Emerging Markets Resistance Surveillance Program Report for Eastern European Nations

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ABSTRACT

Background: In the Eastern European nations (EEU) component of the Emerging Markets Resistance Surveillance program (EMRS) in 2011, 8 countries are monitored for antimicrobial resistance (R) patterns including Bulgaria (BUL), Croatia (CRO), Czech Republic (CZR), Israel (ISR), Poland (POL), Romania (ROM), Slovakia (SLO) and Turkey (TUR).

Methods: Results from testing 1,700 strains were interpreted by CLSI, EUCAST and USA-FDA breakpoints. Samples were reference tested versus potent, marketed agents: linezolid (LZD), vancomycin (VAN), tigecycline (TIG), colistin (COL), cefoperazone/sulbactam (C/S), amikacin (AMK), levofloxacin (LEV) and 21 others. R mechanisms were screened by PCR.

Results: Among EEU *S. aureus* (SA; **Table**), LZD (MIC_{90}, 1 µg/ml), TIG (MIC_{90}, 0.12 µg/ml) and VAN (MIC_{90}, 1 µg/ml) exhibited complete coverage and MRSA rates ranged from 16% (BUL) to 60% (POL, ROM, SLO). A *S. simulans* strain was LZD-R (MIC, 8 µg/ml; from ROM) having L3 mutations (N130D, G152A, F147S, A157R). VRE (79% VanA) were noted in CZR (13%), ISR (4%), ROM (5%) and TUR (20%). ESBL rate for *E. coli* was 27% (range, 10% [CRO, SLO] to 70% [BUL], best inhibited by COL (99%S), TIG (100%) AMK (98%), C/S (90%) and carbapenems (96-98%; R strains in ISR & TUR). *Klebsiella* spp. had greater ESBL rates (66% overall, range 31-100%) as well as carbapenem-R (7% overall, greatest in BUL, ISR, ROM, TUR). Nonfermentors (*P. aeruginosa*, *Acinetobacter* [ACB]) were generally very R except against COL (99-100%S) and TIG (95% S at ≤2 µg/ml; ACB only).

Conclusions: EEU surveillance sampling (EMRS Program) demonstrates a wide array of R isolates, less prevalent among Gram-positives that remain inhibited by available agents (LZD, TIG, VAN). However, β-lactamase-mediated-R has spread widely among Gram-negatives and across the EEU severely limiting infection chemotherapy.

Abstract Table

	EEU S rates for key Gram-positive pathogens (no.).[a]				
Antimicrobials	SA (405)	CoNS (101)	ENT (147)	SPN (115)	BHS (75)
Oxacillin[b]	61	17	69	56	100
LZD	100	99[c]	99[c]	100	100
TIG	100	100	100	100	100
VAN	100	99	93	100	100
Macrolides[d]	55	22	8	57	73
LEV	71	43	45	99	100
TMP/SMX	99	55	46	57	97
Ceftriaxone	61	17	-	70	100

a. ENT=enterococci; SPN=S. pneumoniae; BHS=β-haemolytic streptococci.
b. Ampicillin for ENT and penicillin for the streptococci.
c. Two LZD-R isolates from ROM & TUR.
d. S rates for erythromycin-like agents.

INTRODUCTION

Bacterial strains resistant to commonly used β-lactams, fluoroquinolones and other antimicrobials remain a significant challenge to successful chemotherapy especially in developing nations. β-lactamase-mediated resistances among Gram-negative bacilli and the expansion of Gram-positive resistant species (MRSA, vancomycin-resistant enterococci [VRE], multidrug-resistant [MDR] *Streptococcus pneumoniae*) present the most critical compromise to favorable patient outcomes.

To address these concerns, structured antimicrobial surveillance programs have been organized to 1.) sample key pathogens by nation; 2.) use reference quantitative susceptibility testing methods (Example: Clinical and Laboratory Standards Institute [CLSI]) in regulated central laboratories; and 3.) offer a wide range of tested antimicrobials, usually 20-30 agents. These programs then can be compared to other regional surveillance programs that utilize available "non-reference," often commercial categorical (not quantitative) results. The categorical SIR definitions may vary as well as the quality/accuracy of the methods, therefore structured programs such as the Emerging Markets Resistance Surveillance (EMRS) Program offers expanded, validating information for other programs, where offered.

In the Eastern European (EEU) component of EMRS, eight nations were monitored in 2011 (1,700 isolates), enabling comparison of 28 drugs to that data generated by the EARS-Net for at least four countries.

