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Bacteraemia

Voluntary surveillance of bacteraemia caused by *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. in England: 2011-2015

These analyses are based on data relating to diagnoses of bloodstream infections caused by *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. between 2011 and 2015 in England, extracted on 20 September 2016 from Public Health England's (PHE) voluntary surveillance database Second Generation Surveillance System (SGSS). Data for Wales and Northern Ireland were extracted separately (DataStore on 20 July and CoSurv on 27 July 2016 resepctively) and are included in the geographical and species analyses only.

SGSS comprises a communicable disease module that includes antimicrobial susceptibility data (CDR; formerly CoSurv/LabBase2) and a separate comprehesive antimicrobial resistance module (AMR; formerly AmSurv). Compared to CDR's antimicrobial susceptibility data, the AMR module captures more comprehensive antibiogram data (involving all antibiotics tested); however, until the launch of SGSS in 2014 there was lower laboratory coverage in terms of reporting to the AMR module. Therefore, antimicrobial non-susceptibility trends cannot currently be undertaken using data from the AMR module but data for 2015 were extracted to assess multi-drug resistance rates.

The data presented here for earlier years 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 [1,2]. 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 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

- following a decrease in the rate of bacteraemia reports due to *Enterobacter* spp. from 2011 to 2014 inclusive, a slight increase was seen in England between 2014 and 2015 from 3.2 to 3.4 per 100,000 population respectively.
- following the decrease in the rate of bacteraemia reports due to *Serratia* spp. from 2011 to 2014, a slight increase was seen in England between 2014 and 2015 from 1.4 to 1.5/100,000 respectively.
- the rate for *Citrobacter* spp. was stable from 2011 to 2014 at 1.3/100,000 *per annum* but increased by 18% between from 1.3/100,000 in 2014 1.6/100,000 population in 2015.
- in England the highest proportion of bacteraemia reports identified species to level in 2015 was for *Serratia* spp. (96%) followed by *Enterobacter* spp. (92%) and *Citrobacter* spp. (92%)
- in Wales, the highest proportion was for *Serratia* spp. and for *Citrobacter* spp. (96% each) followed by *Enterobacter* spp. (76%) the latter representing a substantial increase since 2012
- in Northern Ireland, the highest proportion of reports identified to species level was for *Serratia* spp. (100%), then *Enterobacter* spp. (95%) and *Citrobacter* spp. (92%)
- in 2015, the rate of bacteraemia reports was generally higher in males than females and among older adults (≥65 years) and infants (<1 year) across all three genera.
- the highest bacteraemia rates for *Enterobacter* spp. and for *Serratia* spp. were observed in Wales at 4.1 and 3.3/100,000 population respectively in 2015.
- England had the highest rate of *Citrobacter* spp. bacteraemia at 1.6/100,000 population.
- within England, the rate of bacteraemia varied between PHE centres per genus; no single geographical area bore the highest burden across all genera.
- antimicrobial susceptibility trends from 2011 to 2015 were examined for five classes of antibiotics
- a small decrease in non-susceptibility to cefotaxime and to ceftazidime (third-generation cephalosporins) was seen over the five period among *Enterobacter* spp. blood culture isolates reaching 27% and 25% respectively in 2015.
- a small decrease in both cephalosporins was also observed for *Serratia* spp. isolates, reaching 13% and 14% respectively in 2015.
- a small decrease in non-susceptibility to the fluoroquinolone ciprofloxacin was also seen for *Serratia* spp. over the five year period, reaching 7% of bacteraemia isolates in 2015.

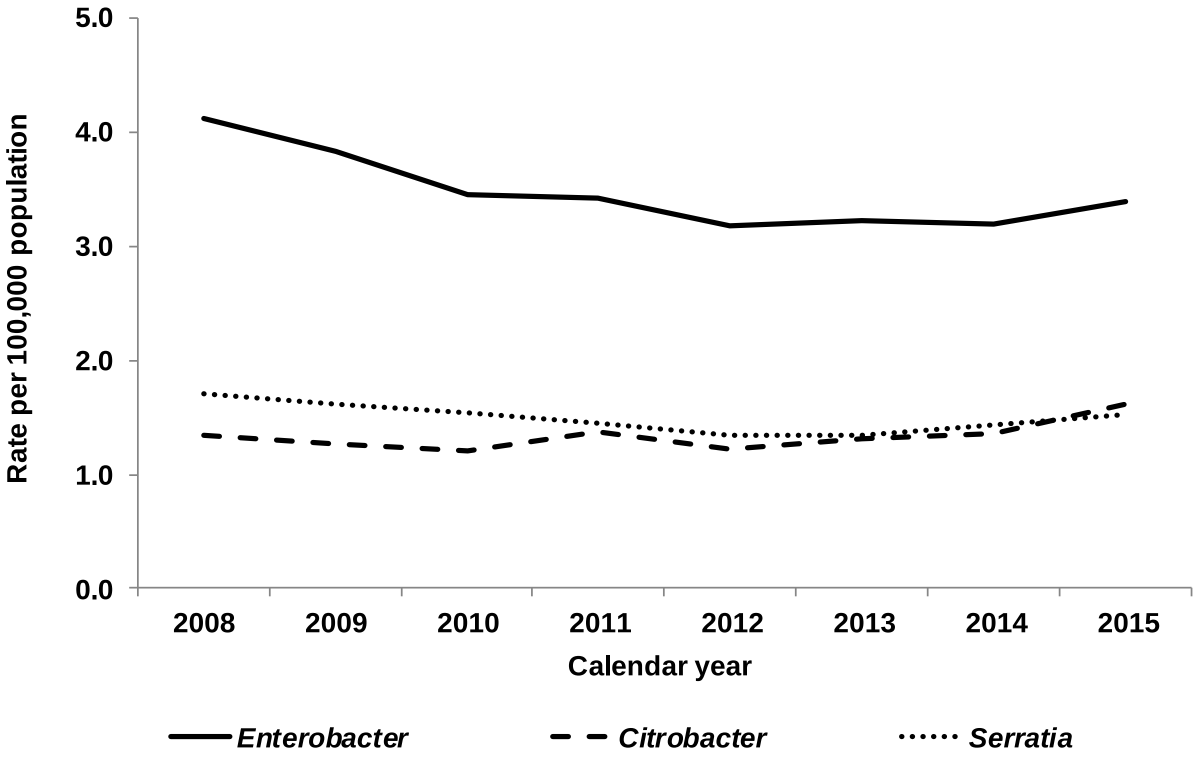
- non-susceptibility to tobramycin (aminoglycoside) increased markedly among *Serratia* spp. isolates from 10% in 2011 to 22% in 2015 and is of concern whereas non-susceptibility to this agent was lower and stable for the other two genera over the same period.
- an increase in non-susceptibility to piperacillin/tazobactam was seen for *Enterobacter* spp. and *Citrobacter* spp., reported in 20% and 10% of isolates in 2015 respectively, possibly reflecting the recent adoption of EUCAST breakpoints.
- non-susceptibility to the carbapenem meropenem remained uncommon (≤1%) across all general over the five year period.
- non-susceptibility to ertapenem (also a carbapenem) was highest only for *Enterobacter* spp. compared to the other two genera, although a small decrease in non-susceptibility to this agent occurred among the Enterobacter spp. isolates reaching 8% in 2015.
- the most common dual non-susceptibility was to ciprofloxacin and third-generation cephalosporins among *Enterobacter* bacteraemia isolates (7.0%).
- the least frequent dual non-susceptibility was to ciprofloxacin and gentamicin (0.4%) among *Serratia* isolates tested.

