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Bacteraemia

Voluntary surveillance of *Klebsiella* spp. bacteraemia in England, Wales and Northern Ireland: 2009-2013

These analyses are based on data relating to diagnoses of *Klebsiella* spp. bloodstream infections during 2009 – 2013 in England, Wales and Northern Ireland (E,W & NI) that were extracted from Public Health England's (PHE) voluntary surveillance database (LabBase2) on 10 April 2014. The data presented here differ in some instances from those in earlier publications due to the inclusion of late reports. Analyses by main species are also included in this report.

As the mid-year resident population estimates for 2013 were not available at the time of producing this report, rates of bacteraemia were calculated using 2012 mid-year resident population estimates based on the 2011 census for England, Wales, and Northern Ireland [1,2]. Geographical analyses were based on the residential postcode of the patient if known (otherwise the GP postcode was used if known or failing that the postcode of the laboratory was used) with cases in England being assigned to the catchment area of one of 15 local PHE centres (PHECs) formed from administrative local authority boundaries.

This report includes analyses of the trends, patient demographic and geographical distribution as well as antimicrobial susceptibility among these bacteraemia episodes.

Key points

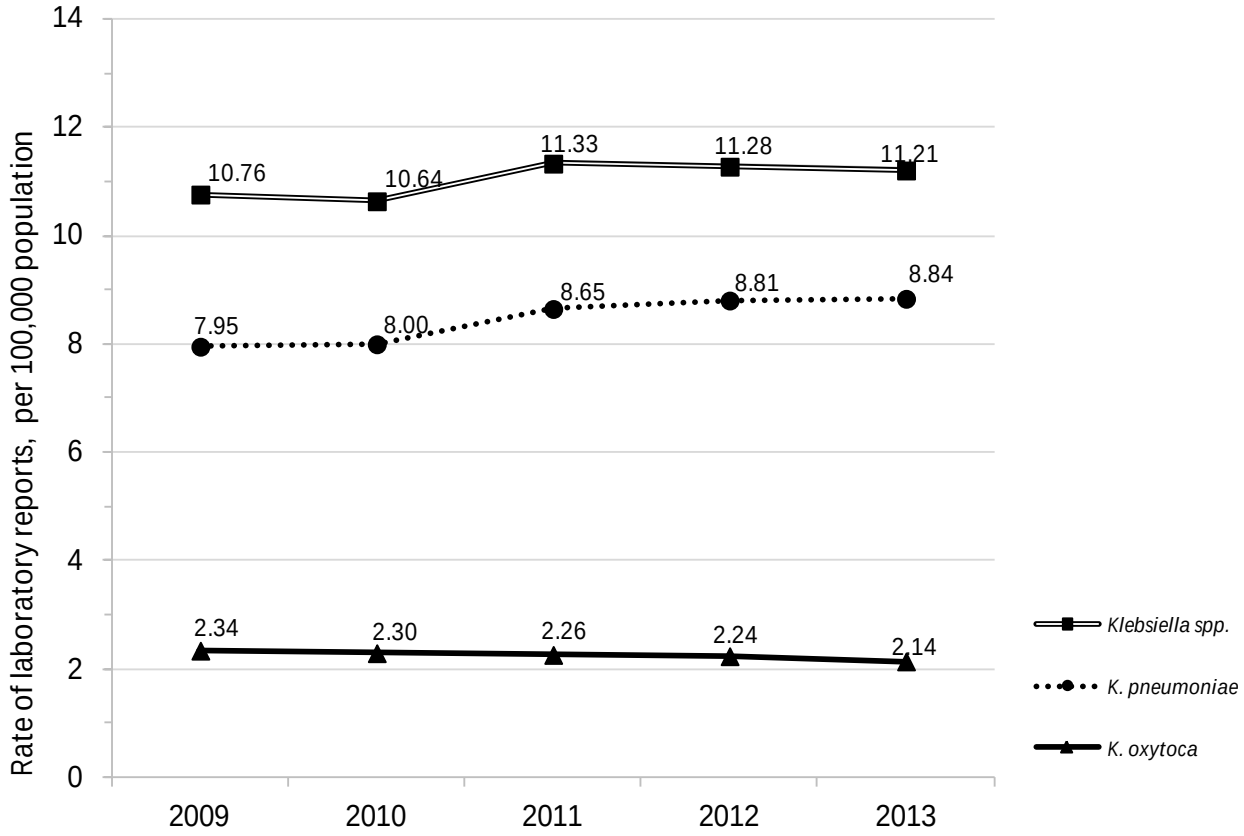
- Between 2012 and 2013 the total number of reports of *Klebsiella* spp. bacteraemia in E,W & NI decreased marginally by 0.6% (from 6,585 to 6,544 episodes respectively).
- The rate of reported *Klebsiella* spp. bacteraemias per 100,000 resident population in E,W & NI was initially stable in 2009 (10.76/100,000) and in 2010 (10.64/100,000). The rate increased by 7% between 2010 and 2011 (11.33/100,000) and remained at this level in 2012 and 2013.
- The rate of bacteraemia due to *K. pneumoniae* was also initially stable in 2009 and 2010 but increased by 8% from 8.00/100,000 in 2010 to 8.65/100,000 in 2011 and remained at this level for the remaining period.
- In 2013, 98% of bacteraemia reports of *Klebsiella* spp. were identified to species level. This represented a continuing improvement in species identification compared with previous years.
- The rate of *Klebsiella* spp. was higher among infants (<1 year) and the elderly than in other age groups. The rate was higher among males and particularly among patients aged ≥75 years.
- At country level, N. Ireland had the highest rate of *Klebsiella* spp bacteraemia (11.95/100,000) followed by England (11.23/100,000) with Wales having the lowest rate (10.34/100,000).
- Within England, Cheshire and Merseyside had the highest rate of *Klebsiella* spp. bacteraemia at 14.98/100,000 followed by Greater Manchester (14.73/100,000). London had the third highest rate at 13.11/100,000. The lowest rate was in Thames Valley (6.75/100,000). This may reflect variation in reporting or case-mix or a combination of both.
- Antimicrobial susceptibility trends from 2009 to 2013 were examined for five classes of antibiotics with results for *Klebsiella* spp. (all species), *K. pneumoniae* and *K. oxytoca*. In general, an increase in resistance was observed across most antibiotic classes except for the fluoroquinolone (ciprofloxacin) where strong evidence of a decrease was observed over the five year period among *K. oxytoca* isolates (from 3% in 2009 to 2% in 2013).
- Of two third-generation cephalosporins examined (cefotaxime and ceftazidime), a significant increase in resistance to cefotaxime was observed (from 8% in 2009 to 10% in 2013). No evidence of change in resistance was found in relation to gentamicin.
- No evidence of change in resistance was found in relation to gentamicin.
- Resistance to piperacillin/tazobactam increased significantly for *Klebsiella* spp. (from 10% in 2009 to 15% in 2013) which may reflect a reduction in the MIC breakpoint from 16 to 8 mg/L for this agent.
- Resistance to the carbapenems remained uncommon, but nonetheless increased significantly over the five-year period with 14 of 4,420 (0.3%) isolates reported resistant in 2009 compared to 42 of 4,941 (0.9%) isolates in 2013.

