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Antimicrobial susceptibility of Gram-negative and Gram-positive bacteria collected from Eastern Europe: Results from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.), 2011–2016

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ABSTRACT

Objectives: The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a global surveillance programme monitoring the in vitro activity of a panel of antimicrobial agents against clinically important bacterial isolates. Data for Gram-positive and Gram-negative isolates collected in Eastern Europe between 2011 and 2016 are presented here.
Methods: Minimum inhibitory concentrations (MICs) were determined by the broth microdilution method using CLSI guidelines. Antimicrobial susceptibility was assessed using EUCAST breakpoints.
Results: Nine Eastern European countries submitted 4289 isolates. Among *Acinetobacter baumannii*, resistance to levofloxacin, amikacin and meropenem was 77.5%, 63.4% and 62.2%, respectively. Multidrug resistance among *A. baumannii* was higher in 2015 than in previous years (44.1% in 2011 and 71.0% in 2015), decreasing to 51.7% in 2016. The multidrug resistance percentage for *Pseudomonas aeruginosa* was 26.9% and was relatively stable over time. The percentage of extended-spectrum β-lactamase (ESBL)-positive isolates among *Escherichia coli* and *Klebsiella pneumoniae* was 20.1% and 55.7%, respectively. Resistance to amikacin, meropenem and tigecycline was low among *E. coli* and *K. pneumoniae* and the ESBL-producing subset (≤5.9%). Among *Staphylococcus aureus* isolates, 36.7% were methicillin-resistant (MRSA); percentages varied year-on-year. No *S. aureus* isolates, including MRSA, were resistant to linezolid, vancomycin or tigecycline. Among *Enterococcus faecium* isolates, resistance was 22.6% to vancomycin and 2.3% to linezolid; no isolates were resistant to tigecycline.
Conclusion: This study shows low resistance to meropenem and tigecycline among Enterobacteriaceae isolates and continued activity of linezolid, vancomycin and tigecycline against Gram-positive organisms. However, antimicrobial resistance continues to be problematic in Eastern Europe and requires continued surveillance.

1. Introduction

Surveillance continues to be an important tool in the fight against increasing antimicrobial resistance. While the initial focus was on the Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), in more recent years the critical importance of increasing resistance among Gram-negative organisms such as *Acinetobacter baumannii* and the Enterobacteriaceae has been recognised [1–3]. The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is an antimicrobial surveillance study that has collected clinical isolates globally since 2004. The broad geographical coverage of the study enables analysis from a global, regional and country perspective. Previous publications of T.E.S.T. data from Eastern Europe have demonstrated high levels of antimicrobial resistance in the region [4]. Furthermore, the European Antimicrobial Resistance Surveillance Network (EARS-Net) study has shown that, for many of the organisms included in T.E.S.T., antimicrobial resistance is generally higher in countries in the eastern and southern parts of Europe compared with countries in the north [2]; therefore, continual monitoring and reporting of the resistance situation in Eastern Europe is warranted.

Eastern European data for isolates collected as part of the T.E.S.T. study between 2004 and 2010 have been published previously [4], and data on resistance for isolates collected between 2004 and 2014 have also been published [5]. The aim of this analysis was to examine percentages of resistant phenotypes and the

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antimicrobial activity of the T.E.S.T. panel of antimicrobial agents against Gram-positive and Gram-negative bacterial isolates collected between 2011 and 2016 in Eastern Europe.

2. Materials and methods

Details of the methodologies used in the T.E.S.T. study have been published previously [5]. Between 2011 and 2016, a total of 20 centres across Eastern Europe submitted isolates to the T.E.S.T. programme. The numbers of participating centres in each country were as follows: the Czech Republic, 4; Croatia, 3; Poland, 3; Romania, 3; Bulgaria, 2; Hungary, 2; Latvia, 1; Lithuania, 1; and the Slovak Republic, 1. Countries did not submit isolates in all study years. Isolates were collected from all body sites and from inpatients and outpatients with hospital-acquired and community-acquired infections.

Minimum inhibitory concentrations (MICs) were determined locally according to Clinical and Laboratory Standards Institute (CLSI) guidelines for broth microdilution methodology [6]. Antimicrobial susceptibility was assessed using breakpoints provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), where available [7].

In this study, multidrug resistance was defined as resistance to three or more classes of antimicrobial agents. The classes used to define multidrug-resistant (MDR) *A. baumannii* were aminoglycosides (amikacin), carbapenems (imipenem or meropenem) and fluoroquinolones (levofloxacin). The classes used to define MDR *Pseudomonas aeruginosa* were aminoglycosides (amikacin), β-lactams [cefepime, ceftazidime or piperacillin/tazobactam (TZP)], carbapenems (imipenem or meropenem) and fluoroquinolones (levofloxacin). Methicillin resistance in *S. aureus* and extended-spectrum β-lactamase (ESBL)-production among *Escherichia coli* and *Klebsiella pneumoniae* were determined by IHMA, Inc. according to CLSI guidelines [8].

3. Results

A total of 4289 isolates were collected between 2011 and 2016 (Table 1), of which 2852 (66.5%) were Gram-negative and 1437 (33.5%) were Gram-positive. The majority of isolates were submitted by two countries, namely the Czech Republic (28.7%) and Croatia (26.9%) (Table 1). Six countries submitted isolates in two or fewer of the 6 years of study [Bulgaria, 2011; Hungary, 2012, 2014; Latvia, 2016; Lithuania, 2016 (1 isolate in 2011); Poland, 2013, 2014; and the Slovak Republic, 2011] and so are not included in the country-by-country analysis, however they are included the analysis of data for Eastern Europe as a whole. Most isolates were collected from inpatients who were not in the intensive care unit, and isolates were most commonly collected from integumentary (25.4%) and respiratory (25.0%) sources (Table 2).

