

Susceptibility and Incidence of Extended-spectrum Beta-lactamase Producing *Escherichia coli* and *Klebsiella pneumoniae* in Intra-abdominal Infections Globally: SMART 2009-2010

P 656

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
Fax: 847.303.5601

R. Badal¹, S. Hawser², S. Bouchillon¹, D. Hoban¹, M. Hackel¹, A. Johnson¹
¹International Health Management Associates, Inc., Schaumburg IL, USA
²IHMA Europe Sàrl, Epalinges, Switzerland

Revised Abstract

Objectives: *E. coli* and *K. pneumoniae* together represent approximately 60-70% of all aerobic gram-negative bacteria (GNB) isolated from intra-abdominal infections (IAI). It is therefore necessary to take their antimicrobial susceptibility into account when treating IAI. One of the goals of the Study for Monitoring Antimicrobial Resistance Trends (SMART), which tracks susceptibility patterns of IAI GNB globally, is to provide physicians with actionable data with which to tailor empiric therapy of IAI. This report provides the latest (2009-2010) susceptibility data and frequency of extended-spectrum beta-lactamase-producing (ESBL+) isolates for these two species.

Methods: 140 hospitals in 35 countries each collected up to 100 consecutive non-selected GNB from IAI; confirmation of identification, susceptibility testing, and phenotypic ESBL determinations were done at a central laboratory (IHMA, Inc.) using custom MicroScan dehydrated MIC panels, following CLSI and manufacturer procedures and quality control guidelines. CLSI M100-S21 breakpoints were used to determine susceptibility.

Results: The following table summarizes ESBL+ rates and susceptibility of *E. coli*, *K. pneumoniae*, and their respective ESBL+ sub-populations.

Organism	n	ESBL+ rate	Etp	Imp	Cpe	Cft	Caaz	Cax	Cfx	AS	PT	AK	CP	LVx
<i>E. coli</i> (all)	8,368	18.7%	98.1	99.2	82.5	76.7	81.2	76.9	88.7	41.6	91.5	97.4	65.8	67.0
<i>E. coli</i> (ESBL+ only)	1,562		95.0	98.7	10.4	0.8	22.6	1.5	78.5	7.6	83.9	90.3	18.8	20.5
<i>K. pneumoniae</i> (all)	2,822	21.9%	92.2	95.7	80.4	75.1	77.5	75.0	81.9	59.9	81.4	93.3	75.6	80.6
<i>K. pneumoniae</i> (ESBL+ only)	617		76.2	87.5	16.7	2.8	11.4	2.4	66.0	2.1	41.2	76.0	21.9	38.1

Conclusions: The two most commonly isolated pathogens of IAI, *E. coli* and *K. pneumoniae*, remain very susceptible to ertapenem, imipenem, and amikacin; even these drugs, however, showed diminished activity against ESBL+ *K. pneumoniae*. The high proportion (roughly 20%) of each of these species that is ESBL+ renders most of the comparators in this study <90% effective *in vitro*, with susceptibility to several <80%. In areas where ESBL+ rates exceed the global average (e.g., Asia/Pacific and Latin America), susceptibility rates are even lower, potentially leaving only the carbapenems and possibly amikacin among drugs studied in SMART as options for empiric therapy of IAI.

Introduction

E. coli and *K. pneumoniae* together represent approximately 60-70% of all aerobic gram-negative bacteria (GNB) isolated from intra-abdominal infections (IAI), making it is necessary to take their antimicrobial susceptibility into account when treating IAI. One of the goals of the Study for Monitoring Antimicrobial Resistance Trends (SMART), which tracks susceptibility patterns of IAI GNB in many countries around the world, is to provide physicians with antimicrobial susceptibility and epidemiologic data which can be used to adapt empiric therapy of IAI to more localized organism population characteristics. This report provides the latest (2009-2010) susceptibility data and frequency of extended-spectrum beta-lactamase-producing (ESBL+) isolates for these two species.