Trends in the number of reports and rates

Between 2012 and 2013, the total number of bacteraemia reports of *Klebsiella* spp. in E,W & NI decreased by 0.6% (from 6,585 to 6,544 respectively) (table 1). In the context of the five year-period under study, the total number of *Klebsiella* spp. bacteraemia reports increased by 7% from 6,138 in 2009 to 6,572 in 2011 and continued to exceed 6,500 for the remaining period. The increase in total *Klebsiella* spp. from 2009 to 2011 was largely accounted for by the increase in *K. pneumoniae* (by 11%) over the corresponding time period. The number of *K. pneumoniae* reports exceeded 5,000 in 2011 and continued at this level into 2012 and 2013.

Figure 1 shows trends in the incidence of bacteraemia for all *Klebsiella* species and by two main named species in E,W &NI between 2009 and 2013. The rate of *Klebsiella* spp. bacteraemia was initially stable in 2009 and 2010 at (10.76/100,000 and 10.64/100,000 respectively). But this increased by 7% from 10.64/100,000 in 2010 to 11.33/100,000 in 2011 and remained at this level for the rest of study period. The rate of bacteraemia due to *K. pneumoniae* was also initially stable in 2009 and 2010 but increased by 8% from 8.00/100,000 in 2010 to 8.65/100,000 in 2011 and remained at this level for the remaining period. The rate for *K. oxytoca* was stable throughout the study period.

