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Laboratory surveillance of *Enterobacter* spp. *Serratia* spp. and *Citrobacter* spp. bacteraemia in England, Wales and Northern Ireland: 2016

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Laboratory surveillance of *Enterobacter* spp. *Serratia* spp. and *Citrobacter* spp. bacteraemia in England, Wales and Northern Ireland: 2016

These analyses are based on data relating to diagnoses of bloodstream infections caused by *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. in England, Wales and Northern Ireland between 2012 and 2016. The surveillance is voluntary.

Data for England were extracted on 11 August 2017 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 9 March and CoSurv on 2 August 2017 respectively).

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 2016 were extracted to assess multi-drug resistance rates. Data from England and Northern Ireland only are included in the antimicrobial susceptibility analysis.

The data presented here may differ from data in previous publications due to inclusion of late reports.

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

This report includes analyses of trends, the age and sex distribution and geographical distribution of cases of *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia in England, Wales and Norrthern Ireland. In addition, five-year trends in antimicrobial susceptibility for England and Northern Ireland have been included in the report, as has a single year of resistance to more than one antibiotic based on England's data reported to the AMR module (previously AmSurv). A web appendix is available featuring the findings of this report including only data submitted via SGSS from laboratories in England.

Key points

- the rate of *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia increased gradually from 2013 to 2016, increasing by 12%, 6% and 12% between 2015 and 2016 to 3.9, 1.8 and 1.8 per 100,000 population, respectively
- in 2016, the rate of bacteraemia reports was generally higher in males than females and among older adults (≥75 years) and infants (<1 year) across all three genera
- at individual country level, the rate of *Enterobacter* spp. bacteraemia in 2016 for England, Wales and Northern Ireland was 3.9, 4.3 and 4.1/100,000 population, respectively
- the rate of *Serratia* spp. bacteraemia in 2016 for England, Wales and Northern Ireland was 1.7, 2.7 and 1.8/100,000 population, respectively
- the rate of *Citrobacter* spp. bacteraemia in 2016 for England, Wales and Northern Ireland was 1.8, 1.9 and 1.2/100,000 population, respectively
- within England, the rate of bacteraemia varied between geographical areas or PHE centres (PHEc) across all three genera
- in 2016, PHEc in England with the highest population rate for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia were East Midlands (4.6/100,000), North West (2.0) and London and South East (2.2 each), respectively
- In 2016, *Citrobacter* spp. bacteraemia appeared to show a regional gradient with local PHE centres in the south having higher rates compared to centres in the north

- antimicrobial susceptibility trends from 2012 to 2016 were examined for five antibiotic classes (England and Northern Ireland data):
    - a small decrease in non-susceptibility to ceftazidime (third-generation cephalosporin) occurred among *Enterobacter* spp. and *Serratia* spp. blood culture isolates decreasing from 30% to 27% and from 15% to 11%, respectively between 2012 and 2016; no trends were detectable for cefotaxime across all three genera
    - 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 2016; whilst non-susceptibility was stable for the other two genera
    - non-susceptibility to tobramycin (aminoglycoside) increased markedly among *Serratia* spp. isolates from 11% in 2012 to 28% in 2016 driven by increases in non-susceptibility for *S. marcescens* (from 13% to 31% in the same period); non-susceptibility being lower but stable for *Citrobacter* spp. and *Serratia* spp.
    - trends in non-susceptibility to piperacillin/tazobactam were not present across all three genera; it was highest but stable for *Enterobacter* spp. bacteraemia isolates, (20% in 2016), possibly reflecting lower EUCAST breakpoints introduced in 2011
    - non-susceptibility to the carbapenem meropenem remained uncommon(≤1%) across all genera
    - of the three genera, non-susceptibility to ertapenem (a carbapenem) was highest but stable for *Enterobacter* spp., being 8% in 2016
    - in 2016, 4% of *Enterobacter* spp. bacteraemia isolates tested were resistant to gentamicin and third generation cephalosporins or to ciprofloxacin and third generation cephalosporins combinations; only 1% of *Citrobacter* spp. were resistant to any two antibiotic combinations under study
    - multi-drug resistance to all four antibiotics (gentamicin, ciprofloxacin, third generation cephalosporins and meropenem) was uncommon ≤1% across all three genera