MATERIALS AND METHODS

Nations and organisms monitored. A total of eight countries were sampled with a target of ≥200 isolates of specific species per nation. The organisms were isolated from a wide variety of clinical infection types/sites including respiratory tract, acute bacterial skin and skin structure, bacteremias and urinary tract. The countries (sample size) were: Bulgaria (100), Croatia (200), Czech Republic (195), Israel (225), Poland (200), Romania (217), Slovakia (200) and Turkey (363). The organisms directed to be sampled (per site) included: *S. aureus* (25), coagulase-negative staphylococci (5), enterococci (10), *S. pneumoniae* (10), viridans and β-haemolytic streptococci (5), *E. coli* (10), *Klebsiella* spp. (10), *Enterobacter* spp. (5), other Enterobacteriaceae (5), *P. aeruginosa* (10) and *Acinetobacter* spp. (5).

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-S22, 2012), USA-Food and Drug Administration (FDA) and EUCAST (2012) criteria; and the results of quality control (QC) tests were dominantly (98.8%) within QC ranges of the CLSI M100-S22 for six control organisms.

The sponsor (Pfizer Inc., New York, New York, USA) directed 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 an additional 16, 18 and 18 drugs were tested, respectively.

RESULTS

- Linezolid was widely active (MIC_{90}, 0.5 or 1 µg/ml) against the 886 tabulated Gram-positive isolates (**Table 1**). CoNS (MIC_{50}, 0.5 µg/ml) and *S. pneumoniae* were generally more linezolid-susceptible. The overall linezolid resistance rate was only 2 of 248 CoNS and enterococci (0.8%). Molecular characterization of these linezolid-resistant strains showed a G2576T mutation in the *E. faecium* from Turkey; and the *S. simulans* (a CoNS from Romania) had four mutations of the L3 ribosomal protein (N130D, G152A, F147S, and A157R).
- All Gram-positive pathogens were susceptible to tigecycline at USA-FDA and EUCAST breakpoint concentration with the following MIC_{90} values (**Table 2**): *S. aureus* (0.12 µg/ml) CoNS (0.12 µg/ml), enterococci (0.06 µg/ml), *S. pneumoniae* (≤0.03 µg/ml), BHS (0.06 µg/ml) and VGS (0.06 µg/ml). Tigecycline susceptibility rates against the Enterobacteriaceae ranged from 87.1% (*P. mirabilis*) to 100.0% (*E. coli* and *Serratia* spp.) and it also inhibited 93.6% of *Acinetobacter* spp. at a MIC of ≤2 µg/ml.
- Piperacillin/tazobactam showed potent activity against methicillin (oxacillin)-susceptible staphylococci (MIC_{90}, ≤0.5-2 µg/ml), *S. pneumoniae* (MIC_{90}, 8 µg/ml), and BHS (MIC_{90}, ≤0.5 µg/ml), see **Table 3**. Against the Enterobacteriaceae, piperacillin/tazobactam inhibited 60.1% (*Klebsiella* spp.) to 96.8% (*P. mirabilis*) of strains at the CLSI breakpoint (≤16 µg/ml); and MIC_{50} results ranged from ≤0.5 to 8 µg/ml. It was also active at ≤16 µg/ml against 63.7% of *P. aeruginosa* but only 17.0% of *Acinetobacter* spp. (MIC_{50}, >64 µg/ml) were susceptible.
- Cefoperazone/sulbactam, an early "third-generation" cephem/β-lactamase inhibitor combination (2:1 ratio), was tested against 763 Gram-negative bacilli (**Table 4**).The addition of sulbactam expanded the cefoperazone susceptible rate against Enterobacteriaceae to 76.3 - 100.0%, achieving coverages comparable or superior to piperacillin/tazobactam and carbapenems. The improved spectrum and coverage of cefoperazone with sulbactam ranged from +7.1% (78.6 to 85.7% susceptible) for *Serratia* spp. to +43.9% (32.4 to 76.3% susceptible) for *Klebsiella* spp.; and coverage of *P. aeruginosa* was 67.4% (MIC_{50}, 16 µg/ml). Against *Acinetobacter* spp., only cefoperazone/sulbactam (MIC_{50}, 16 µg/ml; 54.3% susceptible) was active, influenced by the direct action of sulbactam as an antimicrobial agent.
- Some across nation resistance rates are listed in **Table 5**.

Table 5. Across EEU region variations in key antimicrobial resistance patterns (2011).