Figure 1: Rate of laboratory bacteraemia reports of *Klebsiella* spp. (all species). *K. pneumoniae* and *K. oxytoca* in England, Wales and Northern Ireland per 100,000 resident population, 2009-2013*



* Data extracted 10 April 2014

Table 1 gives a breakdown of the number of reports by species between 2009 and 2013. In 2013, the majority of isolates from blood were identified to species level (98%). The level of species identification in 2013 represents a slight, but continuing improvement over previous years (96% in 2009). It should be noted that the analysis for 'other named species' in Table 1 includes data for the option '*Klebsiella* other named' available in LabBase2 if selected by the reporting laboratory.

In 2013, the predominant *Klebsiella* species causing bacteraemia was *K. pneumoniae* (79%) followed by *K. oxytoca* (19%). Inspection of the other named species revealed that all were reported under the option '*Klebsiella* other named' with no further detail – this group consisted of very small number of reports over the five-year period.

Table 1. Reports of bacteraemia due to *Klebsiella* spp. (England, Wales and Northern Ireland): 2009 to 2013*

	2009		2010		2011		2012		2013	
	No.	%	No.	%	No.	%	No.	%	No.	%
***Klebsiella* spp.**	**6,138**	100%	**6,117**	100%	**6,572**	100%	**6,585**	100%	**6,544**	100%
Klebsiella pneumoniae	4,536	74%	4,599	75%	5,016	76%	5,142	78%	5,161	79%
Klebsiella oxytoca	1,336	22%	1,320	22%	1,313	20%	1,308	20%	1,252	19%
Klebsiella, other named species	3	0%	0	0%	9	0%	10	0%	13	0%
Klebsiella, species not recorded	263	4.3%	198	3.2%	234	3.6%	125	1.9%	118	1.8%

