Public Health England

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News

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Annual updates on voluntarily reported bacteraemias published

Trends in overall rates of bloodstream infections caused by *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. [1], and *Proteus* spp., *Morganella morganii* spp. and *Providencia* spp. [2], respectively, are published in two annual reports in the Infection Reports section of this issue of *HPR* [1,2].

The reports include analyses of the five-year trends in bacteraemia reports, and of age, sex and geographical distribution. Data and commentary on antimicrobial susceptibility among the bacteraemia isolates received are also presented.

Relatively small changes are reported in overall numbers of bacteraemia reports nationally between 2012 and 2013. However, the analyses on antibiotic susceptibility data indicate that for some organisms, significant increases were found in the proportion of isolates resistant to some classes of antibiotics.

References

1. "Voluntary surveillance of bacteraemia caused by *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. in England, Wales and Northern Ireland: 2009-2013", *HPR* **8**(40): infection reports, 17 October 2014.
2. "Voluntary surveillance of bacteraemia caused by *Proteus* spp., *Morganella morganii* spp. and *Providencia* spp., England, Wales and Northern Ireland: 2013", *HPR* **8**(40): infection reports, 17 October 2014.

Legionnaires' disease annual report (England and Wales) for 2013

The latest PHE annual report on Legionnaires Disease in residents of England and Wales has been published describing the epidemiological features of confirmed cases with onset of symptoms in 2013 [1].

A total of 284 confirmed cases were reported in 2013, of which more than two-thirds were deemed to be community-acquired (a category which includes cases that may have been associated with travel within the UK). Thirty one per cent of cases (88) were associated with travel abroad. Five cases (1.8%) were thought to have been healthcare-associated/nosocomial. For the foreign travel-related cases, Spain was the destination associated with the highest number of cases reported (15). However, the destination with the highest incidence rate was India, with 7.6 cases per million visits, followed by Malta, with 6.5 cases per million visits.

Legionnaires' disease remains an important cause of both morbidity and mortality in England and Wales. The elderly continue to account for most infections and deaths, for which the age profile is heavily weighted to the over-sixties. Heart disease continues to be the most commonly recorded underlying condition.

Fewer than half the number of clusters/outbreaks were identified in 2013 compared to 2012 (seven compared with 20 in 2012). No nosocomial outbreaks were identified.

The proportion of cases identified by polymerase chain reaction (PCR) testing has doubled since 2012 (from 18% to more than 36% in 2013).

Reference

1. Legionnaires' disease in England and Wales 2013. (Further analysis of the 2013 data, with regional breakdowns, will be published on the same page in due course.)

Enterovirus 68 detections in the USA and Canada

Following reports of cases of severe respiratory and neurological illness associated with Enterovirus 68 (EV-D68) infection in the USA [1] and Canada, ECDC has issued a Rapid Risk Assessment for Europe including a recommendation there be increased systematic enterovirus testing (including typing) of cases of severe undiagnosed respiratory illness in view of the possibility that EV-D68 may be the causative pathogen [2].

From mid-August to 1 September 2014, 500 individuals (mostly children) from 42 US states were confirmed to have respiratory illness caused by EV-D68, compared with fewer than 100 during the previous four year period. Similarly increased incidence has been reported in Canada. In the UK, 12 cases of laboratory confirmed EV-D68 infection, mainly in young children, have been reported since 2012. As also highlighted by ECDC, there is a moderate risk that EV-D68 is currently circulating in Europe but this will be mostly undetected as cases can often be asymptomatic/mildly symptomatic and the virus is not currently part of routine respiratory screening. Clinicians should be alert to unusual clusters of severe unexplained respiratory or neurological illness.

References

1. "Activity of Enterovirus D68-like Illness in States" (Centres for Disease Control and Prevention), http://www.cdc.gov/non-polio-enterovirus/outbreaks/EV-D68-outbreaks.html.

2. ECDC Rapid Risk Assessment, 26 September 2014, http://www.ecdc.europa.eu/en/publications/Publications/enterovirus-68-USA-Canada-rapid-risk-assessment.pdfhttp://www.ecdc.europa.eu/en/publications/Publications/enterovirus-68-USA-Canada-rapid-risk-assessment.pdf.

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Infection Reports

HCAI / bacteraemia

Bacteraemia

Infection report

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Voluntary surveillance of bacteraemia caused by *Enterobacter* spp. , *Serratia* spp. and *Citrobacter* spp. in England, Wales and Northern Ireland: 2009-2013

These analyses are based on data on diagnoses of bloodstream infections caused by *Enterobacter* spp., *Serratia* spp. or *Citrobacter* spp. during 2009-2013 in England, Wales and Northern Ireland (E,W & NI). Information was extracted from Public Health England's (PHE) voluntary surveillance database (LabBase2) on 12 September 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.

The mid-year resident population estimates for 2013 based on the 2011 census for England, Wales, and Northern Ireland were used to estimate rates of bacteraemia [1,2]. Geographical analyses were based on the residential postcode of the patient if known; otherwise the GP postcode was used or, failing that, the postcode of the laboratory. Cases in England were assigned to the catchment area of one of 15 local PHE centres (PHECs) based upon administrative local authority boundaries.

This report includes analyses of the trends, patient demographics and geographical distributions, as well as antimicrobial susceptibility among these bacteraemia isolates.

Key points

- between 2012 and 2013, relatively small changes in the total number of bacteraemia reports in E, W & NI were observed for each of the three genera examined and are likely to reflect random variation between two years;
- between 2009 and 2013, the rate of reported bacteraemia per 100,000 resident population in E, W & NI decreased at a slow but steady pace for *Enterobacter* spp. (from 3.85/100,000 to 3.30/100,000 respectively). The rate for *Serratia* spp. also decreased in a similar manner (from 1.74/100,000 to 1.42/100,000 respectively). Bacteraemias caused by *Citrobacter* spp. did not show evidence of a trend, with little variation around 1.19/100,000 *per annum*;
- in 2013, 92% or more of bacteraemia isolates were identified to species level within each genus. Improvements in the level of species identification occurred only for Serratia spp. over the five year period (from 93% in 2009 to 97% in 2013);
- for all three genera, the rate was higher among infants (<1 year) and in the two oldest groups (patients aged 45-64 years or ≥65 years) than in the other age groups. The rate was generally higher among males and particularly among patients aged ≥65 years;
- at country level, N. Ireland had the highest bacteraemia rate for *Enterobacter* spp. (4.22/100,000) and *Serratia* spp. (2.08/100,000) For *Citrobacter* spp., England had the highest bacteraemia rate (1.36/100,000);
- within England, Cumbria and Lancashire had the highest rate of bacteraemia for *Enterobacter* spp. (4.22/100,000). For *Serratia* spp., the North East had the highest bacteraemia rate (2.15/100,000). For *Citrobacter* spp. the West Midlands had the highest bacteraemia rate (1.73/100,000). Since these are unadjusted estimates, the differences across PHE centres may reflect variation in reporting or case-mix or both factors;

- antimicrobial susceptibility trends from 2009 to 2013 were examined for five classes of antibiotics. For the two third-generation cephalosporins examined (cefotaxime and ceftazidime), only *Serratia* spp. isolates showed a significantly decreasing trend in resistance to both agents over the five year period (from 30% in 2009 to 18% in 2013; from 20% to 16% in 2013 respectively). *Enterobacter* spp. isolates showed a significantly decreasing trend only for cefotaxime (from 35% in 2009 to 26% in 2013). The different trends observed for the two agents among *Enterobacter* spp. isolates may be due to artefact in testing. *Citrobacter* spp. isolates showed no evidence of a trend for either cephalosporin agent;
- resistance to gentamicin increased significantly only for *Citrobacter* spp. isolates (from 2% in 2009 to 4% in 2013);
- resistance to ciprofloxacin decreased significantly only for *Serratia* spp. isolates (from 12% in 2009 to 8% in 2013);
- resistance to piperacillin/tazobactam increased significantly for *Enterobacter spp.* isolates (from 17% in 2009 to 20% in 2013) and for *Citrobacter* spp. isolates (from 6% in 2009 to 9% in 2013). The increases may reflect a reduced MIC breakpoint from 16 to 8 mg/L for this agent;
- resistance to the carbapenems (imipenem or meropenen) remained uncommon, but nonetheless increased significantly for the first time among *Enterobacter* spp. isolates; in 2009 0.4% (7/1,613) of these isolates were reported resistant compared to 1.3% (20/1,531) of isolates in 2013.

