2016. Asia-Pacific experienced a similar trend with meropenem susceptibility dropping from a high of 84.7% in 1997–2000 to a low of 77.1% in 2009–2012 and rising to 82.8% in the most recent period. Piperacillin-tazobactam susceptibility increased from 69.4% in 2005–2008 to 80.2% in 2013–2016.

DISCUSSION

Over the 20 years of SENTRY Program surveillance, the rates of MDR and other resistant phenotypes for *P. aeruginosa* were highest in 2005–2008 and decreased in the most recent period. Latin America showed the sharpest decrease in MDR rate, which was associated with a rise in susceptibility to aminoglycosides and β-lactams. The metallo-β-lactamase SPM-1 that has been reported in multiple Brazilian institutions may be contributing to the meropenem resistance reported there [9, 10]. Among the 6722 *P. aeruginosa* isolates collected from the Latin American region, 3057 (45.5%) were collected from Brazilian medical centers. The results could have been directly influenced by any changes in the epidemiology within Brazilian medical centers. The high carbapenem resistance rates found in Brazilian hospitals have been mainly caused by the spread of the XDR *P. aeruginosa* ST277 clone, which chromosomally encodes for SPM-1 and RmtD, a 16S ribosomal ribonucleic acid (rRNA)

Table 2. Resistant Phenotype Percentages of *Pseudomonas aeruginosa* Isolates by 4-Year Period Over 20 Years of the SENTRY Program

Resistant Phenotype [a]	1997–2016 (n = 52 022)	1997–2000 (n = 9512)	2001–2004 (n = 7928)	2005–2008 (n = 7170)	2009–2012 (n = 10 951)	2013–2016 (n = 16 461)
Multidrug resistant	24.9%	24.1%	27.3%	27.5%	26.9%	21.8%
Extensively drug resistant	17.6%	15.9%	19.6%	20.2%	19.6%	15.2%
Pandrug resistant	0.1%	0.0%	0.0%	0.1%	0.1%	0.1%
Ceftazidime nonsusceptible	22.5%	22.8%	23.4%	25.1%	25.0%	19.2%
Meropenem nonsusceptible	23.9%	19.3%	24.9%	26.6%	27.3%	22.6%

[a]Criteria as published by European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018.

Table 3. Susceptibilities of *Pseudomonas aeruginosa* for All Regions and Time Periods

Resistant Phenotype Antimicrobial Agent	MIC_{50}[b] (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
All isolates (52 022)									
Amikacin	≤4	16	≤4 to >32	90.5	2.5	7	86.0	4.5	9.5
Aztreonam	8	>16	≤0.12 to >16	64.7	13.8	21.5	4.6	73.9	21.5
Cefepime	4	16	≤0.5 to >16	79.3	10.9	9.8	79.3		20.7
Ceftazidime	≤2	>16	≤2 to >16	77.5	5.2	17.3	77.5		22.5
Ciprofloxacin	≤0.5	>2	≤0.5 to >2	73	4.5	22.6	67.8		32.2
Colistin	1	2	≤0.5 to >4	99.4		0.6	99.4		0.6
Meropenem	0.5	>8	≤0.12 to >8	76.1	6.5	17.4	76.1	13	10.9
Piperacillin-tazobactam	8	>64	≤1 to >64	73.2	12.1	14.8	73.2		26.8
Tobramycin	0.5	>8	≤0.25 to >8	84.6	0.9	14.5	84.6		15.4
Multidrug resistant (12 972)									
Amikacin	8	>32	≤4 to >32	65.0	8.6	26.4	52.7	12.3	35
Aztreonam	>16	>16	≤0.12 to >16	15.6	22.1	62.3	1.1	36.7	62.3
Cefepime	16	>16	≤0.12 to >16	26.8	36.5	36.7	26.8		73.2
Ceftazidime	>16	>16	≤2 to >16	26.3	14.9	58.8	26.3		73.7
Ciprofloxacin	>2	>2	≤0.5 to >2	24.6	7.5	67.9	17.1		82.9
Colistin	1	2	≤0.5 to >4	98.9		1.1	98.9		1.1
Meropenem	8	>8	≤0.12 to >8	27.5	13.4	59.1	27.5	32.1	40.4
Piperacillin-tazobactam	>64	>64	≤0.5 to >64	13.8	34.7	51.4	13.8		86.2
Tobramycin	>8	>8	≤0.25 to >8	45.7	2.8	51.5	45.7		54.3
Extensively drug resistant (9161)									
Amikacin	16	>32	≤4 to >32	55.9	10.3	33.8	42.6	13.3	44.1
Aztreonam	>16	>16	≤0.12 to >16	12	21.6	66.4	0.5	33.1	66.4
Cefepime	16	>16	≤0.12 to >16	14.2	39.4	46.3	14.2		85.8
Ceftazidime	>16	>16	≤2 to >16	16.2	15.6	68.2	16.2		83.8
Ciprofloxacin	>2	>2	≤0.5 to >2	13.6	7.3	79.2	7.8		92.2
Colistin	1	2	≤0.5 to >4	98.7		1.3	98.7		1.3
Meropenem	>8	>8	≤0.12 to >8	17.6	12.4	70	17.6	31.7	50.7
Piperacillin-tazobactam	>64	>64	≤0.5 to >64	5.5	34.7	59.8	5.5		94.5
Tobramycin	>8	>8	≤0.25 to >8	34.2	3.0	62.9	34.2		65.8