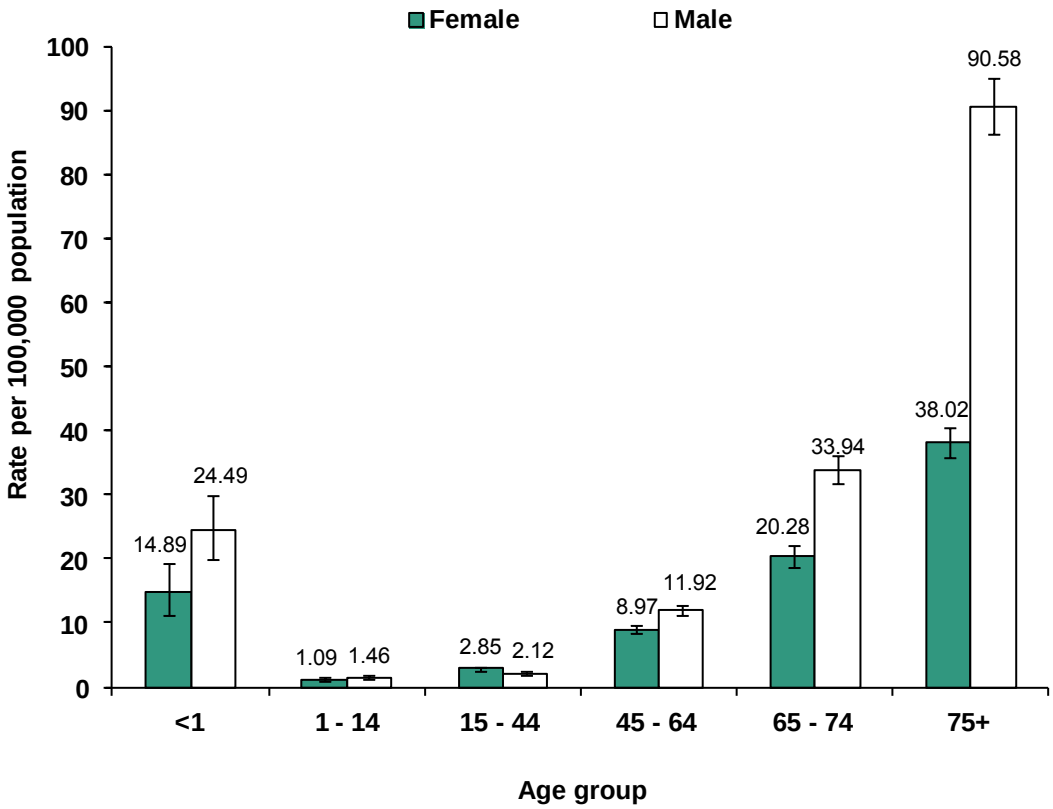
* Data extracted 10 April 2014

Age and sex distribution

Figures 2 to 4 show the age and sex-specific rate of bacteraemia reports in E,W & NI in 2013 per 100,000 resident population for *Klebsiella* spp. and three main *Klebsiella* species. In general, the rate was higher in the infant group (under one year) and in the elderly groups although the rate in the infant group was based on a relatively smaller sample (150 *Klebsiella* spp. reports, of which 101 concerned *K. pneumoniae* and 47 *K. oxytoca*). Across all analyses, the highest rate was among patients aged 75 years or more. The rate of bacteraemia was higher among male patients across all age groups except among those aged 15-44 years where it was higher among female patients.

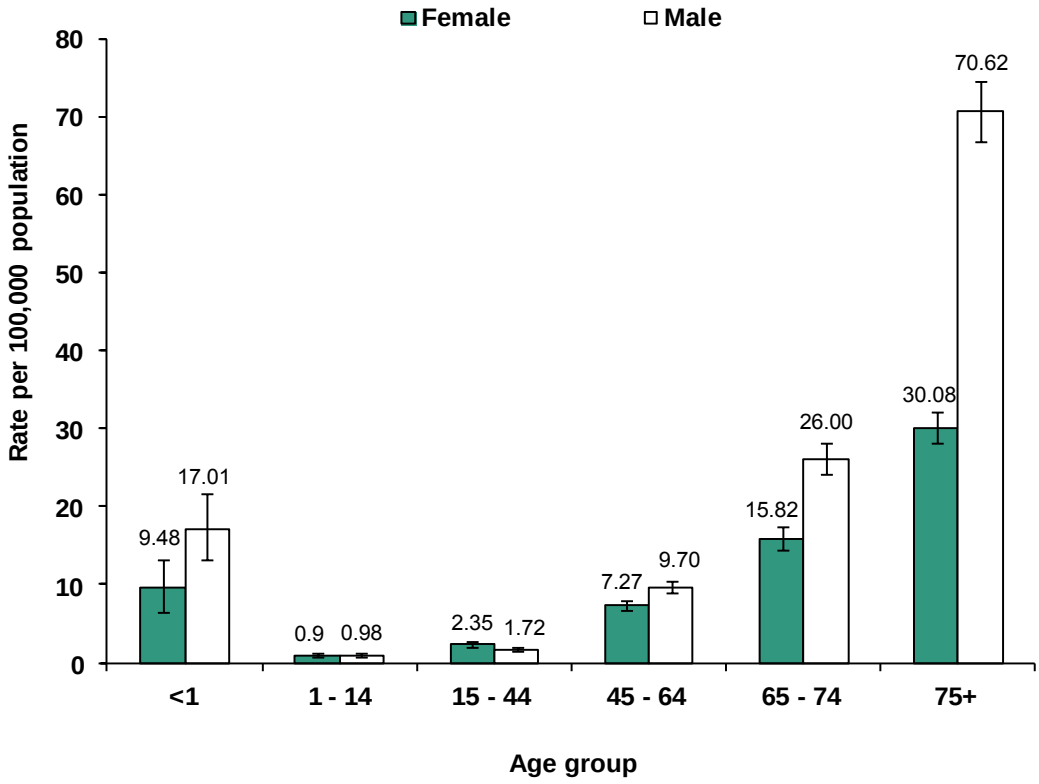
Among the oldest age group (75 years or more), the rate was found to be more than twice as high in males than females. In this age group, the male to female incidence rate ratio was 2.38; 2.35 and 2.44 for *Klebsiella* spp.(all species), *K. pneumoniae* and *K. oxytoca* respectively. Among patients aged 15-44 years the male to female rate ratio was 0.74 for *Klebsiella* spp. (all species); 0.73 for *K. pneumoniae* and 0.72 for *K. oxytoca*.

