Public Health England

Health Protection Report
weekly report

Infection report

Volume 9 Number 45 Published on: 18 December 2015

Surveillance of *Proteus, Morganella* and *Providencia* species causing bacteraemia in England, Wales and Northern Ireland: 2014

These analyses are based on data relating to diagnoses of *Proteus* spp.*, Morganella* spp. *and Providencia* spp. bloodstream infections during 2007 – 2014 in England, Wales and Northern Ireland (E, W & NI) extracted from Public Health England's (PHE) voluntary surveillance database Second Generation Surveillance System (SGSS).

SGSS comprises a communicable disease module (CDR; formerly CoSurv/LabBase2) and an antimicrobial resistance module (AMR; formerly AmSurv). Most analyses presented here are based on data extracted from the CDR module of SGSS data on 3rd December 2015, except for the evaluation of multi-drug resistance data from the AMR module of SGSS. This module captures more comprehensive antibiogram data allowing more robust evaluation of multi-resistance rates. However these data cannot be used for the trend analysis due to the addition of this data collection being relatively recent and therefore a lower laboratory coverage in previous years.

The data presented here will differ in some instances from those in earlier publications partly due to the inclusion of late reports.

Rates of bacteraemia laboratory reports were calculated using mid-year resident population estimates for the respective year and geography [1]. Geographical analyses were based on the residential postcode of the patient if known (otherwise the GP postcode if known or failing that the postcode of the laboratory) with cases in England being assigned to the catchment area of one of 15 local PHE centres (PHECs) formed from administrative local authority boundaries, which were correct at the time the data were reported.

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

Key points

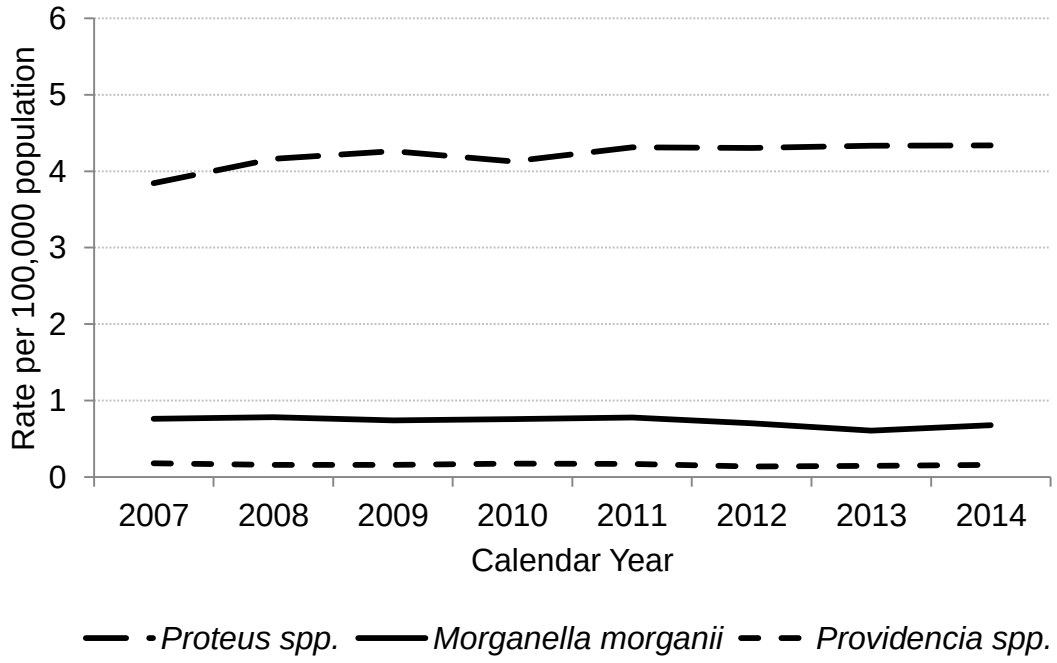
- the overall rate of *Proteus* spp. bacteraemia in England, Wales and Northern Ireland was 4.3 per 100,000 population in 2014, which has steadily increased from 3.8/100,000 population observed in 2007
- the rate of *Morganella morganii* bacteraemia was 0.7/100,000 population in 2014 and has remained consistent since 2007. No other *Morganella* spp. were isolated
- the rate of *Providencia* spp. bacteraemia remained consistent at 0.2/100,000 population between 2007 and 2014
- England had the highest reported incidence rate of *Proteus* spp. in 2014 with 4.4/100,000 population followed by Northern Ireland (4.1) and Wales (3.3)
- England had the highest reported incidence rate of *Morganella morganii* in 2014 with 0.7/100,000 population, where Northern Ireland and Wales both had a rate of 0.4/100,000 population
- the most frequently identified *Proteus* species in blood isolates in 2014 (as in previous years) was *P. mirabilis* (90%)
- the most frequently identified *Providencia* species in blood isolates in 2014 were *P. stuartii* (44%) and *P. rettgeri* (45%)
- the highest rates of *Proteus* spp., *M. morganii* and *Providencia* spp. bacteraemia were observed in those aged 75 years or older and those that were male
- overall the proportion of *P. mirabilis* and *P. vulgaris* bacteraemia reports reported as resistant (defined as reduced- or non-susceptible) to an antimicrobial in 2014 remained steady compared to the previous four years, except for emerging resistance to ertapenem
- a decrease of *M. morganii* resistance to cephalosporins was observed
- all the pathogens in this report were universally susceptible to meropenem in 2014.

