

## Revised Abstract

**Background:** *Enterobacteriaceae* are the most common gram-negative bacilli causing infections in patients worldwide. The Tigecycline Evaluation and Surveillance Trial (TEST) examines the susceptibility of pathogens isolated from multiple infection types in patients in countries worldwide. **Methods:** Clinically significant pathogens from the family *Enterobacteriaceae* were obtained from 93 cumulative sites in 10 countries in Asia 2004- 2010. MICs were determined for 5,115 isolates using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** The % Resistant and MIC<sub>90</sub> for 5,115 *Enterobacteriaceae* isolates versus levofloxacin is shown in the following table:

	% Resistant/MIC <sub>90</sub>						
	2004	2005	2006	2007	2008	2009	2010
<i>E. aerogenes</i> (n=)	3.7/2 27	5.6/1 18	2.0/1 51	13.0/8 100	11.8/8 34	1.7/1 58	20.0/8 30
<i>E. cloacae</i> (n=)	4.5/4 67	20.3/8 59	9.4/4 202	22.6/8 296	20.3/8 153	6.3/4 191	11.4/8 79
<i>E. coli</i> (n=)	43.2/8 125	46.2/8 65	42.5/8 346	50.9/8 438	61.6/8 216	50.7/8 276	58.6/8 116
<i>K. oxytoca</i> (n=)	22.2/8 9	0/4 8	16.7/8 30	29.0/8 38	0/0.12 5	28.6/8 14	0/0.5 11
<i>K. pneumoniae</i> (n=)	17.7/8 123	18.9/8 58	25.6/8 309	29.0/8 399	26.1/8 199	32.9/8 277	10.1/8 109
<i>S. marcescens</i> (n=)	2.1/1 49	4.5/2 22	5.6/4 125	9.2/4 153	10.6/8 90	11.1/8 90	2.2/1 46

**Conclusions:** Levofloxacin resistance (MIC  $\geq 8$ mcg/ml) amongst the *Enterobacteriaceae* varied by species and to a lesser extent by year. Overall, levofloxacin resistance was highest in *E. coli* with resistance  $>42\%$  in every study year. The lowest resistance rates were observed in *S. marcescens*. In Asia, levofloxacin resistance in *Enterobacteriaceae* is common.

## Introduction

Pathogens in the family *Enterobacteriaceae* remain the most common causes of gram negative infections worldwide. They are frequently associated with bacteremia, urinary tract, intra-abdominal and gastro-intestinal infections. Fluoroquinolones such as levofloxacin are potent antimicrobial agents used for the treatment of a wide variety of community- and nosocomial- infections caused by these pathogens. However, increasing resistance to levofloxacin in *Enterobacteriaceae* isolated from community- and hospital-associated infections threatens to restrict the clinical use of this agent [1]. Moreover, infections due to extended-spectrum beta-lactamase (ESBL) - producing *E. coli* and *Klebsiella* spp. are an emerging problem in community and hospital settings, with increasing numbers being reported from various infection sources and countries in Asia [2]. The current report describes susceptibilities and rates of levofloxacin resistance in selected *Enterobacteriaceae* clinical isolates collected as part of the Tigecycline Evaluation and Surveillance Trial (TEST) from Asia during 2004 – 2010 including ESBL-positive and ESBL-negative sub-populations.

## Materials & Methods

- ❖ **Isolates:** Ninety-three cumulative sites in 10 Asian countries collected 5,115 clinical isolates in 2004-2010. These isolates were identified to the species level and tested at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria and isolates were from 2004-2010 from various infection sources in Asia.
- ❖ **Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined by the Clinical Laboratory Standards Institute (CLSI) recommended broth microdilution testing method and interpreted according to CLSI guidelines [3, 4]. Custom broth microdilution panels were supplied by MicroScan (Siemens, West Sacramento, CA, USA) and TREK (TREK Diagnostic Systems, Cleveland, OH, USA).

## References

1. Lin CY, Huang SH, Chen TC, Lu PL, Lin WR, Chen YH. 2008. Risk factors of ciprofloxacin resistance in urinary *Escherichia coli* isolates. J Microbiol Immunol Infect, 41:325-331.
2. Hsueh PR, Badal RE, Hawser SP et al. 2010. Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). Int J Antimicrob Agents. 36: 408 – 414.
3. Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eighth Edition. CLSI document M07-A8 (ISBN 1-56238-689-1). Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2009.
4. Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne PA.