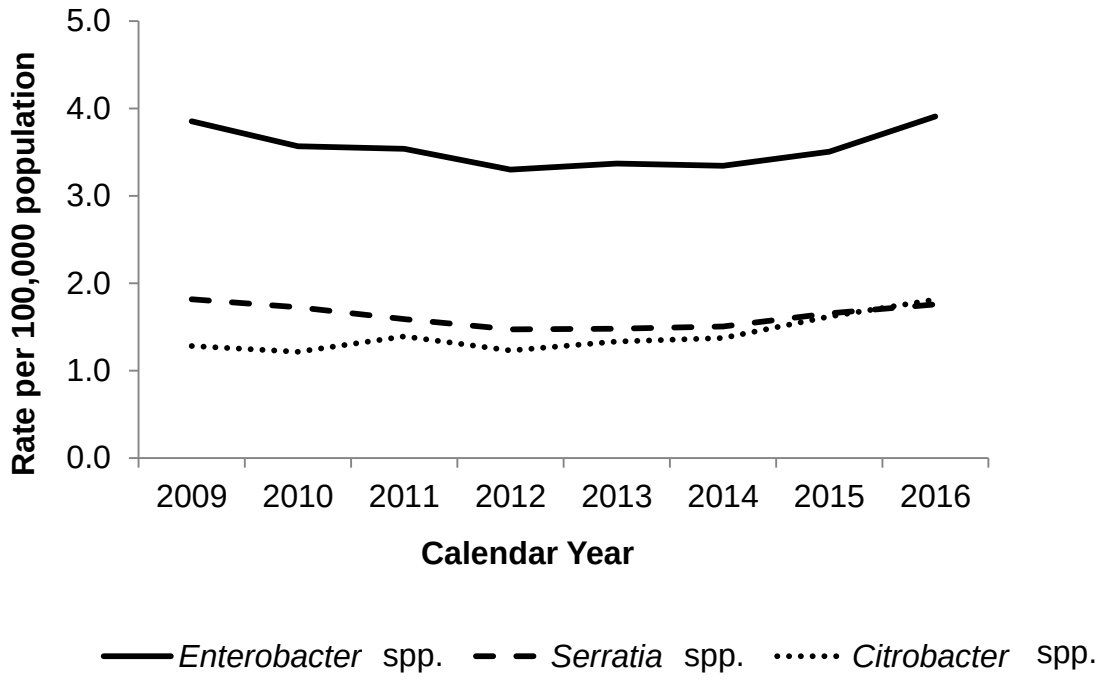
Trends

Figure 1 shows trends in the rate of bacteraemia laboratory reports by genus between 2009 and 2016 per 100,000 resident population.

Between 2009 and 2012, the rate of *Enterobacter* spp. bacteraemia decreased by 14% from 3.9/100,000 to 3.3/100,000 (n=2,197 to n=1,926 cases, respectively) but increased steadily after this. The rate of *Serratia* spp. bacteraemia also decreased over this period; by 19% from 1.8 in 2009 to 1.5/100,000 population (n=1,035 to n=858 cases respectively) but steadily increasing after this. The rate of *Citrobacter* spp. bacteraemia was stable at around 1.3/100,000 population *per annum* between 2009 and 2014 (fluctuating between n=700 and n=800 cases), although increasing afterwards.

Between 2015 and 2016, the bacteraemia rate for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. increased by 12%, 6% and 12% respectively. This was equivalent to an increase in the rate from 3.5 to 3.9/100,000 for *Enterobacter* spp. (n=2,093 to n=2,355 cases, respectively); from 1.7 to 1.8/100,000 for *Serratia* spp. (n=988 to n=1,058 cases, respectively) and from 1.6 to 1.8/100,000 for *Citrobacter* spp. (n=967 to n=1,091 cases respectively).

Figure 1. *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia per 100,000 population (England Wales and Northern Ireland): 2009 to 2016



Geographic distribution

In 2016 the overall rate of laboratory reports of *Enterobacter* spp. bacteraemia for England, Wales and Northern Ireland was 3.9 per 100,000 population. The rates by country were 3.9, 4.3 and 4.1 for England, Wales and Northern Ireland respectively (table 1a). It is important to note that in England and Northern Ireland there are links from different laboratories to SGSS/CoSurv that report clinically significant isolates. Data from Wales are extracted from a single laboratory information system used by all microbiology laboratories, where all positive blood cultures are extracted, including those not thought to be clinically significant.

The overall *Serratia* spp. bacteraemia rate for England, Wales and Northern Ireland in 2016 was 1.8/100,000 population. The rate by country was 1.7, 2.7 and 1.8 per 100,000 population for England, Wales and Northern Ireland, respectively.

The overall *Citrobacter* spp. bacteraemia rate for England, Wales and Northern Ireland in 2016 was 1.8/100,000 population. By individual country, this was 1.8, 1.9 for and 1.2 per 100,000 population for England Wales Northern Ireland, respectively.

Within England, there was variation in the rates between the nine Public Health England centres (PHECs) in 2016 but no consistent pattern emerged across all three genera.

The highest rate of *Enterobacter* spp. bacteraemia in 2016 was in the East Midlands PHEc (4.6/100,000), and the lowest in the Yorkshire and Humber (3.0) (figure 2a; table 1a). For *Serratia* spp. bacteremia, the highest rate in 2016 was in the North West (2.0) (figure 2b; table 1b). The lowest *Serratia* spp. bacteraemia rate in 2016 was in the East Midlands (1.4). For *Citrobacter* spp. (figure 1, table 1c) the highest rate was in London and in South East PHECs (each 2.2). The lowest rate of *Citrobacter* spp. bacteraemia was in North West (1.2/100,000 population). In 2016, *Citrobacter* spp. bacteraemia appeared to show a regional gradient in the rate with PHECs in the south having higher rates compared to centres located further north (figure 2c; table 2c)

No consistent pattern in trends was observed at country level across all genera. However a generally downward trend in *Enterobacter* spp. bacteraemia was observed for Wales and upward trends in *Citrobacter* spp. bacteraemia was observed for all countries.

Notable trends for PHE centres in England were for *Enterobacter* spp. where the most marked increase was observed for East Midlands increasing from 2.8/100,000 in 2012 to 4.6/100,000 population (table 1a).

For *Serratia* spp. bacteraemia a small but steady upward trend was found for Yorkshire and Humber (from 1.0/100,000 to 1.5/100,000 population) (table 1b).

For *Citrobacter* spp. bacteraemia, upward trends in the rate were observed for East of England, London, South East and South West with the most marked increase in the South East bearing a two-fold increase (from 1.0/100,000 in 2012 to 2.2/100,000 in 2016) (table 1c).

The geographical analyses presented here are not corrected for variation in case ascertainment between geographical areas. 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. It is important to note that in England and Northern Ireland there are links from different laboratories to SGSS/CoSurv that report clinically significant isolates. Data from Wales are extracted from a single laboratory information system used by all microbiology laboratories, where all positive blood cultures are extracted, including those not thought to be clinically significant.