Table 1
Number of isolates collected by year from Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) centres in Eastern Europe, 2011–2016.

Country	No. of isolates						
	2011	2012	2013	2014	2015	2016	2011–2016
Bulgaria	185	0	0	0	0	0	185
Croatia	2	0	165	302	356	329	1154
Czech Republic	180	110	0	188	175	580	1233
Hungary	0	225	0	192	0	0	417
Latvia	0	0	0	0	0	47	47
Lithuania	1	0	0	0	0	178	179
Poland	0	0	340	202	0	0	542
Romania	15	0	126	276	0	0	417
Slovak Republic	115	0	0	0	0	0	115
Eastern Europe, total	498	335	631	1160	531	1134	4289

Table 2
Patient demographics and culture source for isolates collected in Eastern Europe, 2011–2016.

Demographic parameter	No. (%) of patients (n = 4289)
Sex	
Male	2381 (55.5)
Female	1869 (43.6)
Unknown	39 (0.9)
Age	
<18 years	530 (12.4)
18–64 years	1932 (45.0)
≥65 years	1773 (41.3)
Unknown	54 (1.3)
Referring ward	
ICU	1230 (28.7)
Non-ICU	2704 (63.0)
Unknown	355 (8.3)
In/out patient	
Inpatient	3249 (75.8)
Outpatient	411 (9.6)
Unknown	629 (14.7)
Culture source	
Body fluids	329 (7.7)
Cardiovascular	482 (11.2)
Genital/urinary	686 (16.0)
Head, ears, eyes, nose, throat	283 (6.6)
Integumentary	1089 (25.4)
Respiratory	1072 (25.0)
Other	335 (7.8)
Unknown	13 (0.3)

ICU, intensive care unit.

3.1. Gram-negative isolates

Over the period 2011–2016, 262 *A. baumannii* isolates were submitted, of which 57.6% were MDR (Table 3). The MDR percentage among *A. baumannii* was 89.2%, 85.4% and 1.9% in Croatia, Romania and the Czech Republic, respectively. Fig. 1a shows that between 2011 and 2015, the percentage of MDR *A. baumannii* isolates for Eastern Europe was higher in 2015 than in previous years (44.1% in 2011 and 71.0% in 2015), decreasing to 51.7% in 2016. Among all *A. baumannii* isolates, resistance to levofloxacin, amikacin and meropenem was 77.5%, 63.4% and 62.2%, respectively (Table 4). Resistance breakpoints for the other agents on the T.E.S.T. panel were not available. The lowest MIC_{90} value among all agents on the T.E.S.T. panel was observed for tigecycline for all *A. baumannii* isolates (2 mg/L), including the MDR subset (2 mg/L).

Of the 454 *P. aeruginosa* isolates submitted, 26.9% were MDR (Table 3). Fig. 1a shows that across Eastern Europe the percentage of *P. aeruginosa* isolates that were MDR was relatively stable between 2011 and 2016, although the percentage in 2011 (36.2%) was higher than in subsequent years. Resistance breakpoints were available for six of the agents on the T.E.S.T. panel. For all *P. aeruginosa* isolates resistance was highest to levofloxacin (52.2%), cefepime (38.1%) and TZP (35.2%), and percentages were higher among MDR isolates (100.0%, 93.4% and 86.9%, respectively) (Table 4). The MIC_{90} value for tigecycline for all *P. aeruginosa* isolates, and for the MDR subset, was 16 mg/L.

Of the 613 *E. coli* isolates submitted, 20.1% were ESBL-producers (Table 3). Fig. 1b shows that the percentage of *E. coli* isolates that were ESBL-producers initially decreased between 2011 and 2012 and was then relatively stable between 2012 and 2016. Among all *E. coli* isolates, resistance was highest to ampicillin (68.4%), amoxicillin/clavulanic acid (AMC) (37.7%) and levofloxacin (33.9%), with higher percentages among ESBL-producing isolates (100.0%, 71.5% and 80.5%, respectively) (Table 4). Resistance was low (≤2.4%) to meropenem, tigecycline and amikacin among all *E. coli* isolates and among the ESBL-producing subset.

Table 3
Number and percentages of resistant phenotypes by country, 2011–2016.

Gram-negative organisms										
Country	*Acinetobacter baumannii*, MDR		*Pseudomonas aeruginosa*, MDR		*Escherichia coli*, ESBL		*Klebsiella pneumoniae*, ESBL		*Haemophilus influenzae*, βL Pos	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%
Croatia	66/74	89.2	45/112	40.2	26/172	15.1	96/148	64.9	9/57	15.8
Czech Republic	1/53	1.9	20/125	16.0	25/160	15.6	58/132	43.9	14/77	18.2
Romania	41/48	85.4	25/57	43.9	12/78	15.4	27/52	51.9	2/5	–[a]
Eastern Europe [b]	151/262	57.6	122/454	26.9	123/613	20.1	270/485	55.7	39/224	17.4

Gram-positive organisms										
Country	*Staphylococcus aureus*, MR		*Enterococcus faecium*, VR		*Streptococcus pneumoniae*, Pen N-S		*S. pneumoniae*, Pen I		*S. pneumoniae*, Pen R	
	n/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%	*n*/*N*	%
Croatia	53/175	30.3	10/22	45.5	19/42	45.2	13/42	31.0	6/42	14.3
Czech Republic	64/205	31.2	5/47	10.6	8/66	12.1	8/66	12.1	0/66	0.0
Romania	44/83	53.0	7/20	35.0	1/1	–	1/1	–	0/1	–
Eastern Europe[b]	257/701	36.7	30/133	22.6	67/217	30.9	49/217	22.6	18/217	8.3

MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase-producing; βL Pos, β-lactamase-positive; MR, methicillin-resistant; VR, vancomycin-resistant; Pen N-S, penicillin non-susceptible; Pen I, penicillin-intermediate; Pen R, penicillin-resistant.