Trends: England

Figure 1 is based on data for England only. This shows the trend in the rates of bacteraemia laboratory reports by genus between 2008 and 2015 per 100,000 resident population. The rate of bacteraemia in England due to *Enterobacter* spp. decreased by 17% from 4.1/100,000 in 2008 to 3.4/100,000 in 2015. The *Serratia* spp. bacteraemia rate also decreased over this period; by 11% from 1.7 in 2008 to 1.5 per 100,000 population in 2015. Although the *Citrobacter* spp. bacteraemia rate was stable at around 1.3/100,000 population *per annum* between 2011 and 2014, it increased to 1.6/100,000 population in 2015.

Between 2014 and 2015, the bacteraemia rate for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. increased by 6%, 7% and 18% respectively. This was equivalent to an increase in the rate from 3.2 to 3.4/100,000 population for *Enterobacter* spp.; from 1.4 to 1.5/100,000 population for *Serratia* spp. and from 1.4 to 1.6/100,000 population for *Citrobacter* spp.

Figure 1. *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia rate per 100,000 population, England: 2008- 2015



Source: PHE, 2016

Geographical distribution: England, Wales and Northern Ireland

The geographical analyses presented here are not corrected for variation in reporting between geographical areas.

In 2015 the overall rate of laboratory reports of *Enterobacter* spp. bacteraemia for England, Wales and Northern Ireland (E,W,NI) was 3.4 per 100,000 population with Wales observing the highest rate (4.1) followed by England (3.4) then Northern Ireland (3.2) (Figure 2, Table 1a).

The *Serratia* spp. bacteraemia rate for E,W,NI in 2015 was 1.6/100,000 population, with the highest rate observed in Wales (3.3), followed by Northern Ireland (1.9) then England (1.5). The *Citrobacter* spp. bacteraemia rate for E,W,NI was 1.6/100,000 population with highest rates in England (1.6) then Northern Ireland (1.5) then Wales (1.0).

Within England, there was variation in the rates between the 15 local PHE centres (PHECs) but no consistent pattern could be discerned across all three genera.

The highest rate of *Enterobacter* spp. bacteraemia in 2015 was in the East Midlands (15.8/100,000), and the lowest in Yorkshire and Humber (2.5) (figure 1; table 1). For *Serratia* spp. bacteremia, the highest rate in 2015 was in Devon, Cornwall and Somerset and in North East PHECs (2.1 each) (figure 1; table 1b). The lowest rate in 2015 for *Serratia* spp. bacteraemia was in South Midlands and Hertfordshire and in Avon, Gloucester and Wilshire PHECs (1.0 each). For *Citrobacter* spp. (figure 1, table 1c) the highest rate was in Devon Cornwall and Somerset and in Kent, Surrey and Sussex (each 1.9). The lowest rate of *Citrobacter* spp. bacteraemia was in Greater Manchester (0.9/100,000 population).

No consistent pattern in trends was observed at country level except for Wales where a generally downward trend was observed for *Citrobacter* spp. bacteraemia. Although no consistent trend was observed for any PHEC over the five-year period, some emerging patterns were seen. For *Enterobacter* spp., Cheshire and Merseyside and Greater Manchester PHECs showed decreasing trends (from 3.6 in 2011 to 3.0 in 2015 and from 4.7 in 2011 to 3.2 in 2015 respectively) (table 1a). For *Citrobacter* spp., Devon, Cornwall and Somerset and Kent, Surrey and Sussex PHECs showed increasing trends (from 1.2 in 2011 to 1.9 in 2015 and from 1.3 in 2011 to 1.9 in 2015 respectively) (table 1c).

Whilst geographical variation may be explained by differences in completeness of reporting between PHECs, local outbreaks, differences in case-mix and variation in the distribution of specialist care units may also influence these rates.

Table 1a. Rate of *Enterobacter* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2011 to 2015

		Rate per 100,000 resident population				
Region	**PHE Centre**	**2011**	**2012**	**2013**	**2014**	**2015**
North of England	Cheshire and Merseyside	3.6	3.1	3.0	3.2	3.0
	Cumbria and Lancashire	2.8	3.0	4.2	3.2	3.2
	Greater Manchester	4.7	3.5	3.7	3.7	3.2
	North East	3.0	3.1	2.9	3.0	3.7
	Yorkshire and Humber	3.3	2.7	2.6	1.9	2.5
Midlands and East of England	Anglia and Essex	3.3	3.3	3.3	3.4	3.6
	East Midlands	4.2	3.1	4.0	3.9	4.7
	South Midlands and Hertfordshire	2.5	2.5	2.4	3.4	2.9
	West Midlands	2.9	3.6	3.3	3.4	3.3
London	London	3.9	3.8	3.8	3.5	3.8
South of England	Avon Gloucestershire and Wiltshire	2.6	2.6	2.4	3.1	3.0
	Devon Cornwall and Somerset	4.0	3.3	3.2	3.6	3.4
	Kent Surrey and Sussex	3.5	3.0	3.3	3.5	3.6
	Thames Valley	2.7	2.6	2.3	2.4	3.0
	Wessex	3.4	3.1	2.8	2.6	3.6
England*		**3.4**	**3.2**	**3.2**	**3.2**	**3.4**
Northern Ireland†		**3.5**	**2.7**	**4.2**	**4.2**	**3.2**
Wales‡		**4.7**	**4.5**	**4.8**	**4.4**	**4.1**
England, Wales and Northern Ireland		**3.5**	**3.2**	**3.3**	**3.3**	**3.4**

* Extracted on 20 September 2016; † extracted on 27 July 2016; ‡ extracted on 20 July 2016.

Source: PHE, 2016

Figure 2a. Geographical distribution of the rate of *Enterobacter* spp., bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2015