Figure 2a. Geographical distribution of the rate of *Enterobacter* spp., bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2016

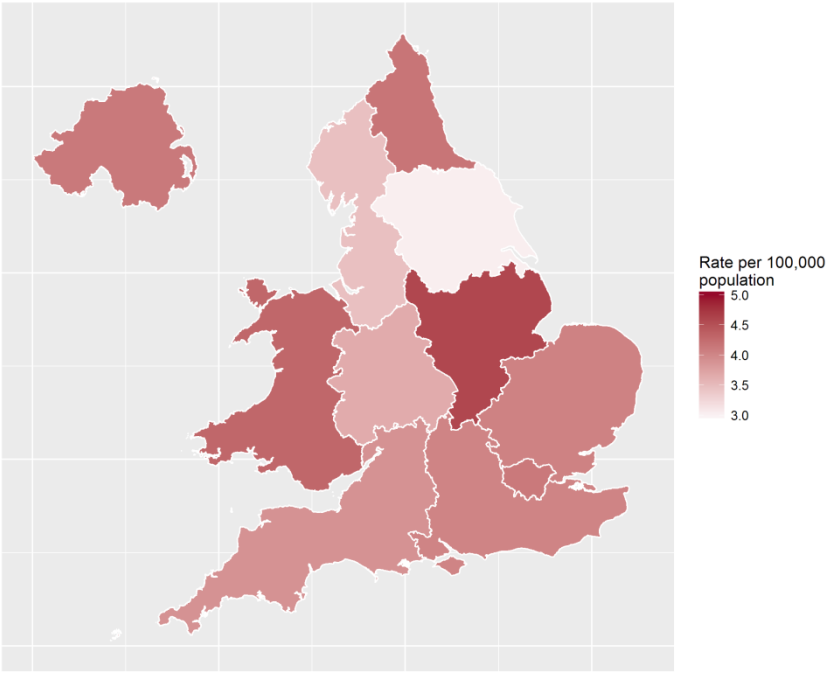


Table 1a. Rate of *Enterobacter* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2011 to 2016

Region	PHE Centre	Rate per 100,000 population				
		2012	2013	2014	2015	2016
North of England	North East	3.9	2.9	3.0	3.7	4.2
	Yorkshire and Humber	2.7	2.6	1.9	2.7	3.0
	North West	3.2	3.6	3.4	3.2	3.5
Midlands and East of England	West Midlands	3.3	3.3	3.4	3.3	3.7
	East Midlands	2.8	3.8	3.6	4.3	4.6
	East of England	3.3	3.2	3.6	3.4	4.1
London	London	3.9	3.8	3.6	3.9	4.1
South of England	South West	3.1	3.1	3.2	3.3	3.9
	South East	2.9	2.8	3.1	3.4	4.0
England*		3.2	3.3	3.2	3.5	3.9
Northern Ireland†		2.7	4.2	4.2	3.2	4.1
Wales‡		4.8	4.9	4.8	4.4	4.3
England, Wales and Northern Ireland		3.3	3.4	3.3	3.5	3.9

* Extracted on 11 August 2017; † extracted on 2 August 2017; ‡ extracted on 9 March 2017

Figure 2b. Geographical distribution of the rate of *Serratia* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2016

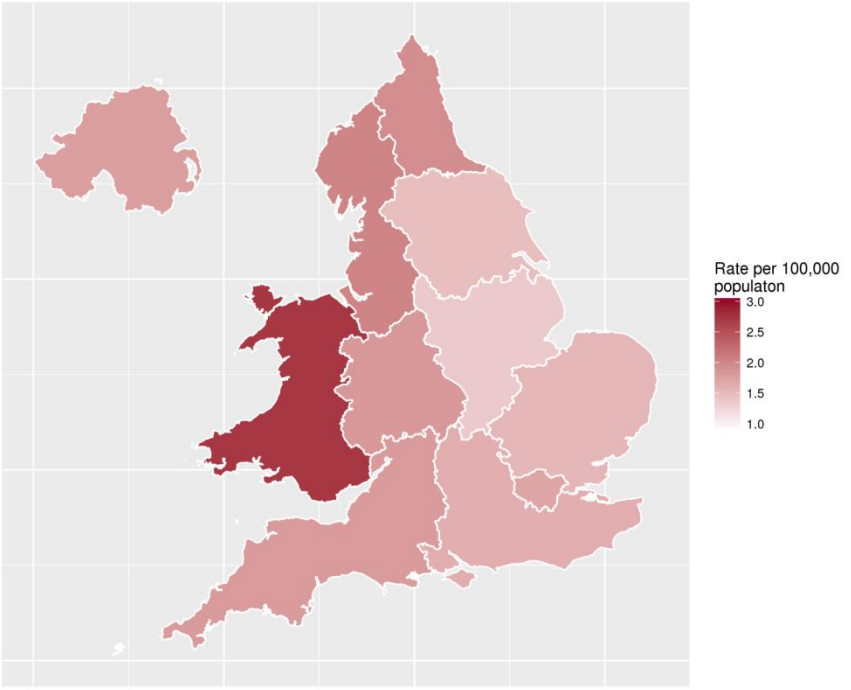


Table 1b. Rate of *Serratia* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2012 to 2016

Region	PHE Centre	Rate per 100,000 population				
		2012	2013	2014	2015	2016
North of England	North East	2.0	2.1	1.8	2.2	1.9
	Yorkshire and Humber	1.0	0.9	1.1	1.1	1.5
	North West	1.7	1.8	1.8	1.7	2.0
Midlands and East of England	West Midlands	1.0	1.3	1.3	1.3	1.8
	East Midlands	1.2	1.3	1.1	1.4	1.4
	East of England	1.3	1.1	1.7	1.4	1.5
London	London	1.6	1.5	1.8	1.8	1.7
South of England	South West	1.7	1.5	1.5	1.5	1.8
	South East	1.1	1.2	1.1	1.6	1.6
England*		1.4	1.4	1.5	1.5	1.7
Northern Ireland†		1.3	2.0	1.4	1.9	1.8
Wales‡		3.5	3.1	2.5	3.4	2.7
England, Wales and Northern Ireland		**1.5**	**1.5**	**1.5**	**1.7**	**1.8**

* Extracted on 11 August 2017; † extracted on 2 August 2017; ‡ extracted on 9 March 2017

