Susceptibility Rates in Latin American Nations: Report from the Emerging Markets Resistance Surveillance Programme

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ABSTRACT

Objective: To establish an Emerging Markets Resistance Surveillance (EMRS) Programme monitoring antimicrobial resistance (R) in 3 geographic regions including Latin America (LATAM; Argentina [ARG], Brazil [BRA], Chile, Colombia [CBA], Costa Rica, Ecuador [ECU], Guatemala [GUA], Mexico [MEX], Panama [PAN], Peru, and Venezuela [VEN]). In 2011, 4,979 organisms were collected from 11 selected nations/20 laboratories for representative antimicrobial susceptibility (S) testing in a central laboratory design.

Methods: Nearly 30 currently marketed agents were S tested by CLSI methods and results interpreted by CLSI, EUCAST and USA-FDA breakpoints. The five most common Gram-positive (*S. aureus* [SA, 921], CoNS [299], *S. pneumoniae* [SPN; 182], β-haemolytic streptococci [115]) and Gram-negative (*E. coli* [EC; 644], *Klebsiella* spp. [KSP; 517], Enterobacters [272], *P. aeruginosa* [PSA; 586], Acinetobacters [ACB; 494]) pathogens were analyzed. Tested agents included: linezolid (LZD), vancomycin (VAN), tigecycline (TIG), colistin (COL), cefoperazone/sulbactam (C/S), and amikacin (AMK). R mechanisms were characterized, where needed.

Results: MRSA rates varied (Table) from 29% (CBA and BRA) to 79% (Peru); but LZD (MIC_{90}, 2 mg/L), TIG (MIC_{90}, 0.12 mg/L) and VAN (MIC_{90}, 1 mg/L) covered all strains as well as the CoNS. Enterococci showed a 14% VRE rate (usually VAN A type), highest in BRA and MEX; all inhibited by TIG and daptomycin, but not LZD (three, non-S with G2576T mutations and a unique *cfr* associated with L3-L4 alterations from PAN in a clonal *E. faecalis*). Penicillin-R among SPN and viridans group streptococci was 51.6 and 41.1%, respectively. LZD overall R rate against Gram-positive cocci was only 0.3%. High ESBL rates were noted in EC (54-71%) and KSP (≥50%) from GUA, MEX and Peru, and six nations, respectively. Carbapenem-R in KSP was 9%, highest rates associate with KPC-2 or -3 in BRA, CBA, ECU, PAN and VEN; also a NDM-1 in KSP from CBA. AMK, TIG, C/S and the carbapenems were the broadest-spectrum agents versus Enterobacteriaceae. Only COL inhibited >90% of PSA, and COL and TIG (≤2 mg/L) covered ≥85% of ACB.

Conclusions: LATAM EMRS nations demonstrated variable, yet high levels of R especially among Enterobacteriaceae (β-lactamase-mediated), PSA and ACB. MRSA (48%), VRE (15%) and multidrug-R SPN were also regional therapeutic challenges needing immediate epidemiologic attention.

Nation	ESBL (%)[a]		CARB–R(%)		VRE (%)		MRSA (%)	
	EC	KSP	KSP	COL/TIG –S	Total	VanA	Total	LZD -S
Argentina	20	53	11-12	96-98	10	100	55	100
Brazil	18	50	17-18	93-99	27	89	29	100
Chile	28	59	0	-	0	-	68	100
Colombia	24	41	9-18	96-100	11	31	29	100
Costa Rica	7	19	0	–	7	100	55	100
Ecuador	20	40	5	100	0	–	31	100
Guatemala	59	69	0	–	9	100	49	100
Mexico	71	56	0	–	26	100	48	100
Panama	37	40	20	100	13	100	47	100
Peru	54	70	0	–	16	100	79	100
Venezuela	10	40	15	90-100	12	67	63	100
All	37	52	9	97	14	91	48	100

a. EC = *E. coli*, KSP = *Klebsiella* spp.; TIG = tigecycline; COL = colistin; CARB=carbapenem; VRE=vancomycin-R enterococci

INTRODUCTION

Recent escalations of β-lactamase-mediated resistances (extended-spectrum β-lactams [ESBL] and metallo-β-lactamases [MBL]) worldwide has complicated antimicrobial therapy of important/common Gram-negative bacillary infections. Already existing resistance challenges among Gram-positive cocci (methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE) and multidrug-resistant pneumococci [MDR]) further emphasize the need for global, regional, national and local surveillance of antimicrobial susceptibility patterns to guide empiric therapy and direct or monitor interventions. These resistant strains increase patient morbidity and mortality, as well as the cost of medical care delivery.

Current surveillance programs, particularly at the global level, have concentrated on larger "developed" nations where fiscal markets and supporting regulatory agencies (USA-FDA, EMA) would recognize the value, and have the resources to sustain monitoring. In contrast, "developing" countries have faced more limited support for drug resistance surveillance, drug patent protection, prescription drug law and antimicrobial stewardship programmes. Beginning in 2011, the Latin American (LATAM) surveillance programmes (SENTRY Antimicrobial Surveillance Programme and several others) administered by JMI Laboratories (North Liberty, Iowa, USA) were expanded to include sites within some countries previously not sampled or having significant reported statistics. This emerging Markets Resistance Surveillance (EMRS) Programme reference test information in several areas of the world including 11 countries in LATAM including seven that are uncommonly sampled (Colombia, Costa Rica, Ecuador, Guatemala, Panama, Peru and Venezuela). Data from testing nearly 5,000 clinical isolates in 2011 are presented here.

