P1540

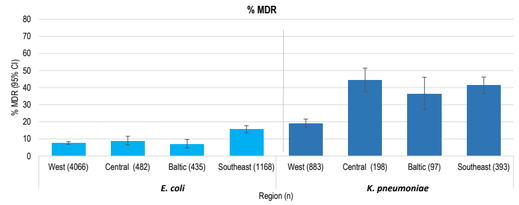
# Resistance patterns among *Escherichia coli* and *Klebsiella pneumoniae* isolates from four European Regions: SMART 2012-2014

S. Lob, K. Kazmierczak, D. Hoban, R. Badal, D. Sahm
IHMA, Inc., Schaumburg, IL, USA

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

## Revised Abstract

**Background:** Large-scale international surveillance studies often contend with limitations regarding relatively low isolate and site counts per country. Solutions have included combining years of data to try to have meaningful numbers at the national level at the expense of longer-term trends, or aggregating data across a large region like Europe at the expense of showing national variations. In this report, we use another approach, combining only the three most recent available years and examining four smaller regions within Europe to assess resistance patterns among *E. coli* and *K. pneumoniae* from intra-abdominal infections (IAI). **Materials/Methods:** 49 hospitals in the West region (France, Germany, Italy, Portugal, Spain, UK; 30 sites), Central (Croatia, Czech Republic, Hungary, Slovenia; 5), Baltic (Estonia, Latvia, Lithuania; 4), and Southeast (Greece, Romania, Serbia, Turkey; 10) collected up to 100 consecutive gram-negative IAI isolates each year 2012-2014 as part of the SMART surveillance program. Susceptibility was determined for 6,151 *E. coli* and 1,571 *K. pneumoniae* using CLSI broth microdilution guidelines and EUCAST breakpoints. MDR was defined as resistance seen in ≥3 drug classes (aminoglycosides, β-lactam/β-lactamase inhibitor combinations, cephems, carbapenems, and quinolones). **Results:** MDR rates with 95% confidence intervals are shown below.




MDR rates also varied within regions, especially for *E. coli* in Southeast, ranging from 7.2% in Romania to 27.6% in Turkey, and *K. pneumoniae* in West from 1.8% in UK to 44.6% in Italy (albeit with small sample sizes).

Only ertapenem, imipenem, and amikacin inhibited >90% of *E. coli* isolates in all regions, and piperacillin-tazobactam in West, Central, and Baltic. Only carbapenems inhibited >90% of MDR *E. coli* in all regions. Susceptibility of *K. pneumoniae* was >90% only to carbapenems and amikacin and only in West, Central, and Baltic. Against MDR *K. pneumoniae* 90% activity was exceeded only by ertapenem and imipenem in Baltic, and imipenem and amikacin in Central. Cephalosporins, quinolones, and piperacillin-tazobactam did not exceed 38% susceptibility anywhere. Among the MDR isolates, CTX-M-15 was the most commonly detected ESBL in all regions and in both species. Among MDR *K. pneumoniae*, the most common carbapenemases were KPC-2/KPC-3 (almost exclusively found in Southeast and West) and OXA-48 (predominantly in Southeast). Carbapenemases in *E. coli* were extremely rare.

**Conclusions:**

- MDR rates varied within regions, but overall rates were high in Southeast for both *E. coli* and *K. pneumoniae*, and in Central and Baltic for *K. pneumoniae*. Susceptibility was especially low to cephalosporins, quinolones, and β-lactam/β-lactamase inhibitor combinations in these regions.
- When local resistance data are unavailable and national estimates may be sub-optimal due to small sample sizes, resistance patterns for smaller regions may be helpful for empiric IAI treatment decision.

## Introduction

Large-scale international surveillance studies often contend with limitations regarding relatively low isolate and site counts per country. Solutions have included combining years of data to try to have meaningful numbers at the national level at the expense of longer-term trends, or aggregating data across a large region like Europe at the expense of showing national variations. In this report, we use another approach, combining only the three most recent available years and examining four smaller regions within Europe to assess susceptibility and multi-drug resistance (MDR) patterns among *E. coli* and *K. pneumoniae* from intra-abdominal infections (IAI).

## Materials & Methods

49 hospitals in the West region (France, Germany, Italy, Portugal, Spain, UK; 30 sites), Central (Croatia, Czech Republic, Hungary, Slovenia; 5), Baltic (Estonia, Latvia, Lithuania; 4), and Southeast (Greece, Romania, Serbia, Turkey; 10) collected up to 100 consecutive gram-negative IAI isolates each year from 2012 to 2014 inclusive as part of the SMART surveillance program. Susceptibility was determined for 6,151 *E. coli* and 1,571 *K. pneumoniae* using CLSI broth microdilution guidelines and EUCAST breakpoints [1-3]. MDR was defined as resistance to agents from ≥3 drug classes (aminoglycosides, β-lactam/β-lactamase inhibitor combinations, cephalosporins, carbapenems, and quinolones).