[a] –, percentage not calculated as $n < 10$.

[b] Includes all countries in Eastern Europe that participated in the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.). Individual data for Bulgaria, Hungary, Latvia, Lithuania, Poland and Slovak Republic are not presented as they submitted isolates in ≤2 years.

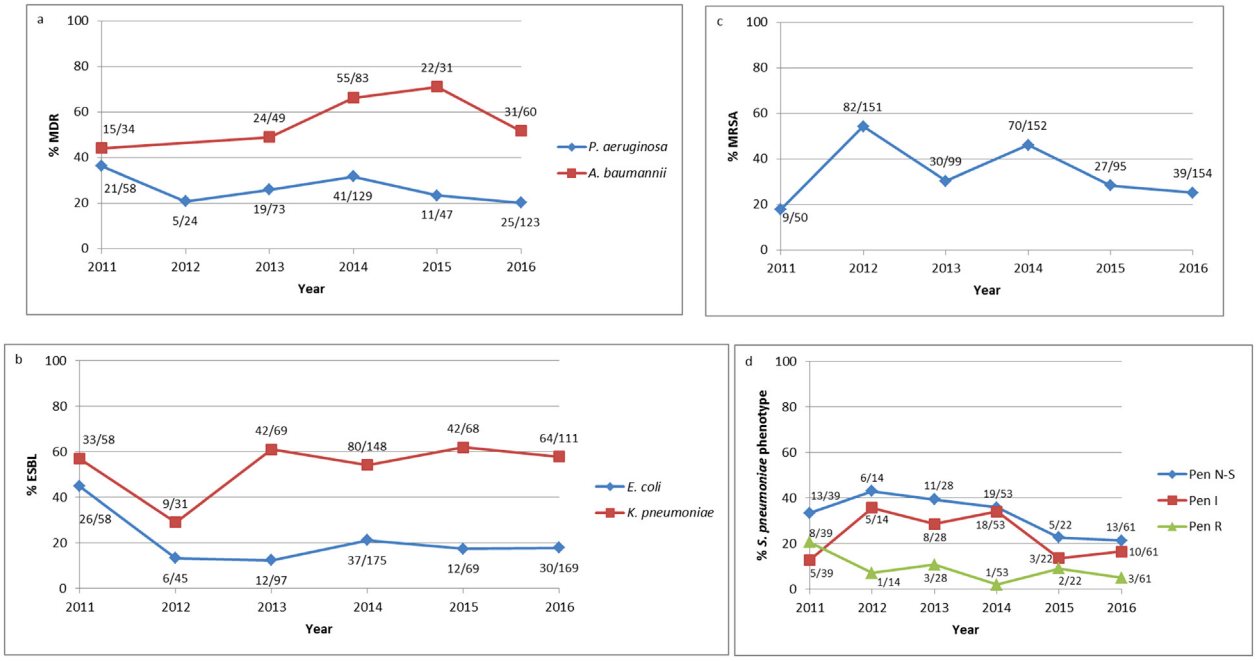

Fig. 1. Percentages of resistant phenotypes collected in Eastern Europe by year, 2011–2016 for (a) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, (b) *Escherichia coli* and *Klebsiella pneumoniae*, (c) *Staphylococcus aureus* and (d) *Streptococcus pneumoniae*. In (a), the data point for *Acinetobacter baumannii* for 2012 is omitted as $n < 10$. MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; Pen N-S, penicillin-non-susceptible; Pen I, penicillin-intermediate; Pen R, penicillin-resistant.

A total of 485 *K. pneumoniae* isolates were submitted, of which 55.7% were ESBL-producers (Table 3). Percentages of ESBL-producing *K. pneumoniae* isolates collected across Eastern Europe were variable between 2011 and 2013 but then stabilised between 2013 and 2016 (Fig. 1b). Of the agents on the T.E.S.T. panel, resistance among all *K. pneumoniae* isolates was highest to ampicillin (98.6%), ceftriaxone (62.7%), AMC (59.4%) and cefepime (57.7%), with higher percentages among ESBL-producers (100.0%, 99.6%, 85.9% and 95.6%, respectively) (Table 4). Resistance to meropenem, amikacin and tigecycline was low against all *K. pneumoniae* isolates (3.1%, 3.7% and 4.7%, respectively) and against the ESBL-producing subset (4.1%, 5.9% and 4.8%, respectively).

A total of 81 *Klebsiella oxytoca* isolates were submitted. Resistance to ampicillin was 90.1% and to all other agents with available breakpoints was ≤19.8%; resistance was lowest to meropenem (0.0%), tigecycline (0.0%) and amikacin (1.2%) (Table 4). Of the 519 *Enterobacter* spp. isolates collected between 2011 and 2016, <5% were resistant to meropenem (0.4%), tigecycline (2.9%) and amikacin (4.6%) (Table 4). Resistance to the remaining agents on the T.E.S.T. panel ranged from 13.7% to 41.4%.

Resistance to meropenem, tigecycline and amikacin was low against the 214 *Serratia marcescens* isolates (0.0%, 0.9%, and 3.7%, respectively) (Table 4). Resistance to the other antimicrobials on the panel ranged from 10.3% to 22.9%.

Table 4
Antimicrobial activity among Gram-negative organisms collected in Eastern Europe, 2011–2016.