METHODS

Nations and organisms sampled. Eleven countries in LATAM (20 sites with 93-503 strains/site) were sampled with a target of ≥250 isolates per nation. The compliance to protocol ranged from 190 [Venezuela, 95%] to >100% for the "developed" countries. The collected organisms were isolated from various types of clinical infections including bloodstream (18.8%), respiratory tract (20.1%), skin and skin structure (13.1%) as well as other or unspecified body sites. The countries (sites; sample size) were: Argentina (two; 498), Brazil (five; 1,588), Chile (two; 467), Colombia (one; 208), Costa Rica (one; 193), Ecuador (one; 192), Guatemala (one; 201), Mexico (three, 1,052), Panama (one; 196), Peru (one; 194) and Venezuela (two, 190); one isolate per patient per infectious episode. The organisms forwarded to the monitoring central laboratory (JMI Laboratories) were as follows: *S. aureus* (921), coagulase-negative *Staphylococcus* species (CoNS; 299), enterococci (218; 92.2% *E. faecalis* or *E. faecium*), *S. pneumoniae* (182), β-haemolytic streptococci (115; 92.2% *S. pyogenes* or *S. agalactiae*), viridans group streptococci (90; more than eight species), *E. coli* (644; 37.3% ESBL phenotype), *Klebsiella* spp. (517; three species, 52.4% ESBL phenotype), *Enterobacter* spp. (272), *P. mirabilis* (74; 24.3% ESBL phenotype), other Enterobacteriaceae (292), *H. influenzae* (128; 29.7% β-lactamase-positive), *M. catarrhalis* (33), *P. aeruginosa* (586), and *Acinetobacter* spp. (494; 94.7% *A. baumannii*). A total of 4,979 isolates were tested, 4,865 or 97.7% presented in Tables 1 and 2.

Organisms detected with resistances to key, marketed agents were tested by various molecular methods such as PCR amplification/sequencing, example ESBLs, MBLs, MDR Gram-negative bacilli or Gram-positive cocci.

Methods and antimicrobials tested. CLSI M07-A9 (2012) methods were applied using validated broth microdilution panels produced by ThermoFisher Scientific Inc., formerly TREK Diagnostics (Cleveland, Ohio, USA). Interpretations of results utilized CLSI (M100-S23, 2013), USA-Food and Drug Administration (FDA) and EUCAST (2013) criteria; and the results of quality control (QC) tests were dominantly (nearly 99.0%) within QC ranges (CLSI M100-S23) for six utilized control organisms.

The sponsor (Pfizer Inc., New York, New York, USA) produced compounds included: linezolid, tigecycline, piperacillin/tazobactam, ampicillin/sulbactam, cefoperazone and cefoperazone/sulbactam. For studying Gram-negative bacilli, Gram-positive cocci, and fastidious respiratory tract species, numerous additional (15-25) drugs were also tested. ESBL patterns were defined for *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* per CLSI (2013) criteria as a MIC of ≥2 mg/L for aztreonam or ceftriaxone or ceftazidime. Carbapenem-resistant Enterobacteriaceae (CRE) were detected by a MIC at ≥2 mg/L for doripenem or imipenem or meropenem.

RESULTS

Antimicrobial profiles of 1,825 Gram-positive pathogens (Table 1)

- *S. aureus* isolates (921, 47.8% MRSA overall) exhibited complete susceptibility (100.0%) to linezolid ($MIC_{50/90}$, 1/2 mg/L), daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L), tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and vancomycin ($MIC_{50/90}$, 1/1 mg/L). Rare resistances to TMP/SMX (1.1%) were observed (Table 1). Aminoglycoside (gentamicin) resistance was approximately 20.0% with highest rates in Peru (72.2%), Chile (30.0%), Argentina (30.7%) and Venezuela (30.6%).
- CoNS samples (299; 83.9% methicillin-resistant) showed common co-resistances and only four agents with >90% susceptibility including linezolid, daptomycin, doxycycline, teicoplanin and vancomycin (94.3 to 100.0% susceptible). The rare occurrences of linezolid non-susceptibility (1.7%) occurred in Brazil (five strains [4.8%]; three species [*S. epidermidis*, three clonal isolates with a G2576 mutation; one *S. hominis* with a G2576, L3 (F147I, M156T) and L4 (S77T) mutations and one *S. lugdunensis* with a G2576 mutation]) with MIC values of 8-32 mg/L; and Mexico (two strains of *S. epidermidis* and *S. haemolyticus* having *cfr* ± L3 or L4 mutations) with MIC values at only 4 mg/L. Teicoplanin non-susceptible results (11.4% by EUCAST breakpoints) were found in Brazil (10 strains, 9.6%), Costa Rica (6 strains, 42.9%), Mexico (8 strains, 8.9%), Panama (2 strains, 15.4%), Peru (2 strains, 14.3%), and Venezuela (5 strains, 45.5%).
- Enterococci (218, either *E. faecalis* or *E. faecium*) had a VRE rate of 14.2-15.1% and 91.4-93.7% with a VAN-A pattern (Table 1). Ten nations had documented VRE (range, 7.1% [Costa Rica] to 25.7-26.5% [Brazil and Mexico]) and the best tested agents (% susceptible) were linezolid (98.6), daptomycin (100.0), teicoplanin (86.2-86.7%) and vancomycin (84.9%). Linezolid non-susceptibility was detected in Brazil (2.9% prevalence overall; G2576 mutations in clonal *E. faecalis*) and in Panama City, Panama (13.3% prevalence; *cfr* clonal occurrences in *E. faecalis*).
- *S. pneumoniae* (182) isolates from LATAM were dominantly penicillin-non-susceptible (51.6%) with highest rates in Mexico (84.8%) and Venezuela (81.2%). Similarly, ceftriaxone non-susceptible rates were elevated (21.1-43.7%) in the same two nations. Poor coverage (susceptible %) were noted for erythromycin (62.6%), tetracycline (63.7-64.8%) and TMP/SMX (45.1-48.4%). The best antimicrobials tested against pneumococci were levofloxacin, linezolid, tigecycline and vancomycin, each inhibiting all strains at published breakpoints (Table 1).