Figure 2. Age and sex-specific rates of bacteraemia reports of *Klebsiella* spp. per 100,000 resident population (England, Wales and Northern Ireland): 2013*



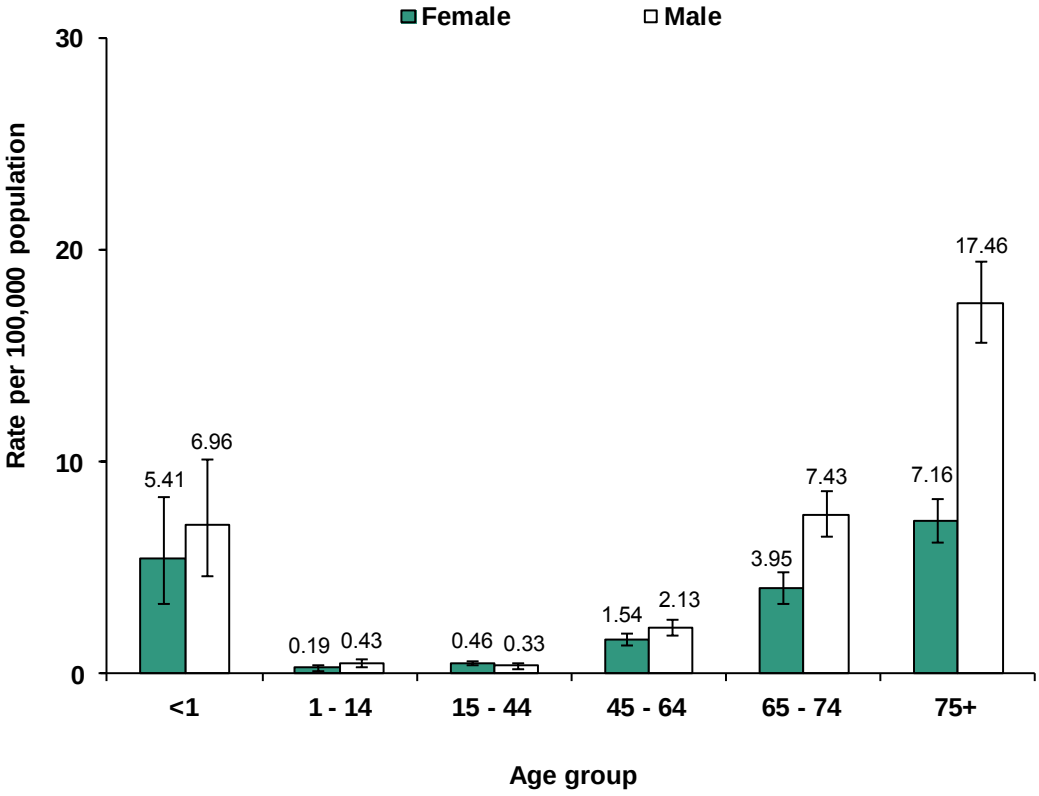
* Data extracted 10 April 2014

Figure 3. Age and sex-specific rates of bacteraemia reports of *K. pneumoniae* per 100,000 resident population (England, Wales and Northern Ireland): 2013*



* Data extracted 10 April 2014

Figure 4. Age and sex-specific rates of bacteraemia reports of *K. oxytoca* per resident 100,000 population (England, Wales and Northern Ireland): 2013*



* Data extracted 10 April 2014

Geographic distribution

Figure 5 shows the reporting rate of bacteraemia based on *Klebsiella* spp. (all reports) reports per 100,000 resident population at country level and at English regional level (Public Health England Centres). This analysis is not corrected for variation in reporting between geographical areas.