Trends

The overall rate of *Proteus* spp. bacteraemia for England, Wales and Northern Ireland was 4.3 per 100,000 population in 2014, which is marginally higher than the 3.8/100,000 population observed in 2007 (13% increase; figure 1). The rate of *Morganella morganii* bacteraemia was 0.7/100,000 population in 2014, representing a decline of 11% since 2007 (0.8/100,000 population; figure 1). No other *Morganella* species were isolated. The rate of *Providencia* spp. bacteraemia remained consistent at 0.2/100,000 between 2007 and 2014 (figure 1).

Proteus spp. accounted for 2.1% of mono-microbial bloodstream infections (BSI; all reported bacteraemia and/or fungaemia) in 2014; making them the ninth most commonly reported cause of mono-microbial BSI. In contrast, *M. morganii* and *Providencia* spp. accounted for 0.3% (ranked 24th) and 0.06% (ranked 41st) of mono-microbial BSI respectively in 2014 [2]. *Proteus* spp,, *M. morganii* and *Providencia* spp. were identified in 7.2%, 1.5% and 0.4% of poly-microbial BSI respectively in 2014.

Figure 1. Eight year trend in *Proteus* spp., *Morganella morganii* and *Providencia* spp. bacteraemia reports per 100,000 population (England Wales and Northern Ireland); 2007 to 2014



Geographic distribution

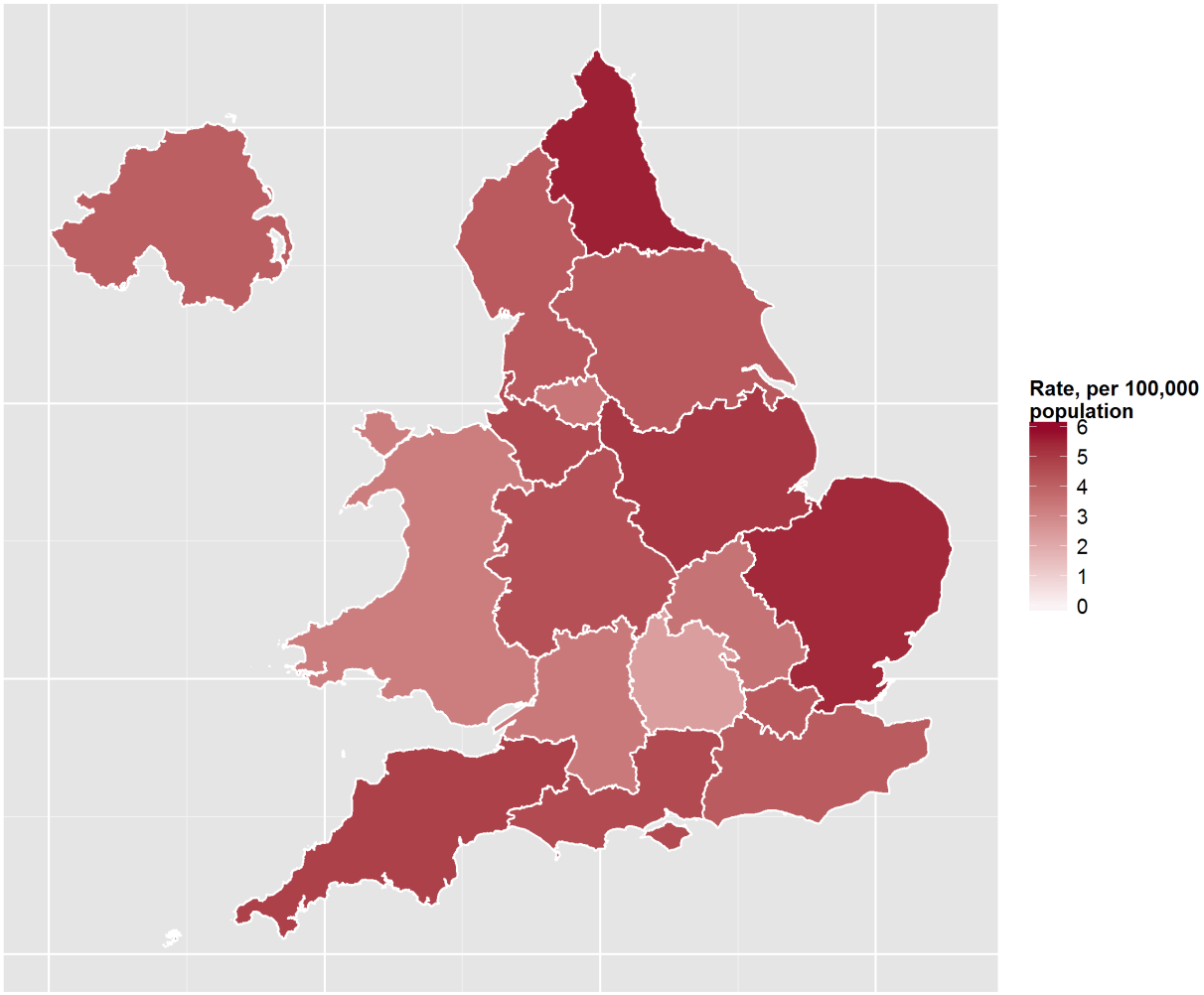
England had the highest reported incidence rate of *Proteus* spp. in 2014 with 4.4/100,000 population followed by Northern Ireland (4.1/100,000) and Wales (3.3/100,000) (table 1a). However, Northern Ireland observed a steep 34% decline of the *Proteus* spp. bacteraemia incidence rate between 2013 and 2014 (6.2 vs. 4.1/100,000 population, respectively; table 1a).