Antimicrobial profiles of Gram-negative bacilli (Tables 2 and 3)

- *E. coli* (644) had an ESBL-phenotype rate of 37.3%, see Table 3. The most active tested agents were amikacin (92.7% susceptible), cefoperazone/sulbactam (92.7%), meropenem (100.0%) and tigecycline (100.0%). The most active cephalosporin was cefepime at 72.4% by CLSI breakpoints (Table 2).
- *Klebsiella* spp. (517) showed very elevated resistance rates (Table 2), with only four drugs inhibiting ≥80.0% of isolates (tigecycline [97.9%], colistin [96.5%], meropenem [90.3%] and amikacin [89.0%]). The ESBL phenotype rate was 52.4% (Table 3), and CRE were identified (no./percentage) in Argentina (6/10.7), Brazil (31/17.3), Colombia (4/18.2), Ecuador (2/10.0), Mexico (1/1.1), Panama (4/20.0) and Venezuela (3/15.0). The following carbapenemases were identified: KPC-2 (Brazil [3], Ecuador [2], Venezuela [3]), KPC-3 (Colombia [2], Panama [3]) and NDM-1 (Colombia [1]).
- *P. mirabilis* (74) showed an ESBL phenotype rate at 24.3% and several UTI-targeted antimicrobials (ampicillin and TMP/SMX) were only 47.3-52.7% effective in vitro.
- Among other enteric bacilli, *Enterobacter* spp. showed a CRE rate at 2.9% with higher rates in Colombia and Venezuela (10.0-12.5%). Amikacin, cefoperazone/sulbactam, cefepime, carbapenems and tigecycline were quite active against these species, as were nearly all tested agents versus *H. influenzae* (128) and *M. catarrhalis* (33).

Antimicrobial profiles of non-fermentative bacilli (Table 2)

- *P. aeruginosa* (586) were most susceptible to amikacin (75.4%), tobramycin (70.1%) and colistin (99.5%). Carbapenem resistance was high due to endemic β-lactamase (SPM-1, usually in Brazil), but the most elevated rates were noted in Guatemala (75.8%), Peru (62.5-68.8%) and Ecuador (55.6%). The most active β-lactam was ceftazidime (65.7%, MIC_{50} at 4 mg/L).
- *Acinetobacter* spp. (494, four species) were significantly inhibited (% susceptible) only by colistin (98.6%), cefoperazone/sulbactam (59.3%), doxycycline (80.4%) and tigecycline (MIC_{90}, 4 mg/L). All carbapenems and aminoglycosides showed susceptibility rates at <50%.

CONCLUSIONS

- Monitoring of nearly 5,000 LATAM pathogens in 2011 documents increasing antimicrobial resistances among nearly all sampled species (Tables 1-3).
- Although methicillin-resistance was elevated among staphylococci (47.8-83.9%), several agents remain active including linezolid, daptomycin, tigecycline and glycopeptides. VRE are expanding (14.2-15.1%, in 10 nations) as are non-susceptible rates for β-lactams in *S. pneumoniae*. Rare linezolid-resistant (<1.0% overall) CoNS and enterococcal were noted with *cfr* and target mutations.
- β-lactamase-mediated (ESBL, MBL [NDM-1], serine carbapenemases) resistance in *E. coli*, *Klebsiella* spp., some other Enterobacteriaceae and non-fermenters continues to evolve (Table 2) to levels of 37.3-52.4% and few drugs remain active at the ≥90% susceptible level.
- Use of combination therapies directed by surveillance programs and patient isolate tests appear needed in LATAM, and interventions to control further escalation are urgently needed across this region.

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Table 1. Activity of selected antimicrobial agents when tested against 1,825 Gram-positive pathogens from Latin America nations (2011).

