

# Klebsiella pneumoniae from Intra-abdominal Infections in Asia/Pacific in 2009-2010: Susceptibility and Incidence of ESBL Phenotypes

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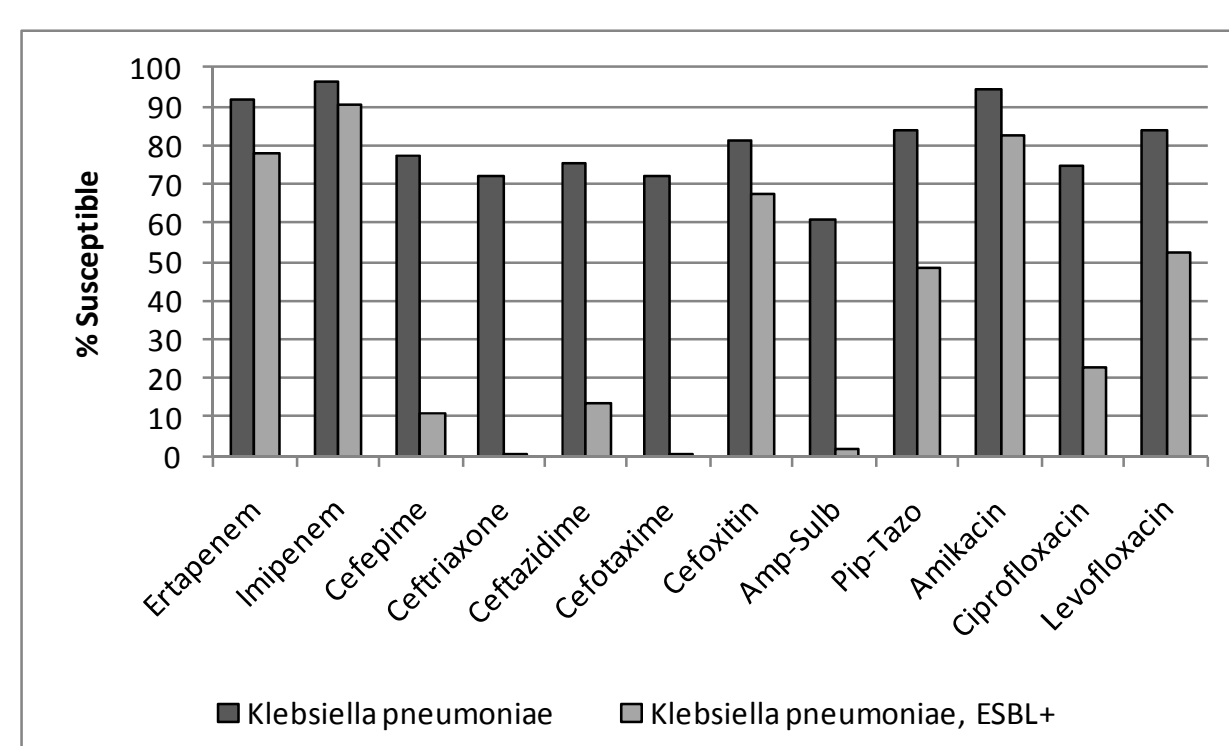
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## Revised Abstract

**Background:** *K. pneumoniae* is the second most common aerobic gram-negative bacillus found in intra-abdominal infection (IAI), after *E. coli*. Numerous reports in the literature have described incidence of ESBL+ isolates, and more recently the appearance of carbapenemases in this species has further added to the challenge of therapy selection. The Study for Monitoring Antimicrobial Resistance Trends (SMART) tracks susceptibility and ESBL rates of IAI pathogens worldwide; this report summarizes the most current susceptibility data for *K. pneumoniae* in the Asia/Pacific region.

**Methods:** 1,076 isolates of *K. pneumoniae* from IAI were collected in hospitals in 11 Asia/Pacific countries in 2009-2010. Susceptibility was determined using custom MicroScan broth microdilution panels, and interpreted using CLSI M100-S21 guidelines. ESBL determination was done using the CLSI phenotypic methodology.

**Results:** 253/1,076 (23.5%) isolates were ESBL+. Susceptibility of all *K. pneumoniae* and ESBL+ isolates to the drugs studied in SMART is shown in the figure below.