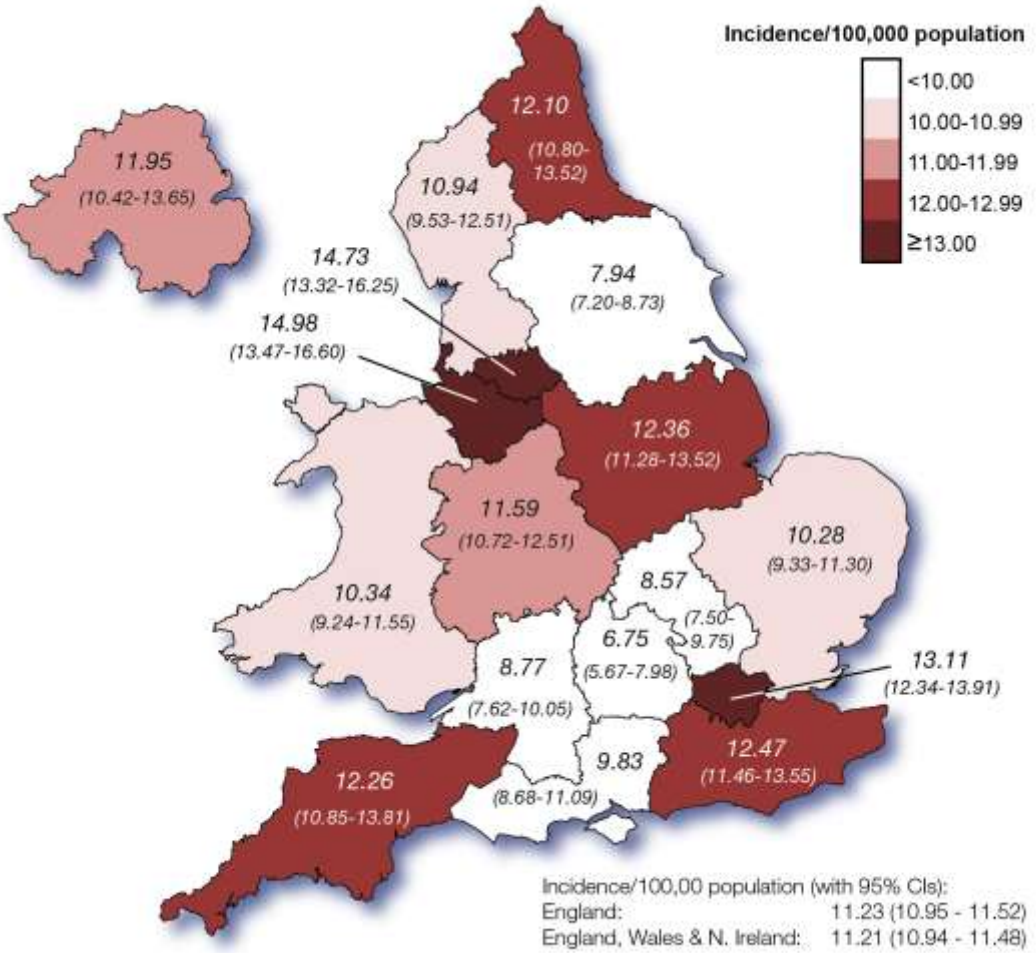
The reported bacteraemia rate for E,W, & NI was 11.21/100,000. Between countries, Northern Ireland had the highest rate at 11.95/100,000 followed by England at 11.23/100,000 then Wales at 10.34/100,000.

In England, variation in the rate between the 15 Public Health Centres (PHECs) was observed. Cheshire and Merseyside was identified as having the highest rate at 14.98/100,000 population, followed by Greater Manchester at 14.73/100,000. Both these PHECs are located in the North West, a region observed to have the highest *Klebsiella* spp bacteraemia rate in previous years [3][4][5].

London was found to have the next highest rate in 2013 at 13.11/100,000. The lowest rate was in Thames Valley at 6.75/100,000.

The geographical variation may be explained by differences in completeness of reporting between PHECs. Other factors include case-mix, accounted for by variation in the distribution of specialist care units. Further work will be undertaken to assess completeness of reporting in order to interpret these variations more robustly in future reports.

Figure 5: Geographic distribution of the rate of bacteraemia reports of *Klebsiella* spp. per 100,000 resident population (England, Wales and Northern Ireland): 2013*



* Data extracted 10 April 2014

Antimicrobial susceptibility data

Tables 2 to 4 present antibiotic susceptibility data for *Klebsiella* spp. blood culture isolates (all species combined), *K. pneumoniae* and *K. oxytoca*. This analysis examines five classes of antibiotics: third-generation cephalosporins (cefotaxime or ceftazidime), carbapenems (imipenem/meropenem), a fluoroquinolone (ciprofloxacin), a penicillin/beta-lactamase inhibitor combination (piperacillin/tazobactam) and an aminoglycoside (gentamicin).