Organism (no. tested/resistance)[b]	% of sample (≥10 only)[-a]								
	BUL	CRO	CZR	ISR	POL	ROM	SLO	TUR	Region
S. aureus (405) - MRSA	16	39	22	44	60[b]	60	60	17	40
CoNS (101)									
MR	-[b]	88	73	92	-	-	71	80	83
Teicoplanin-R	-	19	0	17	-	-	6	15	9
Enterococci (147) - VRE	0	0	13	5	0	5	0	20	7
S. pneumoniae (115)									
PEN-R	-	-	10	13	28	69	10	33	29
ER-R	-	-	10	9	50	77	40	42	44
E. coli (202)									
ESBL	70	10	17	22	53	37	10	37	27
FQR	50	21	23	30	58	37	42	39	37
Klebsiella spp (173)									
ESBL	100	31	67	54	74	72	82	59	66
FQR	60	19	14	46	53	48	59	17	43
CARB-R	10	0	0	17	0	4	0	12	6
P. aeruginosa (135) – CARB-R	30	40	40	20	21	91	40	24	36
Acinetobacter spp (94)	-	100	-	75	55	87	0	90	64

a. Abbreviations: MRSA=methicillin-resistant *S. aureus*; MR=methicillin-resistant; R=resistant; VRE=vancomycin-resistant enterococci; PEN-R=penicillin-resistant (MIC, >2 µg/ml); ER-R=erythromycin-resistant; ESBL=extended spectrum β-lactamase; FQR=fluoroquinolone-resistant; CARB-R=carbapenem-resistant. Countries are: BUL=Bulgaria, CRO=Croatia; CZR=Czech Republic; ISR=Israel; POL=Poland; ROM=Romania; SLO=Slovakia; and TUR=Turkey.
b. Underlined value is the highest resistant rate in the region. "-" = sample size at <10 strains.

Table 1. In vitro activity of linezolid tested by reference methods against six groups of Gram-positive pathogens from the EEU region (886 strains).

	Occurrences at each MIC in µg/ml (cum. % inhibited):								MIC (µg/ml)		
Organism (no. tested)	≤0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}	% susceptible
Staphylococcus aureus (405)	-	1 (0.2)	35 (8.9)	333 (91.1)	36 (100.0)	-	-	-	1	1	100.0
Coagulase-negative staphylococci (101)	-	5 (5.0)	68 (72.3)	27 (99.0)	0 (99.0)	0 (99.0)	1 (100.0)[a]	-	0.5	1	99.0
Enterococcus spp. (147)	1 (0.7)	0 (0.7)	22 (15.6)	109 (89.8)	14 (99.3)	0 (99.3)	0 (99.3)	1 (100.0)[a]	1	2	99.3
Streptococcus pneumoniae (115)	2 (1.7)	1 (2.6)	58 (53.0)	52 (98.3)	2 (100.0)	-	-	-	0.5	1	100.0
Beta-haemolytic streptococci (75)	-	-	18 (24.0)	57 (100.0)	-	-	-	-	1	1	100.0
Viridans group streptococci (43)	-	1 (2.3)	17 (41.9)	22 (93.0)	3 (100.0)	-	-	-	1	1	100.0

a. Linezolid-resistant strain from Romania.
b. Linezolid-resistant strain from Turkey.

Table 2. In vitro activity of tigecycline tested by reference methods against 14 groups of Gram-positive and -negative pathogens from the EEU region (1,649 strains).