Within the English PHECs, the rate of *Proteus* spp. bacteraemia has varied between 2010 and 2014 (table 1a). In 2014, the Thames Valley had the lowest rate of *Proteus* spp. bacteraemia (2.4/100,000 population) compared to the highest rates in Anglia and Essex (5.5/100,000 population) and the North East (5.7/100,000 population; table 1a, figure 2a).

Table 1a. Five year PHE Centre *Proteus* spp. bacteraemia per 100,000 population (England, Wales and Northern Ireland); 2010 to 2014

Region		Rate per 100,000 population				
		2010	**2011**	**2012**	**2013**	**2014**
London	London	3.7	4.5	4.2	4.2	4.3
Midlands	South Midlands and Hertfordshire	2.5	2.3	3.3	3.2	3.6
	East Midlands	5.6	5.4	5.6	5.8	5.2
	Anglia and Essex	4.6	4.8	5.1	5.1	5.5
	West Midlands	4.5	4.7	4.9	4.7	4.5
Northern	Cheshire and Merseyside	3.7	4.9	4.1	5.0	4.7
	Cumbria and Lancashire	2.7	4.0	3.7	4.4	4.3
	Greater Manchester	5.2	3.4	4.6	3.0	3.5
	North East	3.6	4.4	4.3	4.8	5.7
	Yorkshire and Humber	4.6	4.2	4.2	3.7	4.3
Southern	Avon, Gloucestershire and Wiltshire	3.2	4.3	4.1	3.9	3.4
	Devon, Cornwall and Somerset	5.0	4.8	4.4	4.2	4.9
	Wessex	4.0	4.3	4.6	4.4	4.7
	Kent, Surrey and Sussex	4.5	4.1	3.7	4.9	4.2
	Thames Valley	2.9	2.5	2.1	2.0	2.4
England		**4.1**	**4.3**	**4.3**	**4.3**	**4.4**
Northern Ireland		**5.1**	**5.1**	**6.1**	**6.2**	**4.1**
Wales		**3.2**	**4.0**	**3.4**	**3.3**	**3.3**
England, Wales and Northern Ireland		**4.1**	**4.3**	**4.3**	**4.3**	**4.3**

Figure 2a. Geographical distribution of *Proteus* spp. bacteraemia per 100,000 population in England, Wales and Northern Ireland; 2014



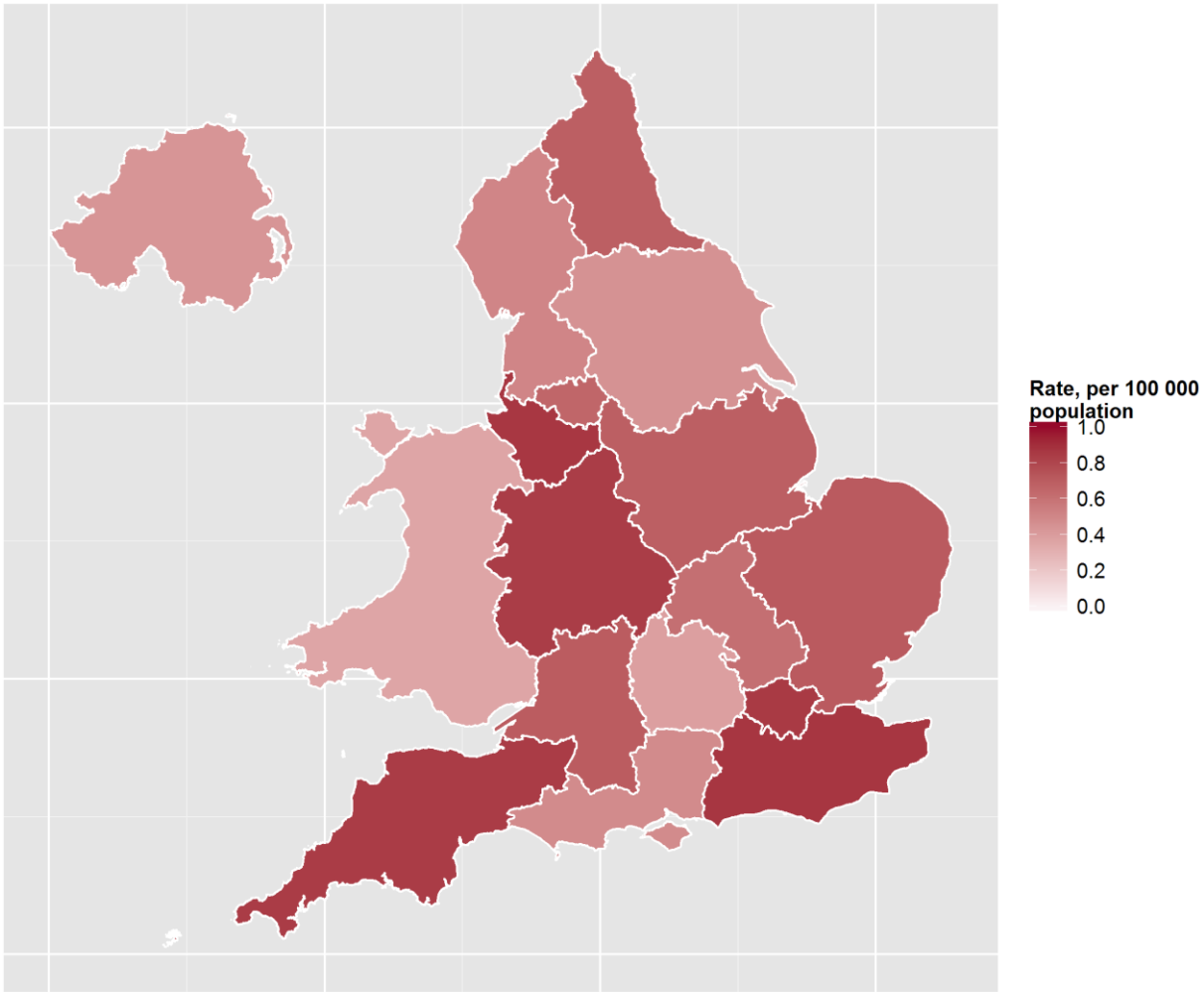
England had the highest reported incidence rate of bacteraemia due to *M. morganii* in 2014 with 0.7/100,000 population, whereas Northern Ireland and Wales both had a rate of 0.4/100,000 population, which was their lowest rate in the five-year period (table 1b).