Materials & Methods

- Participating sites each collected up to 100 consecutive, non-selected isolates of gram-negative aerobic bacilli from intra-abdominal infections (1 isolate per patient) each year of the study; 11,190 clinical isolates of *E. coli* and *K. pneumoniae* were collected in 2009 and 2010 at 140 institutions in 35 countries globally.
- 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 custom 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 chi square test was used to compare each region's ESBL+ rate to the overall global 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

The SMART program is funded by Merck Research Laboratories, Inc. The authors thank all the participants in the SMART program for their continuing contributions to its success.

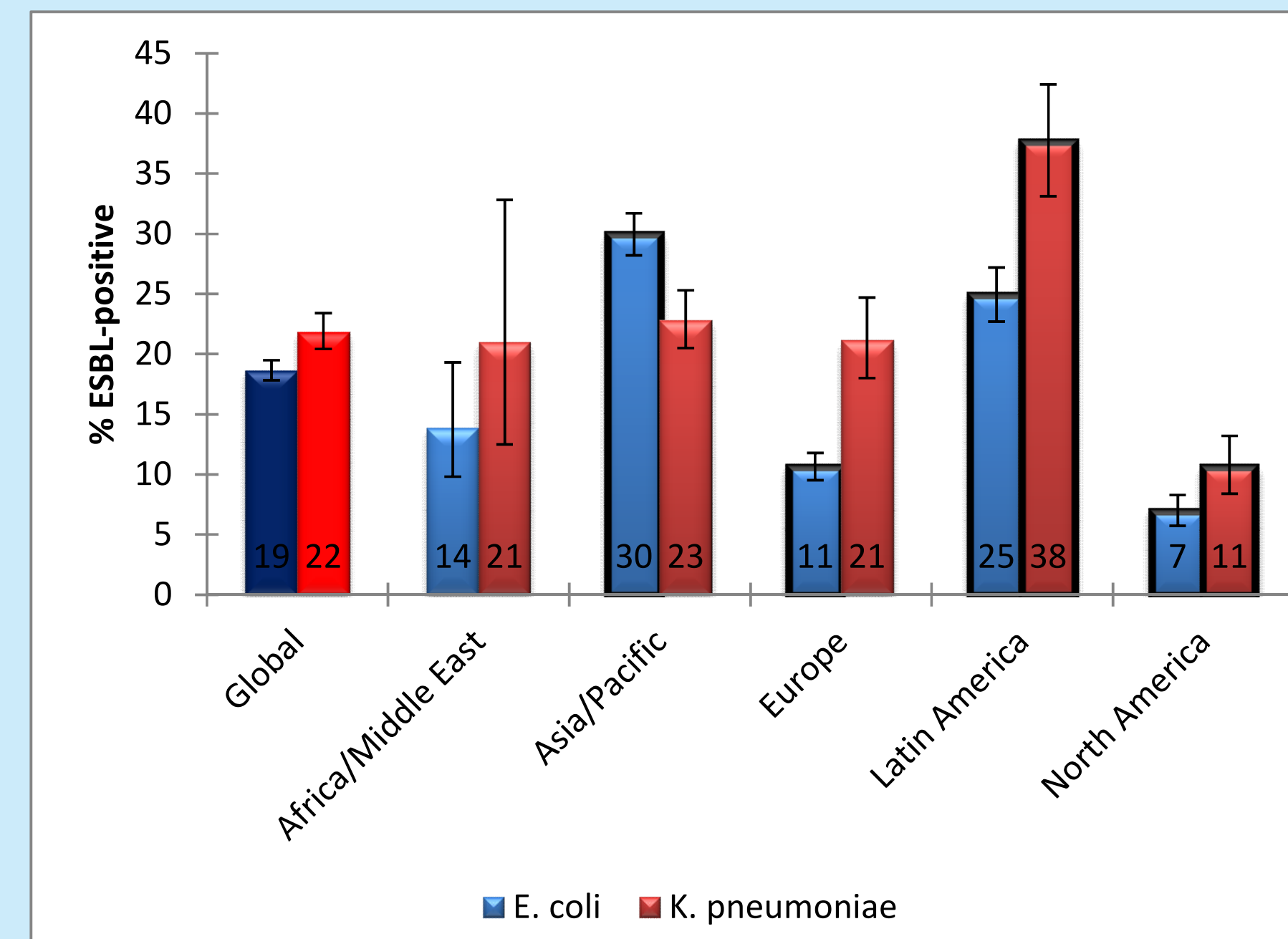
Results

Table 1. Percent susceptible for global *E. coli* and *K. pneumoniae* isolates and their ESBL-positive phenotypes, 2009-10. Values ≥90.0 are green-shaded; values ≥80.0 but <90.0 are yellow-shaded.

Organism	n	ETP	IMP	CPE	CFT	CAZ	CAX	CFX	AS	PT	AK	CP	LVX