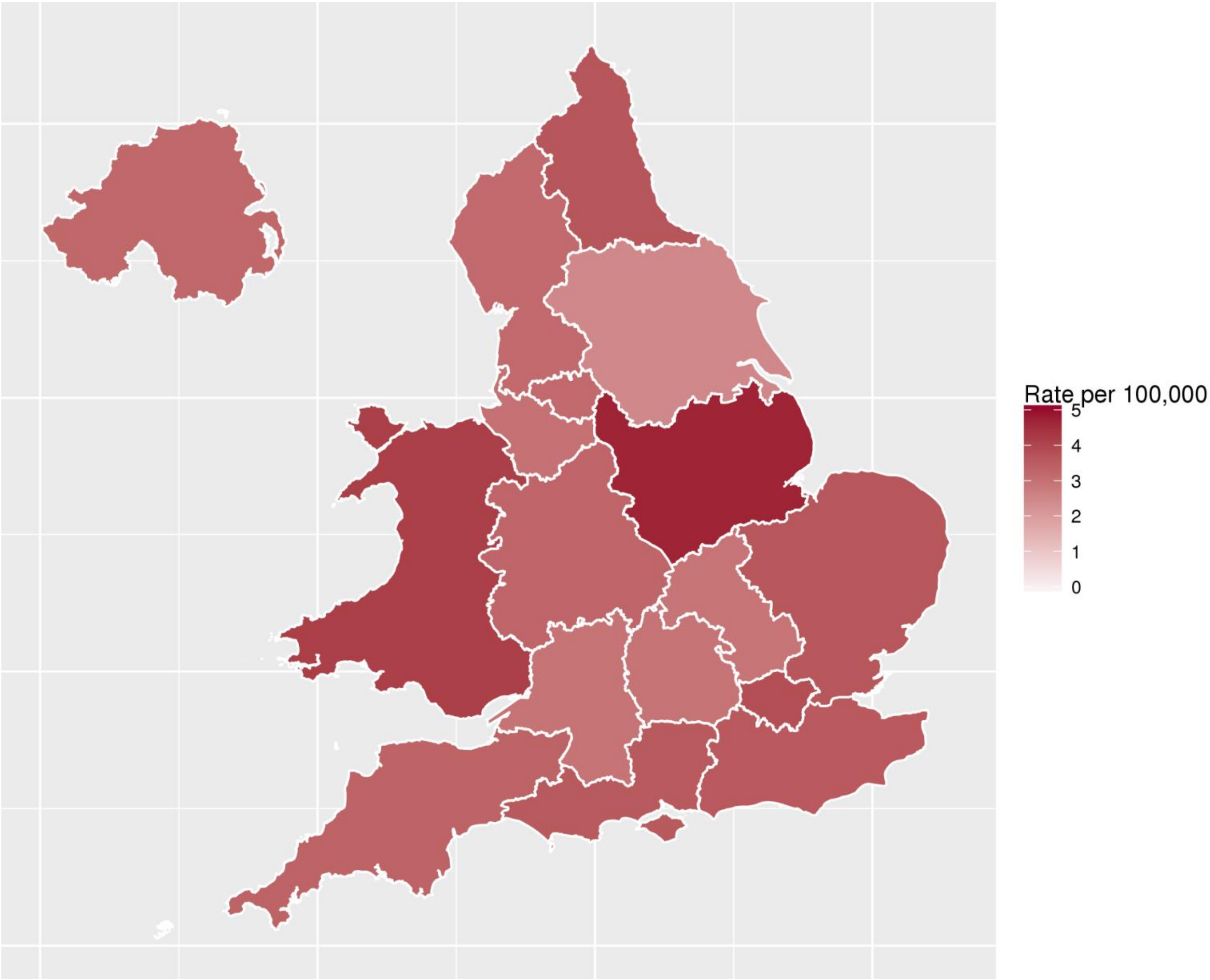


Table 1b. Rate of *Serratia* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2011 to 2015

		Rate per 100,000 resident population				
Region	**PHE Centre**	**2011**	**2012**	**2013**	**2014**	**2015**
North of England	Cheshire and Merseyside	2.0	1.7	2.1	2.0	1.6
	Cumbria and Lancashire	1.6	1.6	1.6	1.8	1.7
	Greater Manchester	1.5	1.9	1.6	1.5	1.8
	North East	2.0	1.6	2.1	1.8	2.1
	Yorkshire and Humber	1.0	1.0	0.9	1.0	1.1
Midlands and East of England	Anglia and Essex	1.5	1.6	1.1	1.8	1.5
	East Midlands	1.8	1.3	1.4	1.2	1.5
	South Midlands and Hertfordshire	1.1	0.6	0.8	1.2	1.0
	West Midlands	1.5	1.0	1.2	1.2	1.3
London	London	1.4	1.5	1.4	1.7	1.8
South of England	Avon Gloucestershire and Wiltshire	0.9	1.2	0.7	1.3	1.0
	Devon Cornwall and Somerset	1.9	2.3	2.1	1.7	2.1
	Kent Surrey and Sussex	1.3	1.1	1.6	1.2	1.9
	Thames Valley	1.2	0.7	0.4	0.9	1.1
	Wessex	1.4	1.4	1.4	1.1	1.3
England*		**1.4**	**1.3**	**1.3**	**1.4**	**1.5**
Northern Ireland†		**2.4**	**1.3**	**2.0**	**1.4**	**1.9**
Wales‡		**3.3**	**3.4**	**3.1**	**2.5**	**3.3**
England, Wales and Northern Ireland		**1.6**	**1.4**	**1.5**	**1.5**	**1.6**

* Extracted on 20 September 2016; † extracted on 27 July 2016; ‡ extracted on 20 July 2016.

Source: PHE, 2016

Figure 2b. Geographical distribution of the rate of *Serratia* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2015

