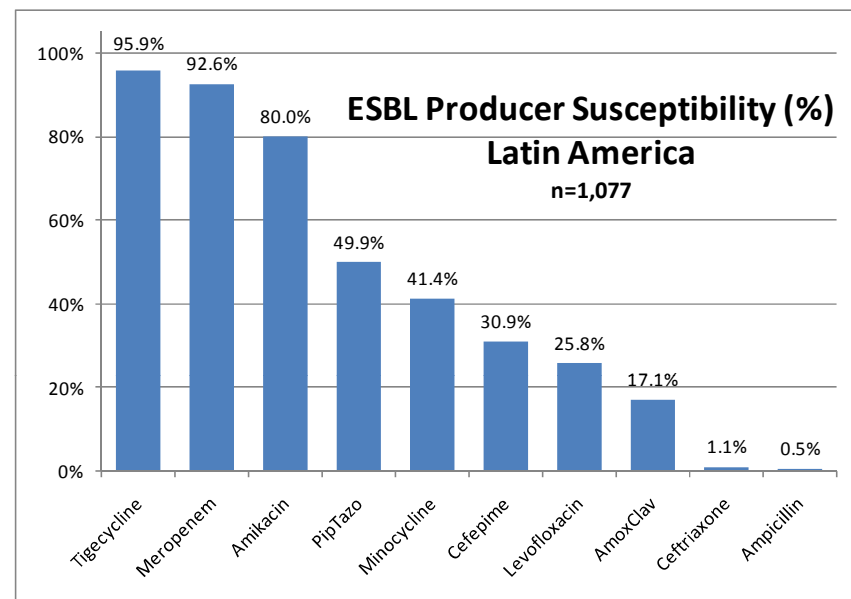


Revised Abstract

Background: The emergence and dissemination of extended spectrum beta-lactamase (ESBL) producing isolates represents an alarming trend in increasing resistance to antimicrobial agents in many countries in recent years. This study looks at ESBL rates from 2008 through 2010 in Latin America and the effect on susceptibilities to common therapeutic agents. This study is part of the larger Tigecycline Evaluation and Surveillance Trial (TEST), an ongoing global surveillance designed to follow trends in antimicrobial activity of tigecycline and comparators. **Methods:** 4,621 clinical isolates from all sources were collected from 133 cumulative investigator sites in Latin America. Evaluations were conducted on ESBL producing strains of *E. coli*, *K. oxytoca*, and *K. pneumoniae*. Clinical isolates were identified to the species level at each participating site and confirmed by the central laboratory. Minimum Inhibitory Concentrations (MICs) were determined by the local laboratory using supplied broth microdilution panels and interpreted according to current CLSI and FDA (tigecycline) guidelines. **Results:** A total of 1,290 (28%) ESBLs were confirmed: 600/2435 (25%) *E. coli*; 30/198 (15%) *K. oxytoca*; 660/1988 (33%) *K. pneumoniae*. Tigecycline *in vitro* activity against all ESBLs demonstrated MIC₅₀, MIC₉₀, and %Sus of 0.5 mcg/ml, 2 mcg/ml, and 95.9%, respectively. % Susceptible of tigecycline and comparators against all ESBLs are presented in the following figure:



Conclusions: The overall ESBL production rate (28%) in *E. coli* and *Klebsiella* spp from Latin America is at the highest level recorded for this region in almost a decade. Tigecycline *in vitro* activity (95.9% Sus) against ESBL producers is comparable to meropenem (92.6% Sus) and greater than that seen for either amikacin or piperacillin-tazobactam (both <80% Sus).

Introduction

Isolates of extended spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* are increasing globally [1,2]. Higher rates of clinical failures and morbidity have been associated with ESBL producing *Enterobacteriaceae* than with non-ESBL producing strains [3]. Therapy with third-generation cephalosporins should be avoided against ESBL producers, and because of the frequent presence of co-resistant genetic determinants, fluoroquinolones, trimethoprim-sulfa, aminoglycosides and tetracyclines find limited use. Tigecycline, a glycylcycline, has been shown to be particularly active against ESBL producing *Enterobacteriaceae* [2].

This study reports the ESBL rate of selected *Enterobacteriaceae* from Latin America as part of the ongoing global Tigecycline Evaluation and Surveillance Trial (TEST) designed to follow trends in antimicrobial activity of tigecycline and comparators.