**Conclusions:** Only imipenem, amikacin, and ertapenem inhibited >90% of all *K. pneumoniae* isolates. Those three drugs also inhibited 91%, 83%, and 78%, respectively, of ESBL+ isolates. All other study drugs inhibited <70% of ESBL+ isolates. Given an ESBL+ rate of 24%, if *K. pneumoniae* is suspected as an IAI pathogen, empiric therapy options in some Asia/Pacific countries among the drugs in SMART may be limited to a carbapenem or amikacin.

## Introduction

**Introduction:** After *Escherichia coli*, *Klebsiella pneumoniae* is the second most common aerobic gram-negative pathogen in intra-abdominal infections (IAI), accounting for approximately 15% of isolates recovered from IAI. As such, it is important for physicians to take its local susceptibility patterns into account when initiating empiric therapy. Production of extended spectrum beta-lactamases (ESBLs) has been reported to be relatively common in this species, especially in parts of Latin America and Asia. More recently, carbapenemases have been reported more and more frequently in *K. pneumoniae* as well as other species, posing more difficult therapeutic challenges.

The Study for Monitoring Antimicrobial Resistance Trends (SMART) has tracked susceptibility and ESBL rates of IAI pathogens worldwide since 2002; this report summarizes the most current susceptibility data for *K. pneumoniae* in the Asia/Pacific region.

## Materials & Methods

- Participating sites each collected up to 100 consecutive, non-selected isolates of gram-negative aerobic bacilli from intra-abdominal infections each year of the study; 1,076 clinical isolates of *K. pneumoniae* were collected in 2009 and 2010 at 37 institutions in 11 countries in the Asia/Pacific region. The numbers of institutions per country were: 1 (South Korea, Thailand), 2 (Malaysia, New Zealand, Philippines, Singapore), 3 (Australia, Vietnam), and 8 (China, India, Taiwan).
- Isolates were sent to a central laboratory (IHMA, Inc., Schaumburg, Illinois, USA) for confirmation of identification and susceptibility testing.
- Minimum inhibitory concentrations (MICs) and production of extended spectrum beta-lactamase (ESBL) were determined using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA), following manufacturer and CLSI guidelines [1,2]. MICs were analyzed using CLSI M100-S21 susceptibility breakpoints [1].
- Quality control was done each day of testing following CLSI guidelines [1].
- The Fisher exact test was used to compare each country's ESBL+ rate to the overall Asia/Pacific rate; 95% confidence intervals were calculated using the adjusted Wald method.

## References

- Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI document M100-S21. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition, in Document M7-A8. Wayne, PA.

## Acknowledgements

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## Results

Table 1. Percent susceptible of all *K. pneumoniae* by country, 2009-2010<sup>1</sup>.

	% Susceptible											
	Asia/Pacific	Australia	China	India	Malaysia	New Zealand	Philippines	Singapore	South Korea	Taiwan	Thailand	Vietnam
Amikacin	94	100	92	68	100	99	99	100	98	98	100	93
Amp-Sulb	61	65	56	21	59	73	54	77	56	75	49	62
Cefepime	77	83	77	30	68	86	76	85	89	94	58	75
Cefotaxime	72	83	71	24	68	85	69	83	65	88	51	73
Cefoxitin	81	83	77	50	91	93	76	94	65	86	93	87
Ceftazidime	76	83	77	28	68	87	73	85	69	91	58	75
Ceftriaxone	72	83	71	24	68	84	72	82	65	88	53	73
Ciprofloxacin	75	87	72	30	73	87	66	85	69	90	62	78
Ertapenem	92	91	90	66	96	100	90	96	77	98	98	96
Imipenem	96	91	94	83	100	100	96	100	92	99	100	100
Levofloxacin	84	91	76	50	94	95	86	90	73	93	84	87
Pip-Tazo	84	91	86	55	71	93	82	92	71	94	84	81
n	1076	23	166	107	66	85	71	110	52	282	45	69

<sup>1</sup> Green shading denotes susceptibility ≥90%.

Table 2. Percent susceptible of ESBL-positive *K. pneumoniae* by country, 2009-2010<sup>1</sup>.