	Occurrences at each MIC in µg/ml (cum. % inhibited):									MIC (µg/ml)		
Organism (no. tested)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	MIC_{50}	MIC_{90}	% susceptible[a]
Staphylococcus aureus (405)	4 (1.0)	330 (82.5)	50 (94.8)	18 (99.3)	3 (100.0)	-	-	-	-	0.06	0.12	100.0
Coagulase-negative staphylococci (101)	15 (14.9)	44 (58.4)	34 (92.1)	8 (100.0)	-	-	-	-	-	0.06	0.12	100.0
Enterococcus spp. (147)	60 (40.8)	82 (96.6)	4 (99.3)	1 (100.0)	-	-	-	-	-	0.06	0.06	100.0
Streptococcus pneumoniae (115)	106 (92.2)	9 (100.0)	-	-	-	-	-	-	-	≤0.03	≤0.03	100.0
Beta-haemolytic streptococci (75)	60 (80.0)	12 (96.0)	3 (100.0)	-	-	-	-	-	-	≤0.03	0.06	100.0
Viridans group streptococci (43)	36 (83.7)	3 (90.7)	3 (97.7)	1 (100.0)	-	-	-	-	-	≤0.03	0.06	100.0
Escherichia coli (202)	-	66 (32.7)	108 (86.1)	26 (99.0)	2 (100.0)	-	-	-	-	0.12	0.25	100.0
Klebsiella spp. (173)	-	2 (1.2)	19 (12.1)	86 (61.8)	40 (85.0)	18 (95.4)	6 (98.8)	2 (100.0)	-	0.25	1	98.8
Enterobacter spp. (84)	-	1 (1.2)	13 (16.7)	49 (75.0)	6 (82.1)	8 (91.7)	6 (98.8)	0 (98.8)	1 (100.0)	0.25	1	98.8
Indole-positive *Proteus* spp. (30)	-	-	1 (3.3)	1 (6.7)	15 (56.7)	7 (80.0)	5 (96.7)	1 (100.0)	-	0.5	2	96.7
Proteus mirabilis (31)	-	-	-	-	1 (3.2)	6 (22.6)	20 (87.1)	4 (100.0)	-	2	4	87.1
Serratia spp. (14)	-	-	-	1 (7.1)	9 (71.4)	4 (100.0)	-	-	-	0.5	1	100.0
Pseudomonas aeruginosa (135)	-	-	-	2 (1.5)	2 (3.0)	1 (3.7)	8 (9.6)	52 (48.1)	70 (100.0)	>4	>4	-
Acinetobacter spp. (94)	1 (1.1)	5 (6.4)	9 (16.0)	3 (19.1)	17 (37.2)	38 (77.7)	15 (93.6)	5 (98.9)	1 (100.0)	1	2	93.6[b]

a. Criteria from the USA-FDA product package insert.
b. % at ≤2 µg/ml.

Table 3. In vitro activity of piperacillin/tazobactam tested by reference methods against 14 groups of Gram-positive and -negative pathogens from the EEU region (1,649 strains).

	Occurrences at each MIC in µg/ml (cum. % inhibited):									MIC (µg/ml)		
Organism (no. tested)	≤0.5	1	2	4	8	16	32	64	>64	MIC_{50}	MIC_{90}	% susceptible
Staphylococcus aureus (405)	17 (4.2)	145 (40.0)	83 (60.5)	14 (64.0)	21 (69.1)	15 (72.8)	18 (77.3)	28 (84.2)	64 (100.0)	2	>64	60.5
Coagulase-negative staphylococci (101)	21 (20.8)	15 (35.6)	10 (45.5)	12 (57.4)	4 (61.4)	8 (69.3)	4 (73.3)	8 (81.2)	19 (100.0)	4	>64	16.8
Enterococcus spp. (147)	1 (0.7)	2 (2.0)	2 (3.4)	55 (40.8)	27 (59.2)	7 (63.9)	6 (68.0)	2 (69.4)	45 (100.0)	8	>64	70.1
Streptococcus pneumoniae (115)	75 (65.2)	5 (69.6)	1 (70.4)	17 (85.2)	17 (100.0)	-	-	-	-	≤0.5	8	-
Beta-haemolytic streptococci (75)	75 (100.0)	-	-	-	-	-	-	-	-	≤0.5	≤0.5	-
Viridans group streptococci (43)	22 (51.2)	3 (58.1)	5 (69.8)	3 (76.7)	4 (86.0)	4 (95.3)	1 (97.7)	1 (100.0)	-	≤0.5	16	-
Escherichia coli (202)	3 (1.5)	35 (18.8)	96 (66.3)	25 (78.7)	11 (84.2)	10 (89.1)	9 (93.6)	4 (95.5)	9 (100.0)	2	32	89.1
Klebsiella spp. (173)	1 (0.6)	10 (6.4)	29 (23.1)	22 (35.8)	34 (55.5)	8 (60.1)	19 (71.1)	14 (79.2)	36 (100.0)	8	>64	60.1
Enterobacter spp. (84)	-	12 (14.3)	28 (47.6)	12 (61.9)	7 (70.2)	1 (71.4)	7 (79.8)	5 (85.7)	12 (100.0)	4	>64	71.4
Indole-positive *Proteus* spp. (30)	20 (66.7)	4 (80.0)	2 (86.7)	0 (86.7)	2 (93.3)	0 (93.3)	1 (96.7)	1 (100.0)	≤0.5	16	93.3	
Proteus mirabilis (31)	18 (58.1)	5 (74.2)	4 (87.1)	1 (90.3)	2 (96.8)	0 (96.8)	0 (96.8)	0 (96.8)	1 (100.0)	≤0.5	4	96.8
Serratia spp. (14)	-	5 (35.7)	4 (64.3)	1 (71.4)	1 (78.6)	1 (85.7)	0 (85.7)	1 (92.9)	1 (100.0)	2	64	85.7
Pseudomonas aeruginosa (135)	1 (0.7)	2 (2.2)	8 (8.1)	39 (37.0)	17 (49.6)	19 (63.7)	7 (68.9)	8 (74.8)	34 (100.0)	16	>64	63.7
Acinetobacter spp. (94)	11 (11.7)	0 (11.7)	3 (14.9)	0 (14.9)	2 (17.0)	0 (17.0)	4 (21.3)	1 (22.3)	73 (100.0)	>64	>64	17.0