Materials & Methods

- Between 2008 and 2010, 4,621 *E. coli* and *Klebsiella* clinical isolates were collected in 133 cumulative sites from 10 countries in Latin America. Isolates were identified to the species level and MICs determined at each participating laboratory using supplied broth microdilution panels. Only one isolate per patient was accepted into the study.
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA) or Sensititre (TREK Diagnostic Systems, Cleveland, OH) panels [4]. All drugs were supplied by the panel manufacturers.
- MIC interpretive criteria are defined by the CLSI and the most recent United States Food and Drug Administration package insert for tigecycline, where applicable [5,6].
- E. coli*, *K. oxytoca* and *K. pneumoniae* were screened for extended spectrum beta-lactamase (ESBL) production by broth microdilution and confirmed using the disc diffusion confirmatory test as recommended by the CLSI [5].
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [5].

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Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation and Surveillance Trial group. This study was sponsored by Pfizer Inc. IHMA is a clinical research organization that has been contracted by Pfizer Inc. to manage the TEST program.

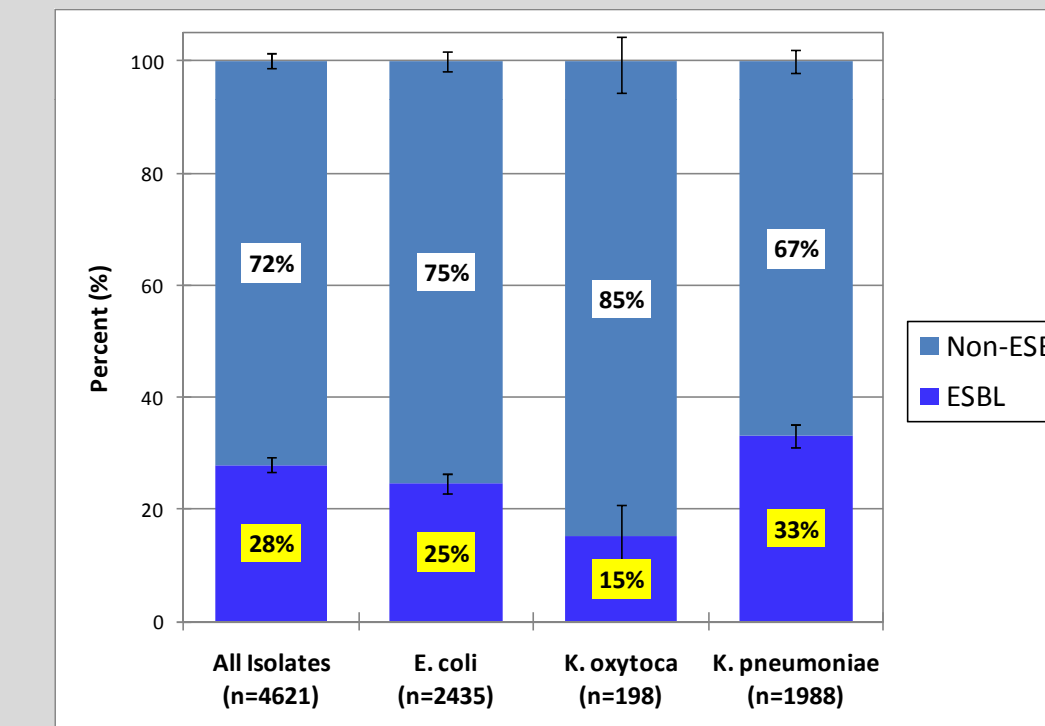
Table 1. *In vitro* activity of tigecycline and comparators against selected ESBL and non-ESBL producing *Enterobacteriaceae* from Latin America, 2008-2010.