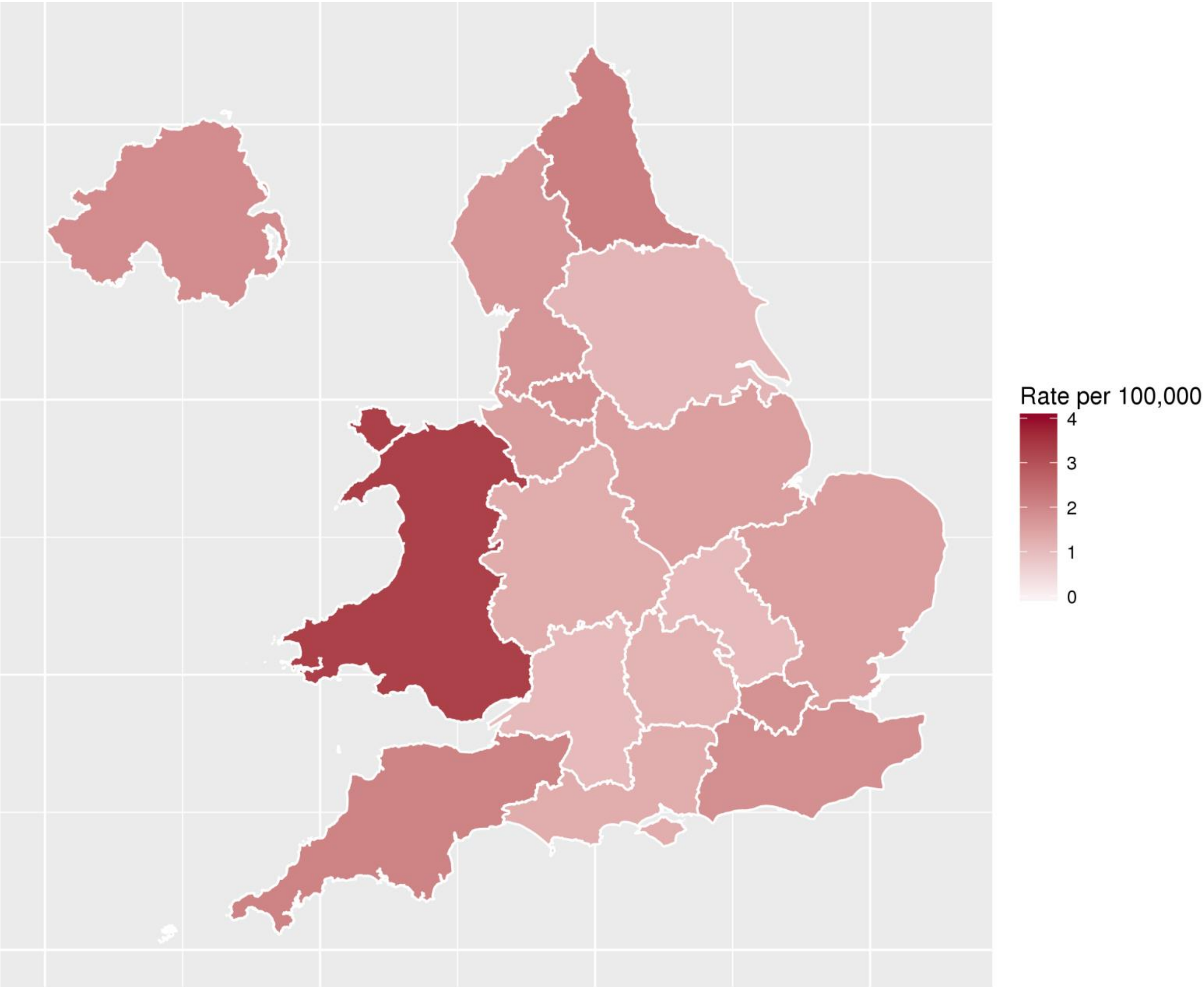


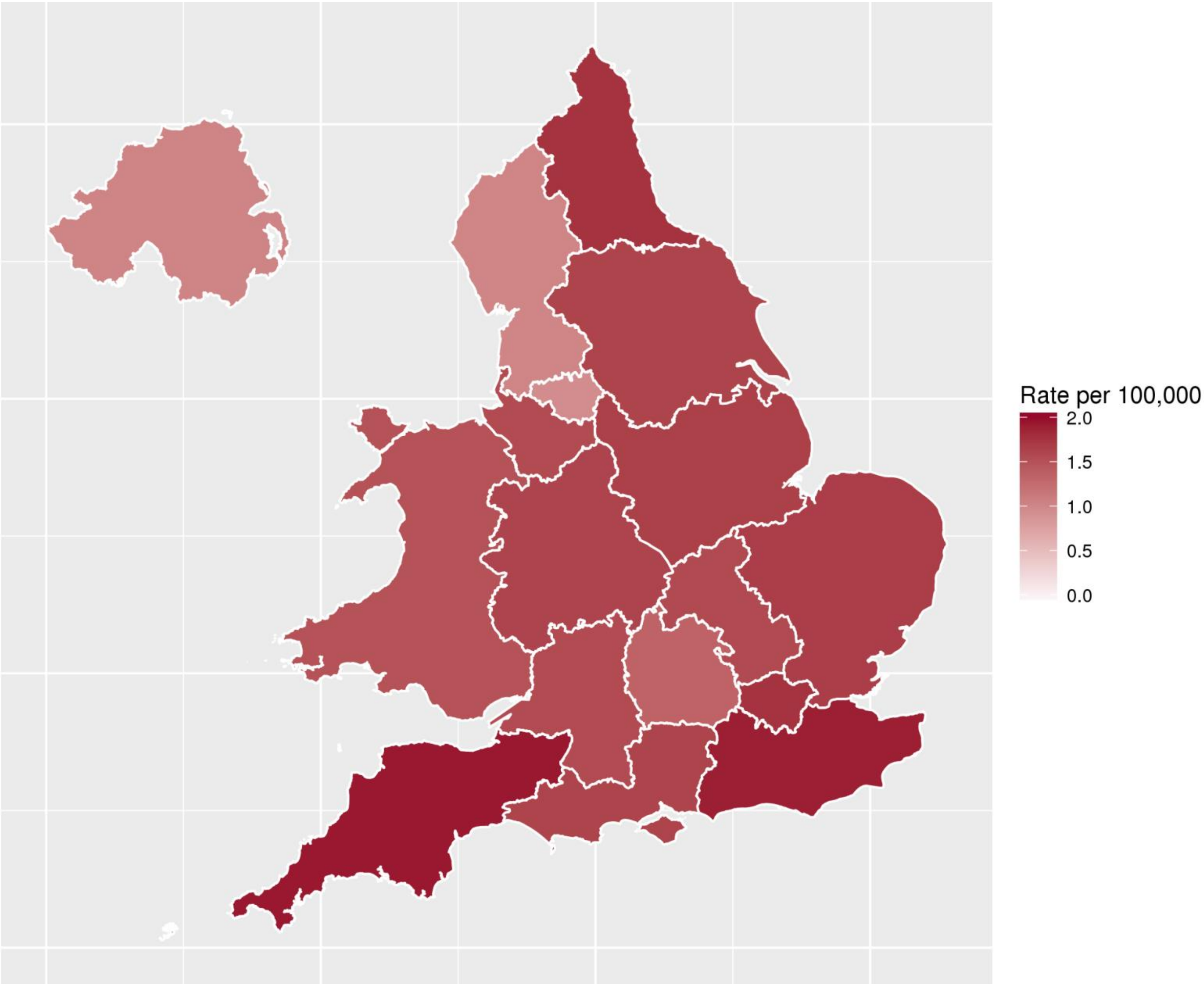
Table 1c. Rate of *Citrobacter* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2011 to 2015

Region		Rate per 100,000 resident population				
		2011	2012	2013	2014	2015
North of England	Cheshire and Merseyside	1.7	1.5	1.4	0.9	1.6
	Cumbria and Lancashire	0.9	1.0	1.2	1.8	1.0
	Greater Manchester	1.0	1.1	0.8	1.0	0.9
	North East	1.2	0.7	1.0	1.1	1.8
	Yorkshire and Humber	1.3	1.0	1.0	0.8	1.6
Midlands and East of England	Anglia and Essex	1.6	1.3	1.7	1.3	1.7
	East Midlands	1.8	1.3	1.4	1.3	1.6
	South Midlands and Hertfordshire	1.2	1.0	1.2	1.7	1.6
	West Midlands	1.5	1.3	1.7	1.7	1.6
London	London	1.6	1.6	1.6	1.7	1.8
South of England	Avon Gloucestershire and Wiltshire	0.9	1.2	0.9	1.4	1.6
	Devon Cornwall and Somerset	1.2	1.3	1.3	1.3	1.9
	Kent Surrey and Sussex	1.3	1.3	1.4	1.6	1.9
	Thames Valley	0.8	0.6	1.1	0.8	1.3
	Wessex	1.4	1.1	1.2	1.3	1.6
England*		**1.4**	**1.2**	**1.3**	**1.4**	**1.6**
Northern Ireland†		**1.0**	**0.7**	**0.7**	**0.8**	**1.0**
Wales‡		**1.7**	**1.4**	**1.5**	**1.4**	**1.5**
England, Wales and Northern Ireland		**1.4**	**1.2**	**1.3**	**1.3**	**1.6**

* Extracted on 20 September 2016; † extracted on 27 July 2016; ‡ extracted on 20 July 2016.

Source: PHE, 2016

Figure 2c. Geographical distribution of the rate of *Citrobacter* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2015



Species distribution: England, Wales and Northern Ireland

In England, the total number of *Enterobacter* spp. bacteraemia reports declined from 1,816 to 1,704 episodes between 2011 and 2012 and remained stable at 1,700 *per annum (*table 2a*).* However, between 2014 and 2015, the number of reports increased by 7% (from 1,737 to 1,864 episodes). In Wales the total number of *Enterobacter* spp. bacteraemia reports decreased by 11% between 2011 and 2015; the decrease between 2014 and 2015 involved a very small number of isolates (n=8). In Northern Ireland, the number of reports were much smaller by comparison with a small inter-year variation (range: 50-78 reports).

In England, the majority of *Enterobacter* spp. from blood specimens in 2015 were identified to species level (94%), a slight improvement compared to previous years (table 2a). Compared to England, species identification for *Enterobacter* spp. blood specimens in Wales was much lower at 76% but slightly higher for Northern Ireland at 95%.

The total number of *Serratia* spp. bacteraemia reports in England increased by 8% between 2011 (n=769) and 2015 (n=837); between 2014 and 2015, the number of reports increased by 7% (table 2b*).* In Wales the total number of *Serratia* spp. bacteraemia reports were much smaller but remained stable at around 100 *per annum*, with the exception of 2014 involving 76 episodes. In Northern Ireland the number of reports were also much smaller by comparison with a small inter-year variation (range: 23-43 reports).

For *Serratia* spp. blood specimens, the majority of reports in 2015 were identified to species level (96%) in England, similar to previous years (table 2b). In Wales, species identification was also 96% but was 100% for Northern Ireland.

It should be noted that in Wales no species-level data were available in 2011 for any of the three genera.

The total number of *Citrobacter* spp. bacteraemia reports in England increased by 17% between 2011 (n=732) and 2015 (n=884); between 2014 and 2015 in particular, the number of reports increased by 16% (table 2c*).* In Wales, the total number of *Cirobacter* spp. bacteraemia reports were much smaller but remained stable at around 50 *per annum*. In Northern Ireland, the number of reports were also much smaller with a small inter-year variation (range: 12-19 reports).

Of the *Citrobacter* spp. blood specimens reported in 2015, 93% were reported to species level in England, a slight increase over previous years (table 2c). In Wales and Northern Ireland, species identification for *Citrobacter* spp. was lower than that for England at 89% and 84%, respectively, and represented a marked decrease since 2013 for each of these two countries.