There was marginal variation in the rate of *M. morganii* bacteraemia within the English PHECs between 2010 and 2014 (table 1b), although the majority of rates remained <1/100,000 population. In 2014, Yorkshire and the Humber and Thames Valley had the lowest rate of *M. morganii* bacteraemia (0.4/100,000 population) compared to the highest rate of 0.9/100,000 population in London, Cheshire and Merseyside, and Kent, Surrey and Sussex (table 1b, figure 2b).

Table 1b. Five year PHE Centre *Morganella morganii* bacteraemia per 100,000 population (England, Wales and Northern Ireland); 2010 to 2014

Region		Rate per 100,000 population				
		2010	**2011**	**2012**	**2013**	**2014**
London	London	0.8	0.8	0.9	0.7	0.9
Midlands	South Midlands and Hertfordshire	0.3	0.5	0.6	0.5	0.6
	East Midlands	1.1	1.1	0.7	0.7	0.7
	Anglia and Essex	0.7	0.8	0.6	0.8	0.7
	West Midlands	0.7	0.8	0.7	0.7	0.8
Northern	Cheshire and Merseyside	0.8	0.5	0.7	0.5	0.9
	Cumbria and Lancashire	0.7	0.7	1.2	0.7	0.5
	Greater Manchester	0.8	0.9	0.7	0.4	0.7
	North East	0.6	0.5	0.6	0.4	0.7
	Yorkshire and Humber	0.9	0.9	0.7	0.4	0.4
Southern	Avon, Gloucestershire and Wiltshire	0.7	0.7	0.4	0.5	0.7
	Devon, Cornwall and Somerset	1.0	0.6	0.5	0.9	0.8
	Wessex	0.5	0.5	0.5	0.5	0.5
	Kent, Surrey and Sussex	0.6	0.9	0.8	0.8	0.9
	Thames Valley	0.6	0.5	0.3	0.3	0.4
England		**0.7**	**0.8**	**0.7**	**0.6**	**0.7**
Northern Ireland		**0.8**	**0.7**	**0.8**	**0.7**	**0.4**
Wales		**1.0**	**1.1**	**0.7**	**0.6**	**0.4**
England, Wales and Northern Ireland		**0.8**	**0.8**	**0.7**	**0.6**	**0.7**

Figure 2b. Geographical distribution of *Morganella morganii* bacteraemia per 100,000 population in England, Wales and Northern Ireland; 2014



Species distribution

Ninety-three per cent of *Proteus* bacteraemia cases were identified to species level in 2014, demonstrating an improving trend from the 90% reported to species level in 2010. The most frequently identified *Proteus* species in blood isolates in 2014 (as in previous years) was *P. mirabilis* (90%; table 2).

The most frequently identified *Providencia* species in blood isolates in 2014 were *P. stuartii* (44%) and *P. rettgeri* (45%; table 2). This is the first year that *P. rettgeri* has been more frequently isolated than *P. stuartii,* for which a 34% decrease in the numbers since 2010 was observed (from 62 isolates in 2010 to 41 isolates in 2014).