	% Susceptible											
	Asia/Pacific	Australia	China	India	Malaysia	New Zealand	Philippines	Singapore	South Korea	Taiwan	Thailand	Vietnam
Amikacin	83	4/4	83	62	100	92	100	100	7/8 <sup>2</sup>	83	100	72
Amp-Sulb	2	0	0	2	0	8	0	0	0	4	5	0
Cefepime	11	0	15	3	0	8	18	6	4/8 <sup>2</sup>	29	10	6
Cefotaxime	1	0	0	0	0	0	6	0	1/8 <sup>2</sup>	0	0	0
Cefoxitin	67	2/4 <sup>2</sup>	73	45	86	100	71	83	3/8 <sup>2</sup>	63	91	72
Ceftazidime	13	0	30	3	0	15	12	6	2/8 <sup>2</sup>	33	14	11
Ceftriaxone	1	0	0	0	0	0	6	0	1/8 <sup>2</sup>	0	0	0
Ciprofloxacin	23	2/4 <sup>2</sup>	38	7	19	31	12	11	3/8 <sup>2</sup>	42	24	28
Ertapenem	78	2/4 <sup>2</sup>	83	62	86	100	77	78	5/8 <sup>2</sup>	88	95	83
Imipenem	91	2/4 <sup>2</sup>	85	80	100	100	100	100	7/8 <sup>2</sup>	96	100	100
Levofloxacin	52	2/4 <sup>2</sup>	45	32	86	77	77	39	3/8 <sup>2</sup>	58	71	56
Pip-Tazo	49	2/4 <sup>2</sup>	65	44	24	69	47	50	3/8 <sup>2</sup>	50	67	28
n	253	4	40	69	21	13	17	18	8	24	21	18

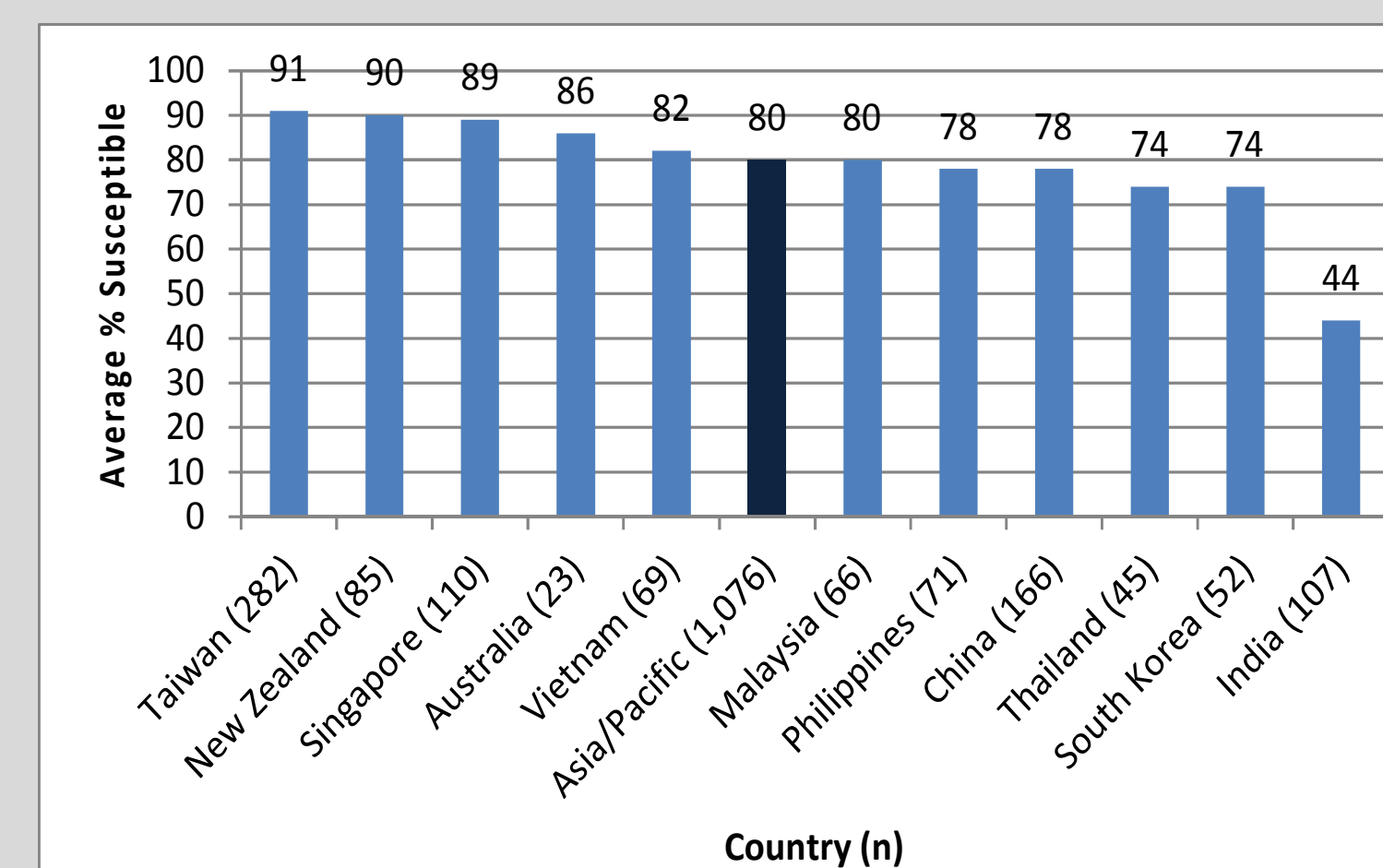
<sup>1</sup> Green shading denotes susceptibility ≥90%; <sup>2</sup>for countries with n<10, results shown as susceptible n/total n.