All ertapenem non-susceptible *E. coli* and *K. pneumoniae* isolates and a random selection of 57% of isolates that tested positive for extended spectrum β-lactamase (ESBL) activity by by combination clavulanic acid-based testing were molecularly characterized for β-lactamase genes. Genes encoding ESBLs (TEM, SHV, CTX-M, VEB, PER, GES), carbapenemases (KPC, NDM, IMP, VIM, SPM, OXA-48-like), and AmpC β-lactamases (CMY, DHA, FOX, MOX, ACC, MIR, ACT) were detected using a combination of microarray (Check-MDR CT101, Check-Points B.V., Wageningen, the Netherlands) and multiplex PCR assays and sequenced.

## Results

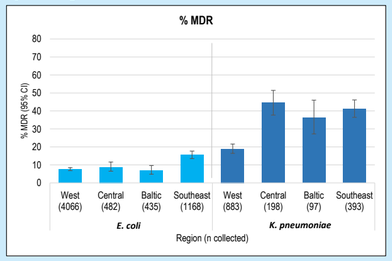
**Table 1. *In vitro* activities of ertapenem and comparator agents against overall and MDR subsets of *E. coli* and *K. pneumoniae* isolates collected in four European sub-regions.**

| Species/region (n tested) | ETP | IPM | FEP | CRO | CTX | CAZ | TZP | SAM | CIP | LVX | AMK |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***E. coli*** | | | | | | | | | | | |
| West (4066) | 99.9 | 99.9 | 89.8 | 87.8 | 87.8 | 88.2 | 91.0 | 45.4 | 75.3 | 77.4 | 97.3 |
| Central (482) | 99.8 | 99.4 | 87.1 | 85.5 | 85.3 | 85.5 | 92.1 | 53.5 | 72.8 | 74.7 | 95.9 |
| Baltic (435) | 100 | 100 | 86.9 | 86.2 | 85.5 | 86.7 | 92.9 | 54.3 | 82.1 | 83.7 | 96.1 |
| Southeast (1168) | 99.3 | 99.9 | 78.2 | 76.7 | 76.9 | 78.0 | 87.9 | 42.0 | 70.4 | 72.3 | 94.7 |
| ***K. pneumoniae*** | | | | | | | | | | | |
| West (883) | 95.0 | 96.6 | 78.3 | 78.1 | 78.9 | 76.6 | 79.8 | 61.2 | 74.9 | 80.2 | 94.5 |
| Central (198) | 95.0 | 99.5 | 52.5 | 51.0 | 51.0 | 51.0 | 64.1 | 43.9 | 52.5 | 59.1 | 95.5 |
| Baltic (97) | 95.9 | 99.0 | 61.9 | 61.9 | 60.8 | 61.9 | 73.2 | 49.5 | 60.8 | 69.1 | 92.8 |
| Southeast (393) | 74.3 | 84.5 | 48.9 | 48.6 | 49.1 | 49.6 | 59.3 | 36.1 | 55.0 | 61.1 | 80.2 |
| ***E. coli* MDR** | | | | | | | | | | | |
| West (309) | 98.7 | 99.4 | 15.1 | 4.2 | 2.9 | 12.5 | 60.9 | 0.0 | 1.0 | 3.5 | 82.1 |
| Central (42) | 97.6 | 95.2 | 9.5 | 0.0 | 0.0 | 2.4 | 61.9 | 0.0 | 2.4 | 2.4 | 71.4 |
| Baltic (30) | 100 | 100 | 10.0 | 6.7 | 3.3 | 10.0 | 53.3 | 0.0 | 6.7 | 10.0 | 66.7 |
| Southeast (181) | 97.8 | 99.5 | 7.2 | 1.7 | 1.7 | 3.3 | 61.9 | 0.0 | 4.4 | 5.5 | 72.9 |
| ***K. pneumoniae* MDR** | | | | | | | | | | | |
| West (167) | 74.3 | 82.0 | 1.2 | 0.6 | 1.2 | 3.0 | 38.3 | 0.0 | 3.0 | 15.0 | 74.3 |
| Central (88) | 88.6 | 98.9 | 2.3 | 0.0 | 0.0 | 0.0 | 23.9 | 1.1 | 1.1 | 11.4 | 90.9 |
| Baltic (35) | 91.4 | 100 | 0.0 | 2.9 | 0.0 | 2.9 | 34.3 | 0.0 | 0.0 | 20.0 | 80.0 |
| Southeast (162) | 40.7 | 63.6 | 0.6 | 0.0 | 0.0 | 0.0 | 19.8 | 0.0 | 2.5 | 12.4 | 52.5 |

Percent susceptible ≥90% are shaded green.