Table 2. Distribution of *Proteus* spp., *Morganella morganii*, and *Providencia* spp. species identified in blood specimens (England, Wales and Northern Ireland); 2010 to 2014

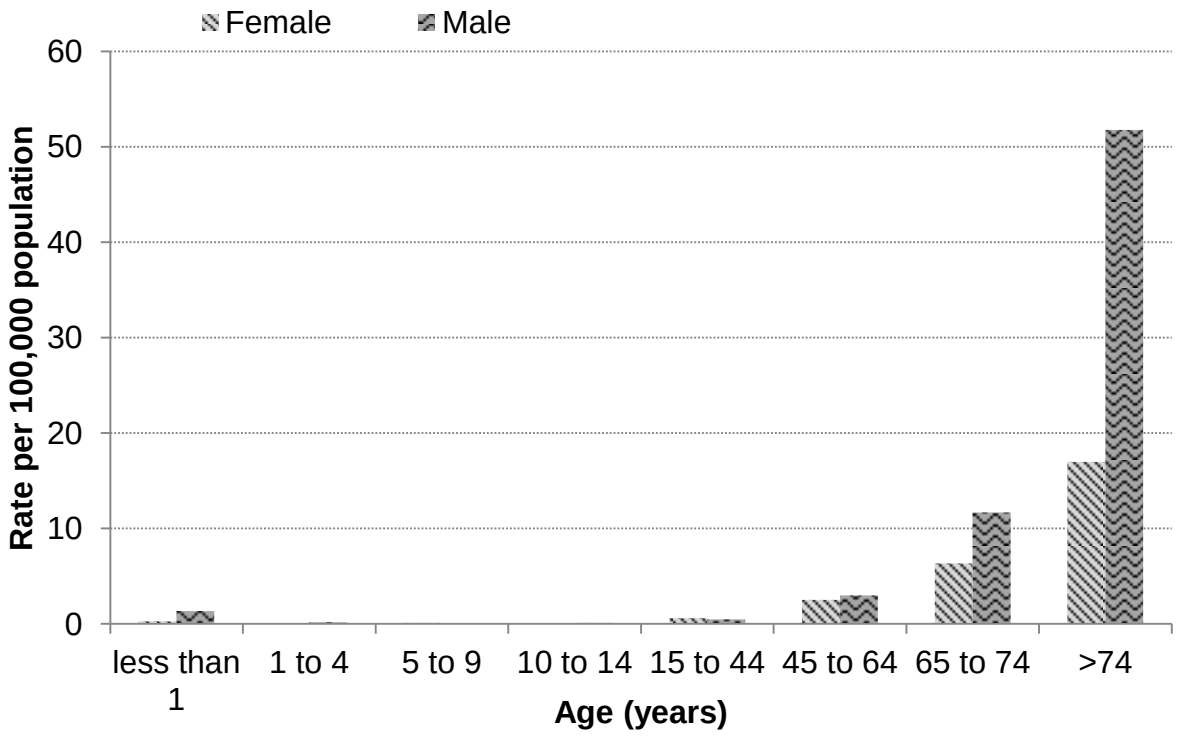
	2010		2011		2012		2013		2014	
Species	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
***Proteus* spp.**	2374	100%	2500	100%	2512	100%	2546	100%	2570	100%
P. mirabilis	2048	86%	2176	87%	2192	87%	2260	89%	2303	90%
P. vulgaris	91	4%	87	3%	88	4%	66	3%	80	3%
Proteus spp., other named	10	0%	4	0%	2	0%	4	0%	7	0%
Proteus spp., sp. not recorded	225	9%	233	9%	230	9%	216	8%	180	7%
Morganella morganii	435	100%	452	100%	412	100%	356	100%	402	100%
***Providencia* spp.**	102	100%	100	100%	80	100%	86	100%	94	100%
P. stuartii	62	61%	56	56%	37	46%	49	57%	41	44%
P. rettgeri	32	31%	27	27%	32	40%	30	35%	42	45%
Providencia spp., other named	3	3%	10	10%	10	13%	7	8%	6	6%
Providencia spp., sp. not recorded	5	5%	7	7%	1	1%	0	0%	5	5%

Age and sex distribution

The age distribution of *Proteus* spp. bacteraemia for 2014 is presented in figure 3a. The highest rates of *Proteus* spp. bacteraemia were observed in those aged 75 years or older (31.5/100,000 population), followed by those aged between 65 and 74 years (8.9/100,000 population; figure 3a). Very few cases were reported in children aged between 0-14 years.