<i>E. coli</i> (all)	8,368	98.1	99.2	82.5	76.7	81.2	76.9	88.7	41.6	91.5	97.4	65.8	67.0
<i>E. coli</i> (ESBL+ only)	1,562	95.0	98.7	10.4	0.8	22.6	1.5	78.5	7.6	83.9	90.3	18.8	20.5
<i>K. pneumoniae</i> (all)	2,822	92.2	95.7	80.4	75.1	77.5	75.0	81.9	59.9	81.4	93.3	75.6	80.6
<i>K. pneumoniae</i> (ESBL+ only)	617	76.2	87.5	16.7	2.8	11.4	2.4	66.0	2.1	41.2	76.0	21.9	38.1

Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Cft=cefotaxime, Caaz=ceftazidime, Cax=ceftriaxone, Cfx=cefuroxime, As=ampicillin-sulbactam, Pt=piperacillin-tazobactam, Ak=amikacin, Cp=ciprofloxacin, Lvx=levofloxacin.

Figure 1: Rate of ESBL-positive *E. coli* and *K. pneumoniae* by region with 95% confidence intervals, 2009-10. Results that are statistically significant from the global average are shown with a black border.



Sample sizes (n *E. coli* / n *K. pneumoniae*): Global (8,368/2,822), Africa/Middle East (2,099/62), Asia/Pacific (2,714/1,154), Europe (2,645/568), Latin America (1,379/412), North America (1,421/626).

Figure 2: Percent susceptible with 95% confidence intervals for *E. coli* and *K. pneumoniae* in the Africa/Middle East region, 2009-2010.