Organism (no. tested) / Antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
S. aureus (921)					
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[b]	0.06	0.12	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Pip/tazo	2	>64	≤0.5 – >64	52.2 / 47.8	52.2 / 47.8
Amox/clav	≤1	>8	≤1 – >8	52.2 / 47.8	52.2 / 47.8
Ceftriaxone	4	>8	1 – >8	52.2 / 47.8	52.2 / 47.8
Clindamycin	≤0.25	>2	≤0.25 – >2	65.4 / 34.6	65.0 / 34.6
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Doxycycline	0.12	0.5	≤0.06 – 8	98.6 / 0.0	95.7 / 2.1
Erythromycin	0.5	>16	≤0.12 – >16	51.6 / 46.9	52.0 / 47.4
Gentamicin	≤1	>8	≤1 – >8	80.5 / 18.9	79.9 / 20.1
Levofloxacin	0.25	>4	≤0.12 – >4	63.1 / 36.3	63.1 / 36.3
Meropenem	0.12	>8	≤0.06 – >8	52.2 / 47.8	52.2 / 47.8
Oxacillin	1	>2	≤0.25 – >2	52.2 / 47.8	52.2 / 47.8
Penicillin	>8	>8	≤0.06 – >8	7.5 / 92.5	7.5 / 92.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	98.4 / 1.6	98.4 / 1.3
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
CoNS (299)[c]					
Linezolid	0.5	1	0.25 – >8	98.3 / 1.7	98.3 / 1.7
Tigecycline[b]	0.06	0.12	≤0.03 – 0.5	- / -	100.0 / 0.0
Pip/tazo	2	>64	≤0.5 – >64	16.1 / 83.9	16.1 / 83.9
Amox/clav	2	>8	≤1 – >8	16.1 / 83.9	16.1 / 83.9
Ceftriaxone	>8	>8	0.5 – >8	16.1 / 83.9	16.1 / 83.9
Clindamycin	0.5	>2	≤0.25 – >2	50.2 / 48.5	48.5 / 49.8
Daptomycin	0.5	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Doxycycline	0.5	2	≤0.06 – >8	94.3 / 2.0	87.6 / 8.7
Erythromycin	>16	>16	≤0.12 – >16	28.8 / 70.2	28.8 / 70.9
Gentamicin	8	>8	≤1 – >8	41.8 / 45.5	35.8 / 64.2
Levofloxacin	4	>4	≤0.12 – >4	41.5 / 54.8	41.5 / 54.8
Meropenem	2	>8	≤0.06 – >8	16.1 / 83.9	16.1 / 83.9
Oxacillin	>2	>2	≤0.25 – >2	16.1 / 83.9	16.1 / 83.9
Penicillin	8	>8	≤0.06 – >8	9.0 / 91.0	9.0 / 91.0
TMP/SMX	2	>4	≤0.5 – >4	50.2 / 49.8	50.2 / 27.1
Vancomycin	2	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Enterococci (218)[d]					
Linezolid	1	2	0.5 – 8	98.6 / 0.5	99.5 / 0.5
Tigecycline[b]	0.06	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Pip/tazo	8	>64	≤0.5 – >64	75.2 / -	75.2 / -
Amox/clav	≤1	>8	≤1 – >8	75.2 / -	75.2 / 24.8
Ampicillin	1	>8	≤0.25 – >8	75.2 / 24.8	73.4 / 24.8
Daptomycin	1	2	≤0.06 – 4	100.0 / -	- / -
Doxycycline	8	>8	≤0.06 – >8	42.7 / 20.2	- / -
Erythromycin	>16	>16	≤0.12 – >16	10.1 / 66.1	- / -
Imipenem	1	>8	≤0.12 – >8	- / -	73.4 / 25.2
Levofloxacin	2	>4	0.5 – >4	54.6 / 40.8	- / -
Teicoplanin	≤2	>16	≤2 – >16	86.7 / 13.3	86.2 / 13.8
Vancomycin	1	>16	0.25 – >16	84.9 / 14.2	84.9 / 15.1
S. pneumoniae					
Penicillin-susceptible (88)					
Linezolid	1	1	0.25 – 1	100.0 / -	100.0 / 0.0
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	- / -
Amox/clav	≤1	≤1	≤1 – 4	98.9 / 0.0	- / -
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 1	100.0 / 0.0	97.7 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.12	8	≤0.12 – 16	87.5 / 12.5	87.5 / 12.5
Levofloxacin	1	1	0.5 – >4	97.7 / 2.3	97.7 / 2.3
Meropenem	≤0.06	≤0.06	≤0.06 – 0.5	98.9 / 0.0	100.0 / 0.0
Penicillin[e]	≤0.06	≤0.06	≤0.06	100.0 / 0.0	- / -
Tetracycline	0.5	>8	≤0.25 – >8	80.7 / 19.3	79.5 / 19.3
TMP/SMX	≤0.5	4	≤0.5 – >4	75.0 / 17.0	81.8 / 17.0
Vancomycin	0.5	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-intermediate (40)					
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	- / -
Amox/clav	≤1	≤1	≤1 – 4	97.5 / 0.0	- / -
Ceftriaxone	0.25	0.5	≤0.06 – 1	100.0 / 0.0	97.5 / 0.0
Clindamycin	≤0.25	>2	≤0.25 – >2	75.0 / 25.0	75.0 / 25.0
Erythromycin	≤0.12	>16	≤0.12 – >16	55.0 / 45.0	55.0 / 45.0
Levofloxacin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	≤0.06	0.25	≤0.06 – 0.5	92.5 / 0.0	100.0 / 0.0
Penicillin[e]	0.25	1	0.12 – 1	100.0 / 0.0	- / -
Tetracycline	0.5	>8	≤0.25 – >8	72.5 / 25.0	70.0 / 27.5
TMP/SMX	2	>4	≤0.5 – >4	35.0 / 40.0	35.0 / 40.0
Vancomycin	0.25	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Penicillin-resistant (54)					
Linezolid	0.5	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	- / -
Amox/clav	2	8	≤1 – 8	50.0 / 31.5	- / -
Ceftriaxone	1	2	0.5 – >8	50.0 / 1.9	5.6 / 1.9
Clindamycin	>2	>2	≤0.25 – >2	42.6 / 55.6	44.4 / 55.6
Erythromycin	>16	>16	≤0.12 – >16	27.8 / 72.2	27.8 / 72.2
Levofloxacin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
Meropenem	0.5	1	0.25 – 1	5.6 / 40.7	100.0 / 0.0
Penicillin[e]	4	4	2 – 4	40.7 / 0.0	- / -
Tetracycline	>8	>8	≤0.25 – >8	33.3 / 66.7	33.3 / 66.7
TMP/SMX	>4	>4	≤0.5 – >4	3.7 / 90.7	3.7 / 90.7
Vancomycin	0.25	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (115)[f]					
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Pip/taz	≤0.5	≤0.5	≤0.5	- / -	100.0 / 0.0
Amox/clav	≤1	≤1	≤1	- / -	100.0 / 0.0
Ceftriaxone	≤0.06	0.12	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	92.2 / 7.8	92.2 / 7.8
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Erythromycin	≤0.12	4	≤0.12 – >16	86.1 / 13.9	86.1 / 13.9
Levofloxacin	0.5	1	0.25 – >4	98.3 / 0.9	93.9 / 1.7
Meropenem	≤0.06	≤0.06	≤0.06	100.0 / -	- / -
Penicillin	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	43.5 / 56.5	42.6 / 56.5
TMP/SMX	≤0.5	≤0.5	≤0.5 – >4	- / -	99.1 / 0.9
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Viridans gr. streptococci (90)[g]					
Linezolid	1	1	0.25 – 2	100.0 / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	- / -
Ceftriaxone	0.25	1	≤0.06 – 2	95.6 / 0.0	87.8 / 12.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.1 / 7.8	92.2 / 7.8
Daptomycin	0.25	1	≤0.06 – 2	98.9 / -	- / -
Erythromycin	≤0.12	4	≤0.12 – >16	50.0 / 50.0	- / -
Levofloxacin	1	2	0.25 – >4	96.7 / 2.2	- / -
Meropenem	≤0.06	0.25	≤0.06 – 2	97.8 / -	100.0 / 0.0
Penicillin	0.12	1	≤0.06 – >8	58.9 / 3.3	82.2 / 3.3
Tetracycline	0.5	>8	≤0.25 – >8	61.1 / 34.4	- / -
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2013] and EUCAST [2013], β-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
c. Includes: *Staphylococcus auricularis* (one strain), *S. capitis* (10 strains), *S. epidermidis* (118 strains), *S. equorum* (one strain), *S. haemolyticus* (48 strains), *S. hominis* (29 strains), *S. lugdunensis* (10 strains), *S.saprophyticus* (six strains), *S. warneri* (three strains), *S. xylosus* (three strains), and unspeciated coagulase-negative staphylococci (70 strains).
d. Includes: *Enterococcus avium* (11 strains), *E. durans* (one strain), *E. faecalis* (142 strains), *E. faecium* (59 strains), *E. gallinarum* (four strains), and *E. hirae* (one strain).
e. Criteria as published by the CLSI [2013] for 'Penicillin parenteral (non-meningitis)'.
f. Includes: *Streptococcus dysgalactiae* (three strains), Group A *Streptococcus* (44 strains), Group B *Streptococcus* (62 strains), Group C *Streptococcus* (one strain), Group F *Streptococcus* (one strain), and Group G *Streptococcus* (four strains).
g. Includes: *Streptococcus anginosus* (five strains), *S. bovis* (one strain), *S. gallolyticus* (seven strains), *S. infantarius* (one strain), *S. mitis* (16 strains), *S. parasanguinis* (one strain), *S. salivarius* (two strains), *S. sanguinis* (two strains), unspeciated *Streptococcus* (one strain), and unspeciated viridans group streptococci (54 strains).
Abbreviations: Pip/taz= Piperacillin/tazobactam, Amox/clav=Amoxicillin/clavulanate, TMP/SMX=Trimethoprim/sullfamethoxazole.