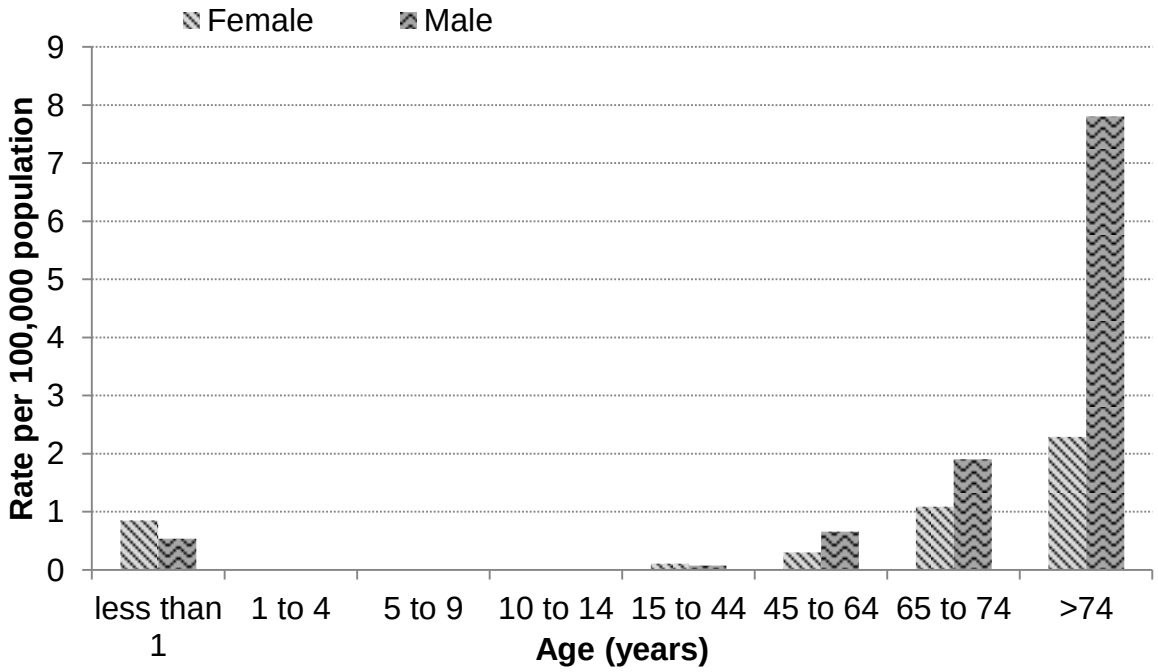
Males had higher rates of *Proteus* bacteraemia than females in all those aged 45 years or more, particularly those aged 75 years or older (51.7 vs. 17.0/100,000 population, respectively).

Figure 3a. Rate per 100,000 population *Proteus* spp. by age and sex (England, Wales and Northern Ireland); 2014



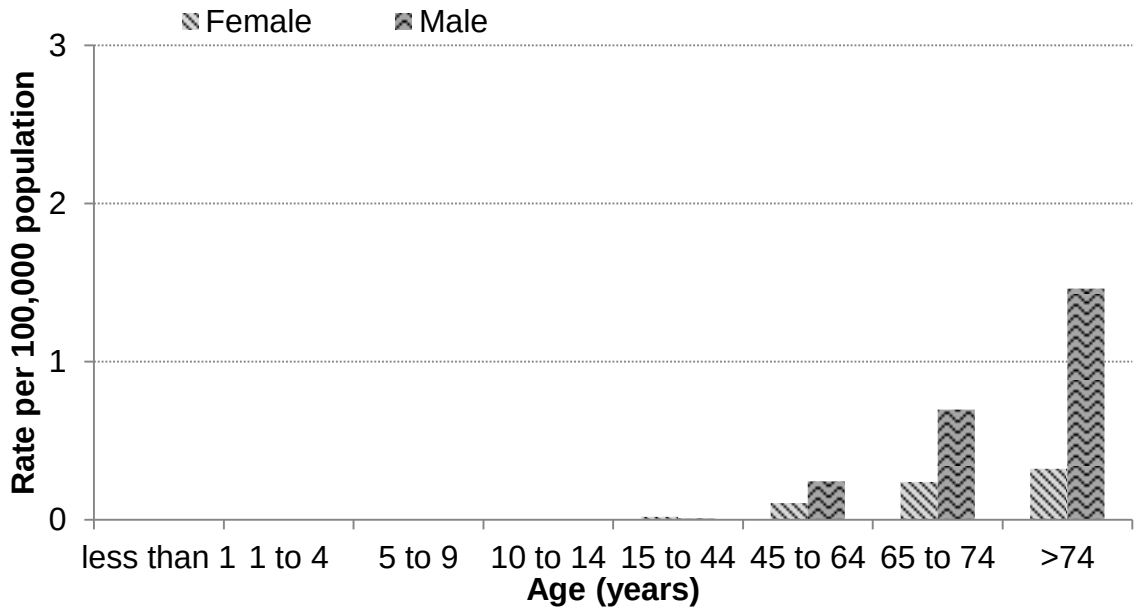
The age distribution of *M. morganii* bacteraemia for 2014 is presented in figure 3b. Those aged 75 years or older had the highest rates of *M. morganii* bacteraemia (4.6/100,000 population; figure 3b); the rate was much higher for males than females in this age-group (7.8 vs.2.3/100,000 population, respectively). Conversely, in children aged <1 year, there was a higher rate in females than males (0.9 vs. 0.5/100,000, respectively). All other age-groups had a rate of <2.0/100,000 population and there were no reported bacteraemias in children aged between 1 and 14 years.

Figure 3b. Population rate by age group for bacteraemia caused by *Morganella morganii* (England, Wales and Northern Ireland); 2014



The age distribution of *Providencia* spp. bacteraemia for 2014 is presented in figure 3c. Those aged 75 years or older had the highest rates of *Providencia* bacteraemia (0.8/100,000 population; figure 3b); the rate was higher for males than females (1.5 vs. 0.3/100,000 population, respectively) in this age-group, as well as the other age-groups. Very few *Providencia* bacteraemia were reported in children aged 14 years or less (<1/100,000 population).

Figure 3c. Population rate by age group for bacteraemia caused by *Providencia* spp. (England, Wales and Northern Ireland); 2014



Antimicrobial resistance

The proportion of *Proteus mirabilis and Proteus vulgaris* isolates with susceptibility test results reported ranged between 44-85% and 40-86% respectively for the key antimicrobials in 2014 (table 3a and 3b).