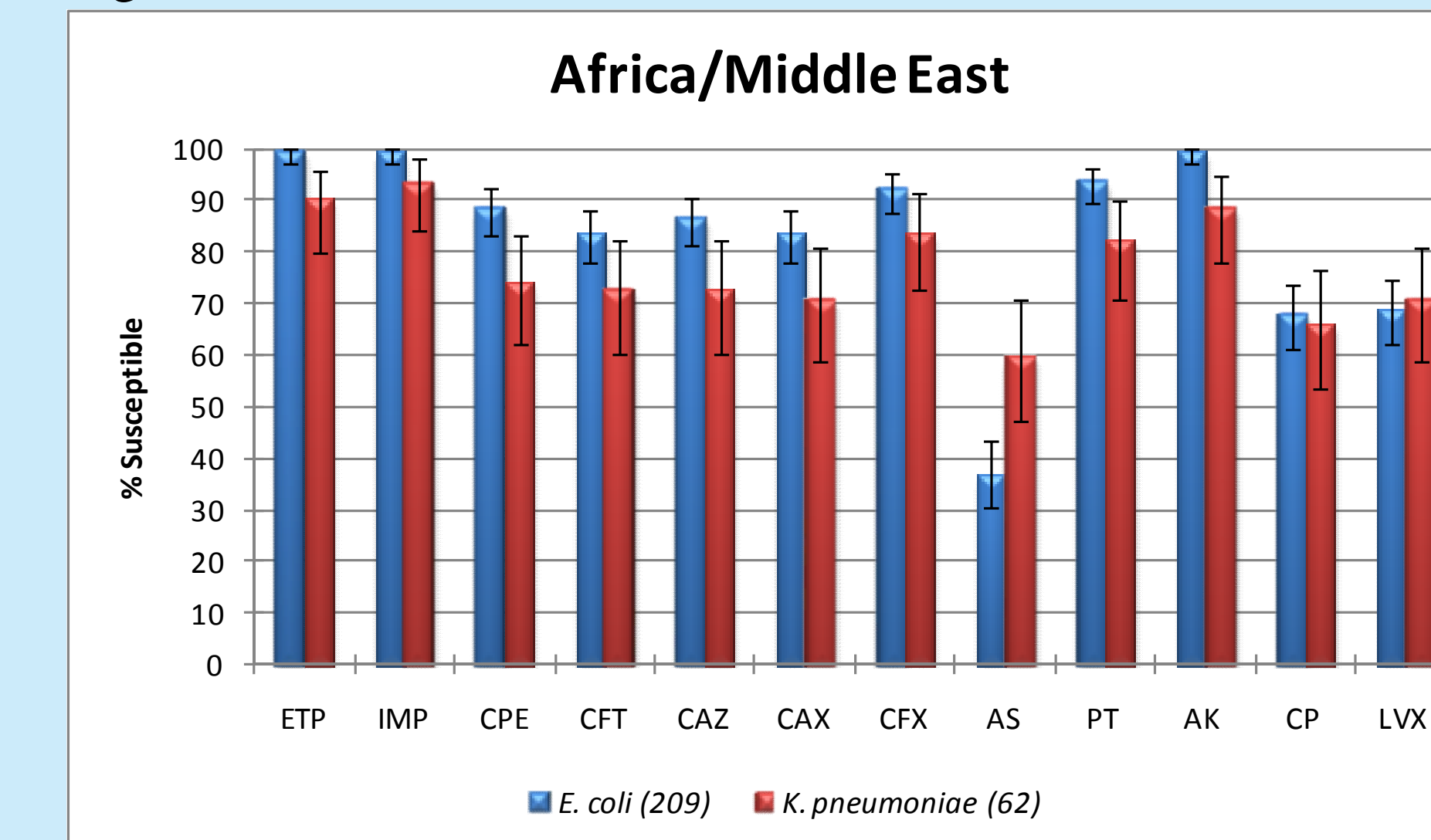


Figure 3: Percent susceptible with 95% confidence intervals for *E. coli* and *K. pneumoniae* in the Asia/Pacific region, 2009-2010.