Species/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Acinetobacter baumannii (*n* = 262)					
Amikacin	64	≥128	1 to ≥128	31.3	63.4
Levofloxacin	8	≥16	0.03 to ≥16	22.1	77.5
Meropenem	≥32	≥32	≤0.06 to ≥32	30.2	62.2
TZP	≥256	≥256	≤0.06 to ≥256	–[a]	–
Tigecycline	1	2	0.015 to 4	–	–
MDR *A. baumannii* (*n* = 151)					
Amikacin	≥128	≥128	32 to ≥128	0.0	100.0
Levofloxacin	8	≥16	4 to ≥16	0.0	100.0
Meropenem	≥32	≥32	16 to ≥32	0.0	100.0
TZP	≥256	≥256	64 to ≥256	–	–
Tigecycline	1	2	0.015 to 4	–	–
Pseudomonas aeruginosa (*n* = 454)					
Amikacin	4	32	≤0.5 to ≥128	76.7	15.9
Cefepime	8	≥64	≤0.5 to ≥64	61.9	38.1
Ceftazidime	4	32	≤1 to 32	67.8	32.2
Levofloxacin	2	≥16	0.06 to ≥16	47.8	52.2
Meropenem	2	≥32	≤0.06 to ≥32	54.8	29.5
TZP	8	128	0.12 to ≥256	64.8	35.2
Tigecycline	8	16	0.25 to 16	–	–
MDR *P. aeruginosa* (*n* = 122)					
Amikacin	32	64	≤0.5 to ≥128	38.5	50.8
Cefepime	32	≥64	8 to ≥64	6.6	93.4
Ceftazidime	32	32	2 to 32	20.5	79.5
Levofloxacin	≥16	≥16	2 to ≥16	0.0	100.0
Meropenem	≥32	≥32	0.5 to ≥32	4.1	93.4
TZP	64	≥256	0.5 to ≥256	13.1	86.9
Tigecycline	16	16	0.5 to 16	–	–
Escherichia coli (*n* = 613)					
Amikacin	2	8	≤0.5 to ≥128	96.4	0.5
AMC	8	32	1 to ≥64	62.3	37.7
Ampicillin	≥64	≥64	≤0.5 to ≥64	31.6	68.4
Cefepime	≤0.5	32	≤0.5 to ≥64	76.3	18.3
Ceftriaxone	≤0.06	64	≤0.06 to 64	74.2	24.8
Levofloxacin	0.06	≥16	≤0.008 to ≥16	64.6	33.9
Meropenem	≤0.06	≤0.06	≤0.06 to ≥32	99.7	0.2
Minocycline	1	8	≤0.5 to ≥32	–	–
TZP	2	16	0.25 to ≥256	87.8	8.6
Tigecycline	0.12	0.5	≤0.008 to 4	99.3	0.2
ESBL-producing *E. coli* (*n* = 123)					
Amikacin	4	16	1 to ≥128	87.0	2.4
AMC	16	32	4 to ≥64	28.5	71.5
Ampicillin	≥64	≥64	64 to ≥64	0.0	100.0
Cefepime	32	≥64	≤0.5 to ≥64	10.6	78.9
Ceftriaxone	64	64	≤0.06 to 64	2.4	95.1
Levofloxacin	8	≥16	≤0.008 to ≥16	19.5	80.5
Meropenem	≤0.06	0.12	≤0.06 to 0.5	100.0	0.0
Minocycline	2	8	≤0.5 to ≥32	–	–
TZP	4	32	0.5 to ≥256	65.0	22.8
Tigecycline	0.25	0.5	0.03 to 2	98.4	0.0
Klebsiella pneumoniae (*n* = 485)					
Amikacin	2	8	≤0.5 to ≥128	91.3	3.7
AMC	16	≥64	1 to ≥64	40.6	59.4
Ampicillin	≥64	≥64	2 to ≥64	1.4	98.6
Cefepime	16	≥64	≤0.5 to ≥64	37.7	57.7
Ceftriaxone	64	64	≤0.06 to 64	37.3	62.7
Levofloxacin	1	≥16	0.015 to ≥16	49.5	45.8
Meropenem	≤0.06	0.25	≤0.06 to ≥32	94.6	3.1
Minocycline	2	≥32	≤0.5 to ≥32	–	–
TZP	8	≥256	0.12 to ≥256	60.2	32.4
Tigecycline	0.5	2	0.06 to 8	84.9	4.7
ESBL-producing *K. pneumoniae* (*n* = 270)					
Amikacin	4	16	≤0.5 to ≥128	89.3	5.9
AMC	16	≥64	2 to ≥64	14.1	85.9
Ampicillin	≥64	≥64	32 to ≥64	0.0	100.0
Cefepime	≥64	≥64	≤0.5 to ≥64	1.9	95.6
Ceftriaxone	64	64	0.12 to 64	0.4	99.6
Levofloxacin	8	≥16	0.03 to ≥16	27.8	66.3
Meropenem	0.12	1	≤0.06 to ≥32	92.2	4.1
Minocycline	4	≥32	≤0.5 to ≥32	–	–
TZP	16	≥256	0.5 to ≥256	42.2	46.3
Tigecycline	0.5	2	0.06 to 8	81.9	4.8
Klebsiella oxytoca (*n* = 81)					
Amikacin	2	4	≤0.5 to ≥128	98.8	1.2

Table 4 (*Continued*)