Among *Enterobacter* spp. isolates in England, the dominant species remained *E. cloacae* accounting for 70% of reports, followed by *E. aerogenes* (18%) (table 2a). *E. cloacae* is part of the *Enterobacter cloacae* complex which includes other related species with the following being reported by England, Wales and Northern Ireland: *E. absuriae*, *E. cloacae*, *E. ludwigii* (England only) and *E. kobaei*. However the distinction between members of the complex is not always reliable. *The E. cloacae* complex was also predominant in Wales and Northern Ireland.

Among *Serratia* spp. isolates in England the most common species was *S. marcescens* accounting for 85% of reports, followed by *S. liquefaciens* (8%) (table 2b). *S. marcescens* was also the predominant species in Wales and Northern Ireland.

Among *Citrobacter* spp. isolates in England, *C. diversus* accounted for 50% of reports, followed by *C. freundii* (35%). Unlike England, *C. freundii* was the most common species reported in both Wales and Northern Ireland. However the smaller number of isolates and the lower level of species identification in these two countries introduce some uncertainty in these data.

Of note, the trends at species level showed that in England, the *E. cloacae* complex decreased albeit modestly from 75% in 2011 to 71% of total *Enterobacter* spp. bacteraemia reports in 2015. In Wales the decrease in the *E. cloacae* complex was more marked (from 82% in 2012 to 55% in 2015), though based on smaller sample sizes. Also of note, *S. marcescens* increased from 78% in 2011 to 85% in 2015 in England. The trends for Northern Ireland were based on much small sample sizes across all genera so trends could not be reliably evaluated.

The expanded list of species being reported for *Enterobacter*/*Serratia*/*Citrobacter* bacteraemia reflects the increased use of automated diagnostic technology (MALDI-TOF) which enables laboratories to distinguish more species. Based on data from SGSS, new species reported in 2015 in England were *E. ludwigii* (n=1) (not shown), *C. sedlakii* (n=1) and *C. werkmanii* (n=4).

Table 2a. Reports of bacteraemia due to *Enterobacter spp.*, (England, Wales and Northern Ireland): 2011 to 2015

	2011		2012		2013		2014		2015	
England	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
E. aerogenes	295	16.2	322	18.9	303	17.4	303	17.4	339	18.2
E. amnigenus	11	0.6	5	0.3	7	0.4	4	0.2	11	0.6
E. cancerogenus	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0
E. gergoviae	5	0.3	2	0.1	6	0.3	4	0.2	5	0.3
E. intermedius	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0
E. cloacae complex*	1,358	74.8	1,218	71.5	1,214	69.9	1,241	71.4	1,329	71.3
Enterobacter spp., other named	49	2.7	44	2.6	70	4.0	68	3.9	62	3.3
Enterobacter spp., sp. not recorded	98	5.4	112	6.6	137	7.9	115	6.6	118	6.3
***Enterobacter* spp.**	**1,816**	100	**1,704**	100	**1,737**	100	**1,737**	100	**1,864**	100
Wales										
E. aerogenes	0	0.0	22	15.8	36	24.3	20	14.7	23	18.0
E. amnigenus	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
E. cancerogenus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
E. gergoviae	0	0.0	0	0.0	1	0.7	0	0.0	1	0.8
E. intermedius	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
E. cloacae complex*	0	0.0	114	82.0	100	67.6	86	63.2	70	54.7
Enterobacter spp., other named	0	0.0	1	0.7	1	0.7	0	0.0	3	2.3
Enterobacter spp., sp. not recorded	144	1.0	1	0.7	10	6.8	30	22.1	31	24.2
***Enterobacter* spp.**	**144**	1.0	**139**	100.0	**148**	100.0	**136**	100.0	**128**	100.0
Northern Ireland										
E. aerogenes	12	19.0	8	16.0	15	19.5	6	7.7	2	3.3
E. amnigenus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
E. cancerogenus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
E. gergoviae	1	1.6	0	0.0	0	0.0	0	0.0	1	1.7
E. intermedius	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
E. cloacae complex*	50	79.4	40	80.0	58	75.3	71	91.0	54	90.0
Enterobacter spp., other named	0	0.0	0	0.0	3	3.9	1	1.3	0	0.0
Enterobacter spp., sp. not recorded	0	0.0	2	4.0	1	1.3	0	0.0	3	5.0
***Enterobacter* spp.**	**63**	100.0	**50**	100.0	**77**	100.0	**78**	100.0	**60**	100.0

*Species of the *Enterobacter cloacae* complex reported: *E. absuriae*, *E. cloacae* (predominant), *E. ludwigii* (England only) and *E. kobaei*

Source: PHE, 2016

Table 2b: Reports of bacteraemia due to *Serratia spp.*, (England, Wales and Northern Ireland): 2011 to 2015

	2011		2012		2013		2014		2015	
England	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
S. ficaria	1	0.1	2	0.3	1	0.1	0	0.0	0	0.0
S. fonticola	6	0.8	8	1.1	8	1.1	3	0.4	2	0.2
S. liquefaciens	95	12.4	73	10.2	56	7.8	66	8.5	68	8.1
S. marcescens	602	78.3	585	81.7	615	85.2	656	84.5	714	85.3
S. odorifera	6	0.8	3	0.4	6	0.8	2	0.3	7	0.8
S. plymuthica	1	0.1	1	0.1	0	0.0	0	0.0	2	0.2
S. proteamaculas	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
S. rubidaea	1	0.1	2	0.3	0	0.0	1	0.1	5	0.6
Serratia spp., other named	9	1.2	11	1.5	8	1.1	19	2.4	2	0.2
Serratia spp., sp. not recorded	48	6.2	31	4.3	28	3.9	29	3.7	36	4.3
***Serratia* spp.**	**769**	100	**716**	100	**722**	100	**776**	100	**837**	100
Wales										
S. ficaria	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
S. fonticola	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. liquefaciens	0	0.0	7	6.6	6	6.3	2	2.6	10	9.8
S. marcescens	0	0.0	95	89.6	82	86.3	70	92.1	88	86.3
S. odrifera	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. plymunthica	0	0.0	3	2.8	1	1.1	0	0.0	0	0.0
S. proteamaculas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. rubidaea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Serratia spp., other named	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Serratia spp., sp. not recorded	101	100.0	1	0.9	6	6.3	3	3.9	4	3.9
***Serratia* spp.**	**101**	100.0	**106**	100.0	**95**	100.0	**76**	100.0	**102**	100.0
Northern Ireland										
S. ficaria	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. fonticola	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. liquefaciens	4	9.3	4	17.4	10	0.3	6	24.0	7	20.0
S. marcescens	36	83.7	19	82.6	27	0.7	19	76.0	28	80.0
S. odrifera	1	2.3	0	0.0	0	0.0	0	0.0	0	0.0
S. plymunthica	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. proteamaculas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
S. rubidaea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Serratia spp., other named	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Serratia spp., sp. not recorded	2	4.7	0	0.0	0	0.0	0	0.0	0	0.0
***Serratia* spp.**	**43**	100.0	**23**	100.0	**37**	1.0	**25**	100.0	**35**	100.0

Source: PHE, 2016

Table 2c: Reports of bacteraemia due to *Citrobacter spp.*, (England, Wales and Northern Ireland): 2011 to 2015