Figure 2c. Geographical distribution of the rate of *Citrobacter* spp. bacteraemia reports per 100,000 population (England, Wales and Northern Ireland): 2016

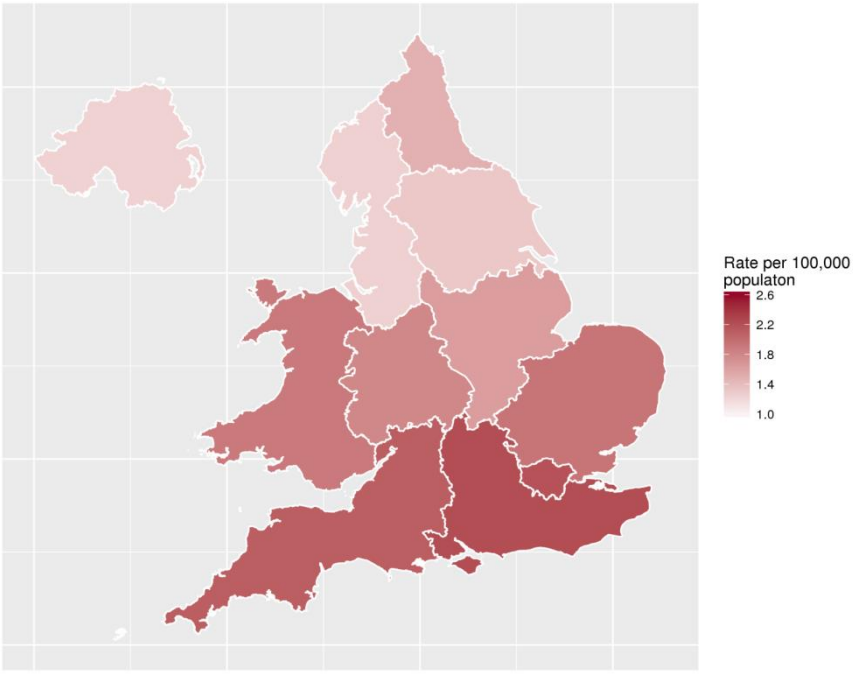


Table 1c. Rate of *Citrobacter* spp. bacteraemia reports per 100,000 population by PHE Centre (England, Wales and Northern Ireland): 2012 to 2016

Region	PHE Centre	Rate per 100,000 population				
		2012	2013	2014	2015	2016
North of England	North East	0.9	1.0	1.1	1.8	1.5
	Yorkshire and Humber	1.1	1.0	0.9	1.7	1.3
	North West	1.2	1.1	1.2	1.2	1.2
Midlands and East of England	West Midlands	1.2	1.8	1.7	1.7	1.8
	East Midlands	1.2	1.2	1.3	1.6	1.6
	East of England	1.3	1.6	1.6	1.7	1.9
London	London	1.6	1.6	1.7	1.8	2.2
South of England	South West	1.4	1.2	1.5	1.9	2.1
	South East	1.0	1.3	1.3	1.6	2.2
England*		1.2	1.3	1.4	1.6	1.8
Northern Ireland†		0.8	0.7	0.8	1.1	1.2
Wales‡		1.4	1.5	1.6	1.5	1.9
England, Wales and Northern Ireland		**1.2**	**1.3**	**1.4**	**1.6**	**1.8**

* Extracted on 11 August 2017; † extracted on 2 August 2017; ‡ extracted on 9 March 2017

Species distribution

In England, Wales and Northern Ireland, the total number of *Enterobacter* spp. bacteraemia reports was steady at just below 2,000 episodes annually between 2012 and 2014 *(*table 2a*).* However, between 2014 and 2015, the number of reports increased by 6% (from 1,981 to 2,093 episodes). A further increase (13%) occurred between 2015 and 2016 (to 2,355 episodes).

In 2016, the majority (92%) of *Enterobacter* spp. from blood specimens were identified to species level. However this followed a small but steady decline seen in the previous three years (table 2). The highest observed in the five period was 94% in 2012.

The total number of *Serratia* spp. bacteraemia reports in England, Wales and Northern Ireland increased steadily between 2012 (n=858) and 2016 (n=1,058) with 23% increase over this period; between 2015 and 2016 in particular, the number of reports increased by 7% (table 2b*).*

For *Serratia* spp. blood specimens, the majority of reports in 2016 identified the organism to species level (97%) representing the highest achieved compared to the previous four years (table 2b).

The total number of *Citrobacter* spp. bacteraemia reports in England increased steadily between 2012 (n=717) and 2016 (n=1,091) with a 52% increase over this period; between 2015 and 2016 in particular, the number of reports increased by 13% (table 2c*).*

Of the *Citrobacter* spp. blood specimens reported in 2016, 93% were reported to species level, a slight decrease over previous year (table 2) but an improvement from earlier years.

All three individual countries in England, Wales and Northern Ireland provided species level data.

Among *Enterobacter* spp. isolates in England, the dominant species remained *E. cloacae* accounting for 73% of reports, followed by *E. aerogenes* (17%) (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 (*England and Wales only*)*, *E. cloacae*, *E. ludwigii* (England and Wales only) and *E. kobaei* (England and Wales only). However the distinction between members of the complex is not always reliable. The *E. cloacae* complex was predominant across all three countries.

Among *Serratia* spp. isolates the most common species remained *S. marcescens* in 2016 accounting for 88% of reports, followed by *S. liquefaciens* (8%) (table 2b).

Among *Citrobacter* spp. isolates, *C. diversus* accounted for 51% of reports in 2016, followed by *C. freundii* (33%) (table 2c). At country level, *C. freundii* was the most common species reported in Wales in 2016 and in most of the preceding years. However the smaller number of total isolates in both Wales and Northern introduce some uncertainty in the species level data.