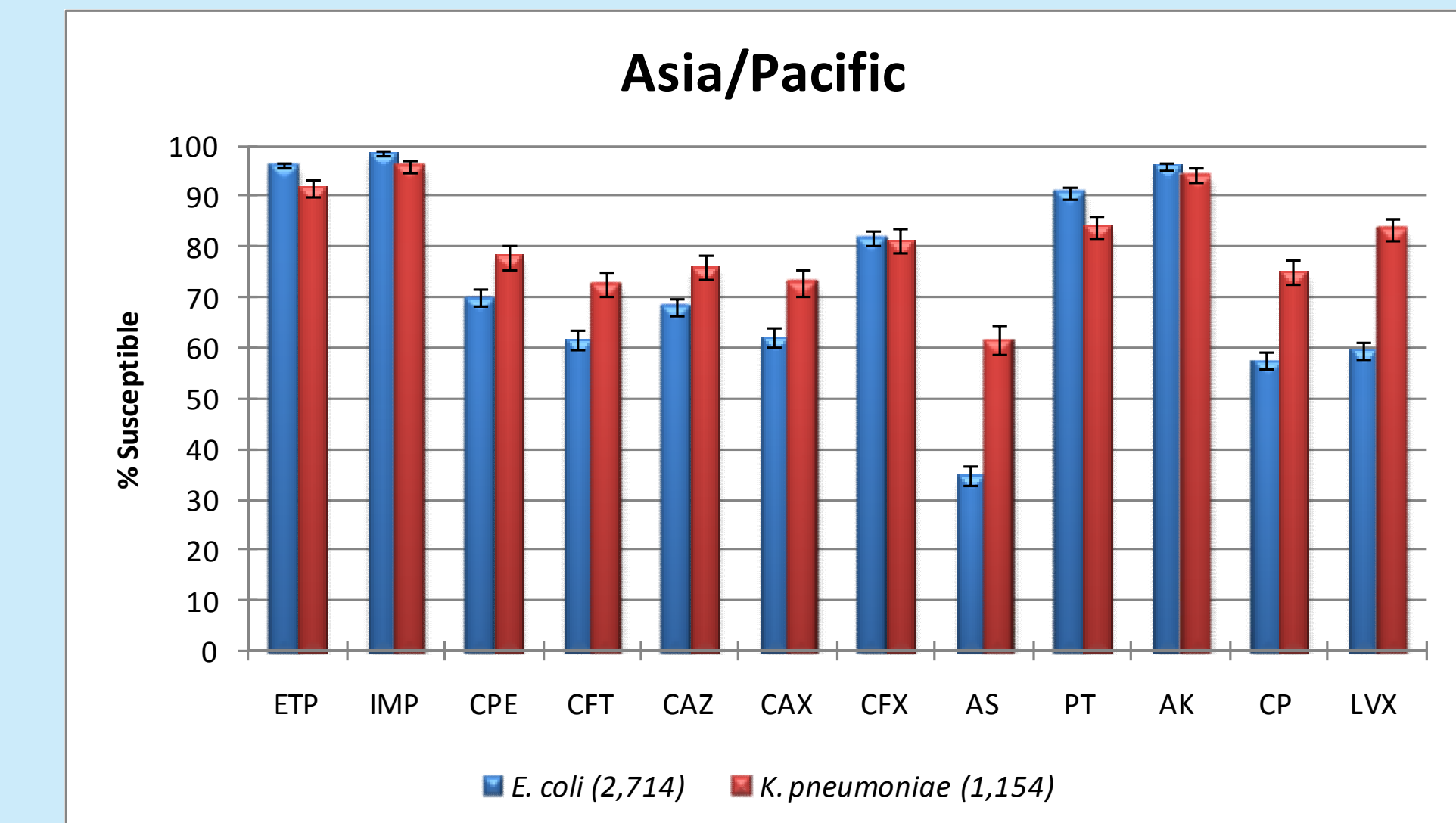


Figure 4: Percent susceptible with 95% confidence intervals for *E. coli* and *K. pneumoniae* in Europe, 2009-2010.

