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Trends in Susceptibility and Multi-Drug Resistance among *K. pneumoniae* from Intra-Abdominal Infections in Western Europe 2009-2014

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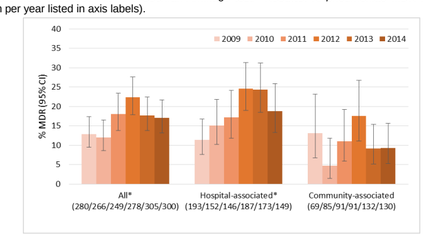
Revised Abstract

Background: Increases in multi-drug resistance (MDR) often associated with extended-spectrum β-lactamases (ESBLs) and carbapenemases have limited in many regions the therapeutic options for intra-abdominal infections (IAI). This report uses data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) to examine resistance patterns in *Klebsiella pneumoniae* from IAI collected in Western Europe from 2009 to 2014. **Materials/Methods:** 34 hospitals in France (6 sites), Germany (5), Italy (4), Portugal (3), Spain (12), and the United Kingdom (UK, 4) collected up to 100 consecutive gram-negative IAI isolates each year. Susceptibility was determined for 1,678 *K. pneumoniae* using CLSI broth microdilution guidelines and EUCAST interpretive breakpoints. MDR was defined as resistance seen in ≥3 drug classes (aminoglycosides, β-lactam/β-lactamase-inhibitor combinations, cephems, carbapenems, and quinolones). An IAI was defined as hospital- or community-associated if cultured ≥48 hours or <48 hours post-admission, respectively. Linear trends in susceptibility and MDR rates were assessed with the Cochran-Armitage test. **Results:** *K. pneumoniae* MDR rates are shown below (n per year listed in axis labels).



A sensitivity analysis using only the 21 sites that submitted isolates in all 6 years showed a similar pattern with % MDR peaking in 2012. Correspondingly, susceptibility trends for individual agents generally showed lowest activity in 2012. Of the tested agents, only susceptibility for cefepime (85.0, 85.7, 79.1, 74.1, 79.7, 80.7% in each year 2009-2014) and ceftriaxone (83.9, 85.7, 79.9, 74.8, 79.7, 79.7%) showed a statistically significant linear decreasing trend, but these agents also demonstrated signs of trend reversal in the last two years. Of the tested agents, only ertapenem, imipenem, and amikacin maintained susceptibility >90% against *K. pneumoniae* across all years. MDR rates in 2013-2014 were 30.2% (19 of 63) in France, 12.1% (13/107) in Germany, 46.6% (41/88) in Italy, 14.5% (10/69) in Portugal, 8.9% (21/235) in Spain, 2.3% (1/43) in UK. The most commonly found β-lactamases in molecularly characterized MDR isolates were CTX-M-15 and KPC-2/KPC-3.

Conclusions:

- Although statistical analysis of *K. pneumoniae* MDR rates in Western Europe from 2009 to 2014 showed a significant linear trend, the increase appeared to be reversing in recent years, including among isolates from hospital-associated IAI, which had shown an especially sharp increase from 2009-2012.
- MDR rates varied widely between countries with highest rates in France and Italy and lowest in Spain and UK.
- Monitoring of MDR rates must continue in Western Europe to confirm that the reversal of the increasing trend in MDR rates continues. National and preferably local resistance patterns should be taken into account when making empiric treatment decisions for IAI patients.

Introduction

Increases in multi-drug resistance (MDR) often associated with carriage of extended-spectrum β-lactamases (ESBLs) and carbapenemases have limited in many regions the therapeutic options for intra-abdominal infections (IAI). This report uses data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) to examine resistance patterns in *Klebsiella pneumoniae* from IAI collected in Western Europe from 2009 to 2014.

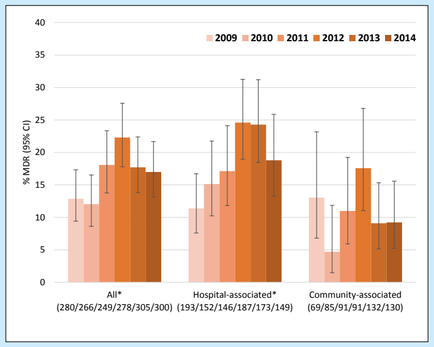
Materials & Methods

34 hospitals in France (6 sites), Germany (5), Italy (4), Portugal (3), Spain (12), and the United Kingdom (UK, 4) collected up to 100 consecutive gram-negative IAI isolates each year from 2009 to 2014. Susceptibility was determined for 1,678 *K. pneumoniae* using CLSI broth microdilution guidelines and EUCAST interpretive 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). An IAI was defined as hospital- or community-associated if cultured ≥48 hours or <48 hours post-admission, respectively. Linear trends in susceptibility and MDR rates were assessed with the Cochran-Armitage test.