Species/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
AMC	4	16	1 to ≥64	80.2	19.8
Ampicillin	≥64	≥64	1 to ≥64	9.9	90.1
Cefepime	≤0.5	4	≤0.5 to ≥64	86.4	9.9
Ceftriaxone	≤0.06	32	≤0.06 to 64	81.5	16.0
Levofloxacin	0.03	1	0.015 to ≥16	86.4	8.6
Meropenem	≤0.06	0.12	≤0.06 to 2	100.0	0.0
Minocycline	1	4	≤0.5 to ≥32	–	–
TZP	1	64	0.12 to ≥256	85.2	12.3
Tigecycline	0.25	0.5	0.03 to 2	97.5	0.0
Enterobacter spp. (*n* = 519)					
Amikacin	2	8	≤0.5 to ≥128	93.8	4.6
Cefepime	≤0.5	≥64	≤0.5 to ≥64	65.3	25.0
Ceftriaxone	0.5	64	≤0.06 to 64	56.5	41.4
Levofloxacin	0.06	4	≤0.008 to ≥16	78.6	13.7
Meropenem	≤0.06	0.25	≤0.06 to 16	98.5	0.4
Minocycline	2	8	≤0.5 to ≥32	–	–
TZP	2	64	≤0.06 to ≥256	71.1	23.1
Tigecycline	0.5	1	0.12 to 8	91.5	2.9
Serratia marcescens (*n* = 214)					
Amikacin	4	8	≤0.5 to ≥128	91.6	3.7
Cefepime	≤0.5	32	≤0.5 to ≥64	81.3	15.0
Ceftriaxone	0.5	64	≤0.06 to 64	70.6	22.9
Levofloxacin	0.12	2	≤0.008 to ≥16	78.5	10.3
Meropenem	0.12	0.25	≤0.06 to 8	98.6	0.0
Minocycline	4	8	≤0.5 to ≥32	–	–
TZP	2	32	≤0.06 to ≥256	83.6	11.2
Tigecycline	1	2	0.06 to 4	78.0	0.9
Haemophilus influenzae (*n* = 224)					
Amikacin	4	8	≤0.5 to 32	–	–
AMC	0.5	1	≤0.12 to 4	98.7	1.3
Ampicillin	≤0.5	16	≤0.5 to ≥64	81.3	18.8
Ceftriaxone	≤0.06	≤0.06	≤0.06 to 0.5	98.2	1.8
Levofloxacin	0.015	0.03	≤0.008 to 8	95.5	4.5
Meropenem	≤0.06	0.12	≤0.06 to 0.5	100.0	0.0
Minocycline	≤0.5	1	≤0.5 to 16	96.0	0.9
TZP	≤0.06	≤0.06	≤0.06 to 0.5	–	–
Tigecycline	0.12	0.25	≤0.008 to 0.5	–	–
β-Lactamase-positive *H. influenzae* (*n* = 39)					
Amikacin	8	8	≤0.5 to 8	–	–
AMC	1	2	0.25 to 4	94.9	5.1
Ampicillin	32	≥64	2 to ≥64	0.0	100.0
Ceftriaxone	≤0.06	≤0.06	≤0.06 to 0.12	100.0	0.0
Levofloxacin	0.015	0.06	≤0.008 to 0.5	97.4	2.6
Meropenem	0.12	0.12	≤0.06 to 0.5	100.0	0.0
Minocycline	≤0.5	1	≤0.5 to 1	100.0	0.0
TZP	≤0.06	≤0.06	≤0.06 to 0.12	–	–
Tigecycline	0.12	0.25	0.03 to 0.5	–	–

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50% and 90% of the isolates, respectively; S, susceptible; R, resistant; TZP, piperacillin/tazobactam; MDR, multidrug-resistant; AMC, amoxicillin/clavulanic acid; ESBL, extended-spectrum β-lactamase.

[a] –, no European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint available.

Of the 224 *Haemophilus influenzae* isolates submitted, 17.4% were β-lactamase-positive (Table 3). Resistance among all *H. influenzae* isolates and among the β-lactamase-positive subset was ≤5.1% to the agents on the T.E.S.T. panel with a resistance breakpoint, with the exception of ampicillin (Table 4). Resistance to ampicillin was 18.8% for all *H. influenzae* isolates and 100.0% for the β-lactamase-positive subset.

3.2. Gram-positive isolates

A total of 701 *S. aureus* isolates were collected between 2011 and 2016, of which 36.7% were MRSA (Table 3). The percentage that were MRSA varied by year of collection, with no clear trend towards increasing or decreasing resistance (Fig. 1c). There were six agents on the T.E.S.T. panel with resistance breakpoints available. None of the *S. aureus* isolates collected (including MRSA) were resistant to linezolid, tigecycline or vancomycin, and resistance to minocycline was low (3.7% for all *S. aureus* isolates and 8.6% for the MRSA subset) (Table 5).

Of the 133 *Enterococcus faecium* isolates collected, 22.6% were vancomycin-resistant (Table 3). Among the agents with breakpoints available, resistance among all *E. faecium* isolates to linezolid was low (2.3%) and no isolates were resistant to tigecycline (Table 5). None of the vancomycin-resistant isolates were resistant to tigecycline, whilst 10.0% were resistant to linezolid.

A total of 215 *Enterococcus faecalis* isolates were collected between 2011 and 2016. None of the *E. faecalis* isolates were resistant to linezolid, tigecycline or vancomycin, and resistance to ampicillin was 0.5% (Table 5). Resistance breakpoints for the other agents on the T.E.S.T. panel were not available.

During the period 2011–2016, 217 *Streptococcus pneumoniae* isolates were submitted, of which 30.9% were penicillin-non-susceptible (Table 3). The percentage of isolates that were

Table 5
Antimicrobial activity among Gram-positive organisms collected in Eastern Europe, 2011–2016.