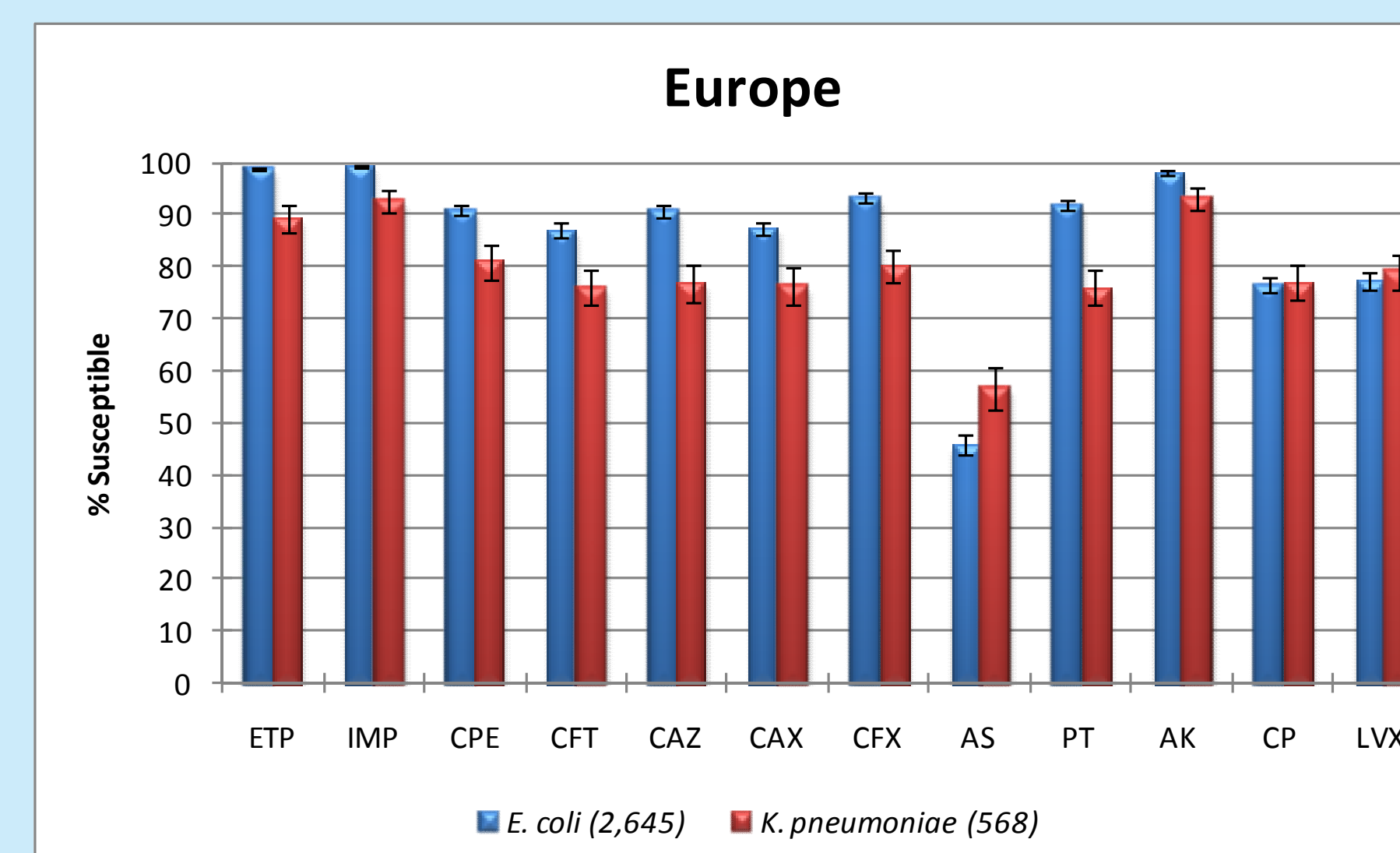


Figure 5: Percent susceptible with 95% confidence intervals for *E. coli* and *K. pneumoniae* in Latin America, 2009-2010.