The percentage of resistant *P. mirabilis* bacteraemia isolates reported was ampicillin/amoxicillin (35%), cefotaxime (2%), ceftazidime (2%), ciprofloxacin (8%), ertapenem (1%), gentamicin (8%) and meropenem (0%). Unlike among *E. coli* and *Klebsiella* spp., cephalosporin resistance remains very unusual in *P. mirabilis* in the UK, although ESBLs or plasmid AmpC have disseminated in the species e.g. in Italy[3]. The percentage of resistant *P. vulgaris* bacteraemia isolates reported was ampicillin/amoxicillin (92%), cefotaxime (8%), ceftazidime (5%), ciprofloxacin (2%), ertapenem (3%), gentamicin (1%) and meropenem (0%).

Overall the proportion of *P. mirabilis* and *P. vulgaris* bacteraemia isolates reported as resistant (defined as reduced- or non-susceptible) to an antimicrobial in 2014 remained steady compared to the previous four years (table 3a). The exception to this was a reported 1% resistance (*P. mirabilis*) and 3% resistance (*P. vulgaris*) to ertapenem that was not seen in previous years; both *Proteus* species remained fully susceptible to meropenem.

For *M. morganii*, the proportion of bacteraemia isolates reported as resistant to an antimicrobial in 2014 also remained steady compared to the previous four years, with a slight decrease observed for the cephalosporins (table 3c). This decrease is consistent with the decrease in resistance reported in *Enterobacter* spp. between 2010-2014 (from 33% to 26% for cefotaxime and 32% to 28% for ceftazidime)[4]. This is notable because the principal mechanism of resistance (derepression of AmpC) is the same in both organisms. Isolates continue to be fully susceptible to meropenem, and in 2014 this was also the case for ertapenem.

Providencia stuartii remained fully susceptible to ertapenem and meropenem, and the other reported rates of resistance remained steady across the five year period (table 3d). 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 [5].

Table 3a. Antimicrobial susceptibility for *Proteus mirabilis* bacteraemia (England, Wales and Northern Ireland); 2010 to 2014

Antimicrobial	2010		2011		2012		2013		2014	
	No. tested	% resistant (%R)*	No. tested	%R*	No. tested	%R*	No. tested	%R*	No. tested	%R*
Ampicillin/Amoxicillin	1651	33%	1761	34%	1875	34%	1867	34%	1795	35%
Cefotaxime	981	1%	1052	2%	1146	2%	1186	3%	1105	2%
Ceftazidime	1354	1%	1482	2%	1486	2%	1476	3%	1441	2%
Ciprofloxacin	1642	6%	1740	8%	1826	9%	1868	8%	1778	8%
Ertapenem	222	0%	469	0%	659	0%	848	0%	1032	1%
Gentamicin	1756	7%	1861	7%	1968	10%	2011	9%	1965	8%
Meropenem	1165	0%	1339	0%	1477	0%	1609	0%	1577	0%
Total reports	**2048**		**2176**		**2192**		**2260**		**2303**	

Table 3b. Antimicrobial susceptibility for *Proteus vulgaris* bacteraemia (England, Wales and Northern Ireland); 2010 to 2014

Antimicrobial	2010		2011		2012		2013		2014	
	No. tested	% resistant (%R)*	No. tested	%R*	No. tested	%R*	No. tested	%R*	No. tested	%R*
Ampicillin/Amoxicillin	70	90%	73	88%	70	94%	57	95%	61	92%
Cefotaxime	47	4%	38	3%	46	9%	32	6%	36	8%
Ceftazidime	58	3%	66	5%	58	7%	40	8%	55	5%
Ciprofloxacin	70	0%	73	3%	65	0%	57	0%	61	2%
Ertapenem	7	0%	16	0%	24	0%	24	0%	32	3%
Gentamicin	72	1%	75	4%	75	7%	59	5%	69	1%
Meropenem	50	0%	56	2%	60	0%	48	0%	61	0%
Total reports	**91**		**87**		**88**		**66**		**80**	

Table 3c. Antimicrobial susceptibility for *Morganella morganii* bacteraemia (England, Wales and Northern Ireland); 2010 to 2014

Antimicrobial	2010		2011		2012		2013		2014	
	No. tested	% resistant (%R)*	No. tested	%R*	No. tested	%R*	No. tested	%R*	No. tested	%R*
Ampicillin/Amoxicillin	343	97%	351	97%	339	98%	279	96%	303	98%
Cefotaxime	215	20%	234	24%	225	20%	176	20%	181	16%
Ceftazidime	290	22%	293	24%	275	21%	241	19%	243	19%
Ciprofloxacin	355	12%	371	11%	339	12%	293	9%	317	12%
Ertapenem	53	2%	97	0%	120	0%	135	1%	177	0%
Gentamicin	379	8%	394	10%	365	9%	315	10%	343	8%
Meropenem	252	0%	295	0%	271	0%	250	0%	286	0%
Total reports	**435**		**452**		**412**		**356**		**402**	

Table 3d. Antimicrobial susceptibility for *Providencia stuartii* bacteraemia (England, Wales and Northern Ireland); 2010 to 2014