Table 2. Activity of selected antimicrobial agents when tested against 3,040 isolates of Gram-negative pathogens from Latin American nations (2011).

Organism (no. tested) / Antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
E. coli (644)					
Amp/sulbactam	16	>32	≤0.25 – >32	30.4 / 49.1	30.4 / 69.6
Cefoperazone	4	>32	≤0.25 – >32	59.6 / 38.2	- / -
Cefoperazone/sulb[b]	2	16	≤0.25 – >32	92.7 / 2.3	- / -
Pip/taz	2	32	≤0.5 – >64	86.5 / 5.0	78.7 / 13.5
Tigecycline[c]	0.12	0.25	≤0.03 – 1	100.0 / 0.0	100.0 / 0.0
Amikacin	4	8	0.5 – >32	97.5 / 0.8	92.4 / 2.5
Amox/clav	8	>8	≤1 – >8	58.4 / 41.6	58.4 / 41.6
Ampicillin	>8	>8	1 – >8	23.3 / 76.7	23.3 / 76.7
Cefepime	≤0.5	>16	≤0.5 – >16	72.4 / 23.9	64.8 / 30.4
Ceftazidime	0.25	32	0.03 – >32	69.6 / 27.2	65.5 / 30.4
Ceftriaxone	0.12	>8	≤0.06 – >8	62.9 / 37.1	62.9 / 37.1
Gentamicin	≤1	>8	≤1 – >8	72.4 / 27.0	70.7 / 27.6
Levofloxacin	4	>4	≤0.12 – >4	49.7 / 47.2	49.4 / 50.3
Meropenem	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	40.4 / 59.3	- / -
Tobramycin	1	>16	0.25 – >16	62.6 / 32.3	61.2 / 37.4
TMP/SMX	>4	>4	≤0.5 – >4	40.0 / 60.0	40.0 / 59.3
Klebsiella spp. (517)[d]					
Ampicillin/sulbactam	32	>32	1 – >32	40.6 / 53.6	40.6 / 59.4
Cefoperazone	>32	>32	≤0.25 – >32	47.2 / 51.1	- / -
Cefoperazone/sulb[b]	4	>32	≤0.25 – >32	71.8 / 21.5	- / -
Pip/taz	4	>64	≤0.5 – >64	66.2 / 25.1	59.0 / 33.8
Tigecycline[c]	0.25	1	≤0.03 – >4	97.9 / 0.2	95.0 / 2.1
Amikacin	2	32	0.5 – >32	89.0 / 6.0	82.8 / 11.0
Amox/clav	8	>8	≤1 – >8	52.4 / 47.6	52.4 / 47.6
Cefepime	1	>16	≤0.5 – >16	62.3 / 32.9	51.8 / 42.4
Ceftazidime	1	>32	≤0.015 – >32	57.3 / 37.3	51.8 / 42.7
Ceftriaxone	8	>8	≤0.06 – >8	48.7 / 51.1	48.7 / 51.1
Gentamicin	≤1	>8	≤1 – >8	68.5 / 27.5	67.1 / 31.5
Levofloxacin	0.25	>4	≤0.12 – >4	68.7 / 30.0	67.1 / 31.3
Meropenem	≤0.06	1	≤0.06 – >8	90.3 / 7.9	92.1 / 5.6
Tetracycline	2	>8	≤0.25 – >8	62.3 / 35.2	- / -
Tobramycin	1	>16	≤0.12 – >16	57.6 / 37.1	56.9 / 42.4
TMP/SMX	≤0.5	>4	≤0.5 – >4	57.1 / 42.9	57.1 / 41.0
P. mirabilis (74)					
Amp/sulbactam	2	32	0.5 – 32	78.4 / 10.8	78.4 / 21.6
Cefoperazone	1	>32	≤0.25 – >32	74.3 / 20.3	- / -
Cefoperazone/sulb[b]	1	4	≤0.25 – 16	100.0 / 0.0	- / -
Pip/taz	≤0.5	1	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tigecycline[c]	2	4	0.5 – >4	85.1 / 1.4	32.4 / 14.9
Amikacin	4	8	1 – >32	95.9 / 2.7	90.5 / 4.1
Amox/clav	≤1	8	≤1 – >8	93.2 / 6.8	93.2 / 6.8
Ampicillin	2	>8	0.5 – >8	52.7 / 47.3	52.7 / 47.3
Cefepime	≤0.5	>16	≤0.5 – >16	81.1 / 17.6	75.7 / 20.3
Ceftazidime	0.06	2	0.03 – >32	94.6 / 5.4	87.8 / 5.4
Ceftriaxone	≤0.06	>8	≤0.06 – >8	75.7 / 23.0	75.7 / 23.0
Gentamicin	≤1	>8	≤1 – >8	78.4 / 21.6	75.7 / 21.6
Imipenem	1	2	≤0.12 – 4	73.0 / 4.1	95.9 / 0.0
Levofloxacin	≤0.12	>4	≤0.12 – >4	73.0 / 23.0	67.6 / 27.0
Meropenem	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / 0.0	100.0 / 0.0
Tobramycin	1	16	0.5 – >16	77.0 / 12.2	73.0 / 23.0
TMP/SMX	>4	>4	≤0.5 – >4	47.3 / 52.7	47.3 / 51.4
Enterobacter spp. (272)[e]					
Cefoperazone	2	>32	≤0.25 – >32	59.9 / 34.9	- / -
Cefoperazone/sulb[b]	1	32	≤0.25 – >32	84.9 / 6.3	- / -
Pip/taz	4	>64	≤0.5 – >64	75.7 / 10.7	69.5 / 24.3
Tigecycline[c]	0.25	1	0.06 – 4	97.8 / 0.0	94.1 / 2.2
Amikacin	2	16	0.5 – >32	94.1 / 4.0	86.8 / 5.9
Cefepime	≤0.5	>16	≤0.5 – >16	84.6 / 12.1	70.2 / 21.0
Ceftazidime	0.5	>32	0.06 – >32	63.2 / 33.5	57.7 / 36.8
Ceftriaxone	0.5	>8	≤0.06 – >8	55.5 / 44.5	55.5 / 44.5
Gentamicin	≤1	>8	≤1 – >8	77.9 / 19.5	76.5 / 22.1
Levofloxacin	≤0.12	>4	≤0.12 – >4	80.9 / 16.5	79.4 / 19.1
Meropenem	≤0.06	0.12	≤0.06 – >8	98.2 / 1.5	98.5 / 0.4
Tetracycline	2	>8	0.5 – >8	74.3 / 19.1	- / -
Tobramycin	0.5	>16	≤0.12 – >16	69.9 / 28.3	69.5 / 30.1
TMP/SMX	≤0.5	>4	≤0.5 – >4	71.0 / 29.0	71.0 / 28.3
Indole-positive *Proteus* spp. (94)[f]					
Cefoperazone	4	>32	≤0.25 – >32	71.3 / 21.3	- / -
Cefoperazone/sulb[b]	2	8	≤0.25 – 32	98.9 / 0.0	- / -
Pip/taz	≤0.5	4	≤0.5 – >64	98.9 / 1.1	97.9 / 1.1
Tigecycline[c]	0.5	2	0.25 – 4	94.7 / 0.0	89.4 / 5.3
Amikacin	2	8	0.5 – >32	94.7 / 4.3	92.6 / 5.3
Cefepime	≤0.5	16	≤0.5 – >16	89.4 / 4.3	80.9 / 13.8