Organism	Drug	mcg/ml			%Sus*	%Int	%Res
		MIC ₅₀	MIC ₉₀	Range			
ALL ESBL-producing Isolates Combined n=1290	Tigecycline	0.5	2	≤0.008 - 16	95.9	3.0	1.1
	Amikacin	4	64	≤0.5 - >64	80.0	7.2	12.8
	Amox-Clav	16	>32	0.25 - >32	17.1	36.9	46.1
	Ampicillin	>32	>32	1 - >32	0.5	0.2	99.3
	Cefepime	32	>32	≤0.5 - >32	30.9	12.6	56.4
	Ceftriaxone	>64	>64	1 - >64	1.1	1.5	97.4
	Levofloxacin	>8	>8	0.03 - >8	25.8	3.9	70.3
	Meropenem	≤0.06	1	≤0.06 - >16	92.6	1.6	5.9
	Minocycline	8	>16	≤0.5 - >16	41.4	17.1	41.6
	Pip-Tazo	32	>128	≤0.06 - >128	49.9	20.8	29.4
	<i>E. coli</i> , ESBL n=600	Tigecycline	0.25	1	≤0.008 - 4	99.8	0.2
Amikacin		4	32	≤0.5 - >64	88.7	6.2	5.2
Amox-Clav		16	32	0.25 - >32	19.5	43.7	36.8
Ampicillin		>32	>32	1 - >32	1.2	0.3	98.5
Cefepime		32	>32	≤0.5 - >32	30.5	13.3	56.2
Ceftriaxone		>64	>64	1 - >64	1.7	1.8	96.5
Levofloxacin		>8	>8	0.03 - >8	10.3	3.0	86.7
Meropenem		≤0.06	0.25	≤0.06 - >16	96.3	1.2	2.5
Minocycline		8	>16	≤0.5 - >16	45.7	15.2	39.2
Pip-Tazo		16	128	0.25 - >128	68.0	19.0	13.0
<i>E. coli</i> , non-ESBL n=1835		Tigecycline	0.25	0.5	≤0.008 - >16	99.7	0.3
	Amikacin	2	8	≤0.5 - >64	96.7	1.5	1.9
	Amox-Clav	8	32	0.25 - >32	59.0	22.6	18.4
	Ampicillin	>32	>32	≤0.5 - >32	26.3	1.9	71.9
	Cefepime	≤0.5	4	≤0.5 - >32	94.0	2.1	3.9
	Ceftriaxone	≤0.06	32	≤0.06 - >64	80.9	2.3	16.8
	Levofloxacin	0.5	>8	≤0.008 - >8	57.3	2.8	40.0
	Meropenem	≤0.06	0.12	≤0.06 - >16	98.9	0.1	1.0
	Minocycline	4	>16	≤0.5 - >16	58.2	15.4	26.5
	Pip-Tazo	2	32	≤0.5 - >128	87.6	5.6	6.8
	<i>K. oxytoca</i> , ESBL n=30	Tigecycline	0.5	1	0.06 - 2	100.0	0.0
Amikacin		4	32	1 - >64	86.7	6.7	6.7
Amox-Clav		16	32	0.25 - >32	30.0	43.3	26.7
Ampicillin		>32	>32	32 - >32	0.0	0.0	100.0
Cefepime		16	>32	≤0.5 - >32	46.7	16.7	36.7
Ceftriaxone		>64	>64	1 - >64	3.3	3.3	93.3
Levofloxacin		>8	>8	0.06 - >8	40.0	3.3	56.7
Meropenem		≤0.06	0.25	≤0.06 - 4	96.6	0.0	3.5
Minocycline		4	>16	1 - >16	50.0	30.0	20.0
Pip-Tazo		16	>128	≤0.06 - >128	63.3	20.0	16.7
<i>K. oxytoca</i> , non-ESBL n=168		Tigecycline	0.25	1	0.06 - 4	98.2	1.8
	Amikacin	2	8	≤0.5 - >64	96.4	1.2	2.4
	Amox-Clav	4	32	0.5 - >32	73.8	9.5	16.7
	Ampicillin	>32	>32	≤0.5 - >32	1.8	7.7	90.5
	Cefepime	≤0.5	8	≤0.5 - >32	91.1	3.6	5.4
	Ceftriaxone	≤0.06	32	≤0.06 - >64	79.2	2.4	18.5
	Levofloxacin	0.06	>8	≤0.008 - >8	83.3	1.8	14.9
	Meropenem	≤0.06	0.12	≤0.06 - 16	97.0	1.8	1.2
	Minocycline	2	16	≤0.5 - >16	78.6	7.1	14.3
	Pip-Tazo	2	128	0.25 - >128	83.9	5.4	10.7
	<i>K. pneumoniae</i> , ESBL n=660	Tigecycline	0.5	2	0.06 - 16	92.1	5.8
Amikacin		8	>64	≤0.5 - >64	71.8	8.2	20.0
Amox-Clav		32	>32	1 - >32	14.2	30.5	55.3
Ampicillin		>32	>32	32 - >32	0.0	0.0	100.0
Cefepime		32	>32	≤0.5 - >32	30.6	11.8	57.6
Ceftriaxone		>64	>64	1 - >64	0.5	1.1	98.5
Levofloxacin		8	>8	0.03 - >8	39.2	4.7	56.1
Meropenem		≤0.06	2	≤0.06 - >16	89.1	2.0	8.9
Minocycline		8	>16	≤0.5 - >16	37.1	18.2	44.7
Pip-Tazo		64	>128	0.5 - >128	32.7	22.4	44.9
<i>K. pneumoniae</i> , non-ESBL n=1328		Tigecycline	0.5	2	≤0.008 - >16	96.7	2.4
	Amikacin	1	8	≤0.5 - >64	92.7	2.3	5.0
	Amox-Clav	4	>32	≤0.12 - >32	65.3	10.8	23.9
	Ampicillin	>32	>32	1 - >32	1.2	8.0	90.8
	Cefepime	≤0.5	16	≤0.5 - >32	87.3	3.0	9.7
	Ceftriaxone	0.12	>64	≤0.06 - >64	74.8	1.4	23.8
	Levofloxacin	0.12	>8	≤0.008 - >8	78.3	2.6	19.1
	Meropenem	≤0.06	0.5	≤0.06 - >16	94.3	1.0	4.7
	Minocycline	4	>16	≤0.5 - >16	58.9	13.3	27.9
	Pip-Tazo	4	>128	≤0.06 - >128	75.5	7.8	16.6

* Susceptibility breakpoints defined in CLSI document M100-S21 (2011), where available; tigecycline breakpoints defined by FDA (Tygacil®, 2010).