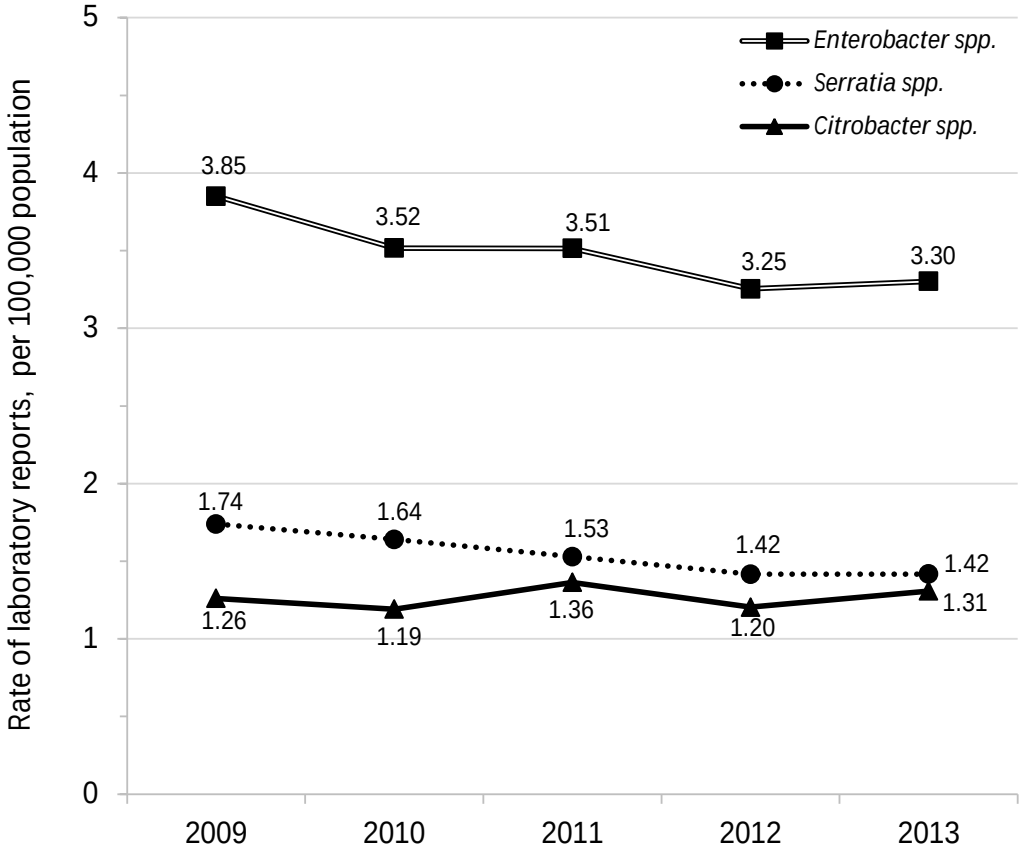
Trends in the number of reports and rates

Between 2012 and 2013, small changes in the total number of bacteraemia reports in E, W & NI were observed for each of the three genera (table 1). For *Enterobacter* spp. the number of bacteraemia reports decreased by 2.2%, though this represented a decrease of just 40 reports. For *Serratia* spp. an increase of 0.73% occurred over the same time period, equating to only six reports. For *Citrobacter* spp. the number of reports increased by 9.4%, amounting to an increase of 66 reports. In the context of the overall annual numbers, the small changes observed between two years may reflect random fluctuation.

Evaluating changes over a five year period may be more useful. Between 2009 and 2013, the total number of laboratory bacteraemia reports in E, W & NI decreased at a slow but steady pace for two of the three genera examined. Bacteraemia reports of *Enterobacter* spp. decreased by 11.6% over this time (from 2,196 in 2009 to 1,941 in 2013) (table 1). *Serratia* spp. also decreased over this period (by 16.0%). Although bacteraemia reports of *Citrobacter* spp. increased by 7.0% this represented an increase of only 50 reports overall with small fluctuations in the intervening period. By comparison, the overall number of bacteraemia reports increased by 4% between 2009 (92,713) and 2013 (96,264) (provisional as of 4 April 2014).

Figure 1 shows trends in the incidence of bacteraemia per genus. *Enterobacter* spp. had the highest rate per 100,000 population in E, W & NI followed by *Serratia* spp. and then *Citrobacter* spp. The rate of laboratory bacteraemia reports decreased at a slow but steady pace for *Enterobacter* spp. (from 3.85/100,000 in 2009 to 3.30/100,000 in 2013). The rate of laboratory bacteraemia reports also decreased at a slow but steady rate for *Serratia* spp. (from 1.74/100,000 in 2009 to 1.42/100,000 in 2013). No trend was detected for *Citrobacter* spp. bacteraemia with small fluctuations in the rate ranging from 1.19 to 1.36 per 100,000 population over this period.

Figure 1: Rate of laboratory bacteraemia reports of *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. in England, Wales and N Ireland per 100,000 resident population: 2009 - 2013



Source: PHE, 2014

Table 1 gives a breakdown of the number of reports by species between 2009 and 2013. Although the majority of isolates from blood were identified to species level across the three genera in 2013 (>91%), improvements in the level of species identification occurred only for *Serratia* spp. over the five year period (from 93% in 2009 to 97% in 2013). It should be noted that the analysis for 'other named species' in table 1 includes data on the option for 'other named' available in LabBase2, if selected by the reporting laboratory. The range of minor species reported in recent years is likely to be due to the effect of laboratories increasingly adopting MALDI-TOF technology (matrix assisted laser desorption/ionisation time of flight). These systems automate microbial identification more rapidly than conventional methods.

In 2013, the predominant *Enterobacter* spp. species causing bacteraemia was *E. cloacae* (71%) followed by *E. aerogenes* (18%). *E. cloacae* decreased at a slow rate in terms of the number of episodes and as a proportion of all *Enterobacter* spp. episodes reported over the five year period. *E. aerogenes* remained broadly unchanged. Inspection of the other named species revealed that overall >70% of these were reported under the option '*Enterobacter* other named' with no further details. The named species reported were *E. amnigenus*, *E. gergoviae* and *E. intermedius* whose numbers were very small (<15 annually) and broadly unchanged during the five-year period.

The predominant *Serratia* spp. species in 2013 was *S. marcescens* (85%) followed by *S. liquefaciens* (9%). The number of reports remained stable for the former but decreased slowly for the latter. The other named species reported were *S. ficaria, S. fonticola, S. odorifera, S. plymuthica*, *S. proteamaculans* and *S. rubidaea* all representing very few reports annually (<15)

and with unchanging trends. The option '*Serratia* other named' was used involving very small numbers but had broadly unchanging trends over the five year period.

For *Citrobacter* spp. the predominant species in 2013 was *C. koseri* (*diversus*) (52%) followed by *C. freundii* (31%). In terms of other named species, the majority (92%) were reported under '*Citrobacter* other named' but the numbers were small and broadly unchanged. The only named species reported was *C. amalonaticus* involving very small numbers but unchanged in the five year period.

Table 1. Reports of bacteraemia due to *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. by species (England, Wales and N Ireland): 2009 to 2013

	2009		2010		2011		2012		2013	
	No.	%	No.	%	No.	%	No.	%	No.	%
***Enterobacter* spp.**	**2,196**	100%	**2,022**	100%	**2,038**	100%	**1,900**	100%	**1,941**	100%
Enterobacter cloacae	1,684	77%	1,520	75%	1,528	75%	1,372	72%	1,371	71%
Enterobacter aerogenes	315	14%	334	17%	339	17%	360	19%	349	18%
Enterobacter sakazakii	27	1%	28	1%	21	1%	19	1%	28	1%
Enterobacter spp., other named species	60	3%	53	3%	48	2%	36	2%	63	3%
Enterobacter spp., species not recorded	110	5%	87	4%	102	5%	113	6%	130	7%
***Serratia* spp.**	**992**	100%	**943**	100%	**887**	100%	**827**	100%	**833**	100%
Serratia marcescens	776	78%	775	82%	704	79%	683	83%	707	85%
Serratia liquefaciens	123	12%	102	11%	107	12%	81	10%	72	9%
Serratia spp., other named species	27	3%	17	2%	28	3%	31	4%	26	3%
Serratia spp., species not recorded	66	7%	49	5%	48	5%	32	4%	28	3%
***Citrobacter* spp.**	**719**	100%	**685**	100%	**791**	100%	**703**	100%	**769**	100%
Citrobacter koseri (C. diversus)	317	44%	320	47%	384	49%	328	47%	403	52%
Citrobacter freundii	282	39%	254	37%	285	36%	267	38%	240	31%
Citrobacter spp., other named species	51	7%	49	7%	64	8%	53	8%	62	8%
Citrobacter spp., species not recorded	69	10%	62	9%	58	7%	55	8%	64	8%