All ertapenem non-susceptible *K. pneumoniae* isolates and a random selection of 58% of ertapenem-susceptible isolates that tested positive for extended spectrum β-lactamase (ESBL) activity 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.

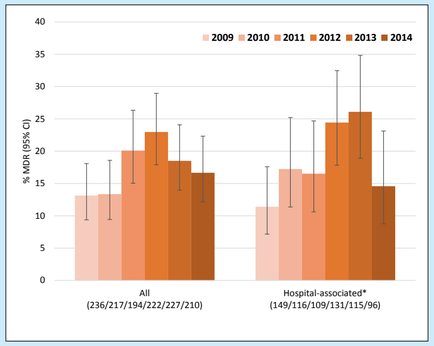
Results

Figure 1. Trends in MDR rates among *K. pneumoniae* isolates collected in Western Europe.



* Significant increasing linear trend (p<0.05).
Bars indicate 95% confidence interval.
Sample size per year listed in axis labels.

Figure 2. Sensitivity analysis of trends in MDR rates among *K. pneumoniae* from Western Europe, using only sites that submitted isolates in all study years.



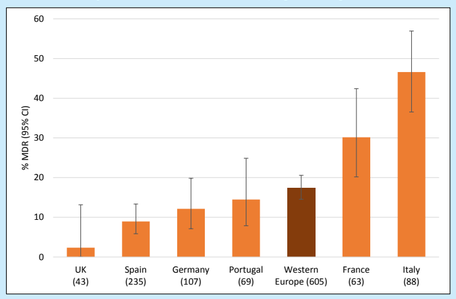
* Significant increasing linear trend (p<0.05).
Bars indicate 95% confidence interval.
Sample size per year listed in axis labels.
Sample sizes were too small for meaningful analysis of isolates from community-associated infections.

Table 1. Trends in *in vitro* activities of ertapenem and comparators against *K. pneumoniae* isolates collected in Western Europe.

	% Susceptible[a]										
Year (n)	ETP	IPM	FEP	CRO	CTX	CAZ	TZP	SAM	CIP	LVX	AMK
All											
2009 (280)	95.4	98.6	**85.0**	**83.9**	83.9	78.6	78.6	59.6	79.3	84.3	95.0
2010 (266)	98.9	99.6	**85.7**	**85.7**	85.3	83.1	82.7	64.7	81.2	83.1	95.1
2011 (249)	91.2	92.4	**79.1**	**79.9**	79.9	78.3	77.5	61.0	74.7	81.9	93.2
2012 (278)	95.0	95.7	**74.1**	**74.8**	75.2	72.3	80.2	56.5	70.9	76.6	92.5
2013 (305)	96.1	97.4	**79.7**	**79.7**	81.3	80.0	82.3	63.9	75.4	80.7	94.4
2014 (300)	94.0	96.7	**80.7[b]**	**79.7[b]**	80.0	77.0	77.0	62.7	78.0	83.0	96.3
Hospital-associated											
2009 (193)	97.4	99.0	**87.1**	**85.5**	**85.0**	**80.8**	79.3	61.7	**80.3**	**87.1**	95.3
2010 (152)	98.7	100	**81.6**	**81.6**	**81.6**	**77.6**	77.0	56.6	**75.7**	**79.0**	94.1
2011 (146)	92.5	92.5	**78.1**	**79.5**	**79.5**	**76.7**	76.0	55.5	**74.7**	**82.9**	93.2
2012 (187)	93.6	94.1	**70.1**	**71.1**	**71.7**	**67.9**	77.0	50.3	**67.4**	**75.4**	90.4
2013 (173)	94.8	96.0	**72.3**	**73.4**	**75.7**	**72.8**	77.5	54.9	**67.1**	**72.8**	92.5
2014 (149)	94.6	98.0	**78.5[b]**	**77.2[b]**	**77.9[b]**	**73.8[b]**	72.5	54.4	**76.5[b]**	**81.9[b]**	96.6
Community-associated											
2009 (69)	94.2	97.1	84.1	84.1	85.5	78.3	81.2	62.3	81.2	82.6	98.6
2010 (85)	98.8	98.8	94.1	94.1	94.1	94.1	94.1	78.8	90.6	90.6	97.7
2011 (91)	96.7	98.9	89.0	89.0	89.0	89.0	87.9	75.8	82.4	89.0	100
2012 (91)	97.8	98.9	82.4	82.4	82.4	81.3	86.8	69.2	78.0	79.1	96.7
2013 (132)	97.7	99.2	89.4	87.9	88.6	89.4	88.6	75.8	86.4	90.9	97.0
2014 (130)	97.7	97.7	87.7	88.5	88.5	86.2	86.2	76.2	84.6	90.0	99.2