Species/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Staphylococcus aureus (*n* = 701)					
AMC	1	≥16	≤0.03 to ≥16	–[a]	–
Ampicillin	8	≥32	≤0.06 to ≥32	–	–
Ceftriaxone	4	≥128	≤0.03 to ≥128	–	–
Levofloxacin	0.25	16	≤0.06 to ≥64	69.2	30.8
Linezolid	2	2	≤0.5 to 4	100.0	0.0
Meropenem	0.25	8	≤0.12 to ≥32	–	–
Minocycline	≤0.25	≤0.25	≤0.25 to 8	95.7	3.7
Penicillin	8	≥16	≤0.06 to ≥16	16.7	83.3
TZP	1	≥32	≤0.25 to ≥32	–	–
Tigecycline	0.12	0.25	0.03 to 0.5	100.0	0.0
Vancomycin	0.5	1	≤0.12 to 2	100.0	0.0
Methicillin-resistant *S. aureus* (MRSA) (*n* = 257)					
Levofloxacin	8	32	≤0.06 to ≥64	21.0	79.0
Linezolid	2	2	1 to 4	100.0	0.0
Minocycline	≤0.25	0.5	≤0.25 to 8	90.7	8.6
Tigecycline	0.12	0.25	0.06 to 0.5	100.0	0.0
Vancomycin	0.5	1	0.25 to 2	100.0	0.0
Enterococcus faecium (*n* = 133)					
Ampicillin	≥32	≥32	0.5 to ≥32	6.0	94.0
Levofloxacin	≥64	≥64	≤0.06 to ≥64	–	–
Linezolid	2	2	≤0.5 to ≥16	97.7	2.3
Minocycline	1	8	≤0.25 to ≥16	–	–
Tigecycline	0.06	0.12	≤0.008 to 0.25	100.0	0.0
Vancomycin	1	≥64	0.25 to ≥64	77.4	22.6
Vancomycin-resistant *E. faecium* (*n* = 30)					
Ampicillin	≥32	≥32	1 to ≥32	3.3	96.7
Levofloxacin	≥64	≥64	2 to ≥64	–	–
Linezolid	2	2	≤0.5 to ≥16	90.0	10.0
Penicillin	≥16	≥16	4 to ≥16	–	–
TZP	≥32	≥32	8 to ≥32	–	–
Tigecycline	0.06	0.25	≤0.008 to 0.25	100.0	0.0
Enterococcus faecalis (*n* = 215)					
Ampicillin	1	2	≤0.06 to ≥32	99.5	0.5
Levofloxacin	1	≥64	0.12 to ≥64	–	–
Linezolid	2	2	1 to 2	100.0	0.0
Meropenem	4	8	≤0.12 to ≥32	–	–
Penicillin	2	8	≤0.06 to ≥16	–	–
TZP	2	8	≤0.25 to ≥32	–	–
Tigecycline	0.12	0.25	0.03 to 0.5	99.5	0.0
Vancomycin	1	2	0.25 to 4	100.0	0.0
Streptococcus pneumoniae (*n* = 217)					
AMC	≤0.03	2	≤0.03 to ≥16	–	–
Ampicillin	≤0.06	4	≤0.06 to 16	83.9	12.4
Azithromycin [b]	0.06	64	≤0.03 to ≥128	75.5	24.5
Ceftriaxone	≤0.03	1	≤0.03 to 8	87.1	0.5
Clarithromycin [b]	0.03	64	≤0.015 to ≥128	75.9	22.6
Clindamycin [b]	0.03	≥128	≤0.015 to ≥128	84.4	15.6
Erythromycin [b]	0.06	64	≤0.015 to ≥128	75.5	24.5
Levofloxacin	1	1	≤0.06 to 8	99.1	0.9
Linezolid	≤0.5	1	≤0.5 to 2	100.0	0.0
Meropenem	≤0.12	1	≤0.12 to 2	100.0	0.0
Minocycline	0.5	8	≤0.25 to ≥16	59.0	29.0
Penicillin	≤0.06	2	≤0.06 to 8	69.1	8.3
TZP	≤0.25	2	≤0.25 to 8	–	–
Tigecycline	0.015	0.03	≤0.008 to 0.06	–	–
Vancomycin	0.25	0.5	≤0.12 to 1	100.0	0.0
Penicillin-resistant *S. pneumoniae* (*n* = 18)					
AMC	4	8	2 to ≥16	–	–
Ampicillin	8	16	4 to 16	0.0	100.0
Azithromycin	64	≥128	0.06 to ≥128	16.7	83.3
Ceftriaxone	2	2	0.5 to 8	5.6	5.6
Clarithromycin	64	≥128	0.03 to ≥128	16.7	83.3
Clindamycin	≥128	≥128	0.03 to ≥128	27.8	72.2
Erythromycin	64	≥128	0.03 to ≥128	16.7	83.3
Levofloxacin	1	1	0.5 to 1	100.0	0.0
Linezolid	≤0.5	1	≤0.5 to 1	100.0	0.0
Meropenem	1	2	0.5 to 2	100.0	0.0
Minocycline	8	≥16	0.5 to ≥16	11.1	88.9
TZP	4	8	2 to 8	–	–
Tigecycline	0.015	0.03	0.015 to 0.03	–	–
Vancomycin	0.25	0.5	≤0.12 to 0.5	100.0	0.0
Penicillin-intermediate *S. pneumoniae* (*n* = 49)					
AMC	0.25	4	≤0.03 to 4	–	–

Table 5 (*Continued*)