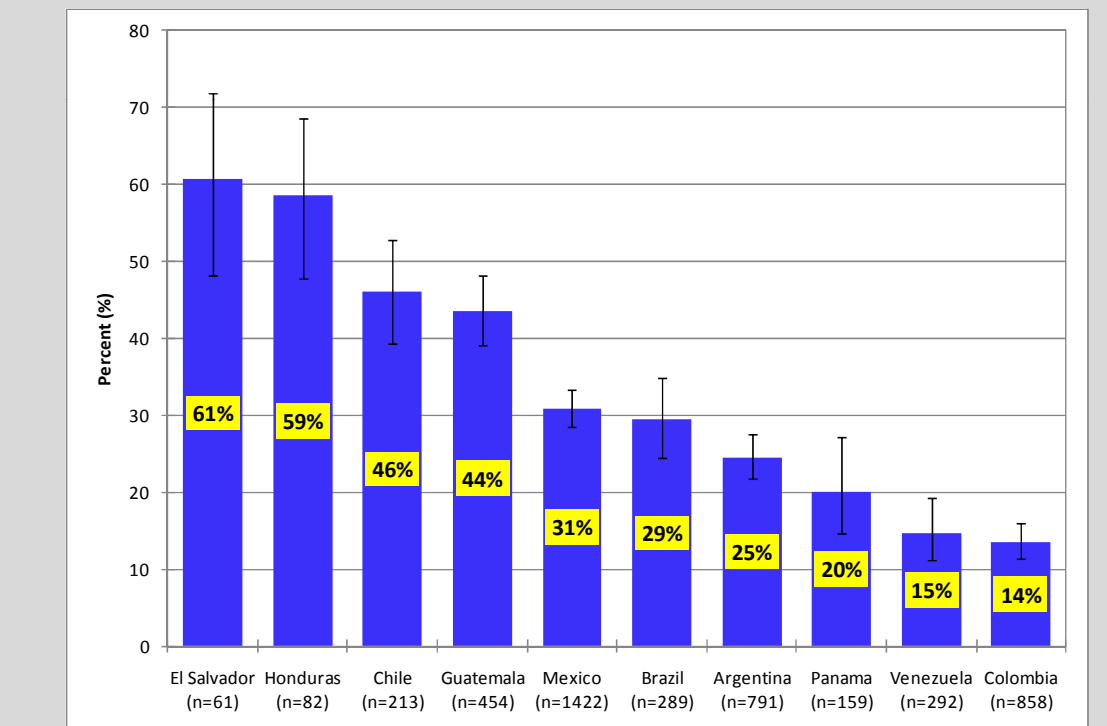
Results

Figure 1. Prevalence of ESBL compared to non-ESBL producing *Enterobacteriaceae* in Latin America, 2008-2010.



CI = 95% Confidence Intervals; adjusted Wald method.

Figure 2. Prevalence of ESBL-producing *Enterobacteriaceae* in Latin America by country (total n), 2008-2010.



CI = 95% Confidence Intervals; adjusted Wald method.

Conclusions

- The TEST program reports the current ESBL production rate to be 28% (95% confidence interval (CI): 27%- 29%) for all *E. coli*, *K. oxytoca*, and *K. pneumoniae* combined in Latin America during the years 2008 through 2010. The rates varied by country and were highest in Honduras (59%; 95% CI: 48-69%) and El Salvador (61%; 95% CI: 48-72%) and lowest in Venezuela (15%; 95% CI: 11-19%) and Colombia (14%; 95% CI:11-16%).
- Tigecycline, amikacin, and meropenem inhibited >90% of all non-ESBL producing isolates *in vitro* at their respective susceptible breakpoints. Cefepime inhibited >90% of all non-ESBL producing *E. coli* and *K. oxytoca* but not *K. pneumoniae*. Tigecycline and meropenem were the only two study drugs with activity >90% against ESBL producing *E. coli* and *K. oxytoca* while only tigecycline retained activity >90% against *K. pneumoniae*, followed closely by meropenem (89%).
- The increasing prevalence of ESBL producing *Enterobacteriaceae* in Latin America poses a serious challenge to clinicians with increasingly limited therapeutic options against these difficult to treat pathogens.