The data for England, Wales and Northern Ireland shows that *E. cloacae* trends remained stable in the five year period. Trends were similarly stable for *C. diversus*. Trends for *C. freundii*. tended to show small inter-year variability although marginal decreases occurred from 2014 onwards. Although the *C. braakii* proportion increased from <1% in 2012 to 2% in 2016, this was based on a small number of episodes

Of note, relative to the other *Serratia* species, *S. marcescens* increased faster; from 83% of reports in 2012 (n=711) to 88% of reports in 2016 (n=926).

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 the data feed to SGSS, new species reported in England in 2016 was *S. ureilytica* (n=3).

Of the top 20 most frequent organisms involved in monomicrobial bacteraemia (BSI, bacterial and fungal bloodstream pathogens) only the leading species of *Enterobacter spp.*, *E. cloacae*, featured, ranked as fourteenth in 2016, making up 0.9% of these infections [2]. None of the *Serratia* or *Citrobacter* species featured in this ranking [2].

Table 2a. Reports of *Enterobacter* spp. bacteraemia by species (England, Wales and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2016	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
***Enterobacter* spp.**	**1,926**	**100**	**1,980**	**100**	**1,981**	**100**	**2,093**	**100.0**	**2,355**	**100**
E. aerogenes	361	18.7	355	17.9	334	16.9	369	17.6	395	16.8
E. amnigenus	6	0.3	7	0.4	4	0.2	11	0.5	6	0.3
E. cancerogenus	0	0.0	0	0.0	1	0.1	0	0.0	2	0.1
E. cloacae complex*	1,394	72.4	1,388	70.1	1422	71.8	1,507	72.0	1,714	72.8
E. gergoviae	3	0.2	7	0.4	4	0.2	7	0.3	6	0.3
E. intermedius	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
E. sakazakii	18	0.9	28	1.4	13	0.7	6	0.3	2	0.1
Enterobacter spp., other named	27	1.4	46	2.3	56	2.8	34	1.6	36	1.5
Enterobacter spp., species not recorded	116	6.0	149	7.5	146	7.4	159	7.6	194	8.2

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

Table 2b. Reports of *Serratia* spp. bacteraemia by species (England, Wales and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2016	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
***Serratia* spp.**	**858**	**100**	**869**	**100**	**891**	**100**	**988**	**100**	**1,058**	**100**
S. ficaria	2	0.2	1	0.1	1	0.1	0	0.0	0	0.0
S. fonticola	8	0.9	8	0.9	3	0.3	2	0.2	7	0.7
S. liquefaciens	84	9.8	73	8.4	74	8.3	86	8.7	87	8.2
S. marcescens	711	82.9	735	84.6	757	85.0	842	85.2	926	87.5
S. odorifera	3	0.3	6	0.7	2	0.2	7	0.7	4	0.4
S. plymuthica	4	0.5	1	0.1	0	0.0	2	0.2	0	0.0
S. proteamaculas	0	0.0	1	0.1	0	0.0	1	0.1	0	0.0
S. rubidaea	2	0.2	0	0.0	1	0.1	5	0.5	1	0.1
S. ureilytica	0	0.0	0	0.0	0	0.0	0	0.0	3	0.3
Serratia spp., other named	12	1.4	10	1.2	20	2.2	2	0.2	0	0.0
Serratia spp., species not recorded	32	3.7	34	3.9	33	3.7	41	4.1	30	2.8

Table 2c. Reports of *Citrobacter* spp. bacteraemia by species (England, Wales and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2,016	
	No.	%	No.	%	No.	%	No.	%	No.	%
***Citrobacter* spp.**	**717**	**100**	**782**	**100**	**812**	**100**	**967**	**100**	**1,091**	**100**
C. amalonaticus	7	1.0	3	0.4	4	0.5	5	0.5	5	0.5
C. braakii	4	0.6	2	0.3	4	0.5	23	2.4	25	2.3
C. diversus	339	47.3	405	51.8	369	45.4	478	49.4	561	51.4
C. farmeri	1	0.1	0	0.0	2	0.2	4	0.4	4	0.4
C. freundii	269	37.5	245	31.3	303	37.3	337	34.9	357	32.7
C. koseri	2	0.3	8	1.0	5	0.6	6	0.6	9	0.8
C. sedlakii	0	0.0	0	0.0	0	0.0	1	0.1	1	0.1
C. werkmanii	0	0.0	0	0.0	0	0.0	4	0.4	1	0.1
C. youngae	0	0.0	0	0.0	1	0.1	3	0.3	7	0.6
Citrobacter spp., other named	44	6.1	58	7.4	53	6.5	42	4.3	46	4.2
Citrobacter spp., species not recorded	51	7.1	61	7.8	71	8.7	64	6.6	75	6.9

Age and sex distribution

Figures 3a-c show the age and sex-specific bacteraemia rates in 2016 by genus. The distribution follows a J-shaped curve across all genera due to the elderly (≥65 years) and the infant group (<1 year) having higher rates of bacteraemia per 100,000 population. There were no *Serratia* spp. bacteraemia episodes for the age group 10-14 years and no *Citrobacter* spp. bacteraemia episodes for males aged 5-14 years.

Across all genera the rate was higher among males in most age groups with the largest disparity among patients aged ≥75 years. In this age group, the incidence rate among males was 3.5-fold, 3.1-fold and 4.7-fold higher than in females for *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp. bacteraemia respectively.