Species/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Ampicillin	0.5	4	≤0.06 to 4	67.3	16.3
Azithromycin	0.12	≥128	≤0.03 to ≥128	63.3	36.7
Ceftriaxone	0.25	1	≤0.03 to 2	79.6	0.0
Clarithromycin	0.03	64	≤0.015 to ≥128	65.3	28.6
Clindamycin	0.03	≥128	≤0.015 to ≥128	79.6	20.4
Erythromycin	0.06	64	≤0.015 to ≥128	63.3	36.7
Levofloxacin	1	1	0.5 to 8	98.0	2.0
Linezolid	1	1	≤0.5 to 2	100.0	0.0
Meropenem	0.25	1	≤0.12 to 2	100.0	0.0
Minocycline	0.5	8	≤0.25 to ≥16	51.0	38.8
TZP	≤0.25	4	≤0.25 to 4	–	–
Tigecycline	0.015	0.03	0.015 to 0.06	–	–
Vancomycin	0.25	0.5	≤0.12 to 1	100.0	0.0
Streptococcus agalactiae (*n* = 171)					
AMC	0.06	0.12	≤0.03 to 0.12	–	–
Ampicillin	0.12	0.12	≤0.06 to 0.25	–	–
Ceftriaxone	0.06	0.12	≤0.03 to 2	–	–
Levofloxacin	0.5	1	0.25 to 2	100.0	0.0
Linezolid	1	1	≤0.5 to 2	100.0	0.0
Meropenem	≤0.12	≤0.12	≤0.12 to 0.25	–	–
Minocycline	8	≥16	≤0.25 to ≥16	18.7	80.1
Penicillin	≤0.06	0.12	≤0.06 to 0.12	100.0	0.0
TZP	≤0.25	≤0.25	≤0.25 to 0.5	–	–
Tigecycline	0.03	0.25	≤0.008 to 2	95.3	4.7
Vancomycin	0.5	0.5	0.25 to 1	100.0	0.0

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50% and 90% of isolates, respectively; S, susceptible; R, resistant; AMC, amoxicillin/clavulanic acid; TZP, piperacillin/tazobactam.

[a] –, no European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint available.

[b] *n* = 212.

penicillin-non-susceptible was 33.3% in 2011 and then decreased from 42.9% in 2012 to 21.3% in 2016 (Fig. 1d). None of the *S. pneumoniae* isolates were resistant to linezolid, meropenem or vancomycin (Table 5). Resistance to ceftriaxone and levofloxacin was low among all *S. pneumoniae* isolates (0.5% and 0.9%, respectively) and among the penicillin-resistant subset (5.6% and 0.0%, respectively). Resistance to the other agents on the T.E.S.T. panel ranged from 12.4% to 29.0% for all isolates, and percentages were higher among isolates in the penicillin-resistant subset (72.2%–100.0%).

Of the 171 *Streptococcus agalactiae* isolates collected, none were resistant to levofloxacin, linezolid, penicillin or vancomycin and 4.7% were resistant to tigecycline (Table 5).

4. Discussion

This study reports on the in vitro antimicrobial resistance and resistant phenotypes among organisms collected in Eastern Europe between 2011 and 2016. There are few reports on antimicrobial resistance focusing on this region, however high levels of resistance have been demonstrated [2,4]. Furthermore, carbapenemase-producing Enterobacteriaceae continue to spread in Europe [9–11], and the European Centre for Disease Prevention and Control (ECDC) reported increased consumption of polymyxins in eight European countries (2011–2015), including Bulgaria, Hungary and Romania [12]. Reports from surveillance programmes focusing on Eastern Europe are therefore essential, and here we provide a follow-up to a T.E.S.T publication that reported on the 2004–2010 time period in this region [4].

In the present study, resistance to the three antimicrobials on the T.E.S.T. panel with EUCAST breakpoints for *A. baumannii* (levofloxacin, amikacin and meropenem) was high (77.5%, 63.4% and 62.2%, respectively). These values are higher than the population-weighted mean results reported by the EARS-Net study for 2016 for fluoroquinolones, aminoglycosides and carbapenems against *Acinetobacter* spp. for European Union/European Economic Area (EU/EEA) countries (39.0%, 35.2% and 35.1%, respectively). This demonstrates the higher level of resistance seen in Eastern Europe compared with Europe as a whole [2], although the different time periods of isolate collection could also be a factor. In this study, the overall percentage of *A. baumannii* isolates that were MDR for the period 2011–2016 was 57.6%, which again is higher than the population-weighted mean percentage for combined resistance of *Acinetobacter* spp. to fluoroquinolones, aminoglycosides and carbapenems (the T.E.S.T definition of MDR) reported by the EARS-Net study for EU/EEA countries in 2015 and 2016 (37.8% and 31.7%, respectively) [2]. Yearly data from the T.E.S.T. study showed percentages of MDR *A. baumannii* isolates increased year on year between 2011 and 2015, but then decreased in 2016. The EARS-Net study also reported a decrease in the population-weighted mean percentage for combined resistance between 2015 and 2016 for Europe overall [2].

This analysis presents country-specific data for three countries, namely Croatia, the Czech Republic and Romania. Focusing on the Eastern European countries that are included both in this analysis and the EARS-Net study, data from the EARS-Net study showed that percentages of combined resistance among *Acinetobacter* spp. to fluoroquinolones, aminoglycosides and carbapenems varied widely between the countries [2]. Using EARS-Net data from 2016 as an example, percentages ranged from 0.0% in the Czech Republic to 82.9% in Romania and 81.1% in Croatia. This wide variation between countries was also observed among *A. baumannii* isolates in this T.E.S.T. study of pooled data collected between 2011 and 2016, with percentages of multidrug resistance ranging from 1.9% in the Czech Republic to 85.4% in Romania and 89.2% in Croatia (other countries submitted isolates in ≤2 years of the study and so were not included in the country-by-country analysis). The differences between Croatia, the Czech Republic and Romania, although marked in some cases, were less extreme for the other resistant phenotypes reported in this T.E.S.T. study. This was also

the case in the EARS-Net study for MRSA, vancomycin-resistant *E. faecium* and penicillin-non-susceptible *S. pneumoniae* (other resistant phenotypes were not reported by EARS-Net) [2]. However, the number of isolates submitted to the T.E.S.T study in some countries was low and countries did not participate every year, limiting the interpretation of these results.