Table 3. Proportion of *K. pneumoniae* that is ESBL-positive by country, 2009-2010. Each country's rate is compared to the overall Asia/Pacific rate; significantly different rates are boldfaced (p<0.05).

	n	% ESBL+	(95% CI) <sup>1</sup>	p
<b>India</b>	107	64.5	(55-73)	<b>&lt;0.0001</b>
<b>Thailand</b>	45	46.7	(33-61)	<b>0.016</b>
Malaysia	66	31.8	(22-44)	0.262
Vietnam	69	26.1	(17-38)	0.675
China	166	24.1	(18-31)	0.924
Philippines	71	23.9	(15-35)	0.89
<b>Asia/Pacific</b>	<b>1076</b>	<b>23.5</b>	<b>(21-26)</b>	<b>--</b>
Australia	23	17.4	(6-38)	0.804
Singapore	110	16.4	(11-25)	0.191
South Korea	52	15.4	(8-28)	0.314
New Zealand	85	15.3	(9-25)	0.18
<b>Taiwan</b>	282	8.5	(6-12)	<b>&lt;0.0001</b>

<sup>1</sup>CI= confidence interval

Figure 1. Average percent susceptible\* of *K. pneumoniae* in Asia/Pacific countries in 2009-2010.



\*Average of susceptibility percentages of all drugs studied in SMART, using CLSI M100-S21 breakpoints.

## Conclusions

- Only imipenem, amikacin, and ertapenem inhibited ≥90% of all *K. pneumoniae* isolates in the Asia/Pacific region. Those three drugs also inhibited 91%, 83%, and 78%, respectively, of ESBL+ isolates. All other study drugs inhibited <70% of ESBL+ isolates.
- Rates of ESBL-positive *K. pneumoniae* varied by country, with India and Thailand showing significantly higher rates than the Asia/Pacific average (p<0.05), while the rate in Taiwan was significantly lower (p<0.05).
- The *in vitro* activity of the studied antimicrobials varied by country, with India, South Korea, and Thailand generally showing lower % susceptible than the other countries in the Asia/Pacific region. The Korea and Thailand data should be interpreted with some caution, since only one site per country participated in SMART in 2009-2010. The susceptibility rates in India, however, are extremely alarming, with only imipenem >80%, and only three other drugs (amikacin, ertapenem, and piperacillin-tazobactam) exceeding 50%.
- Although India and Thailand had the two highest ESBL+ rates in Asia, the ertapenem susceptibility rates in the two countries were very different; additionally, South Korea — despite having one of the lowest ESBL+ rates in Asia — had the second lowest ertapenem %S value. Further study and molecular characterization of these isolates is necessary to understand the underlying mechanisms of non-susceptibility, as ESBLs are not known to confer resistance to ertapenem without the presence of other mechanisms. Many of these isolates — especially in India — may well elaborate other beta-lactamases (multiple ESBLs, ampCs, and carbapenemases including NDM-1) and/or have altered outer membrane porins which might help explain the unusually low rate of susceptibility to many of the drugs in SMART.
- With a regional ESBL+ rate of 24%, if *K. pneumoniae* is suspected as an IAI pathogen, options for empiric therapy in some countries of Asia/Pacific — at least among the drugs studied in SMART — may be limited to a carbapenem or amikacin; options in India appear to be even more limited.