Among *Klebsiella* spp. the most common mechanism of resistance to third-generation cephalosporins (cefotaxime or ceftazidime) is plasmid-mediated extended-spectrum β-lactamase (ESBL) production. For the analysis based on *Klebsiella* spp. isolates (all species), resistance to cefotaxime increased significantly albeit slowly from 8% in 2009 to 10% in 2013 ($p<0.05$). By comparison, there was no evidence that the increase in resistance to ceftazidime was significant ($p=0.240$). A similar result was found for *K. pneumoniae,* where a significant increase was observed for cefotaxime from 9% in '09 to 12% in '13 ($p<0.05$), but with no evidence of change for ceftazidime ($p=0.487$). The analysis for *K. oxytoca*, showed no evidence of change in resistance to either cefotaxime or ceftazidime ($p=0.815$ and $p=0.817$, respectively). The different susceptibility trends observed for cefotaxime and ceftazidime among *Klebsiella* spp. isolates is worrying given that the same ESBL enzymes are expected to affect both cephalosporin compounds in the same way. The different results are more likely to be due to artefact (e.g. differences between laboratories in testing one agent over the other or susceptibility testing errors) rather than a genuine increase in specific ESBLs among *Klebsiella* spp. that predominantly attack cefotaxime but are weak against ceftazidime.

Table 2: Antibiotic susceptibility data on all *Klebsiella* spp. bacteraemia isolates, England, Wales and Northern Ireland: 2009-2013

	2009		2010		2011		2012		2013	
	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant
Piperacillin/ Tazobactam	4,482	10%	4,635	11%	5,217	12%	5,430	13%	5,427	15%
Imipenem/ Meropenem*†	4,420	<1%	4,407	<1%	4,851	<1%	4,975	<1%	4,941	<1%
Cefotaxime	3,130	8%	3,061	9%	3,393	9%	3,487	10%	3,373	10%
Ceftazidime	4,007	9%	4,195	9%	4,618	9%	4,651	10%	4,420	10%
Ciprofloxacin	4,741	9%	4,897	8%	5,374	8%	5,526	8%	5,440	9%
Gentamicin	5,195	6%	5,276	6%	5,859	6%	5,934	6%	5,859	7%
Total *Klebsiella* spp. reports	6,138		6,117		6,572		6,585		6,544	

*0.3% in 2009; 0.4% in 2010; 0.8% in 2011; 0.7% in 2012; 0.9% in 2013

† Ertapenem not included due to the small number of test results reported

Table 3: Antibiotic susceptibility data on *K pneumoniae* bacteraemia isolates, England, Wales and Northern

	2009		2010		2011		2012		2013	
	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant
Piperacillin/ Tazobactam	3,319	10%	3,433	10%	3,941	13%	4,223	13%	4,232	16%
Imipenem/ Meropenem*†	3,237	<1%	3,292	<1%	3,675	1.0%	3,849	<1%	3,857	<1%
Cefotaxime	2,341	9%	2,323	10%	2,617	10%	2,730	11%	2,669	12%
Ceftazidime	2,916	10%	3,126	11%	3,514	11%	3,621	11%	3,484	12%
Ciprofloxacin	3,461	10%	3,641	10%	4,064	10%	4,285	10%	4,248	11%
Gentamicin	3,832	6%	3,944	7%	4,442	7%	4,599	7%	4,569	8%
Total *K. pneumoniae* reports	4,536		4,599		5,016		5,142		5,161	

*0.4% in 2009; 0.5% in 2010; 0.8% in 2012; 0.9% in 2013

† Ertapenem not included due to the small number of test results reported

Table 4: Antibiotic susceptibility data on *K oxytoca* bacteraemia isolates, England, Wales and Northern Ireland: 2009-2013

	2009		2010		2011		2012		2013	
	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant	No. tested	% resistant
Piperacillin/ Tazobactam	1,009	12%	1,015	12%	1,029	12%	1,046	11%	1,038	13%
Imipenem/ Meropenem*†	950	<1%	932	<1%	953	<1%	984	<1%	951	<1%
Cefotaxime	650	6%	638	4%	651	4%	661	5%	625	5%
Ceftazidime	872	4%	887	2%	881	3%	910	3%	826	4%
Ciprofloxacin	1,039	3%	1,056	2%	1,058	2%	1,080	2%	1,038	2%
Gentamicin	1,106	2%	1,123	2%	1,156	1%	1,161	2%	1,129	1%
Total *K. oxytoca* reports	1,336		1,320		1,313		1,308		1,252	