Ceftazidime	0.25	16	0.03 – >32	80.9 / 13.8	70.2 / 19.1
Ceftriaxone	0.12	>8	≤0.06 – >8	68.1 / 25.5	68.1 / 25.5
Gentamicin	≤1	>8	≤1 – >8	68.1 / 27.7	61.7 / 31.9
Imipenem	2	2	0.25 – 4	35.1 / 6.4	93.6 / 0.0
Levofloxacin	1	>4	≤0.12 – >4	62.8 / 25.5	55.3 / 37.2
Meropenem	≤0.06	0.12	≤0.06 – 1	100.0 / 0.0	100.0 / 0.0
Tobramycin	1	16	0.25 – >16	73.4 / 14.9	68.1 / 26.6
TMP/SMX	>4	>4	≤0.5 – >4	43.6 / 56.4	43.6 / 56.4
Serratia spp. (142)[g]					
Cefoperazone	2	>32	0.5 – >32	78.9 / 14.1	- / -
Cefoperazone/sulb[b]	2	16	0.5 – >32	90.8 / 4.9	- / -
Pip/taz	2	32	≤0.5 – >64	89.4 / 7.0	85.9 / 10.6
Tigecycline[c]	0.5	1	0.25 – >4	95.8 / 0.7	90.1 / 4.2
Amikacin	2	16	0.5 – >32	90.8 / 5.6	85.9 / 9.2
Cefepime	≤0.5	4	≤0.5 – >16	92.3 / 7.0	84.5 / 9.2
Ceftazidime	0.12	16	0.06 – >32	84.5 / 13.4	81.0 / 15.5
Ceftriaxone	0.25	>8	≤0.06 – >8	75.4 / 23.2	75.4 / 23.2
Gentamicin	≤1	>8	≤1 – >8	85.2 / 13.4	83.1 / 14.8
Levofloxacin	≤0.12	4	≤0.12 – >4	88.7 / 7.7	83.1 / 11.3
Meropenem	≤0.06	0.12	≤0.06 – 4	98.6 / 0.7	99.3 / 0.0
Tobramycin	4	>16	0.25 – >16	73.9 / 19.7	45.8 / 26.1
TMP/SMX	≤0.5	>4	≤0.5 – >4	84.5 / 15.5	84.5 / 12.7
Citrobacter spp. (56)[h]					
Cefoperazone	1	>32	≤0.25 – >32	69.6 / 25.0	- / -
Cefoperazone/sulb[b]	0.5	16	≤0.25 – >32	91.1 / 7.1	- / -
Pip/taz	4	64	1 – >64	80.4 / 5.4	76.8 / 19.6
Tigecycline[c]	0.25	0.5	0.06 – 2	100.0 / 0.0	96.4 / 0.0
Amikacin	2	32	0.5 – >32	89.3 / 5.4	83.9 / 10.7
Cefepime	≤0.5	>16	≤0.5 – >16	87.5 / 10.7	76.8 / 16.1
Ceftazidime	0.5	>32	0.06 – >32	71.4 / 25.0	66.1 / 28.6
Ceftriaxone	0.25	>8	≤0.06 – >8	66.1 / 32.1	66.1 / 32.1
Gentamicin	≤1	4	≤1 – >8	91.1 / 8.9	83.9 / 8.9
Levofloxacin	≤0.12	1	≤0.12 – >4	92.9 / 5.4	92.9 / 7.1
Meropenem	≤0.06	≤0.06	≤0.06 – 4	98.2 / 1.8	98.2 / 0.0
Tetracycline	1	4	1 – >8	91.1 / 8.9	- / -
Tobramycin	1	>16	0.25 – >16	80.4 / 19.6	78.6 / 19.6
TMP/SMX	≤0.5	>4	≤0.5 – >4	76.8 / 23.2	76.8 / 23.2
H. influenzae (128)					
Pip/taz	≤0.5	≤0.5	≤0.5	100.0 / 0.0	- / -
Tigecycline[c]	0.25	0.5	0.06 – 1	86.7 / -	- / -
Amox/clav	≤1	2	≤1 – 2	100.0 / 0.0	100.0 / 0.0
Ampicillin	0.25	>8	≤0.12 – >8	70.3 / 28.9	70.3 / 29.7
Cefepime	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / -	99.2 / 0.8
Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -	100.0 / 0.0
Meropenem	≤0.06	0.12	≤0.06 – 0.25	100.0 / -	100.0 / 0.0
Tetracycline	0.5	0.5	≤0.12 – >16	98.4 / 1.6	98.4 / 1.6
TMP/SMX	≤0.5	>4	≤0.5 – >4	61.7 / 35.2	61.7 / 37.5
M. catarrhalis (33)					
Tigecycline[c]	0.06	0.06	0.03 – 0.06	- / -	- / -
Amox/clav	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Cefepime	1	2	≤0.5 – 4	- / -	100.0 / 0.0
Ceftriaxone	0.25	0.5	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.12	≤0.12	≤0.12 – 1	100.0 / -	100.0 / 0.0
Meropenem	≤0.06	≤0.06	≤0.06	- / -	100.0 / 0.0
Tetracycline	0.25	0.25	≤0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
P. aeruginosa (586)					
Cefoperazone	32	>32	0.5 – >32	49.3 / 39.4	- / -
Cefoperazone/sulb[b]	16	>32	0.5 – >32	55.8 / 25.4	- / -
Pip/taz	16	>64	≤0.5 – >64	58.5 / 22.9	58.5 / 41.5
Amikacin	4	>32	≤0.25 – >32	75.4 / 20.5	71.3 / 24.6
Cefepime	8	>16	≤0.5 – >16	63.8 / 25.9	63.8 / 36.2
Ceftazidime	4	>32	0.25 – >32	65.7 / 29.4	65.7 / 34.3
Colistin	1	2	≤0.25 – 4	99.5 / 0.0	99.5 / 0.5
Gentamicin	2	>8	≤1 – >8	67.4 / 29.4	67.4 / 32.6
Imipenem	2	>8	≤0.12 – >8	52.9 / 44.9	55.1 / 28.5
Levofloxacin	2	>4	≤0.12 – >4	56.8 / 38.2	47.8 / 43.2
Meropenem	2	>8	≤0.06 – >8	54.4 / 38.4	54.4 / 28.2
Tobramycin	0.5	>16	≤0.12 – >16	70.1 / 29.0	70.1 / 29.9
Acinetobacter spp. (494)[i]					
Cefoperazone/sulb[b]	16	32	≤0.25 – >32	59.3 / 8.1	- / -
Tigecycline	1	4	≤0.03 – >4	- / -	- / -
Amikacin	>32	>32	0.5 – >32	25.3 / 67.6	23.1 / 74.7
Colistin	0.5	2	≤0.25 – >4	98.0 / 2.0	98.0 / 2.0
Doxycycline	1	>8	≤0.06 – >8	80.4 / 18.6	- / -
Gentamicin	>8	>8	≤1 – >8	29.2 / 58.9	29.2 / 70.9
Imipenem	>8	>8	≤0.12 – >8	22.9 / 75.7	22.5 / 75.7
Meropenem	>8	>8	≤0.06 – >8	23.1 / 75.5	21.9 / 75.5
Tetracycline	8	>8	0.5 – >8	27.3 / 43.3	- / -
Tobramycin	16	>16	0.25 – >16	47.8 / 51.6	47.8 / 52.2
TMP/SMX	>4	>4	≤0.5 – >4	22.1 / 77.9	22.1 / 75.3