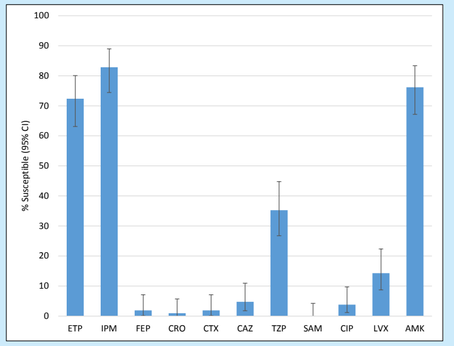
[a] Percent susceptible ≥90% are shaded.
[b] Statistically significant decreasing trends between 2009 and 2014 are bolded (p<0.05).
ETP, ertapenem; IPM, imipenem; FEP, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CAZ, ceftazidime; TZP, piperacillin-tazobactam; SAM, ampicillin-sulbactam; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin

Figure 3. MDR rates among *K. pneumoniae* isolates collected in Western Europe in 2013-2014 combined, by country.



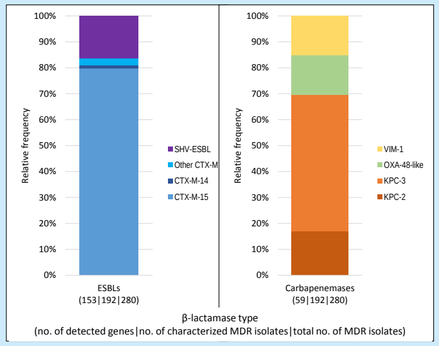
Sample size per country or region listed in axis labels.
Bars indicate 95% confidence interval.

Figure 4. *In vitro* activities of ertapenem and comparators against MDR *K. pneumoniae* isolates (n=105) collected in Western Europe in 2013-2014 combined.



Bars indicate 95% confidence interval.
ETP, ertapenem; IPM, imipenem; FEP, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CAZ, ceftazidime; TZP, piperacillin-tazobactam; SAM, ampicillin-sulbactam; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin

Figure 5. Distribution of ESBLs and carbapenemases detected among molecularly characterized MDR *K. pneumoniae* isolates collected in Western Europe in 2009-2014.



Some isolates carried more than one β-lactamase gene: 6 isolates carried CTX-M-15 and OXA-48-type genes; 6 isolates carried CTX-M-15 and SHV-ESBL; 3 isolates carried CTX-M-15 and KPC; 2 isolates carried CTX-M-15, SHV-ESBL, and KPC; 2 carried KPC and SHV-ESBL; 2 carried OXA-48 and CTX-M-14; 1 carried OXA-48, CTX-M-9, and SHV-ESBL, 1 carried VIM and DHA-type AmpC; and 1 carried VIM, DHA-type AmpC, and SHV-ESBL.

Results Summary

- Although statistical analysis of *K. pneumoniae* MDR rates in Western Europe from 2009 to 2014 showed a significant linear increase, the trend appeared to be reversing in recent years (Figure 1).
- Sensitivity analyses using only isolates from study sites participating in all years (2009-2014) found similar trends (Figure 2).
- Susceptibility to most antimicrobials showed the reverse pattern with lowest levels observed in 2012. Of the tested agents, only ertapenem, imipenem, and amikacin maintained >90% activity (Table 1).
- Aggregating the data from 2013-2014 yielded sample sizes large enough to examine MDR rates among *K. pneumoniae* from each country as well antimicrobial susceptibility profiles of MDR isolates from the region.
  - o MDR rates among recent *K. pneumoniae* isolates varied widely between countries, with the lowest percentage of MDR isolates observed in the UK and the highest in Italy (Figure 3).
  - o Susceptibility of recent MDR isolates to the majority of tested agents was <15%. Only ertapenem, imipenem, and amikacin were active *in vitro* against >70% of MDR *K. pneumoniae* (Figure 4).
- The most commonly found β-lactamases in molecularly characterized MDR isolates were CTX-M-15 and KPC-2/KPC-3 (Figure 5).

Conclusions

- Monitoring of susceptibility must continue in Western Europe to confirm that the recent decrease in resistance continues. Furthermore, efforts should be made to elucidate the possible reasons for the reversal in the trend (e.g. antibiotic stewardship programs, infection control practices), as this may inform strategies to further reduce resistance rates.
- Current national and ideally local resistance patterns should be taken into account when making empiric treatment decisions for IAI patients.

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.
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