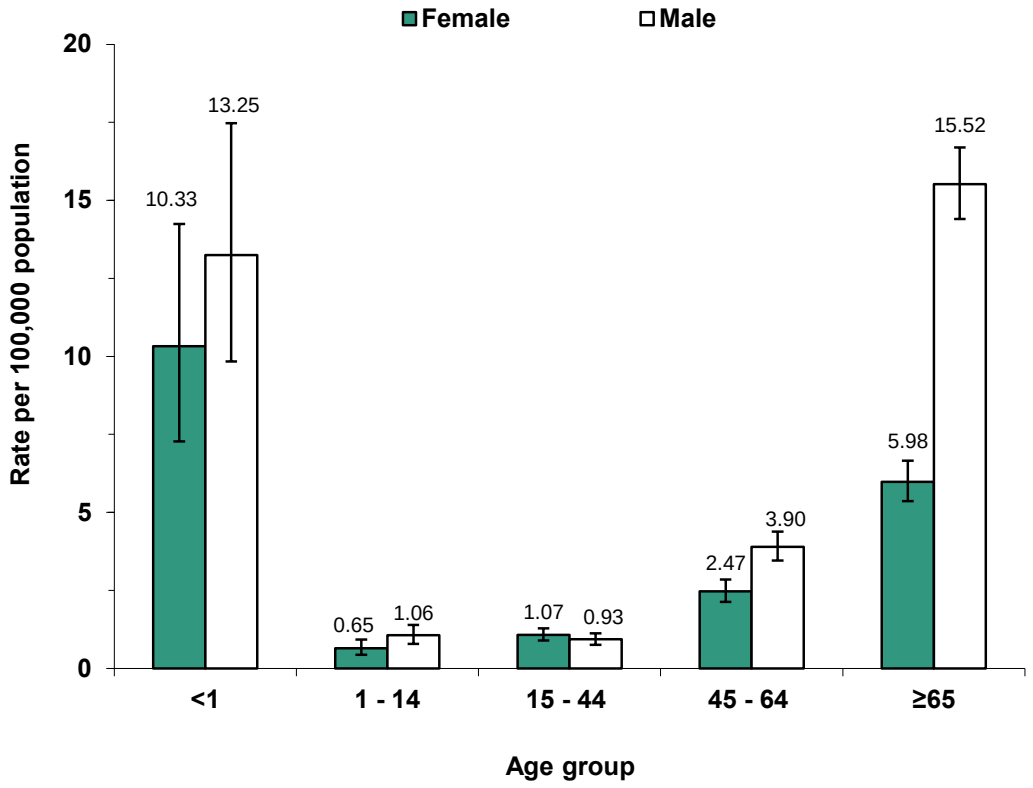
Source: PHE, 2014

Age and sex distribution

Figures 2 to 4 show the age and sex-specific rates of bacteraemia reports in E, W & NI in 2013 per 100,000 resident population for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. In general, the rate was higher in the infant group (under one year) and in the elderly group although the rate in the infant group was based on a relatively smaller sample (<100 reports for each organism under analysis). The highest rate was among patients aged 65 years or more. The rate of bacteraemia was consistently higher among male infants and for males in the two oldest groups (patients aged 45-64 years or those aged ≥65 years).

Among the oldest age group (patients aged 65 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 2.60; 2.34 and 3.82 for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. respectively.

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



Source: PHE, 2014

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

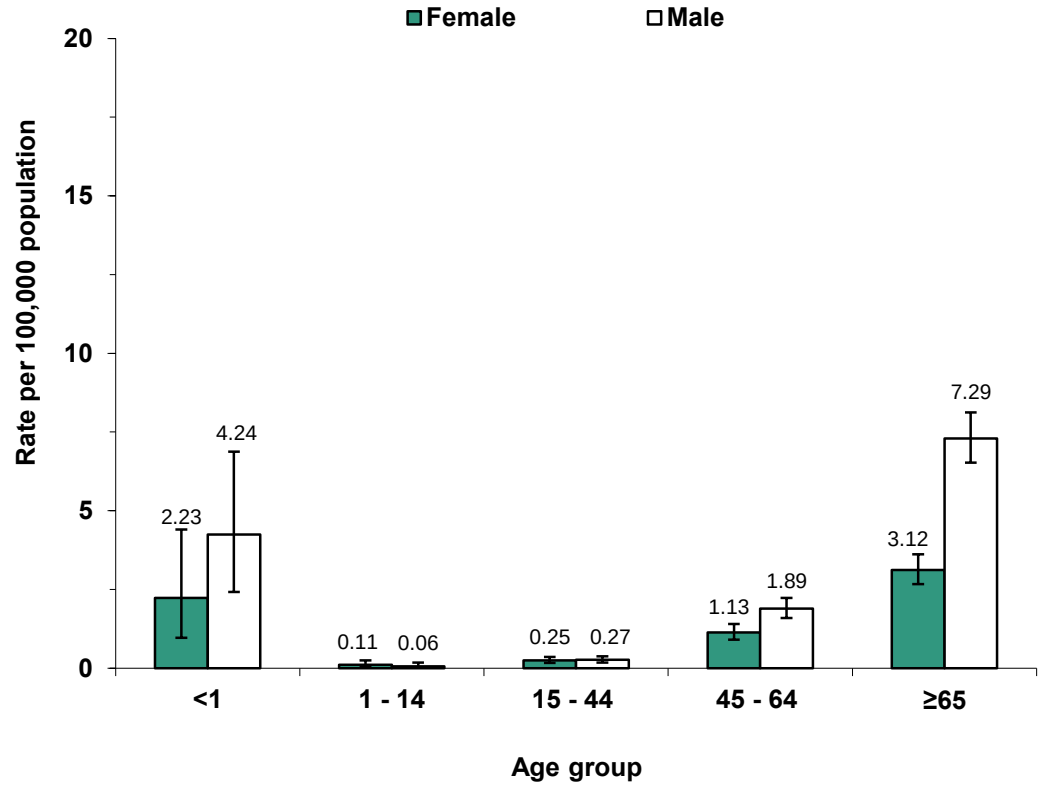
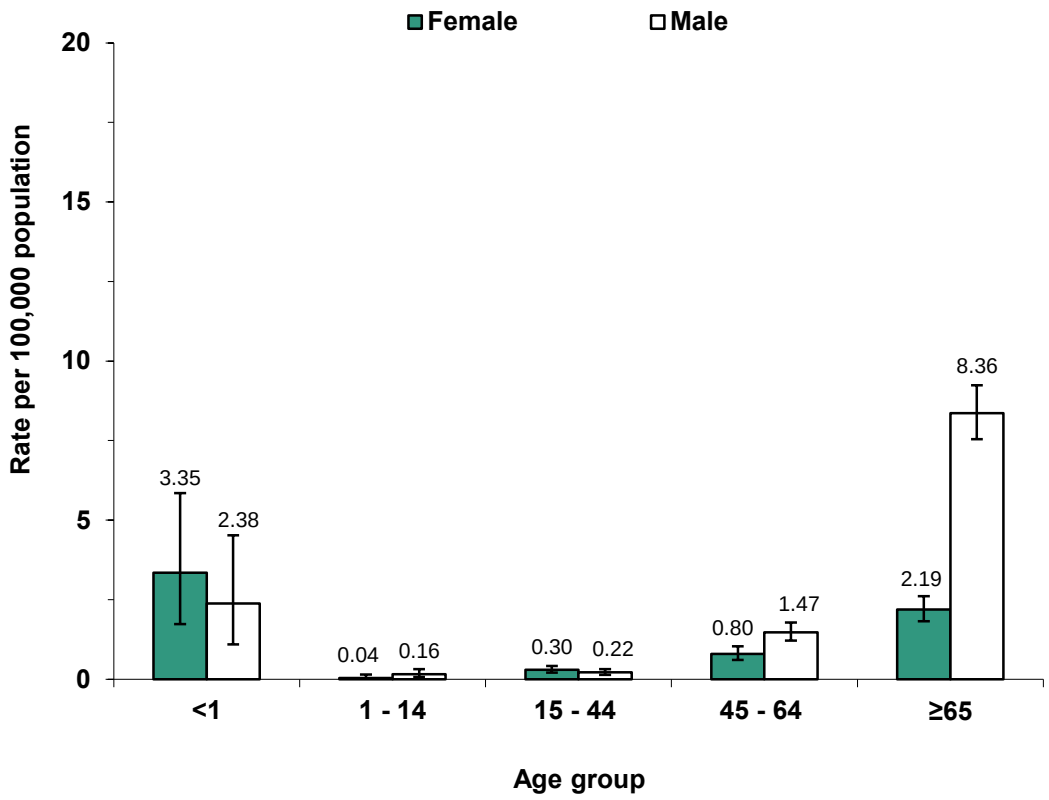


Figure 4. Age and sex-specific rates of bacteraemia reports of *Cirobacter* spp. per resident 100,000 population (England, Wales and N Ireland): 2013



Source: PHE, 2014

Geographic distribution

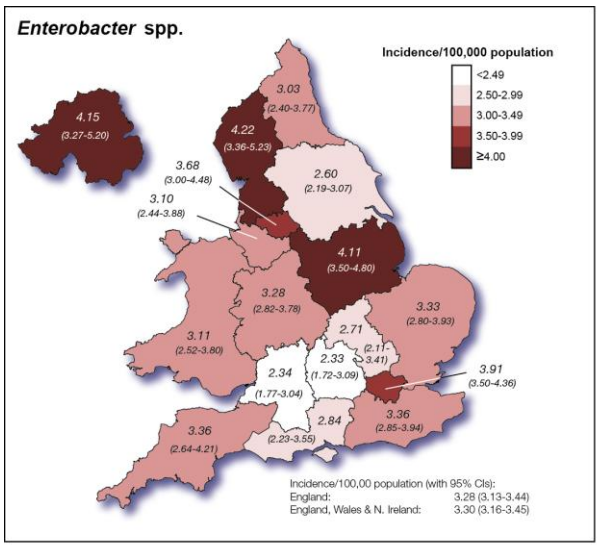
Figures 5 shows the reporting rate of bacteraemia for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. per 100,000 resident population at country level and at English regional level (Public Health England Centres). This analysis is not corrected for variation in reporting between geographical areas.