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## Results

Table 1. Levofloxacin percent resistance and MIC<sub>90</sub> (mcg/ml) for 5,115 *Enterobacteriaceae* spp.

Year	Organism	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	%I	%R
2004	<i>E. aerogenes</i>	27	0.06	2	92.6	3.7	3.7
	<i>E. cloacae</i>	67	0.06	4	89.6	5.9	4.5
	<i>E. coli</i>	125	0.5	>8	52.8	4.0	43.2
	<i>K. oxytoca</i>	9	0.06	>8	77.8	0	22.2
	<i>K. pneumoniae</i>	123	0.12	8	79.7	3.3	17.1
	<i>S. marcescens</i>	49	0.12	1	95.9	2.0	2.1
2005	<i>E. aerogenes</i>	18	0.03	1	94.4	0	5.6
	<i>E. cloacae</i>	59	0.25	>8	76.3	3.4	20.3
	<i>E. coli</i>	65	2	>8	50.8	3.1	46.2
	<i>K. oxytoca</i>	8	0.03	4	87.5	12.5	0
	<i>K. pneumoniae</i>	58	0.06	>8	77.6	3.5	18.9
	<i>S. marcescens</i>	22	0.5	2	95.5	0	4.5
2006	<i>E. aerogenes</i>	51	0.06	1	94.1	3.9	2.0
	<i>E. cloacae</i>	202	0.06	4	88.1	2.5	9.4
	<i>E. coli</i>	346	0.5	>8	52.3	5.2	42.5
	<i>K. oxytoca</i>	30	0.06	>8	80.0	3.3	16.7
	<i>K. pneumoniae</i>	309	0.12	>8	72.2	2.3	25.6
	<i>S. marcescens</i>	125	0.25	4	83.2	11.2	5.6
2007	<i>E. aerogenes</i>	100	0.06	8	81.0	6.0	13.0
	<i>E. cloacae</i>	296	0.25	>8	71.6	5.8	22.6
	<i>E. coli</i>	438	8	>8	46.8	2.3	50.9
	<i>K. oxytoca</i>	38	0.06	>8	68.4	2.6	29.0
	<i>K. pneumoniae</i>	399	0.5	>8	63.7	6.3	30.1
	<i>S. marcescens</i>	153	0.25	4	85.6	5.2	9.2
2008	<i>E. aerogenes</i>	34	0.06	>8	88.2	0	11.8
	<i>E. cloacae</i>	153	0.12	>8	77.8	2.0	20.3
	<i>E. coli</i>	216	>8	>8	37.0	1.4	61.6
	<i>K. oxytoca</i>	5	0.06	0.12	100	0	0
	<i>K. pneumoniae</i>	199	0.5	>8	67.3	6.5	26.1
	<i>S. marcescens</i>	94	0.25	8	88.3	1.1	10.6
2009	<i>E. aerogenes</i>	58	0.06	1	98.3	0	1.7
	<i>E. cloacae</i>	191	0.06	4	89.0	4.7	6.3
	<i>E. coli</i>	276	8	>8	43.8	5.4	50.7
	<i>K. oxytoca</i>	14	0.06	>8	71.4	0	28.6
	<i>K. pneumoniae</i>	277	0.5	>8	63.9	3.3	32.9
	<i>S. marcescens</i>	90	0.25	8	84.4	4.4	11.1
2010	<i>E. aerogenes</i>	30	0.25	8	70.0	10.0	20.0
	<i>E. cloacae</i>	79	0.06	8	86.1	2.5	11.4
	<i>E. coli</i>	116	8	>8	38.8	2.6	58.6
	<i>K. oxytoca</i>	11	0.06	0.5	100	0	0
	<i>K. pneumoniae</i>	109	0.12	8	84.4	5.5	10.1
	<i>S. marcescens</i>	46	0.25	1	95.6	2.2	2.2

Figure 1. Levofloxacin resistant *E. coli* in Asia 2004-2010.