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. Criteria as published by the CLSI [2013] for cefoperazone used for cefoperazone/sulbactam.
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
d. Includes: *Klebsiella oxytoca* (51 strains), *K. ozaenae* (two strains), *K. pneumoniae* (460 strains), and unspeciated *Klebsiella* (four strains).
e. Includes: *Enterobacter aerogenes* (47 strains), *E. cloacae* (202 strains), *E. gergoviae* (two strains), and unspeciated *Enterobacter* (21 strains).
f. Includes: *Morganella morganii* (72 strains), *Proteus vulgaris* (12 strains), *P. rettgeri* (five strains), *P. stuartii* (four strains), and unspeciated *Providencia* (one strain).
g. Includes: *Serratia liquefaciens* (one strain), *S. marcescens* (131 strains), and unspeciated *Serratia* (10 strains).
h. Includes: *Citrobacter amalonaticus* (two strains), *C. braakii* (two strains), *C. freundii* (39 strains), *C. koseri* (12 strains), and *C. sedlakii* (one strain).
i. Includes: *Acinetobacter baumannii* (468 strains), *A. haemolyticus* (two strains), *A. lwoffii* (11 strains), *A. ursingii* (four strains), and unspeciated *Acinetobacter* (nine strains); only drugs with >20% susceptibility are listed.