Figure 3a. *Enterobacter* spp. bacteraemia rates by age and sex (England, Wales and Northern Ireland): 2016

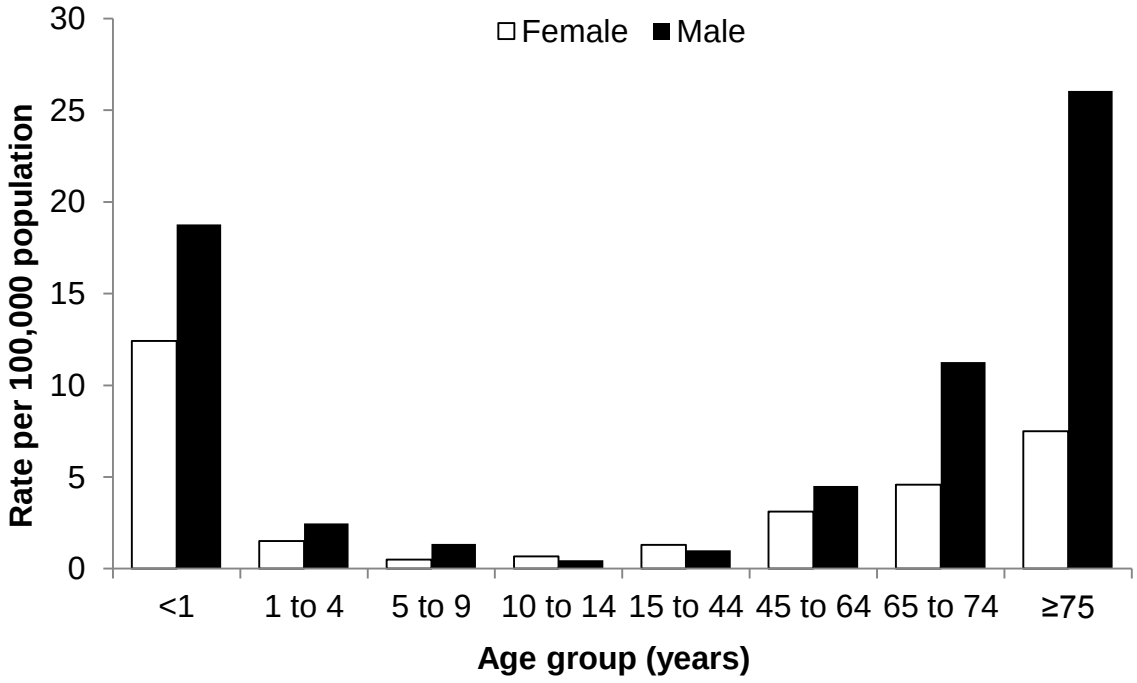


Figure 3b. *Serratia* spp. bacteraemia rates by age and sex (England, Wales and Northern Ireland): 2016

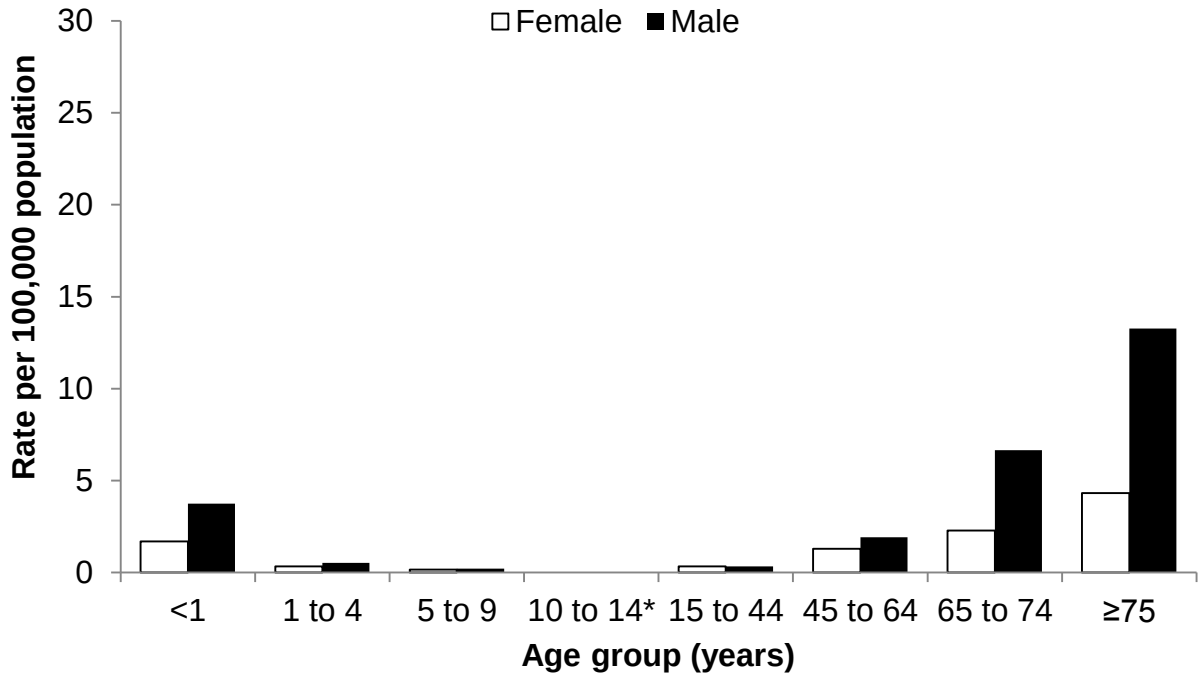
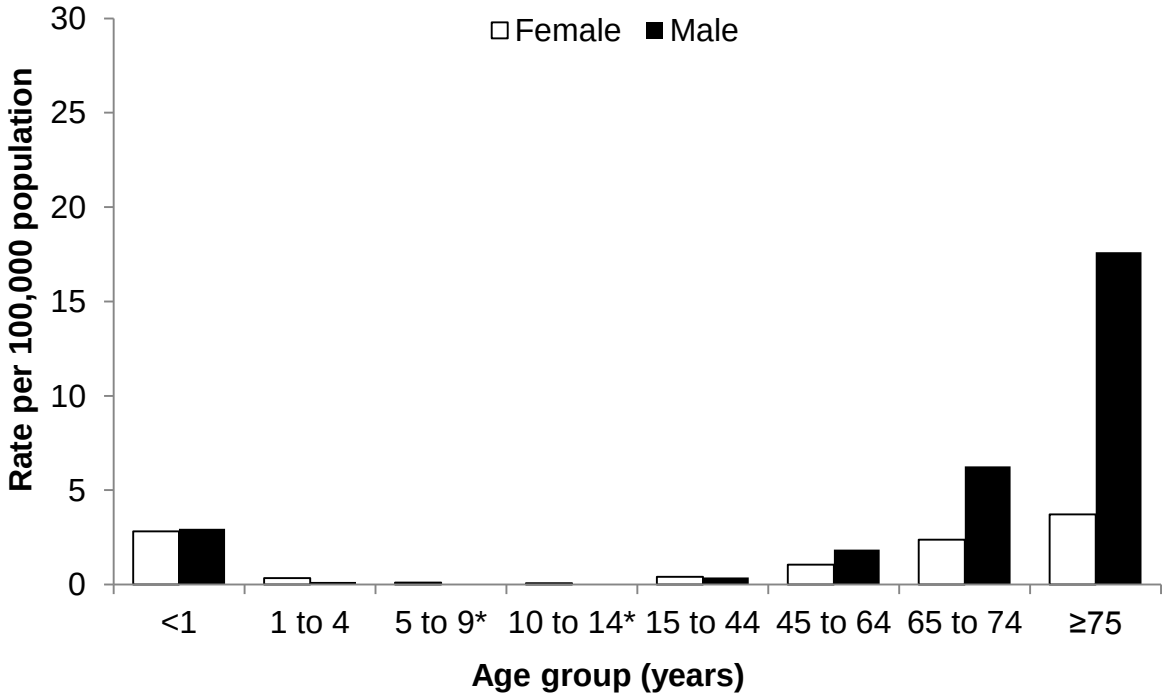