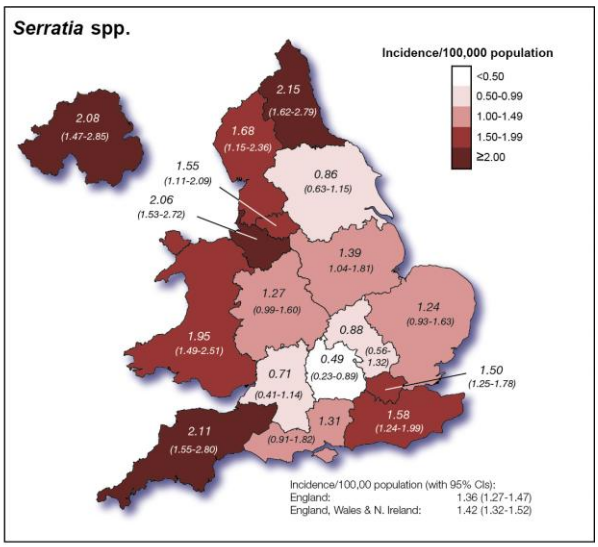
Of all three organisms examined, *Enterobacter* spp. had the highest rate in general. For this organism, the reported bacteraemia rate for E, W, & NI combined was 3.30/100,000. At country level, Northern Ireland had the highest rate at 4.15/100,000 followed by England and then Wales.

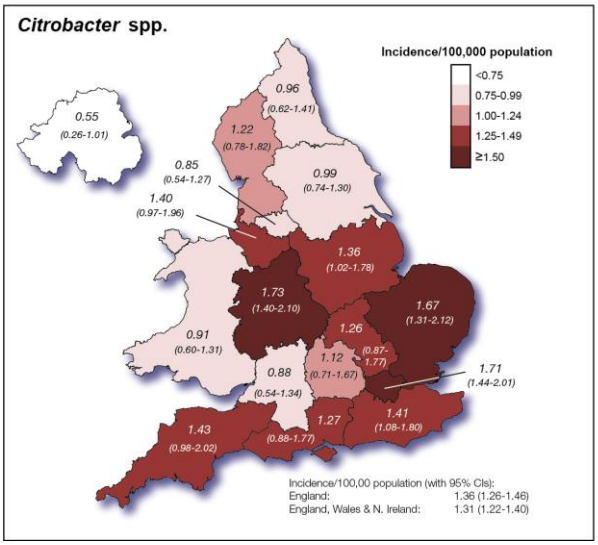
In England, variation in the rate between the 15 Public Health Centres (PHECs) was observed for each of three organisms. For *Enterobacter* spp., Cumbria and Lancashire was identified as having the highest rate at 4.22/100,000 with the lowest rate in Thames Valley at 2.33/100,000. For *Serratia* spp., the North East was identified as having the highest rate at 2.15/100,000, with the lowest rate observed for Thames Valley at 0.49/100,000. For *Citrobacter* spp., the West Midlands was identified as having the highest rate, at 1.73/100,000, with the lowest rate observed for Greater Manchester at 0.85/100,000.

Despite similarity in resistance across the three genera, the geographical variation osberved may be explained by differences in completeness of reporting between PHECs. Other factors include variation in case-mix or 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 *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. per 100,000 resident population (England, Wales and N Ireland): 2013







Source: PHE, 2014

Antimicrobial susceptibility data

Tables 2 to 4 present antibiotic susceptibility data on blood culture isolates for *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp. 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).

Cephalosporins are the antibiotic group to which all three genera show the greatest level of resistance compared with the other antibiotics examined. Among *Enterobacter* spp., resistance to cefotaxime and ceftazidime commonly reflects de-repression of chromosomal AmpC β-lactamase. The analysis for bacteraemia isolates relating to *Enterobacter* spp. showed a year on year decrease in resistance to cefotaxime from 35% in 2009 to 26% in 2013 which was found to be significant ($p<0.0005$). By comparison, no evidence of a trend was found with regards to resistance to ceftazidime ($p=0.138$). Among *Serratia* spp. isolates, year on year decreases in resistance to cefotaxime and ceftazidime was observed which were found to be significant ($p<0.001$; $p<0.01$ respectively). Among *Citrobacter* spp. isolates, no evidence of a trend was found for either cefotaxime or ceftazidime ($p=0.139$; $p=0.942$ respectively).

The different susceptibility trends for cefotaxime and ceftazidime among *Enterobacter* spp. isolates are perplexing, given that AmpC enzymes are expected to affect both cephalosporin compounds similarly and that only a small minority of *Enterobacter* spp. isolates have ESBLs e.g. CTX-M-9/-14 that confer much more obvious resistance to cefotaxime than to ceftazidime (BSAC data). The different results observed in this analysis are more likely to be due to artefact (e.g. differences between laboratories in testing one agent over the other or susceptibility testing errors). Decreases in AmpC-mediated resistance probably reflect reduced cephalosporin usage, since de-repression, previously, was a mode of resistance often selected de novo during cephalosporin therapy.

Table 2: Antibiotic susceptibility data on all *Enterobacter* 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	1,546	17%	1,478	18%	1,576	17%	1,492	20%	1,595	20%
Imipenem/ Meropenem*†	1,613	<1%	1,520	1%	1,556	1%	1,480	1%	1,531	1%
Cefotaxime	1,076	35%	989	33%	1,011	29%	997	26%	952	26%
Ceftazidime	1,368	32%	1,366	32%	1,386	30%	1,313	29%	1,294	31%
Ciprofloxacin	1,684	6%	1,633	5%	1,676	5%	1,579	5%	1,647	6%
Gentamicin	1,834	7%	1,716	5%	1,794	6%	1,700	6%	1,741	6%
Total *Enterobacter* spp. reports	**2,196**		**2,022**		**2,038**		**1,900**		**1,941**	

*0.4% in 2009; 0.8% in 2010; 0.8% in 2011; 0.7% in 2012; 1.3% in 2013

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

Table 3: Antibiotic susceptibility data on *Serratia* 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	712	12%	712	15%	707	10%	657	8%	676	12%
Imipenem/ Meropenem*†	780	<1%	735	1%	701	<1%	675	<1%	677	1%
Cefotaxime	541	30%	497	29%	458	21%	454	19%	443	18%
Ceftazidime	647	20%	681	21%	643	16%	620	14%	576	16%
Ciprofloxacin	800	12%	794	12%	756	11%	709	9%	725	8%
Gentamicin	855	3%	838	2%	824	1%	762	1%	760	2%
Total *Serratia* spp. reports	992		943		887		827		833	

*0.1% in 2009; 0.5% in 2010; 0.4% in 2011; 0.4% in 2012; 0.6% in 2012.

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

Table 4: Antibiotic susceptibility data on *Citrobacter* 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	501	6%	504	7%	620	7%	562	9%	631	9%
Imipenem/ Meropenem*†	505	<1%	490	0%	582	0.0%	527	0%	576	<1%
Cefotaxime	322	18%	320	14%	375	13%	364	12%	388	13%
Ceftazidime	446	15%	467	13%	525	12%	502	13%	510	14%
Ciprofloxacin	545	3%	540	4%	645	3%	578	2%	628	3%
Gentamicin	607	2%	575	4%	686	3%	611	5%	676	4%
Total *Citrobacter* spp. reports	992		943		887		827		833	

*0.2% in 2009; 0 cases in 2010, 2011 and 2012; 0.2% in 2013

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

Source: PHE, 2014

The proportion of isolates reported as being resistant to piperacillin/tazobactam increased significantly over the five-year period for two of the three genera. One of these was *Enterobacter* spp. (with resistance increasing from 17% of isolates in 2009 to 20% in 2013; p<0.05). For *Citrobacter* spp. isolates, resistance increased from 6% in 2009 to 9% in 2013; p<0.01). These results may reflect the revised (EUCAST vs BSAC) MIC breakpoint from 16 to 8 mg/L for this agent with regards to Enterobacteriaceae. No evidence of change in resistance to this antibiotic was found among *Serratia* spp. isolates (p=0.064).

In terms of ciprofloxacin resistance, only *Serratia* spp. showed evidence of a trend. The proportion of these isolates reported as being resistant to this agent decreased significantly over the five-year period (from 12% in 2009 to 8% in 2013; p<0.005).

For gentamicin resistance, only *Citrobacter* spp. showed evidence of a trend. The proportion of these isolates reported as being resistant to this agent increased significantly over the five year period (from 2% in 2009 to 4% in 2013; p<0.025).

Resistance to carbapenems (imipenem/meropenem) was uncommon in the five-year period, at 1% or less among the three genera examined in this report. However despite the small underlying numbers, for the first time in these analyses, *Enterobacter* spp. showed evidence of a slow but significant increase in resistance to this class of antibiotic from 0.4% (7/1,613) in

2009 to 1.3% (20/1,531) in 2013; p<0.05). The majority (35%; 22/62) of these resistant isolates were reported by laboratories in the Midlands and East of England. No evidence of a trend in carbapenem resistance was found for the other two genera.

A similar small but increasing trend to imipenem and meropenem resistance among bacteraemia isolates of *Klebsiella* spp. has been reported previously [3][4][[5]. Despite the small underlying numbers, the increase among these bacteraemia isolates is of concern given that this class of antibiotic is a powerful last-line treatment for serious infections caused by Gram-negative bacteria. Moreover these increases are occurring in the context of the emergence of resistance to these antibiotics among Enterobacteriaceae reported internationally in recent years [6][7].