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

[a]Criteria as published by CLSI 2018 and EUCAST 2018.

[b]MIC, minimum inhibitory concentration; S, susceptible, I, intermediate, R, resistant.

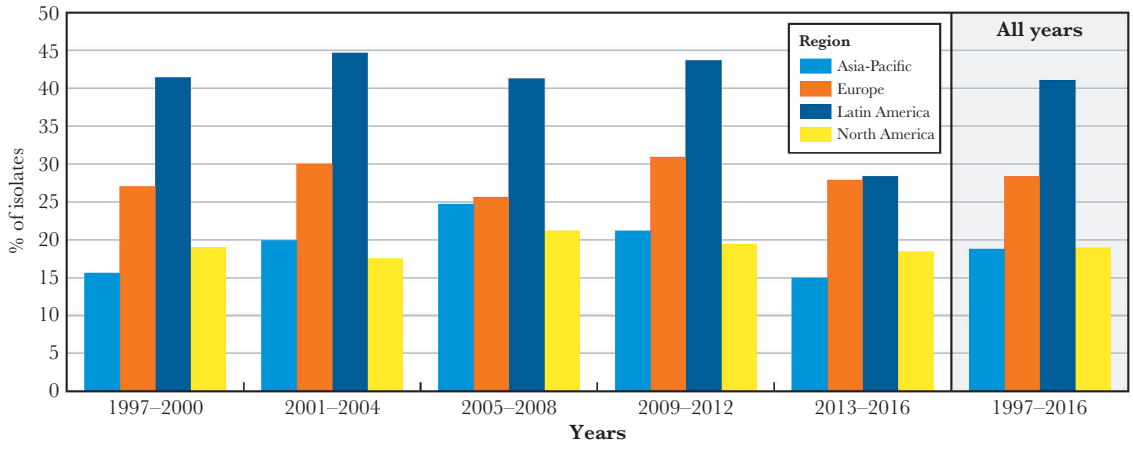

Figure 2. Percentage of multidrug-resistant *Pseudomonas aeruginosa* in 4 regions over the 20-year SENTRY Program study period.

Table 4. Susceptibilities of *Pseudomonas aeruginosa* Isolates in Each 4-Year Period for 4 Regions

Region Antimicrobial Agent	Susceptibility % by Time Period[a]					
	1997–2000	2001–2004	2005–2008	2009–2012	2013–2016	Overall
All regions (n)	(9512)	(7928)	(7170)	(10 951)	(16 461)	(52 022)
Amikacin	89.3	88.4	88.9	90.3	93.1	90.5
Cefepime	79	77.0	77.8	76.5	83.1	79.3
Ceftazidime	77.2	76.6	74.9	75.0	80.8	77.5
Ciprofloxacin	74	69.9	70.8	71.7	75.7	73
Colistin[b]	N/A	N/A	99.4	99.2	99.5	99.4
Meropenem	80.7	75.1	73.4	72.7	77.4	76.1
Piperacillin-tazobactam	73.4	70.6	70.7	70.1	77.4	73.2
Tobramycin	83.4	80.4	81.6	84.2	88.8	84.6
North America (n)	(4380)	(2763)	(2129)	(4351)	(8847)	(22 470)
Amikacin	95.4	96.7	96.1	97.1	96.7	96.4
Cefepime	83.1	85.5	83.7	83.4	86.1	84.7
Ceftazidime	80.7	85.6	81.4	82.7	85.1	83.5
Ciprofloxacin	76.8	74.5	75.7	76.3	78.0	76.8
Colistin	N/A	N/A	99.9	99.1	99.6	99.5
Meropenem	85.2	83.2	79	80.3	81.8	82.1
Piperacillin-tazobactam	78.5	79.7	77.1	77.5	81.6	79.5
Tobramycin	91.9	92.7	90.5	92.4	93.0	92.4
Europe (n)	(2380)	(2947)	(2712)	(3762)	(5620)	(17 421)
Amikacin	85.7	87.9	90.5	87.2	87.8	87.8
Cefepime	77.2	75.2	79.6	73.4	78.2	76.7
Ceftazidime	77.1	74.8	76.1	70.1	74.4	74.2
Ciprofloxacin	71.3	69.3	72.2	68.3	70.9	70.3
Colistin	N/A	N/A	99.6	99.4	99.5	99.5
Meropenem	76.5	73.3	74.2	68.9	70.6	72.1
Piperacillin-tazobactam	71.9	68.6	73.4	66.2	70.8	70.0
Tobramycin	75.1	75.9	81.3	78.5	82.3	79.3
Asia-Pacific (n)	(1243)	(792)	(811)	(1327)	(1236)	(5409)
Amikacin	96.5	94.4	91.6	94.2	95.0	94.5
Cefepime	84.8	82.2	77.4	79.0	86.8	82.3
Ceftazidime	81.2	81.4	75.2	77.5	81.9	79.6
Ciprofloxacin	85.8	82.1	77.3	80.8	83.6	82.2
Colistin	N/A	N/A	97.2	98.6	99.1	98.5
Meropenem	84.7	80.8	79.4	77.1	82.8	81.1
Piperacillin-tazobactam	77.7	74.2	69.4	71.8	80.2	75.1
Tobramycin	92.0	88.5	87.8	91.8	93.7	91.2
Latin America (n)	(1509)	(1426)	(1518)	(1511)	(758)	(6722)
Amikacin	71.4	70.2	74.8	74.9	86.8	74.4
Cefepime	65.1	61.4	66.5	62.3	77.2	65.4
Ceftazidime	64.2	60.1	63.2	62.8	74.6	64.0
Ciprofloxacin	60.5	55.7	57.9	58.8	71.1	59.7
Colistin	N/A	N/A	99.8	99.4	99.1	99.5
Meropenem	70.8	59.7	61.2	56.2	67.7	62.7
Piperacillin-tazobactam	57.3	54.7	57.7	57.4	73.1	58.7
Tobramycin	64.5	61.2	66.2	68	80.6	66.8