Antimicrobial	2010		2011		2012		2013		2014	
	No. tested	% resistant (%R)*	No. tested	%R*	No. tested	%R*	No. tested	%R*	No. tested	%R*
Ampicillin/Amoxicillin	48	85%	43	98%	28	93%	39	87%	28	100%
Cefotaxime	28	4%	25	8%	18	6%	31	6%	23	9%
Ceftazidime	41	5%	36	6%	28	7%	35	6%	26	12%
Ciprofloxacin	45	13%	48	8%	31	3%	42	12%	31	13%
Ertapenem	4	0%	14	0%	12	0%	18	0%	18	0%
Gentamicin	50	50%	45	51%	29	62%	45	56%	33	64%
Meropenem	35	0%	34	0%	24	0%	38	0%	25	0%
Total reports	**62**		**56**		**37**		**49**		**41**	

Tables 4a-d show the dual resistance of *P. mirabilis, P. vulgaris, M. morganii* and *P. stuartii* respectively to third-generation cephalosporin, gentamicin or ciprofloxacin. Dual resistance in these pathogens is rare, and was seen for only 0-3% of all bacteraemias due to *Proteus* spp., 3-7% due to *M. morganii* and 3-6% of *Providencia* spp. In other European countries, individual resistance of *M. morganii* to ciprofloxacin (9-20%), gentamicin (6-16%) and 3rd generation cephalosporins (3-30% depending on the individual antimicrobial) have been reported.[6] Isolates of *Providencia* spp. are inherently resistant to gentamicin, which is why there is a dual resistance of 3-6%.

No dual resistance, when including meropenem, was detected (results not shown).

Table 4a. Pair-Wise antimicrobial testing and resistance summary for *Proteus mirabilis* (England); 2014

Antimicrobial	3rd generation cephalosporin*		Ciprofloxacin		Gentamicin	
	No. tested	% Resistant (R)	No. tested	% R	No. tested	% R
3rd generation cephalosporin*						
Ciprofloxacin	1541	<1%				
Gentamicin	1562	<1%	1608	3%		

***Cefotaxime or Ceftriaxone or Ceftazidime or Cefpodoxime**

Table 4b. Pair-Wise antimicrobial testing and resistance summary for *Proteus vulgaris* (England); 2014

Antimicrobial	3rd generation cephalosporin*		Ciprofloxacin		Gentamicin	
	No. tested	% Resistant (R)	No. tested	% R	No. tested	% R
3rd generation cephalosporin*						
Ciprofloxacin	52	0%				
Gentamicin	53	0%	54	0%		

***Cefotaxime or Ceftriaxone or Ceftazidime or Cefpodoxime**

Table 4c. Pair-Wise antimicrobial testing and resistance summary for *Morganella morganii* (England); 2014

Antimicrobial	3rd generation cephalosporin*		Ciprofloxacin		Gentamicin	
	No. tested	% Resistant (R)	No. tested	% R	No. tested	% R
3rd generation cephalosporin*						
Ciprofloxacin	256	4%				
Gentamicin	260	3%	276	7%		

*Cefotaxime or Ceftriaxone or Ceftazidime or Cefpodoxime

Table 4d. Pair-Wise antimicrobial testing and resistance summary for *Providencia stuartii* (England); 2014

Antimicrobial	3rd generation cephalosporin*		Ciprofloxacin		Gentamicin	
	No. tested	% Resistant (R)	No. tested	% R	No. tested	% R
3rd generation cephalosporin*						
Ciprofloxacin	34	3%				
Gentamicin	33	3%	34	6%		

*Cefotaxime or Ceftriaxone or Ceftazidime or Cefpodoxime

For advice on treatment of antibiotic-resistant infections due to these opportunistic pathogens or for reference services including species identification and confirmation of susceptibility testing results, laboratories should contact the Medical Microbiologists at PHE's Bacteriology Reference Department at Colindale on colindalemedmicro@phe.gov.uk and PHE's Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit in London [7].

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. The support from colleagues within Public Health England, and the ARMHAI Reference Unit, in particular, is valued in the preparation of the report. 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. Mid-year population estimates for England, Wales and Northern Ireland. Available: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/index.html
2. PHE. Poly-microbial bacteraemia and fungaemia in England, Wales and Northern Ireland, 2014. Health Protection Report [serial online] 2015; 9(21): Infection Report
3. Luzzaro *et al.* Trends in production of extended-spectrum ß-lactamases among enterobacteria of medical interest: report of the seconf Italian nationwide survey. J Clin Microbiol 2006;44:1659-1664
4. Public Health England. Health Protection Report: *Enterobacter* spp*., Serratia* spp*.*, and *Citrobacter* spp. bacteraemia (EWNI): 2014. Vol 9, no 37. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/469137/hpr3715_ntrbctr.pdf
5. 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
6. Wenzel *et al.* In vitro susceptibilities of Gram-negative bacteria isolated from hospitalized patients in four European countries, Canada, and the United States in 2000-2001 to expanded-spectrum cephalosporins and comparator antimicrobials: implications for therapy. Antimicrob agents chemother 2003;47:3089-3098
7. Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI), https://www.gov.uk/amrhai-reference-unit-reference-and-diagnostic-services.