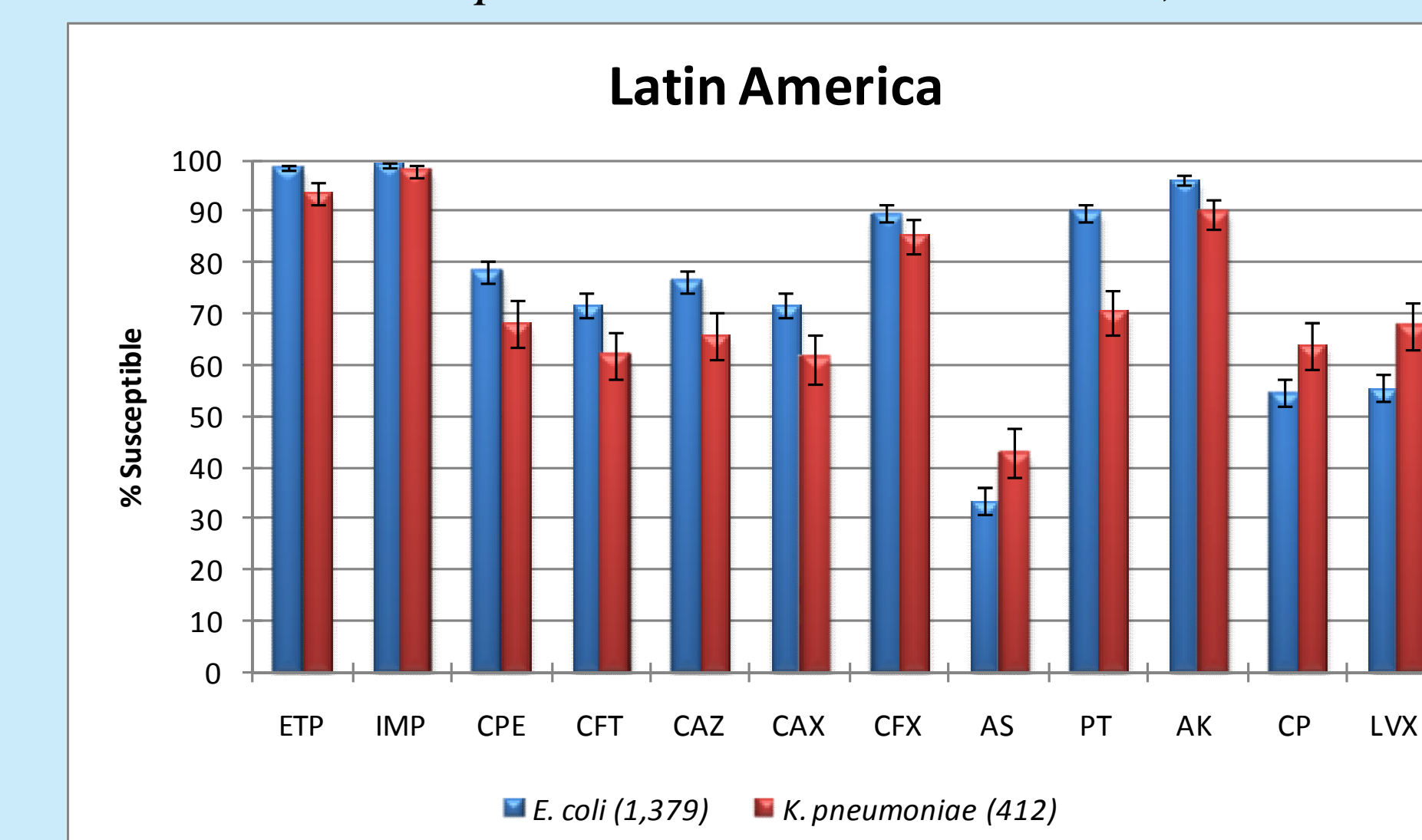
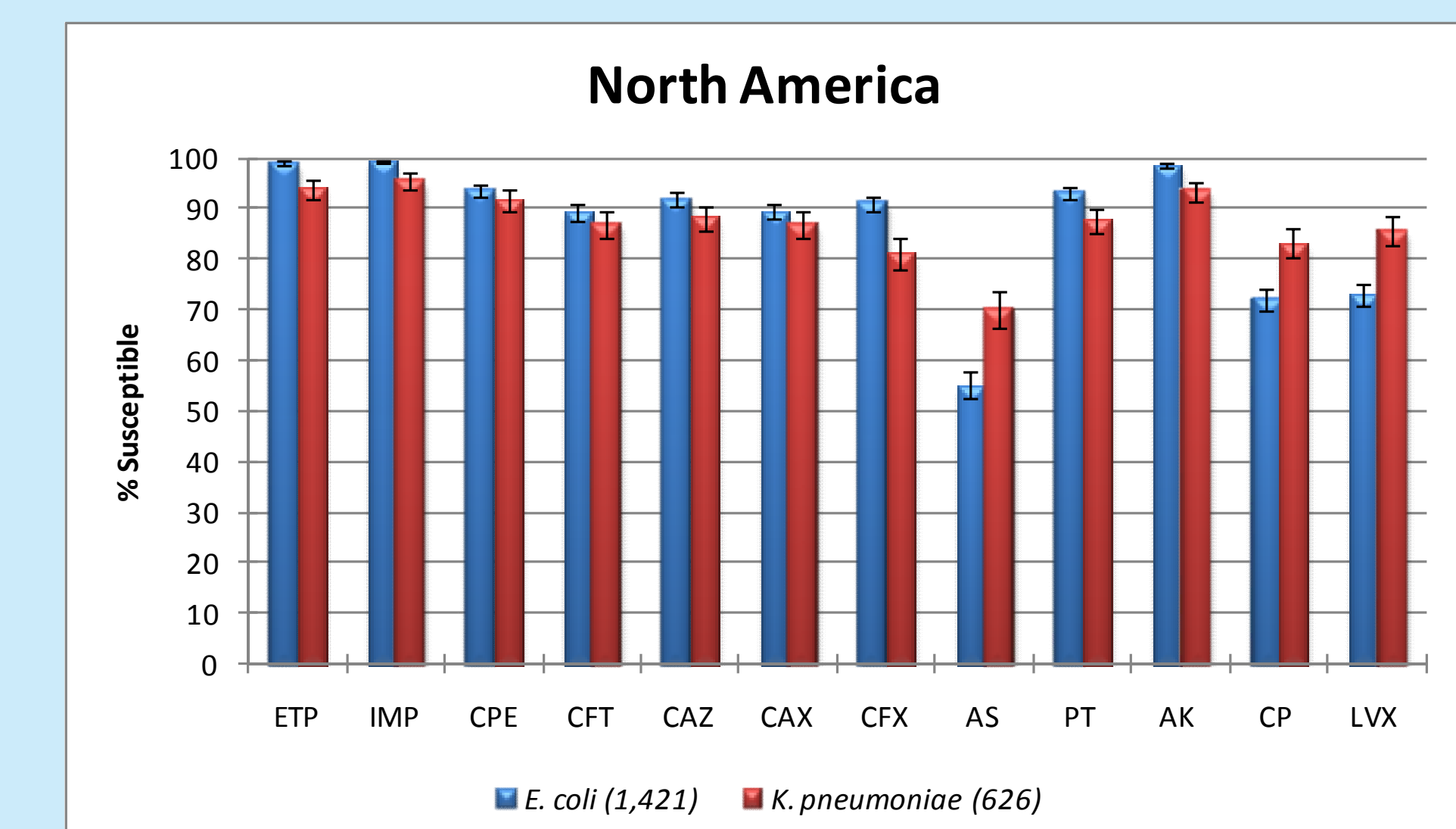


Figure 6: Percent susceptible with 95% confidence intervals for *E. coli* and *K. pneumoniae* in North America, 2009-2010.



Conclusions

- The two most commonly isolated pathogens of IAI, *E. coli* and *K. pneumoniae*, remain very susceptible to ertapenem, imipenem, and amikacin; even these drugs, however, showed diminished activity against ESBL+ *K. pneumoniae*. The high proportion (roughly 20%) of each of these species that is ESBL+ renders most of the comparators in this study <90% effective *in vitro*, with susceptibility to several <80%. The somewhat lower beta-lactam %S values of *K. pneumoniae* are probably due to carbapenemases, ampCs, and outer membrane porin loss combined with ESBLs.
- The fluoroquinolones continue to show diminished activity, especially against *E. coli*, with all regions showing %S values of <80%; outside of Europe and North America, %S values were <70% or even <60%.
- In areas where ESBL+ rates exceed the global average (e.g., Asia/Pacific for *E. coli*, and Latin America for both *E. coli* and *K. pneumoniae*), susceptibility rates for many drugs are lower still, potentially leaving only the carbapenems and possibly amikacin among drugs studied in SMART as viable options for empiric therapy of IAI.