Data based on specimens referred to PHE's national reference laboratory indicate an increasing trend in carbapenamase-producing Enterobacteriaceae (CPE) from 2008, although sporadic cases were reported as far back as 2003. A total of 2,794 Enterobacteriaceae, from all specimen types, were identified as carbapenemase producing by PHE between 2003 and 2013. *Klebsiella* spp. accounted for the majority of these isolates (79%), followed by *E. coli* (12%) then *Enterobacter* spp. (7%). Approximately 10% of confirmed carbapenemase producers were isolated from bacteraemias; PHE's Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit found them to variously produce carbapenemases belonging to the KPC, OXA-48-like, NDM, VIM and IMP families. Although carbapenem resistance among Enterobacteriaceae in general (and particularly in *Enterobacter* spp.) may also be mediated by ESBL or AmpC production combined with impermeability (porin loss), the proportion of resistant isolates with carbapenemases is growing.

In recognition of the importance of carbapenemase-producing Enterobacteriaceae, 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 carbapenemase-producing Enterobacteriaceae 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].

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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.

References

1. Office for National Statistics (ONS) mid-year population estimates for England and Wales. Available: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-england-and-wales/mid-2012/mid-2012-population-estimates-for-england-and-wales.html

2. Northern Ireland Statistcs and Research Agency (NISRA) mid-year population esitmates for Northern Ireland. Available: http://www.nisra.gov.uk/demography/default.asp17.htm

3. HPA. Voluntary surveillance of *Klebsiella*, *Enterobacter*, *Serratia* and *Citrobacter* bacteraemia in England, Wales and Northern Ireland: 2011. Health Protection Report [serial online] 2012; 6(42). Available: http://webarchive.nationalarchives.gov.uk/20140505162355/http://www.hpa.org.uk/hpr/archives/2012/hpr4212_klbsll.pdf

4. HPA. Voluntary surveillance of *Klebsiella*, *Enterobacter*, *Serratia* and *Citrobacter* bacteraemia in England, Wales and Northern Ireland: 2012. Health Protection Report [serial online] 2013; 7(42). Available:

http://webarchive.nationalarchives.gov.uk/20140505162355/http://www.hpa.org.uk/hpr/archives/2013/hpr4213_klbsll.pdf

5. PHE. Voluntary surveillance of *Klebsiella* spp. bacteraemia in England, Wales and Northern Ireland: 2009-2013. Health Protection Report [serial online] 2014; 8(19). Available:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/346847/hpr1914_klbsll.pdf

6. Pitout JD, Laupland KB. Extended-spectrum β-lactamase–producing *Enterobacteriaceae:* an emerging public health concern. Lancet Infect Dis. 2008;8:159–66. Available: http://www.sciencedirect.com/science/article/pii/S1473309908700410

7. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis*. 2011;17(10):1791–8. Available: http://wwwnc.cdc.gov/eid/article/17/10/11-0655_article.htm

8. PHE. Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae. London: Public Health England

https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts

9. Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI): https://www.gov.uk/amrhai-reference-unit-reference-and-diagnostic-services#contact.

Bacteraemia

Infection report

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Voluntary surveillance of bacteraemia caused by *Proteus spp., Morganella morganii* spp. and *Providencia* spp., England, Wales and Northern Ireland: 2009-2013

These analyses are based on data extracted from the Public Health England (PHE) voluntary surveillance database, LabBase2, on 2 September 2014 for the period 2009 to 2013. The data presented here may differ from previous reports due to the inclusion of late reports.

Rates were calculated using 2013 mid-year resident population estimates based on the 2011 census for England, Wales, and Northern Ireland [1]. English sub-national geographical analyses were based on the residential location of the patient with reference to PHE Centre geographies; Wales and Northern Ireland were each analysed as a whole.

The report includes analyses on the trend, age and sex distribution, geographical distribution and the antimicrobial susceptibility in reported cases of *Proteus* spp., *Morganella morganii* and *Providencia* spp.

Key points

- the annual incidence of *Proteus* spp. (4.0 per 100,000 population), and *Providencia* spp. (0.2 per 100,000 per population) bacteraemia remained steady between 2009 and 2013
- the incidence of *Morganella morganii* reduced from 0.8 in 2011 to 0.6 in 2013;
- in 2013, most *Proteus* spp. bacteraemias were attributed to *Proteus mirabilis* (90%);
- the majority of *Providencia* isolates determined to species level in 2013 were identified as *Providencia stuartii*, which accounted for 57% of these reports;
- the majority of infections caused by Proteeae were in the eldest patient age group (≥75 years old); the number of reports decreased with age, with the exception of children aged <1 year who had the highest paediatric rate. *Proteus* spp. dominated in each age group;
- the rate of Proteeae bacteraemia was higher in male than female patients except for those aged 15-44 years;
- regionally, Northern Ireland and the East Midlands had the highest rates of *Proteus* spp. (6.3 and 5.7 per 100,000 population respectively) compared to the lowest regional rate from the Thames Valley (2.1 per 100,000 population);
- the region with the highest incidence of *M. morganii* bacteraemia was Devon, Cornwall and Somerset (1.0/100,000); Thames Valley (0.3/100,000) had the lowest incidence;
- with the exception of amoxicillin, resistance of *P. mirabilis* has remained at <10% for cefuroxime, cefotaxime, ceftazidime, ciprofloxacin, gentamicin, meropenem;
- the only statistically significant change ($P<0.025$) in antimicrobial susceptibility observed for *M. morganii* was the sudden increase in resistance (intermediate and full resistance) to imipenem (from 0% in 2012 to 16% in 2013);
- dual resistance of third-generation cephalosporin and gentamicin in these pathogens is rare and was seen for only 2% of *Proteus spp.* and *M. morganii* bacteraemias in 2013.

Trends in episode numbers and rates

The annual reported incidence of *Proteus* spp. (4.4 per 100,000 population), and *Providencia* spp. (0.2 per 100,000 per population) bacteraemia remained steady between 2009 and 2013 (figure 1). Between 2009 and 2013, there was little fluctuation in the total number of reports of *Proteus* spp. (from 2,490 to 2,565 reports) and *Providencia* spp. (from 93 to 86 reports) bacteraemia; there has been a slight decrease in *Morganella morganii* reports from 432 to 362 over the same period. In comparison, the total number of bacteraemia reports increased by 4% overall between 2009 (92,713) and 2013 (96,264).

Figure 1. *Proteus* spp., *Morganella morganii*, and *Providencia* spp. bacteraemia reports (England, Wales and Northern Ireland): 2009 to 2013

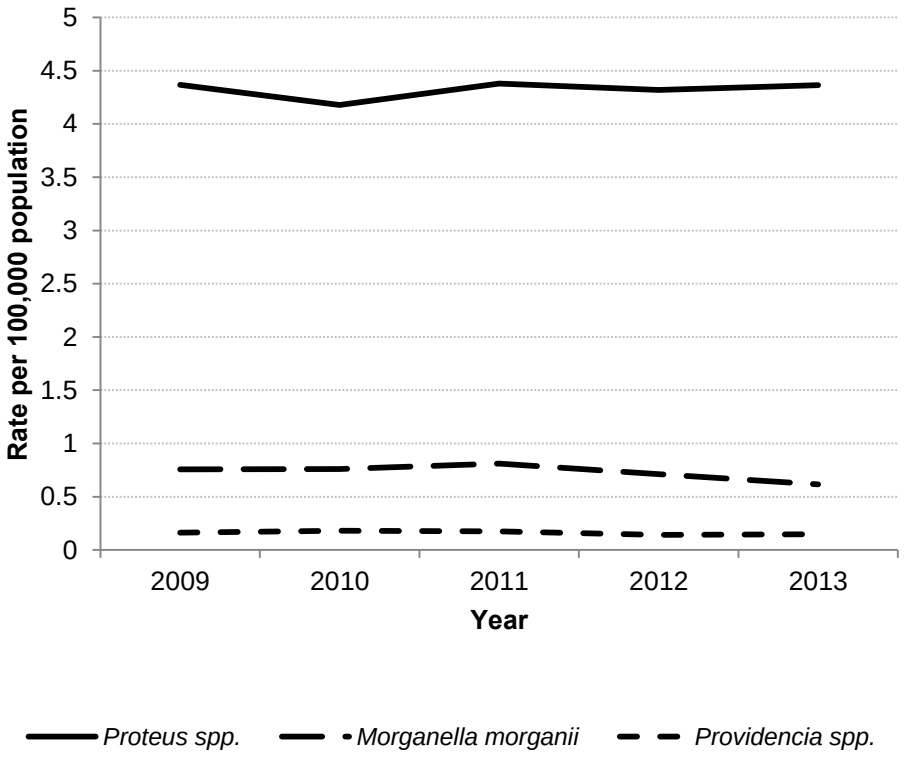


Table 1 gives a breakdown of reported Proteeae bacteraemias by species from 2009 to 2013. In 2013, as previously, most *Proteus* spp. bacteraemias were attributed to *Proteus mirabilis* (90%). The majority of *Providencia* isolates determined to species level in 2013 were identified as *Providencia stuartii*, which accounted for 57% of these reports.