Figure 3b. *Citrobacter* spp. bacteraemia rates by age and sex (England, Wales and Northern Ireland): 2016



Antimicrobial resistance: England

Tables 3a-c present antibiotic susceptibility trends from 2012 to 2016 for blood culture isolates based on data from England and Northern Ireland. Five classes of antibiotics were examined: 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 or amikacin).

Tables 4a-c describe multiple resistance among isolates in England, 2016 based on a defined combination of antibiotics using data from SGSS's AMR module. Trends using data from this module cannot be undertaken at present owing to lower laboratory coverage in earlier years.

In the single resistance analysis, the highest level of non-susceptibility was in the cephalosporin class across all three genera (tables 3a-3c). Among *Enterobacter* spp., the mechanism of resistance to third-generation cephalosporins commonly reflects de-repression of chromosomal AmpC β- lactamase. A small decline in non-susceptibility to ceftazidime was observed among *Enterobacter* spp. and *Serratia* spp. bacteraemia isolates between 2012 and 2016 (from 30% to 27%; and from 15% to 11% respectively) (tables 3a and 3b). Non-susceptibility to cefotaxime was stable for *Enterobacter* spp. bacteraemia isolates (27% in 2016) whilst for *Serratia* spp., no trends could be identified due to inter-year fluctuations. Among *Citrobacter* spp. bacteraemia isolates, trends in non-susceptibility to ceftazidime or cefotaxime were not found (table 3c).

The declining trends in non-susceptibility to ceftazidime among *Enterobacter* spp. and *Serratia* spp. bacteraemia isolates could reflect decreased beta-lactam use in clinical practice. However, the lack of trends in non-susceptibility to either cephalosporin agent among *Citrobacter* spp. bacteraemia isolates may reflect the varied AmpC β-lactamase characteristics at species-level (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, from 7% in 2012 to 5% in 2016 (table 3b). 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 gentamicin (an aminoglycoside) was lowest among *Serratia* spp. at 2% in 2016 (table 3b). Among *Enterobacter* spp. isolates, non-susceptibility to this agent remained stable over the five year period at 5% in 2016 (table 3b) whilst for *Citrobacter* spp. no trends were detectable due to small inter-year variation reaching 3% in 2016 (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 (≤2%) among *Enterobacter* spp. and *Citrobacter* spp. isolates, with no evidence of change from 2012 to 2016.

Non-susceptibility to tobramycin (also an aminoglycoside) increased markedly among *Serratia* spp. bacteraemia isolates from 11% in 2012 to 28% in 2016 (table 3b) but was lower and stable for the other two genera (8% and 4% in 2016 for *Enterobacter* spp. and *Citrobacter* spp. respectively). Further analysis showed that this increase in *Serratia* spp. was driven by *S. marcescens* where non-susceptibility to this agent increased from 13% of isolates in 2012 to 31% in 2016 (data not shown). This is a large increase and may in part be explained by the increasing number of *S. marcescens* reports relative to the other *Serratia* species (see table 2b). The increase in non-susceptibility for *S. marcescens* is of concern and demands vigilance.

Non-susceptibility to piperacillin/tazobactam remained high but stable at 20% of *Enterobacter* spp. bacteraemia isolates in most years of the five year period (table 3a). Non-susceptibility to this antibiotic was lower for *Serratia* spp. and *Citrobacter* spp. bacteraemia isolates with small inter-year variation, each genus reaching 9% in 2016 (tables 3b-3c). Non-susceptibility to piperacillin/tazobactam increased after 2011 for *Enterobacter* spp. bacteraemia isolates in particular. This could reflect laboratories switching from the CLSI MIC breakpoint of 16 mg/L to the EUCAST breakpoint of 8 mg/L in 2011 for this agent in regard to Enterobacteriaceae [4].

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-c). Non-susceptibility to ertapenem was also uncommon across all genera (0%-3%) except among *Enterobacter* spp. isolates where it was relatively higher, although a small decrease in non-susceptibility occurred from 9% in 2012 to 8% in 2016. Although a small increase in non-susceptibility to ertapenem occurred in 2014 among *Citrobacter* spp. isolates, this was not sustained in 2015 and 2016. 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 carbapenamase producing Enterobacteriaceae (CPE) based on all specimen types observed by PHE's ARMHAI is in line with the emerging non-susceptibility to these antibiotics among Enterobacteriaceae reported internationally in recent years [6,7].