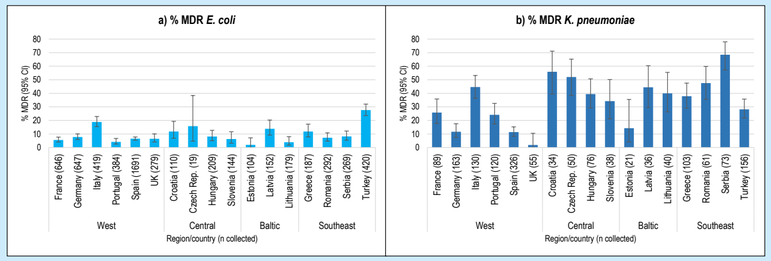
ETP=ertapenem, IPM=imipenem, FEP=cefepime, CRO=ceftriaxone, CTX=cefotaxime, CAZ=ceftazidime, TZP=piperacillin-tazobactam, SAM=ampicillin-sulbactam, CIP=ciprofloxacin, LVX=levofloxacin, AMK=amikacin.
**West**: France, Germany, Italy, Portugal, Spain, UK; **Central**: Croatia, Czech Republic, Hungary, Slovenia; **Baltic**: Estonia, Latvia, Lithuania; **Southeast**: Greece, Romania, Serbia, Turkey.

**Figure 1. Percentages of MDR *E. coli* and *K. pneumoniae* isolates collected in Europe, by sub-region.**



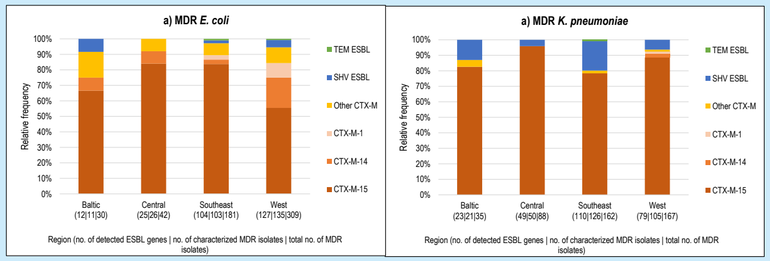

Bars indicate 95% confidence interval.

**Figures 2a and b. Percentages of MDR *E. coli* and *K. pneumoniae*, by country.**




Bars indicate 95% confidence interval.

**Figures 3a and b. Distribution of ESBL enzyme types and variants detected among molecularly characterized MDR *E. coli* and *K. pneumoniae*.**




Some isolates carried more than one ESBL gene.

**Table 2. Distribution of carbapenemase enzyme types and variants detected among molecularly characterized MDR *E. coli* and *K. pneumoniae*.**

| | Total no. of MDR isolates | No. of characterized MDR isolates | KPC-2 | KPC-3 | OXA-48 | NDM-1 | VIM-type |
|---|---|---|---|---|---|---|---|
| ***E. coli*** | | | | | | | |
| West | 309 | 135 | | | | | |
| Central | 42 | 26 | | | | | |
| Baltic | 30 | 11 | | | | | |
| Southeast | 181 | 103 | | | 3 | | |
| ***K. pneumoniae*** | | | | | | | |
| West | 167 | 105 | 6 | 22 | 5 | | 3 |
| Central | 88 | 50 | 1 | | 1 | | 2 |
| Baltic | 35 | 21 | | | | | |
| Southeast | 162 | 126 | 29 | | 31 | 14 | 3 |

VIM-type: West, VIM-1 (n=3); Central, VIM-4 (n=2); Southeast, VIM-1 (n=2) and VIM-19 (n=1).

## Results Summary

- *E. coli* isolates showed reduced susceptibility (generally <80%) to cephalosporins, quinolones, and β-lactam/β-lactamase inhibitor combinations in the Southeast sub-region. The susceptibility *K. pneumoniae* to these agents was even lower (<70%) in the Southeast, Central, and Baltic regions (Table 1).
- Correspondingly, the percentages of MDR *E. coli* identified in the Southeast and MDR *K. pneumoniae* found in the Southeast, Central, and Baltic sub-regions were elevated (15% and 35-45%, respectively) (Figure 1). MDR rates also varied *within* the regions, but sample sizes were often small and confidence intervals wide (Figure 2).
- Among the MDR isolates, CTX-M-15 was the most commonly detected ESBL in all regions and in both species (Figure 3).. Among MDR *K. pneumoniae*, the most commonly detected carbapenemases were KPC-2 and KPC-3, found almost exclusively in the Southeast and West, and OXA-48-like β-lactamases, found predominantly in the Southeast. Only 3 MDR *E. coli* (of 562, 0.5%) carried carbapenemases (Table 2).

## Conclusions

- Susceptibilities to antimicrobial agents, MDR rates, and β-lactamase content among *E. coli* and *K. pneumoniae* from IAI varied substantially between four European sub-regions.
- When local resistance data are unavailable and national estimates may be sub-optimal due to small sample sizes, resistance patterns observed for smaller sub-regions may be helpful in making empiric treatment decision.

**References and Acknowledgments:**

1. Clinical and Laboratory Standards Institute. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 10th ed. Approved standards M7-A10. Clinical and Laboratory Standards Institute, Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2015. Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement. CLSI document M100-S25. Clinical and Laboratory Standards Institute, Wayne, PA.
3. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, version 5.0, 2015 http://www.eucast.org.

The SMART surveillance program is funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Kenilworth, NJ. The authors thank all the participants in the SMART program for their continuing contributions to its success.