Table 1. Reports of *Proteus* spp., *Morganella morganii*, and *Providencia* spp. bacteraemia, by species: 2009-2013

	2009		2010		2011		2012		2013	
	No.	%	No.	%	No.	%	No.	%	No.	%
***Proteus* spp.**	2490	100%	2403	100%	2539	100%	2523	100%	2565	100%
Proteus mirabilis	2133	86%	2091	87%	2220	87%	2241	89%	2314	90%
Proteus vulgaris	98	4%	94	4%	89	4%	90	4%	66	3%
Proteus spp., other named species	9	0%	10	0%	4	0%	2	0%	4	0%
Proteus spp., species not recorded	250	10%	208	9%	226	9%	190	8%	181	7%
Morganella morganii	432	100%	437	100%	471	100%	415	100%	362	100%
***Providencia* spp.**	93	100%	103	100%	101	100%	82	100%	86	100%
Providencia stuartii	56	60%	63	61%	57	56%	39	48%	49	57%
Providencia rettgeri	25	27%	32	31%	27	27%	32	39%	30	35%
Providencia spp., other named species	3	3%	3	3%	10	10%	10	12%	7	8%
Providencia spp., species not recorded	9	10%	5	5%	7	7%	1	1%	0	0%

Age and sex distribution

Figure 2 shows the age distribution for cases of bacteraemia due to Proteeae in 2013. The majority of infections were in the eldest age group (≥75 years old), with rates reduced in younger agegroups. Children aged <1 year had the highest paediatric rates compared to the other age-groups: by contrast, there were no reports of Proteeae bacteraemias for children aged 5-9 years, and no *M. morganii* or *Providencia* spp. bacteraemias reported for children aged 1-4 years or 10-14 years. Similarly to previous years, *Proteus* spp. dominated in each age group where reported.

Figure 3 illustrates the division of Proteeae bacteraemia between female and male patients. The rate of bacteraemias caused by Proteeae species was more than double in male patients compared to female patients in the two oldest age groups (65-74 years and ≥75 years old) and in children aged <1 year. The only age-group where the rate was higher in females was in the 15 to 44 year olds.

Figure 2. *Proteus* spp., *M. morganii*, and *Providencia* spp. bacteraemia reports by age: 2013

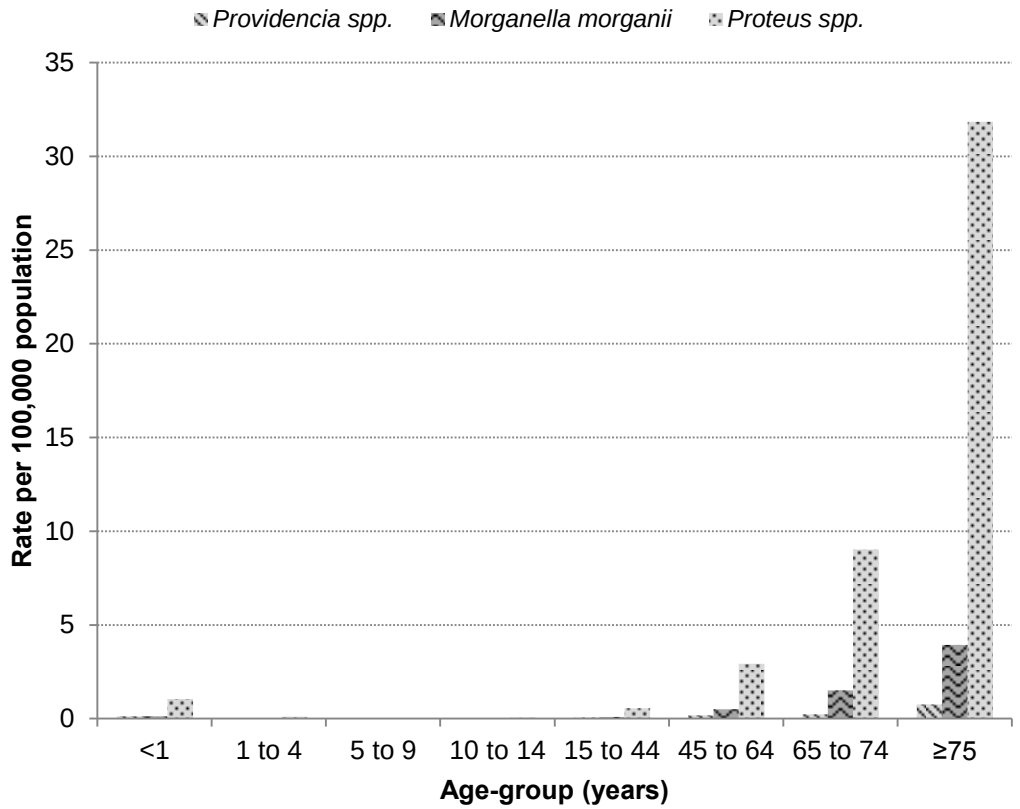
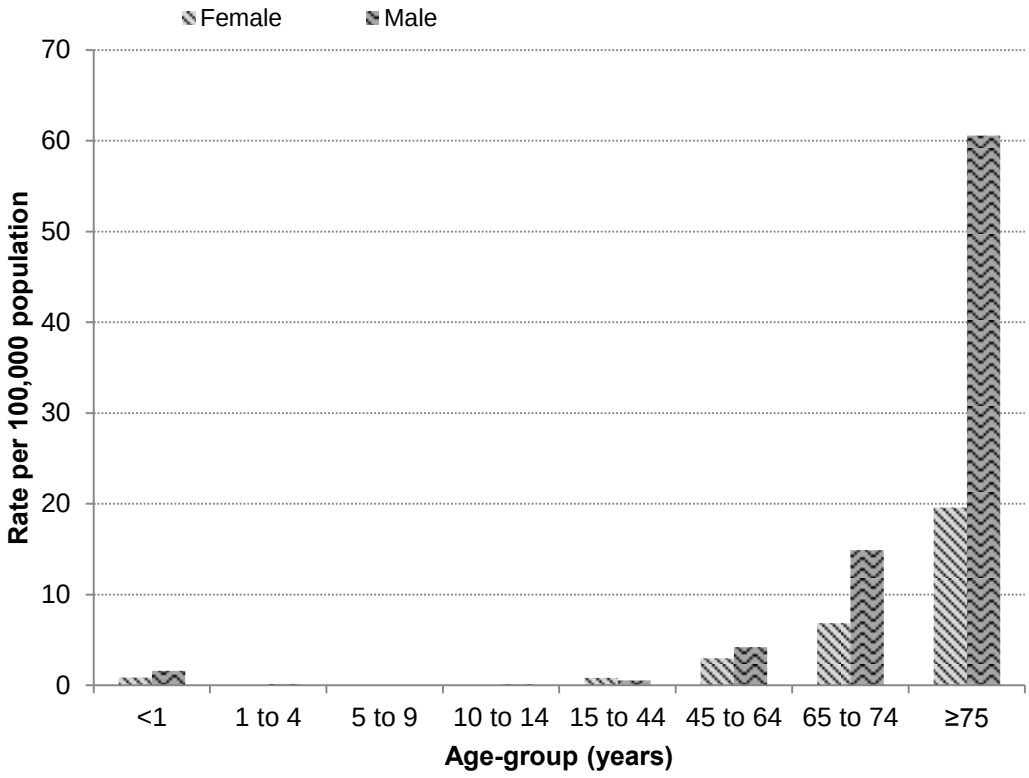