	2011		2012		2013		2014		2015	
England	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
C. amalonaticus	3	0.4	5	0.8	3	0.4	4	0.5	4	0.5
C. braakii	0	0.0	0	0.0	0	0.0	3	0.4	13	1.5
C. diversus	366	50.0	319	48.9	373	52.9	346	46.7	444	50.2
C. farmeri	0	0.0	0	0.0	0	0.0	2	0.3	4	0.5
C. freundii	250	34.2	240	36.8	213	30.2	269	36.3	306	34.6
C. sedlakii	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
C. werkmanii	0	0.0	0	0.0	0	0.0	0	0.0	4	0.5
C. youngae	0	0.0	0	0.0	0	0.0	1	0.1	2	0.2
Citrobacter spp., other named	60	8.2	44	6.7	58	8.2	53	7.2	50	5.7
Citrobacter spp., sp. not recorded	53	7.2	45	6.9	58	8.2	63	8.5	56	6.3
***Citrobacter* spp.**	**732**	100.0	**653**	100.0	**705**	100.0	**741**	100.0	**884**	100.0
Wales										
C. amalonaticus	0	0.0	0	0.0	0	0.0	0	0.0	1	2.2
C. diversus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
C. freundii	0	0.0	19	44.2	28	59.6	23	52.3	17	37.0
C. farmeri	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
C. youngae	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Citrobacter spp., other named	0	0.0	20	46.5	17	36.2	16	36.4	23	50.0
Citrobacter spp., sp. not recorded	51	100.0	3	7.0	2	4.3	5	11.4	5	10.9
***Citrobacter* spp.**	**51**	100.0	**43**	100.0	**47**	100.0	**44**	100.0	**46**	100.0
Northern Ireland										
C. amalonaticus	0	0.0	2	15.4	0	0.0	0	0.0	0	0.0
C. diversus	2	11.1	2	15.4	8	66.7	5	35.7	6	31.6
C. freundii	14	77.8	8	61.5	3	25.0	8	57.1	9	47.4
C. farmeri	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
C. youngae	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Citrobacter spp., other named	1	5.6	0	0.0	0	0.0	0	0.0	1	5.3
Citrobacter spp., sp. not recorded	1	5.6	1	7.7	1	8.3	1	7.1	3	15.8
***Citrobacter* spp.**	**18**	100.0	**13**	100.0	**12**	100.0	**14**	100.0	**19**	100.0

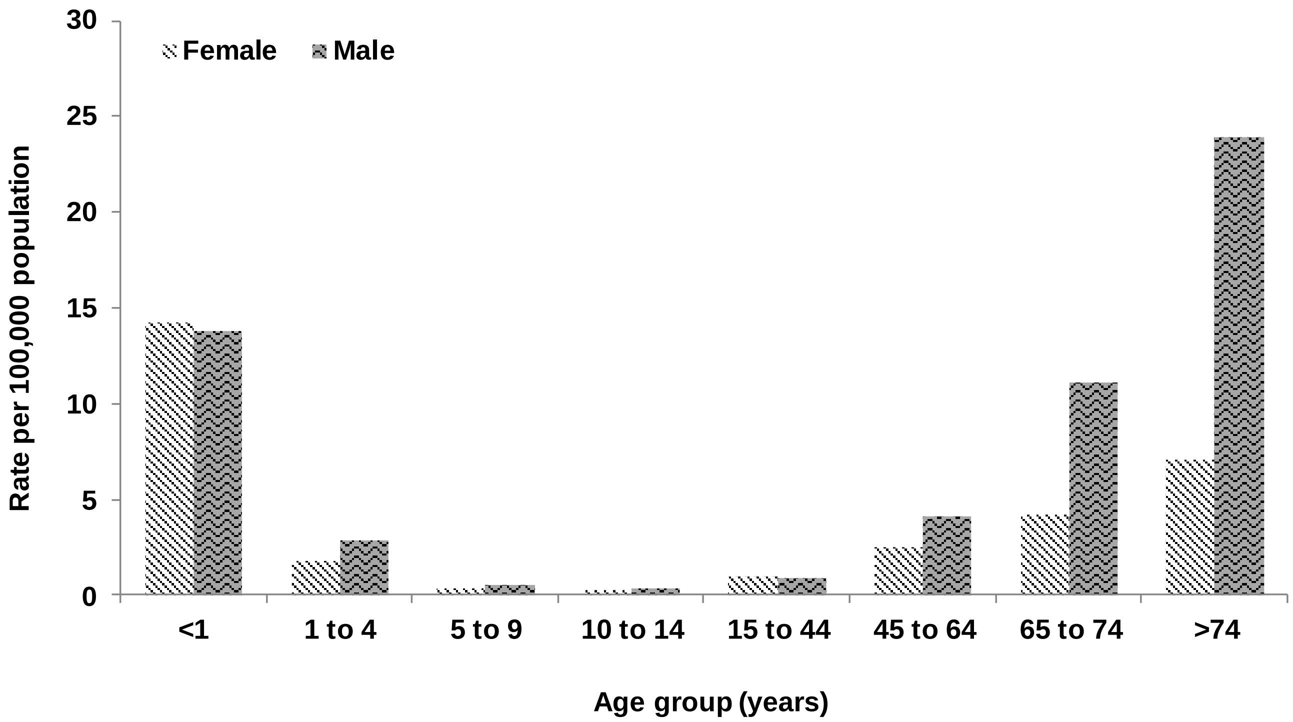
Source: PHE, 2016

Age and sex distribution: England

Figures 3a-c show the age and sex-specific rates of bacteraemia reports in England in 2015 per 100,000 resident population by genus. The rates were highest in adults over 65 years and in infants (under one year) across all genera. For *Citrobacter* spp., there were no data for the age group 10-14 years in 2015.

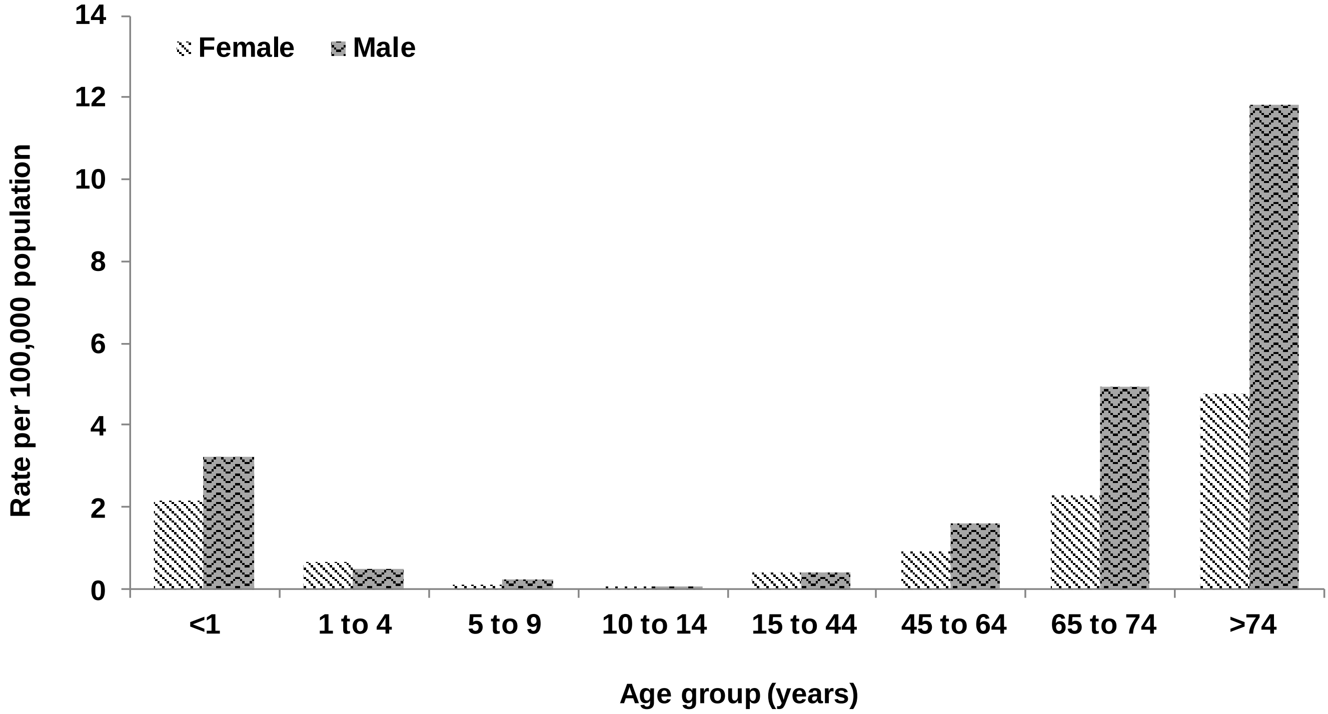
For *Enterobacter* spp. bacteraemia, the incidence rate ratio (IRR) comparing males to females was highest among patients aged ≥75 years (IRR=3.4), indicating that the rate for males was more than three times higher than for females. For *Serratia* spp. and *Citrobacter* spp., the IRR was also highest among patients aged ≥75 years (2.5 and 6.1 respectively).