Carbapenem-resistant *A. baumannii* and carbapenem-resistant *P. aeruginosa* have been identified by the World Health Organization (WHO) as critical priority one pathogens, meaning they are in a group of pathogens for which globally the urgency for research and development for new antimicrobials is greatest [3]. For the pooled time period, the percentage of *A. baumannii* and *P. aeruginosa* isolates that were resistant to meropenem in this study was 62.2% and 29.5%, respectively.

The percentages of ESBL-producers in the current study (2011–2016) among *E. coli* (20.1%) and *K. pneumoniae* (55.7%) were higher than those reported by T.E.S.T. for 2004–2010 (15.3% and 39.3%, respectively) [4], although this could be in part due to the different countries and numbers of centres in each study. Carbapenem-resistant Enterobacteriaceae have also been identified by the WHO as critical priority pathogens [3]. Importantly, meropenem resistance among *E. coli* in the current study was low, as was the case for the population-weighted mean percentage of carbapenem resistance in all the countries in the EARS-Net study [2]. The percentage of *K. pneumoniae* isolates that were resistant to meropenem in this T.E.S.T. analysis was 3.1%. This was similar to the percentage of isolates that were carbapenem-resistant in eight of the nine Eastern European countries that are included in both this T.E.S.T. analysis and the EARS-Net study (≤4.4% in 2016; 31.4% in Romania in 2016).

MRSA and vancomycin-resistant *E. faecium* are both considered high priority in the WHO list of pathogens [3]. In this surveillance programme, the percentage of *S. aureus* isolates that were MRSA was variable over time across Eastern Europe and there was no clear trend to increasing or decreasing resistance. The EARS-Net study continues to report decreasing population-weighted mean MRSA percentages for the whole of Europe (EU/EEA) although this is not always seen at a country level, with some countries reporting flat or increasing trends [2]. In particular, Croatia and the Czech Republic (which make up >50% of isolates submitted to T.E.S.T.) showed no marked change in the percentages of MRSA in the EARS-Net study between 2013 and 2016. MRSA remains a concern across Europe as it is common for MRSA to be resistant to multiple antimicrobial agents [2]. Approximately one-third of *S. aureus* isolates collected in Eastern Europe in T.E.S.T. were MRSA, which is higher than the value (25%) reported by T.E.S.T. for 2004–2010 [4]. However, all of the MRSA isolates were susceptible to linezolid, vancomycin and tigecycline, as also seen in the report by Balode et al. [4]. This was also the case in a study of MRSA isolates collected in Eastern Europe in 2014 [13]; however, in a study of MRSA isolates collected in countries across Europe in 2012, tigecycline susceptibility was 99.3% (100% for linezolid and vancomycin) [14].

No vancomycin resistance was reported among *E. faecalis* from Eastern Europe, but 22.6% of *E. faecium* were resistant to vancomycin. Resistance to vancomycin among *E. faecium* is highly variable across Europe with many countries reporting no such isolates; however, countries in Eastern Europe are a notable exception to this and many have reported increasing rates of vancomycin resistance among *E. faecium* [2]. The percentage of vancomycin-resistant *E. faecium* reported here (22.6%) is higher than the previous T.E.S.T. study of isolates collected in Eastern Europe between 2004 and 2010 [4]. These higher percentages of vancomycin-resistant *E. faecium* in the Eastern countries of Europe limit treatment options caused by these pathogens. As found previously [4], all isolates of *E. faecalis* were susceptible to linezolid and tigecycline. Against *E. faecium*, all isolates were susceptible to tigecycline and 97.7% to linezolid.

7The EARS-Net reported on percentages of penicillin non-susceptibility among *S. pneumoniae* in Europe between 2013 and 2016 [2]. Of the nine Eastern European countries included in Eastern Europe for this T.E.S.T. study, two were reported by the EARS-Net study to have significantly changed percentages of penicillin non-susceptibility among *S. pneumoniae* (2013–2016), with an increase reported in Hungary and a decrease in Poland. We report that penicillin non-susceptibility among *S. pneumoniae* in this study in Eastern Europe decreased from 2011 (33.3%) to 2016 (21.3%). Resistance to ceftriaxone and levofloxacin among all *S. pneumoniae* isolates was low in this T.E.S.T. study (0.5% and 0.9%, respectively). The Survey of Antibiotic Resistance (SOAR) study reported ceftriaxone and levofloxacin resistance among *S. pneumoniae* for five of the countries included in T.E.S.T. (Bulgaria, Romania, Croatia, the Slovak Republic and the Czech Republic) for 2014–2016, and also reported that resistance was low [15–17].

Surveillance studies play an important role in the charting of antimicrobial resistance; however, as with all large-scale studies, T.E.S.T. has limitations. The study centres were not the same over the entire study period, with centres not contributing in each year of study; this impacts the longitudinal analysis as each study centre will have its own pattern of antimicrobial resistance. However, by pooling together the contribution from a number of centres across countries, the aim is that the study gives a picture of the situation across Eastern Europe. In addition, identification of MDR isolates among the *A. baumannii* collected was limited as there are only three antimicrobials in the T.E.S.T. panel with EUCAST breakpoints against *A. baumannii* (amikacin, meropenem and levofloxacin).

Antimicrobial resistance continues to be an issue in Eastern Europe, particularly in terms of MDR *A. baumannii*, ESBL-producing Enterobacteriaceae and MRSA. This study shows continued activity of linezolid, vancomycin and tigecycline against Gram-positive organisms including MRSA. Among Gram-negative organisms, resistance to meropenem and tigecycline was low among the Enterobacteriaceae, and the MIC_{90} for tigecycline against *A. baumannii* was low (2 mg/L). Continued surveillance of antimicrobial resistance in this region is required to monitor antimicrobial susceptibility and emerging resistance in this region.

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Competing interests

MJD is a current employee of Pfizer Inc. EC declares no competing interests.

Ethical approval

Not required.

Data availability

The data sets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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