*0.1% in 2009; 0.0% in 2010 due to 0 cases; 0.1% in 2011; 0.4% in 2012; 0.5% in 2013

† Ertapenem not included due to the small number of test results reported

Source: PHE, 2014

The proportion of isolates reported resistant to piperacillin/tazobactam increased significantly over the five-year period based on all *Klebsiella* isolates (from 10% in 2009 to 15% in 2013) (p<0.001). The analysis for *K. pneumonie* also showed a significant increase from 10% in 2009 to 16% in 2013 (p<0.001). These results may reflect the revised MIC breakpoint from 16 to 8 mg/L for this agent with regards to Enterobacteriaceae. However there was no evidence of change in resistance in relation to this antibiotic among *K. oxytoca* isolates (p=0.929).

In terms of ciprofloxacin, no trend in resistance was found between 2009 and 2013 for either *Klebsiella* spp. (all species) or for *K. pneumoniae* (p=0.539; p=0.366, respectively). However, the analysis for *K. oxytoca* indicated that resistance to this antibiotic decreased year on year over the five-year period from 3% in 2009 to 2% in 2013 with strong evidence that this decreasing trend was significant (p<0.01).

No evidence of change in resistance to gentamicin was found based on all *Klebsiella* spp. isolates (p=0.067). At species level, no evidence of change was found for either *K. pneumoniae* (p=0.058) or for *K. oxytoca* (p=0.225).

Resistance to carbapenems was uncommon in the five-year period at less than 1% of isolates (except for *K. pneumoniae* where it reached 1%). However, despite the small underlying numbers, a slow but steady increase in the proportion of isolates resistant to this class of antibiotic was observed between 2009 and 2013. This increase was significant across the three analyses: p<0.001 for *Klebsiella* spp. (all species); p<0.001 for *K. pneumoniae* and p=0.025 for *K. oxytoca*.

The increase in resistance to carbapenems based on *Klebsiella* spp. (all species) was first identified using data available up to 2011 where the year on year increase observed from 2009 to 2011 was found to be significant [4]. Resistance to carbapenems was observed prior to 2009 among isolates of all specimen types referred to PHE's national reference laboratory. Despite the small underlying numbers the increase among bacteraemia isolates also raised concerns given that this class of antibiotic is a powerful last-line treatment for serious infections. The trend in E,W & NI occurred in the context of the recent emergence of resistance to this antibiotic reported internationally [6][7]. In this report, the data for E,W & NI indicated a further but small increase in 2013 (*n*=42). Further analysis of these resistant isolates showed that 51% (75/146) were reported by laboratories from London, Greater Manchester and Cheshire and Merseyside. The patient sex breakdown showed a higher proportion among males at 65% (78/120) compared to 35% among females (42/120). The additional breakdown by age showed that among females the 45-64 year age group was the most affected (38%; 16/42) whilst for males the oldest groups (65-74 years and ≥75 years) were the most affected (23%; 18/78 per group).

Despite the small overall number of carbapenem-resistant isolates involved, the trend in carbapenem-resistant *Klebsiella* spp. warrants close vigilance. Although carbapenem resistance in *Klebsiella* spp. may be mediated by ESBL production combined with impermeability (porin loss), a growing number of isolates referred to PHE's Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit produce carbapenemases belonging to the KPC, OXA-48-like, NDM, VIM and IMP families. *Klebsiella* spp. is the commonest hosts of these enzymes. However approximately only 10% of confirmed carbapenemase producers are isolated from bacteraemias.

In recognition of the importance of carbapenemase-producing Enterobacteriaceae (CPE), PHE issued a Toolkit in December 2013 on the identification and management of affected patients in acute healthcare settings [8]. This Toolkit includes a risk assessment to identify those individuals who should be screened for colonisation or infection with CPE as part of the routine admission procedure. A Toolkit for non-acute settings is to follow.

For advice on treatment of antibiotic resistant infections due to these organisms or for reference services including species identification and confirmation of sensitivity testing results, laboratories should contact PHE's AMRHAI Reference Unit in London [9].

Acknowledgements

These reports would not be possible without the weekly contributions from microbiology colleagues in laboratories across England, Wales, and Northern Ireland, without whom there would be no surveillance data. Feedback and specific queries about this report are welcome and can be sent to: hcai.amrdepartment@phe.gov.uk.

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