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; N/A, not available.

[a]Susceptible based on criteria as published by CLSI 2018.

[b]Agent added in 2006.

methylase [10, 11]. This clone also possesses mutations on the quinolone-resistant determining regions of *gyrA* and *parC*, and it harbors *sul1* and aminoglycoside-modifying enzyme-encoding genes such as *aac(6′)-Ib-cr* and *aadA7* [11]. In general, SPM-1-producing *P. aeruginosa* ST277 isolates are susceptible only to polymyxins. Although no studies that include isolates from all Brazilian regions have been carried out, studies evaluating isolates from specific regions or single institutions have shown a decrease in the frequency of SPM-1-producing *P. aeruginosa* isolates [12, 13]. These studies may support the increase

in the antimicrobial susceptibility rates in Latin America, especially for aminoglycosides and carbapenems, observed by the SENTRY Program study in the 2013–2016 period. Cacci et al [13] also found that as the frequency of the SPM-1 clone decreased, carbapenem-resistant isolates displayed the more commonly observed resistance mechanisms overall, including porin loss and efflux overproduction [14].

The Asia-Pacific region had an overall lower frequency of MDR *P. aeruginosa* than Latin America and Europe (Figure 2). The region saw an increase in MDR *P. aeruginosa*, from 15.6% in 1997–2000 to 24.7% in 2005–2008 and decreased to 15.0% in 2013–2016. A study by Pfaller et al [15] found that frequency of meropenem-resistant *P. aeruginosa* varied by country in the period 2013–2015, with South Korea having the highest rate (46.3%). Studies in the Asia-Pacific region have shown an increasing prevalence of metallo-β-lactamases and carbapenemases in *P. aeruginosa,* particularly the ST235 clone, which may explain the increase in MDR seen in 2005–2008 [16–18]. Because strain typing was not performed in this study, it is unknown whether the decrease in resistance is due to a decrease in the prevalence of ST235 or other causes. The European and North American medical centers had a stable frequency of MDR *P. aeruginosa*, with the North American and European rates ranging from 17.5% to 21.2% and 25.6% to 30.9%, respectively, over the 20-year period. Isolates from both regions showed a decrease in meropenem susceptibility in 2009–2012, although susceptibility improved in the most recent time period for both regions. The ST235 clone and others that have been globally disseminated may have contributed to the increase in meropenem resistance and, perhaps, to the variations observed [19].

CONCLUSIONS

This study has shown variation in the resistance rates over time and over geography; however, MDR *P. aeruginosa* remains a cause of serious infections. The improved activities of newer agents, such as ceftolozane-tazobactam and ceftazidime-avibactam, against *P. aeruginosa* including MDR isolates have been published elsewhere, and those agents may be effective treatment options, especially for patients with infections caused by meropenem-resistant isolates [20, 21]. Whether the trend of decreasing resistance in *P. aeruginosa* is maintained will be documented in future SENTRY Program and other international surveillance studies.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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