Figure 3a. Age and sex-specific rates of *Enterobacter* spp. bacteraemia reports per 100,000 population (England): 2015



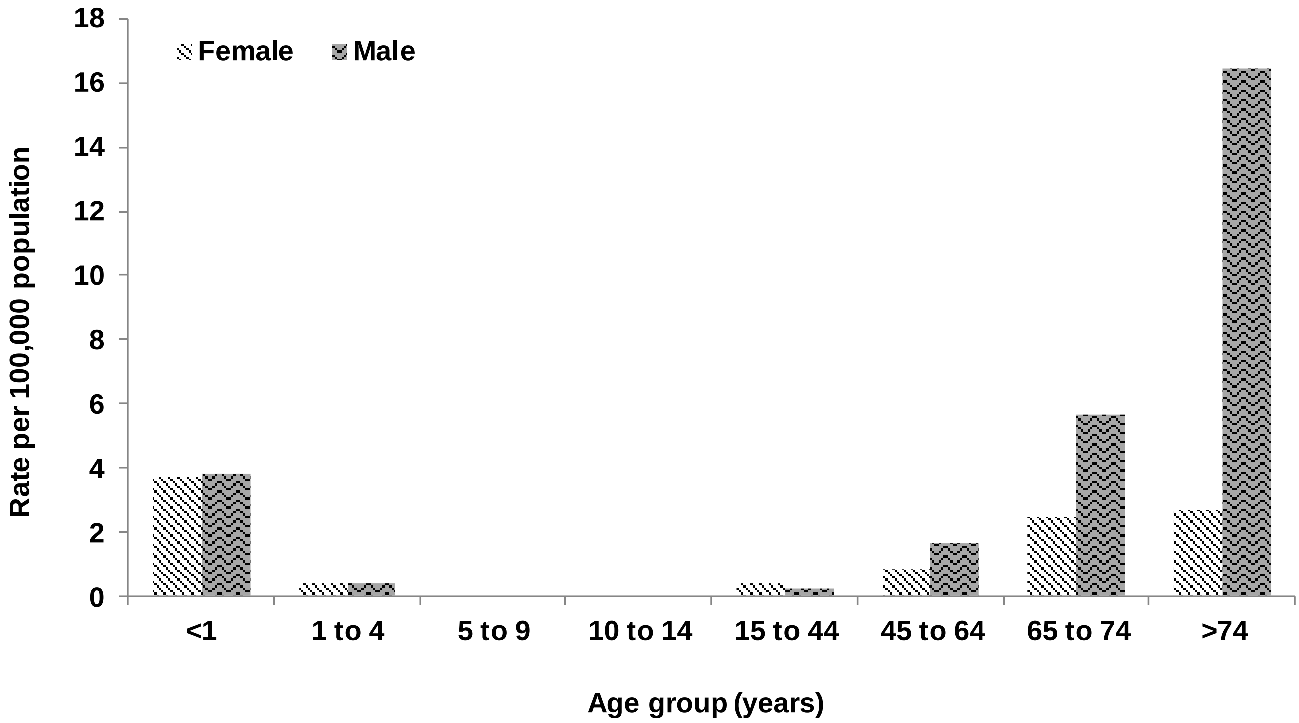
Source: PHE, 2016

Figure 3b. Age and sex-specific rates of *Serratia* spp. bacteraemia reports per 100,000 population (England): 2015



Source: PHE, 2016

Figure 3c. Age and sex-specific rates of *Citrobacter* spp. bacteraemia reports per 100,000 population (England): 2015



Source: PHE, 2016

Antimicrobial susceptibility data: England

Tables 3a-c present antibiotic susceptibility trends from 2011 to 2015 in England for blood culture isolates using data from the CDR module of SGSS. This analysis examines five classes of antibiotics: third-generation cephalosporins (cefotaxime or ceftazidime), carbapenems (meropenem or ertapenem), a fluoroquinolone (ciprofloxacin), a penicillin/beta-lactamase inhibitor combination (piperacillin/tazobactam), and aminoglycosides (gentamicin, tobramycin and amikacin).

Table 4 shows dual resistance in England in 2015 based on a defined combination of antimicrobial drugs based on data from SGSS's AMR module. Trends using data from this module cannot be undertaken at present owing to lower laboratory coverage in previous years.

In this analysis, the highest level of non-susceptibility was found in the cephalosporin class across all three genera (table 3a to table 3c). Among *Enterobacter* spp., the mechanism of resistance to third-generation cephalosporins commonly reflects de-repression of chromosomal AmpC β- lactamase. Among *Enterobacter* spp. bacteraemia isolates, a small decline in non-susceptibility to both agents was observed between 2011 and 2015, from 29% to 27% respectively for ceftazidime and from 27% to 25% for cefotaxime (table 3a). Small but decreasing trends in non-susceptibility were also found for *Serratia* spp. reaching 13% for ceftazidime and 14% for cefotaxime in 2015 (table 3b). These trends most likely reflect decreased beta-lactam exposure in clinical practice. No evidence of change in resistance was observed among *Citrobacter* spp. bacteraemia isolates (table 3c). The latter result may reflect the varied AmpC β-lactamase characteristics among *Citrobacter* species (e.g. *C. diversus* does not have AmpC β-lactamase hence cannot become de-repressed and *C. freundii* behaves like *Enterobacter* spp. with the risk of AmpC β-lactamase de-repression.

A small decrease in non-susceptibility to the fluoroquinolone ciprofloxacin was observed among *Serratia* spp. blood culture isolates during the five year period, from 9% in 2011 to 7% in 2015 (table 3b). However the proportion of isolates reported as non-susceptible to this agent was stable for the other two genera.

The proportion of bacteraemia isolates reported as non-susceptible to the aminoglycoside agent gentamicin was lowest among *Serratia* spp. (2% in 2015 (table 3b). Among *Enterobacter* spp. isolates, non-susceptibility to this agent remained stable over the period (table 3b) whilst for *Citrobacter* spp. small inter-year variation in non-susceptibility occurred reaching 3% in 2015 (table 3c). Non-susceptibility to amikacin (another aminoglycoside) was assessed only for

Enterobacter spp. and *Citrobacter* spp. (table 3a and table 3c respectively). This is because *S. marcescens* (which accounts for the majority of *Serratia* spp.) produces a chromosomally encoded AAC(6) enzyme which can become derepressed via mutation, which affects the activity of amikacin [3]. Non-susceptibility to amikacin was rare among *Enterobacter* spp. and *Citrobacter* spp. isolates, with no evidence of change from 2011 to 2015. Non-susceptibility to tobramycin (also an aminoglycoside) increased markedly among *Serratia* spp. isolates from 10% in 2011 to 22% in 2015 (table 3b) but was lower and stable for the other two genera. The increase in non-susceptibility to tobramycin among *Serratia* spp. isolates is of concern. Further analysis shows that this increase appears to be driven by *S. marcescens* where non-susceptibility to this agent increased from 11% of isolates in 2011 to 24% in 2015 (not shown).