Abbreviations: Amp/sulbactam=Ampicillin/sulbactam; Cefoperazone/sulb=Cefoperazone/sulbactam, Pip/taz=Piperacillin/tazobactam, Amox/clav=Amoxicillin/clavulanate, TMP/SMX=Trimethoprim/sulfamethoxazole.

Table 3. Activity of 12 antimicrobial agents when tested against ESBL-phenotype *Escherichia coli* and *Klebsiella* spp. isolated in Latin American medical centres (511 strains cultured in 2011).

Organism (no. tested) / Antimicrobial agent	MIC (mg/L) 50%	90%	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
E. coli (240)					
Cefoperazone/sulb[b]	8	32	≤0.25 – >32	81.3 / 6.3	- / -
Pip/taz	8	64	≤0.5 – >64	72.5 / 8.3	52.9 / 27.5
Tigecycline[c]	0.12	0.25	0.06 – 1	100.0 / 0.0	100.0 / 0.0
Amikacin	8	16	1 – >32	93.8 / 2.1	82.1 / 6.3
Cefepime	>16	>16	≤0.5 – >16	25.8 / 64.2	8.8 / 81.3
Colistin	0.5	0.5	≤0.25 – 2	- / -	100.0 / 0.0
Gentamicin	>8	>8	≤1 – >8	46.3 / 52.9	43.8 / 53.8
Levofloxacin	>4	>4	≤0.12 – >4	16.3 / 81.3	16.3 / 83.8
Meropenem	≤0.06	≤0.06	≤0.06 – 0.5	100.0 / 0.0	100.0 / 0.0
Tetracycline	>8	>8	≤0.25 – >8	20.8 / 79.2	- / -
Tobramycin	>16	>16	0.5 – >16	22.5 / 71.7	20.8 / 77.5
TMP/SMX	>4	>4	≤0.5 – >4	24.2 / 75.8	24.2 / 74.2
Klebsiella spp. (271)[d]					
Cefoperazone/sulb[b]	32	>32	≤0.25 – >32	46.5 / 41.0	- / -
Pip/taz	64	>64	1 – >64	38.0 / 46.9	25.8 / 62.0
Tigecycline[c]	0.25	1	≤0.03 – 4	97.0 / 0.0	92.3 / 3.0
Amikacin	4	>32	0.5 – >32	79.7 / 11.4	67.9 / 20.3
Cefepime	>16	>16	≤0.5 – >16	28.0 / 62.7	8.1 / 80.8
Colistin	0.5	1	≤0.25 – >4	- / -	93.4 / 6.6
Gentamicin	>8	>8	≤1 – >8	42.8 / 50.6	40.2 / 57.2
Levofloxacin	>4	>4	≤0.12 – >4	43.9 / 54.2	41.3 / 56.1
Meropenem	≤0.06	>8	≤0.06 – >8	81.6 / 15.1	84.9 / 10.7
Tetracycline	8	>8	≤0.25 – >8	46.5 / 49.1	- / -
Tobramycin	16	>16	≤0.12 – >16	21.8 / 69.0	20.7 / 78.2
TMP/SMX	>4	>4	≤0.5 – >4	31.0 / 69.0	31.0 / 66.1

a. Criteria as published by the CLSI [2013] and EUCAST [2013].
b. Criteria as published by the CLSI [2013] for cefoperazone used for cefoperazone/sulbactam.
c. USA-FDA breakpoints were applied when available [Tygacil Product Insert, 2012].
d. Includes: *Klebsiella oxytoca* (16 strains), *K. ozaenae* (one strain), *K. pneumoniae* (252 strains), and unspeciated *Klebsiella* (two strains).
Abbreviations: Cefoperazone/sulb=Cefoperazone/sulbactam, Pip/taz=Piperacillin/tazobactam, TMP/SMX=Trimethoprim/sulfamethoxazole.