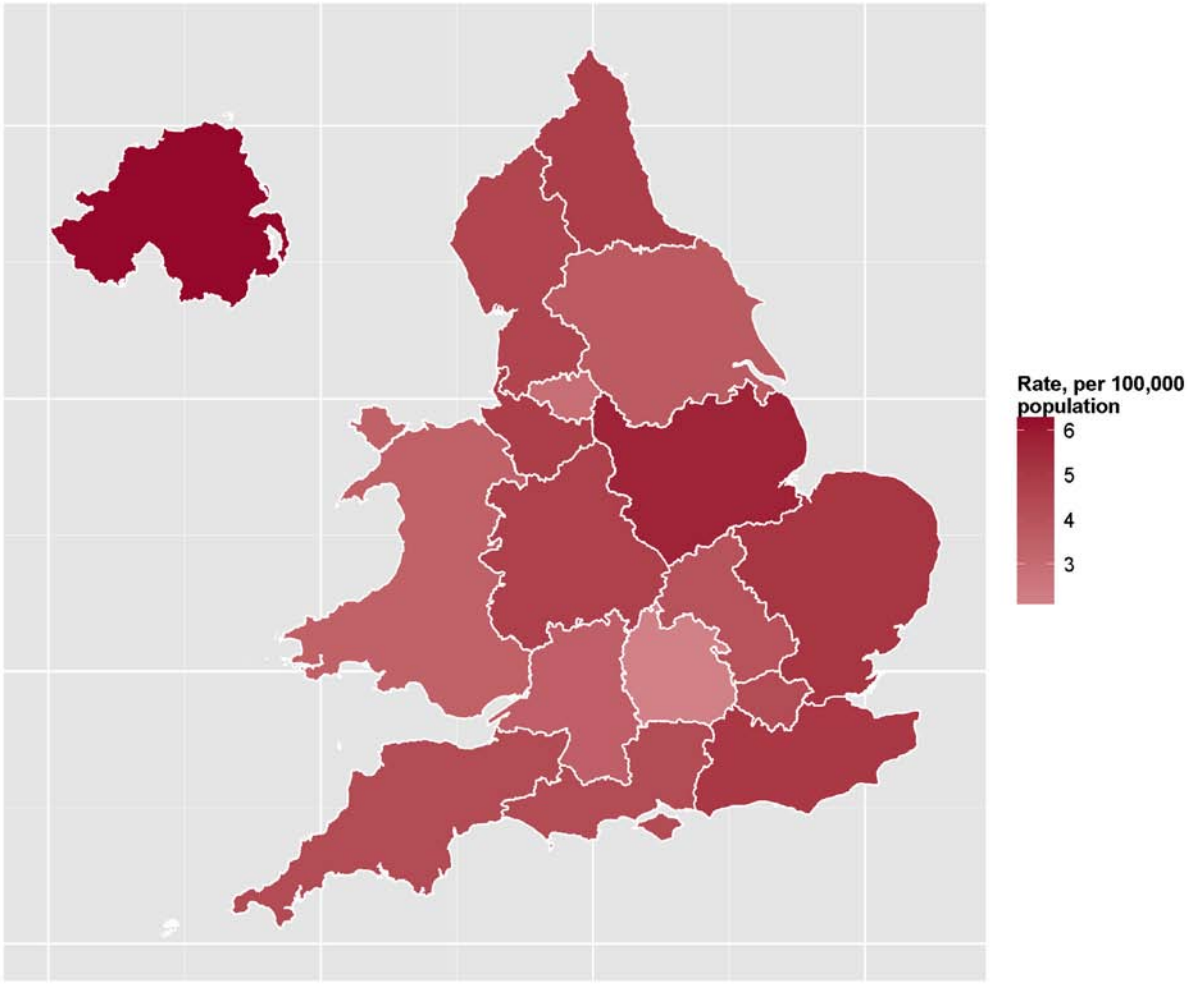
Figure 3. *Proteus* spp., *M. morganii*, and *Providencia* spp. bacteraemia reports by sex: 2013



Distribution by region

Figures 4 and 5 show regional distribution of *Proteus* spp. and *M. morganii* bacteraemia in 2013 with adjoining summary tables of the rate by region for the previous 5 years.

Figure 4. Region-specific rates [1] of *Proteus* spp. bacteraemia: England, Wales, and Northern Ireland, 2013



The regions/countries with the highest incidence of *Proteus* spp. bacteraemia in 2013 included Northern Ireland (6.3 cases per 100,000 population) and the East Midlands (5.7/100,000). Regions with low incidence included Thames Valley (2.1/100,000) and Greater Manchester (2.9/100,000). The overall reported incidence for England, Wales, and Northern Ireland was 4.0 per 100,000 population. It is important to note that regional incidence rates are affected by completeness of regional reporting.

Table 2. Five year reporting rate trend for *Proteus* spp. by Public Health England Centre and country in England Wales and Northern Ireland; 2009 to 2013

	Rate per 100,000 population				
PHE Centre	2009	2010	2011	2012	2013
London	4.5	3.8	4.6	4.4	4.3
South Midlands and Hertfordshire	4.4	3.1	2.9	4.1	4.0
East Midlands	5.7	5.6	5.5	5.2	5.7
Anglia and Essex	4.4	4.7	4.8	5.0	5.1
West Midlands	5.4	4.6	4.8	5.0	4.7
Cheshire and Merseyside	3.0	3.6	4.9	4.0	4.8
Cumbria and Lancashire	3.5	2.8	4.2	3.7	4.5
Greater Manchester	4.7	5.2	3.5	4.7	2.9
North East	4.7	3.6	4.4	4.3	4.8
Yorkshire and Humber	5.3	4.5	4.2	4.1	3.7
Avon, Gloucestershire and Wiltshire	2.3	3.1	4.2	3.8	3.5
Devon, Cornwall and Somerset	5.1	5.1	4.9	4.2	4.3
Wessex	3.2	4.0	4.4	4.5	4.3
Kent, Surrey and Sussex	4.6	4.5	4.1	3.7	5.0
Thames Valley	3.0	2.9	2.6	2.1	2.1
England	4.5	4.2	4.4	4.3	4.3
Wales	2.5	3.2	4.1	3.4	3.4
Northern Ireland (NI)	4.2	5.2	5.3	6.2	6.3
England, Wales and NI	4.4	4.2	4.4	4.3	4.4

Due to the smaller number of reports of *M. morganii*, the range in region-specific rates (figure 4) was small. The region with the highest incidence of *M. morganii* bacteraemia was Devon, Cornwall and Somerset (0.9/100,000), whereas Thames Valley (0.3/100,000) had the lowest incidence. The overall reported incidence for England, Wales, and Northern Ireland was 0.6 per 100,000 population in 2013. It is important to note that regional incidence rates are affected by completeness of regional reporting as well as the regional distribution of specialist care units.

Figure 5. Region-specific rates [1] of *M. morganii* bacteraemia: England, Wales, and Northern Ireland, 2013

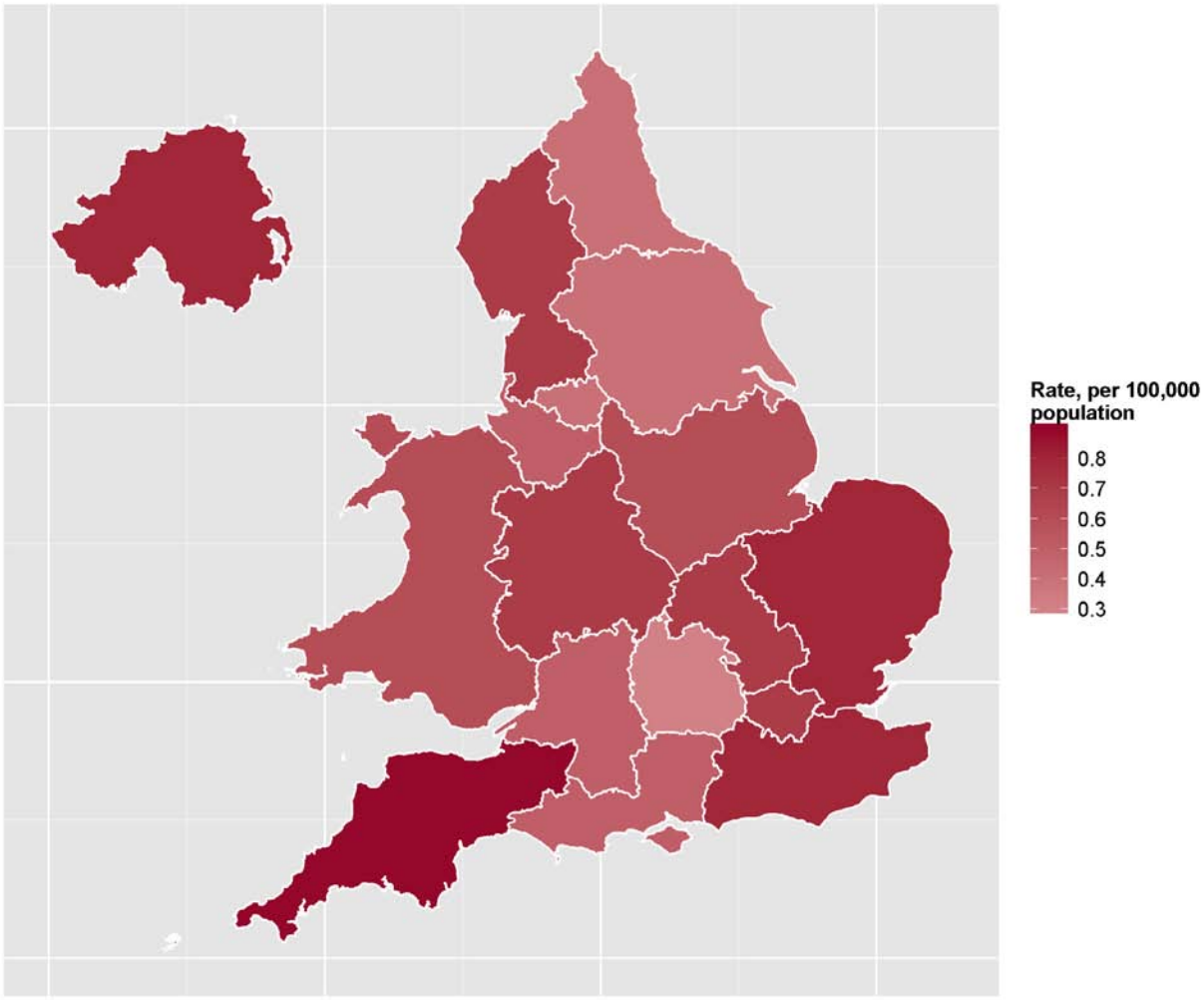


Table 3. Five year reporting rate trend for *M. morganii* by Public Health England Centre and country in England Wales and Northern Ireland; 2009 to 2013