Non-susceptibility to piperacillin/tazobactam showed a gradual increase over the five year period among *Enterobacter* spp. bacteraemia isolates (from 16% to 20%) (table 3a). This was also true forfor *Citrobacter* spp. isolates (from 7% to 10%) (table 3c). These results are likely to reflect laboratories switching from the CLSI MIC breakpoint of 16 mg/L to the EUCAST breakpoint of 8 mg/L for this agent relating to Enterobacteriaceae introduced in 2011 [4]. However, among *Serratia* spp., non-susceptibility to this agent was stable, exhibiting small inter-year variation reaching 10% in 2015 (table 3b).

Of the two carbapenems examined, non-susceptibility to meropenem remained uncommon in the study period across all genera with 1% or fewer of isolates reported as resistant (tables 3a to 3c). Non-susceptibility to ertapenem was also uncommon across all genera (1%-3%) except among *Enterobacter* spp. isolates where it was relatively higher although a small decrease in non-susceptibility occurred from 10% in 2011 to 8% in 2015. Although a small increase in non-susceptibility to ertapenem was observed among *Citrobacter* spp. isolates in 2014, this was not sustained in 2015. It should be noted that the underlying number of isolates reported as non-susceptible to the carbapenems was small.

It should be noted that EUCAST's clinical breakpoint for determining susceptibility to ertapenem is lower than that for meropenem (0.5mg/L vs 2mg/L respectively) [5]. However, the ertapenem compound is more prone to resistance due to de-repressed AmpC β-lactamase together with porin deficiency arising via mutation. Meropenem resistance is rarer owing to the higher breakpoint and lower vulnerability to this combination of mechanisms. Consequently resistance to meropenem is more likely to be due to true carbapenemases, hence of public health concern.

Non-susceptibility to the carbapenem class warrants close vigilance given that this class of antibiotics is a powerful last-line treatment for serious infections caused by Gram-negative bacteria. The increases in CPE based on all specimen types observed by PHE's ARMHAI are occurring in the context of the emerging non-susceptibility to these antibiotics among Enterobacteriaceae reported internationally in recent years [6,7].

In recognition of the importance of 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 was issued in June 2015 [9].

As CPE pose significant treatment and public health challenges, PHE launched an enhanced surveillance of CPE in May 2015 to better understand the epidemiology of these organisms. A web-based electronic reporting system (https://cro.phe.nhs.uk/) has been designed to enable laboratories in NHS Trusts in England to capture specimen, demographic, healthcare setting and risk factor details as part of the core and enhanced dataset [10].

Table 3a. Antibiotic susceptibility of *Enterobacter* spp. bacteraemia isolates, England: 2011-2015

	2011		2012		2013		2014		2015	
	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*
Gentamicin	1,594	6%	1,518	5%	1,551	6%	1,503	6%	1,676	6%
Ciprofloxacin	1,485	5%	1,399	5%	1,464	6%	1,402	6%	1,591	5%
Ceftazidime	1,227	29%	1,174	30%	1,142	31%	1,139	29%	1,366	27%
Cefotaxime	865	27%	859	27%	833	26%	839	27%	935	25%
Meropenem	1,260	1%	1,258	1%	1,304	1%	1,333	1%	1,579	1%
Ertapenem	442	10%	618	9%	730	9%	839	9%	1,284	8%
Tobramycin	454	8%	473	8%	482	8%	472	11%	563	8%
Amikacin	890	2%	906	1%	938	1%	930	1%	1,033	1%
Piperacillin/Tazobactam	1,454	16%	1,382	21%	1,472	20%	1,389	21%	1,593	20%
Total *Enterobacter* spp. reports	**1,816**		**1,704**		**1,737**		**1,737**		**1,864**	

*defined as reduced- or non-susceptible

Source: PHE, 2016

Table 3b. Antibiotic susceptibility of *Serratia* bacteraemia isolates, England: 2011-2015

	2011		2012		2013		2014		2015	
	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*	No. Tested	% Resistant*
Gentamicin	717	1%	663	1%	655	2%	684	2%	760	2%
Ciprofloxacin	654	9%	610	6%	619	7%	635	5%	717	7%
Ceftazidime	564	15%	534	16%	498	17%	523	14%	592	13%
Cefotaxime	386	17%	373	19%	374	18%	386	13%	399	14%
Meropenem	567	0%	542	0%	556	1%	603	0%	706	1%
Ertapenem	207	1%	271	1%	323	2%	376	1%	578	2%
Tobramycin	207	10%	221	12%	227	20%	202	19%	246	22%
Piperacillin/Tazobactam	634	9%	602	8%	610	12%	640	9%	707	10%
Total *Serratia* spp. reports	**769**		**716**		**722**		**776**		**837**	

*defined as reduced- or non-susceptible

Source: PHE, 2016

Table 3c. Antibiotic susceptibility of *Citrobacter* bacteraemia isolates, England: 2011-2015

	2011		2012		2013		2014		2015	
	No. Tested	**% Resistant***	**No. Tested**	**% Resistant***	**No. Tested**	**% Resistant***	**No. Tested**	**% Resistant***	**No. Tested**	**% Resistant***
Gentamicin	639	4%	566	5%	616	4%	643	2%	802	3%
Ciprofloxacin	600	3%	531	2%	571	3%	593	4%	746	3%
Ceftazidime	492	12%	464	13%	461	14%	458	13%	631	14%
Cefotaxime	342	13%	326	11%	348	12%	350	15%	423	14%
Meropenem	494	0%	449	0%	507	0%	549	0%	722	0%
Ertapenem	166	2%	193	1%	277	0%	365	3%	598	1%
Tobramycin	181	5%	175	5%	194	5%	183	3%	265	5%
Amikacin	365	<1%	335	<1%	359	1%	374	1%	464	1%
Piperacillin/Tazobactam	591	7%	653	8%	585	9%	601	10%	760	10%
Total *Citrobacter* spp. reports	**732**		**653**		**705**		**741**		**884**	

*defined as reduced- or non-susceptible

Source: PHE, 2016

The SGSS AMR data was used to examine multi-drug non-susceptibility among bacteraemia isolates. The analysis was based on combinations of two different defined antibiotics (table 4). *Enterobacter* spp. exhibited the highest frequency of dual non-susceptibility. *Serratia* spp. exhibited the lowest dual resistance except in relation to the pair-wise combination of third generation cephalosporins and ciprofloxacin.

Among *Enterobacter* spp. bacteraemia isolates, the most common dual resistance was to third generation cephalosporins and ciprofloxacin (7.0%). The least common dual resistance was among *Serratia spp.* isolates to ciprofloxacin and gentamicin at <0.5% of isolates tested.

Non-susceptibility to all of third generation cephalosporins, ciprofloxacin, gentamicin and meropenem was uncommon (<1%) among bacteraemia isolates due to *Enterobacter* spp. (8/981), *Serratia* spp. (1/410) and *Citrobacter* spp. (zero cases in 439 isolates) (data not shown).

Table 4. Pair-Wise antimicrobial testing and non-susceptibility among isolates of bacteraemia due to *Enterobacter* spp., *Serratia* spp. *or Citrobacter* spp., England, 2015

	Gentamicin and ciprofloxacin		Gentamicin and 3rd-generation cephalosporin*		Ciprofloxacin and 3rd generation cephalosporin*	
	No. tested	% Resistant	No. tested	% Resistant	No. tested	% Resistant
Enterobacter spp.	1,687	2.9	1,039	7.7	1,018	7.0
Serratia spp.	742	0.4	438	2.5	428	5.6
Citrobacter spp.	811	1.0	480	3.3	466	3.6

* Any of cefotaxime, ceftazidime, cefpodoxime or ceftriaxone

Source: PHE, 2016

For advice on treatment of antibiotic-resistant infections due to these organisms or for reference services including species identification and confirmation of susceptibility testing results, laboratories should contact PHE’s AMRHAI Reference Unit in London [11].

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