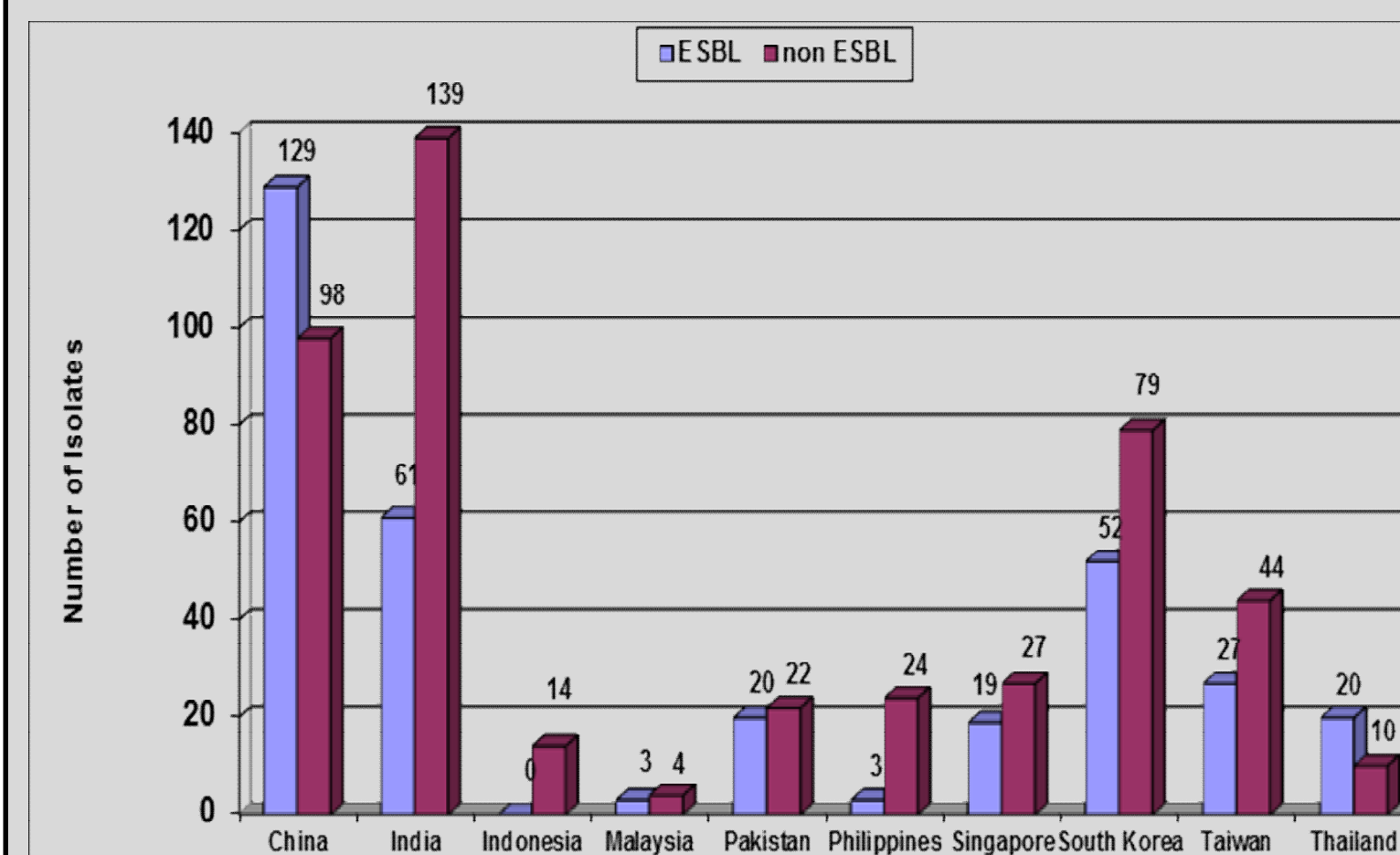
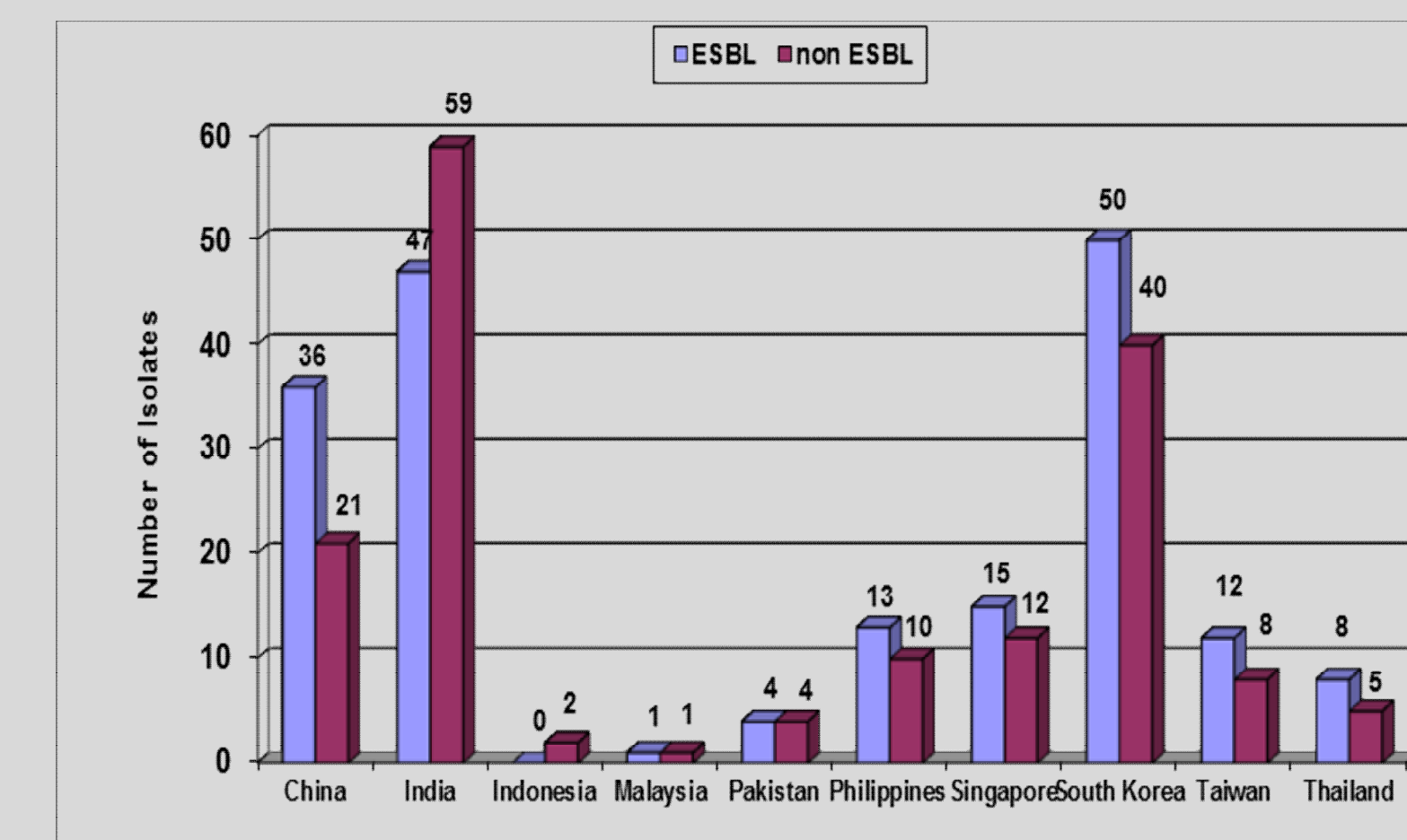


Figure 2. Levofloxacin resistant *K. pneumoniae* in Asia 2004-2010.



## Conclusions

- ❖ Levofloxacin resistance in *Enterobacteriaceae* spp. isolated in Asia over the past 7 years continues to increase.
- ❖ *E. coli* demonstrates the highest levels of levofloxacin resistance and in 2010 was greater than 50%.
- ❖ Isolate counts of ESBL-positive *E. coli* and *K. pneumoniae* document the increased prevalence of this phenotype.
- ❖ ESBL-positive *E. coli* are increasingly fluoroquinolone resistant (ciprofloxacin and levofloxacin).