	Rate per 100,000 population				
PHE Centre	**2009**	**2010**	**2011**	**2012**	**2013**
London	0.8	0.8	0.9	1.0	0.7
South Midlands and Hertfordshire	0.5	0.4	0.6	0.6	0.7
East Midlands	0.7	1.0	1.1	0.6	0.6
Anglia and Essex	0.5	0.7	0.9	0.6	0.8
West Midlands	0.9	0.7	0.8	0.7	0.7
Cheshire and Merseyside	0.5	0.8	0.5	0.7	0.5
Cumbria and Lancashire	0.8	0.7	0.7	1.2	0.7
Greater Manchester	0.9	0.8	0.9	0.7	0.4
North East	0.7	0.6	0.5	0.6	0.4
Yorkshire and Humber	1.0	0.9	1.0	0.7	0.4
Avon, Gloucestershire and Wiltshire	0.3	0.7	0.7	0.4	0.5
Devon, Cornwall and Somerset	1.2	0.9	0.6	0.5	0.9
Wessex	0.6	0.5	0.5	0.5	0.5
Kent, Surrey and Sussex	1.0	0.6	0.9	0.8	0.8
Thames Valley	0.8	0.6	0.5	0.3	0.3
England	0.8	0.7	0.8	0.7	0.6
Wales	0.7	1.0	1.2	0.7	0.6
Northern Ireland (NI)	0.8	0.8	0.7	0.8	0.8
England, Wales and NI	0.8	0.8	0.8	0.7	0.6

Antibiotic susceptibility data

Tables 4 to 8 present antibiotic susceptibility data for each of the four main species. Trend analysis was carried out using the Chi-square test in Stata.

Table 4. Antibiotic susceptibility data for reports of *Proteus mirabilis* bacteraemia, England, Wales, and Northern Ireland: 2009 to 2013

	2009		2010		2011		2012		2013	
Antimicrobial	**No. tested**	**% resistant (%R)***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***
Amoxicillin	1660	32%	1690	33%	1793	34%	1911	34%	1911	34%
Cefuroxime	1323	1%	1311	2%	1458	2%	1479	1%	1507	2%
Cefotaxime	1044	0%	1005	1%	1074	2%	1163	2%	1221	3%
Ceftazidime	1380	1%	1383	1%	1518	2%	1515	2%	1521	2%
Ciprofloxacin	1622	6%	1677	5%	1776	7%	1860	9%	1912	8%
Gentamicin	1779	6%	1795	7%	1898	7%	2003	10%	2058	9%
Imipenem	524	6%	407	8%	339	9%	247	5%	230	8%
Meropenem	1113	0%	1183	0%	1364	0%	1500	0%	1649	0%
Total *P. mirabilis*	2133		2091		2220		2241		2314	

*reported as reduced- or non-susceptible

With the exception of amoxicillin, resistance of *P. mirabilis* to the other antibiotics has remained at <10%. The observed increase in the non-susceptibility of *P. mirabilis* to gentamicin (6-9%) and imipenem (6-8%) between 2009 and 2013 was statistically significant ($P<0.005$ and $P<0.025$ respectively). Although not statistically significant, appears to be an upward creep in resistance to cefotaxime. *Proteus* spp. are inherently among the least susceptible Enterobacteriaceae to imipenem, meaning that the reporting of some non-susceptibility by laboratories is not surprising. Unlike among *E. coli* and *Klebsiella*, cephalosporin resistance remains exceptional in *P. mirabilis* in the UK, although ESBLs or plasmid AmpC have disseminated in the species e.g. in Italy.

Table 5. Antibiotic susceptibility data for reports of *Proteus vulgaris* bacteraemia, England, Wales, and Northern Ireland: 2009 to 2013

	2009		2010		2011		2012		2013	
Antimicrobial	**No. tested**	**% resistant (%R)***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***
Cefotaxime	50	6%	50	4%	39	3%	47	9%	32	6%
Ceftazidime	60	2%	61	3%	68	4%	59	7%	40	8%
Ciprofloxacin	63	5%	73	0%	75	3%	66	0%	57	0%
Gentamicin	78	3%	74	1%	77	4%	77	6%	59	5%
Imipemen	26	4%	18	6%	22	18%	8	0%	5	0%
Meropenem	43	0%	52	0%	57	0%	61	0%	48	0%
Total *P. vulgaris*	98		94		89		90		66	

*reported as reduced- or non-susceptible

There were no statistically significant changes in the susceptibility of isolates reported in 2013 compared to 2012; the 18% of *P. vulgaris* resistance to imipenem observed in 2011 is most likely due to a testing fluctuation; there has been no further evidence of imipenem-resistant isolates, although the number of tested isolates has remained fewer than 30 in all years.

Table 6. Antibiotic susceptibility data for reports of *Morganella morganii* bacteraemia, England, Wales, and Northern Ireland: 2009 to 2013

	2009		2010		2011		2012		2013	
Antimicrobial	**No. tested**	**% resistant (%R)***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***
Cefotaxime	180	18%	216	21%	244	23%	224	19%	178	20%
Ceftazidime	253	22%	292	22%	309	24%	276	22%	245	19%
Ciprofloxacin	329	11%	358	12%	387	11%	341	11%	299	10%
Gentamicin	350	8%	382	8%	410	10%	367	9%	321	9%
Imipemen	117	3%	106	4%	85	4%	54	0%	49	16%
Meropenem	216	0%	255	0%	309	0%	272	0%	255	0%
Total *M. morganii*	432		437		471		415		362	

*reported as reduced- or non-susceptible

The only statistically significant change ($P<0.025$) in antimicrobial resistance observed for *M. morganii* was the sudden increase in resistance to imipenem (from 0% in 2012 to 16% in 2013). Of the eight isolates non-susceptible to imipenem, six had reduced (intermediate) susceptibility (four were from the same laboratory but from different patients) and two were fully resistant; this is again most likely due to a testing fluctuation and borderline sensitivity. This proportion may be due to unrepresentative testing as the numbers of tested isolates has more than halved since 2009. The relatively unchanging proportion of isolates non-susceptible to cephalosporins contrasts the decrease in resistance reported in *Enterobacter* spp. between 2008-2012 (from 38% to 26% for cefotaxime and 36% to 29% for ceftazidime)[2]. This is notable because the principal mechanism of resistance (derepression of AmpC) is the same in both organisms.

Table 7. Antibiotic susceptibility data for reports of *Providencia stuartii* bacteraemia, England, Wales, and Northern Ireland: 2009 to 2013

	2009		2010		2011		2012		2013	
Antimicrobial	**No. tested**	**% resistant (%R)***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***	**No. tested**	**%R***
Cefotaxime	29	3%	28	4%	25	8%	18	6%	31	6%
Ceftazidime	36	3%	41	5%	36	6%	28	7%	35	6%
Ciprofloxacin	42	10%	45	13%	48	8%	31	3%	42	12%
Gentamicin	43	21%	51	49%	46	52%	31	61%	45	56%
Imipemen	15	0%	11	0%	9	0%	6	0%	5	20%
Meropenem	25	0%	36	0%	34	0%	24	0%	37	0%
Total *P. stuartii*	56		63		57		39		49	

*reported as reduced- or non-susceptible

There were no statistically significant resistance trends for *P. stuartii.* *P. stuartii* remained universally susceptible to meropenem and the number of isolates tested for imipenem is very small, so the results should be interpreted with caution. Inherent resistance to gentamicin in this species is not very reliably detected, though EUCAST advises that all isolates should be reported as resistant to aminoglycosides except for amikacin and streptomycin owing to the production of a chromosomally mediated acetyltransferase [3].

Table 8. Combined third-generation cephalosporin and gentamicin susceptibility data for reports of *Proteus* spp. and *Morganella morganii* bacteraemia, England, Wales, and Northern Ireland: 2009 to 2013

Pathogen	2009		2010		2011		2012		2013	
	No. tested	% resistant (%R)*	No. tested	%R*	No. tested	%R*	No. tested	%R*	No. tested	%R*
Proteus spp.	1631	0%	1562	0%	1765	1%	1826	2%	1823	2%
Morganella morganii	267	3%	306	4%	331	3%	307	4%	261	2%

*reported as reduced- or non-susceptible

Dual resistance of third-generation cephalosporin and gentamicin in these pathogens is very rare, and was seen for only 2-4% of all bacteraemias due to *Proteus spp.* and *M. morganii* between 2009 and 2013. Isolates of *Providencia* spp. were excluded from this analysis because they are inherently resistant to gentamicin.

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References

1. Regional rates were calculated using mid-year 2011 resident population estimates published by the Office for National Statistics (ONS) (http://www.statistics.gov.uk)

2. Public Health England. Health Protection Report: Voluntary surveillance of *Klebsiella, Enterobacter, Serratia*, and *Citrobacter* spp. bacteraemia in England, Wales and Northern Ireland: 2012. Vol 7, no 42. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/KlebsiellaSpecies/EpidemiologicalData/

3. Leclercq *et al.* EUCAST expert rules in antimicrobial susceptibility testing. CLin Microbiol Infect 2011;19:141-60 http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/EUCAST-Expert-rules-v2-CMI.pdf