Table 4. In vitro activity of cefoperazone/sulbactam tested by reference methods against eight groups of Gram-negative pathogens from the EEU region (763 strains).

	Occurrences at each MIC in µg/ml (cum. % inhibited):								MIC (µg/ml)		
Organism (no. tested)	≤0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}	% susceptible[a]
Escherichia coli (202)	71 (35.1)	20 (45.0)	27 (58.4)	25 (70.8)	21 (81.2)	16 (89.1)	12 (95.0)	6 (98.0)	4 (100.0)	1	16	95.0
Klebsiella spp. (173)	31 (17.9)	6 (21.4)	12 (28.3)	9 (33.5)	11 (39.9)	30 (57.2)	33 (76.3)	20 (87.9)	21 (100.0)	8	>32	76.3
Enterobacter spp. (84)	37 (44.0)	8 (53.6)	5 (59.5)	0 (59.5)	9 (70.2)	3 (73.8)	6 (81.0)	7 (89.3)	9 (100.0)	0.5	>32	81.0
Indole-positive *Proteus* spp. (30)	1 (3.3)	4 (16.7)	13 (60.0)	5 (76.7)	0 (76.7)	4 (90.0)	3 (100.0)	-	-	1	8	100.0
Proteus mirabilis (31)	-	11 (35.5)	5 (51.6)	4 (64.5)	2 (71.0)	6 (90.3)	2 (96.8)	1 (100.0)	-	1	8	96.8
Serratia spp. (14)	-	4 (28.6)	4 (57.1)	2 (71.4)	1 (78.6)	0 (78.6)	1 (85.7)	2 (100.0)	-	1	32	85.7
Pseudomonas aeruginosa (135)	-	-	2 (1.5)	2 (3.0)	36 (29.6)	26 (48.9)	25 (67.4)	14 (77.8)	30 (100.0)	16	>32	67.4
Acinetobacter spp. (94)	1 (1.1)	4 (5.3)	8 (13.8)	7 (21.3)	2 (23.4)	13 (37.2)	16 (54.3)	25 (80.9)	18 (100.0)	16	>32	54.3

a. Susceptibility criteria used for cefoperazone tested alone (≤16 µg/ml).

CONCLUSIONS

- Linezolid and tigecycline showed sustained and near complete coverage of Gram-positive pathogens (only two linezolid-resistant organisms). No evidence of MIC creep or emerging resistant clones was observed against either drug.
- Both monitored β-lactamase inhibitor combinations exhibited broad-spectrum coverage of Gram-positive (not MRSA) and -negative pathogens. Approximately 90.0% of all enteric bacilli were susceptible to piperacillin/tazobactam and cefoperazone/sulbactam. Non-fermentative Gram-negative bacilli were less susceptible with rates ranging from 17.0 to 67.4% at ≤16 µg/ml for both agents.
- Some serious emerging resistances have become endemic in the EEU Region:
  - ESBL in *E. coli* (9.7 - 70.0%; average at 27.2%) and *Klebsiella* spp. (31.3 - 100.0%; average at 65.9%!); highest in Bulgaria and Poland.
  - Fluoroquinolones (ciprofloxacin or levofloxacin) were less effective in vitro with 20.7 - 57.9% resistance rates among *E. coli*.
  - Carbapenem resistances in Enterobacteriaceae were observed, as well as among the non-fermentative bacilli.
  - Colistin non-susceptible organisms were noted in a number of enteric bacilli, but in only 0.7% of *P. aeruginosa* among non-fermentative bacilli (Romania).
- Clearly a potential for even greater emergence of MDR pathogens was demonstrated in several nations where carbapenem and colistin resistances have become more prevalent. Newer antimicrobials or inhibitor combinations will be necessary to address the extremely high contemporary ESBL rates among Enterobacteriaceae in EEU, rates much higher than those encountered in North America and several Western EU nations.

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