The analysis on multi-drug resistance testing was based on combinations of two or more defined antibiotics (tables 4a-c). *Enterobacter* spp. exhibited the highest frequency of multi-drug resistance for all tested antibiotic combinations compared to the other two genera.

The analysis on defined pair-wise antibiotic resistance showed that 4% of *Enterobacter* spp. bacteraemia isolates were resistant to gentamicin and third generation cephalosporins or to ciprofloxacin and third generation cephalosporins (table 4a). Only 1% of *Citrobacter* spp. bacteraemia isolates exhibited resistance to any two defined antibiotic combinations (table 4c).

Non-susceptibility to all three defined antibiotics: gentamicin, ciprofloxacin and third generation cephalosporins was highest for *Enterobacter* spp. bacteraemia isolates at 2% (compared to <1% for each of the other two genera (tables 3a-c).

Non-susceptibility to all of third generation cephalosporins, ciprofloxacin, gentamicin and meropenem was uncommon (<1%) among bacteraemia isolates due to *Enterobacter* spp. (2/1,945), *Serratia* spp. (0/826) and *Citrobacter* spp. (0/903).

In recognition of the importance of CPE, PHE issued a toolkit in December 2013 to aid 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 the electronic reporting system (ERS) for the enhanced surveillance of carbapenem resistance in Gram-negative bacteria 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. Antimicrobial susceptibility for *Enterobacter* spp. bacteraemia (England and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2016	
Antimicrobial agent	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***
Gentamicin	1,587	5	1,634	6	1,591	5	1,755	6	1,994	5
Ciprofloxacin	1,463	5	1,538	6	1,479	6	1,672	5	1,932	6
Ceftazidime	1,221	30	1,202	31	1,204	28	1,417	27	1,597	27
Cefotaxime	905	27	876	26	904	26	978	26	1,081	27
Meropenem	1,321	1	1,384	1	1,413	1	1,655	1	1,897	1
Ertapenem	623	9	739	9	844	9	1,315	8	1,502	8
Tobramycin	509	7	522	7	526	10	593	8	735	8
Amikacin	956	1	995	1	996	1	1,073	1	1,303	2
Piperacillin/Tazobactam	1,450	20	1,557	20	1,475	21	1,675	20	1,839	20
Total *Enterobacter* spp. bacteraemia reports	**1,778**		**1,830**		**1,834**		**1,956**		**2,221**	

* Defined as reduced or non-susceptibility

Table 3b. Antimicrobial susceptibility for Serratia spp. bacteraemia (England and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2016	
Antimicrobial agent	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***
Gentamicin	695	1	705	2	715	2	806	2	898	2
Ciprofloxacin	640	7	667	7	663	5	759	7	864	5
Ceftazidime	557	15	532	17	546	13	619	12	694	11
Cefotaxime	396	18	401	17	408	13	426	14	459	17
Meropenem	574	<1	605	1	631	<1	744	1	858	<1
Ertapenem	276	1	330	2	382	1	589	2	686	1
Tobramycin	230	11	238	19	207	20	250	22	297	28
Piperacillin/Tazobactam	634	8	658	12	668	9	752	10	776	9
Total *Serratia* spp. bacteraemia reports	**751**		**772**		**814**		**884**		**973**	

* Defined as reduced or non-susceptibility

Table 3c. Antimicrobial susceptibility for *Citrobacter* spp. bacteraemia (England and Northern Ireland): 2012 to 2016

	2012		2013		2014		2015		2016	
Antimicrobial agent	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***	**No. tested**	**% resistant***
Gentamicin	585	5	646	4	665	2	839	4	920	3
Ciprofloxacin	548	2	599	3	612	4	781	3	877	3
Ceftazidime	477	12	486	13	471	13	661	14	741	11
Cefotaxime	338	11	370	12	363	15	439	15	508	11
Meropenem**	465	0	535	<1	568	<1	754	<1	851	0
Ertapenem	195	1	283	0	370	3	609	1	709	<1
Tobramycin	183	4	210	5	194	3	274	5	346	4
Amikacin	346	<1	383	1	390	1	484	1	568	1
Piperacillin/Tazobactam	550	8	614	8	623	10	793	10	839	9
Total *Citrobacter* spp. bacteraemia reports	**675**		**735**		**764**		**919**		**1,032**	

* Defined as reduced or non-susceptibility; ** 0% indicates zero bacteraemia episodes in underlying data that were found to be resistant for the antibiotic tested

Table 4a. Multi-drug antimicrobial testing and non-susceptibility among isolates of bacteraemia due to *Enterobacter* spp., England, 2016

Organism	Antimicrobial combinations	No. tested	% resistant†
Enterobacter spp.	Gentamicin and ciprofloxacin	2,024	2
	Gentamicin and 3rd-generation cephalosporin*	2,030	4
	Ciprofloxacin and 3rd generation cephalosporin*	2,014	4
	Gentamicin, ciprofloxacin and 3rd generation cephalosporin*	1,990	2
	Gentamicin, ciprofloxacin, 3rd generation cephalosporin*and meropenen	1,935	<1

* Any of cefotaxime, ceftazidime, cefpodoxime or ceftriaxone; †defined as reduced or non-susceptibility

Table 4b. Multi-drug antimicrobial testing and non-susceptibility among isolates of bacteraemia due to *Serratia* spp., England, 2016

Organism	Antimicrobial combinations	No. tested	% resistant†
Serratia spp.	Gentamicin and ciprofloxacin	868	1
	Gentamicin and 3rd-generation cephalosporin*	866	2
	Ciprofloxacin and 3rd generation cephalosporin*	864	3
	Gentamicin, ciprofloxacin and 3rd generation cephalosporin*	849	<1
	Gentamicin, ciprofloxacin, 3rd generation cephalosporin*and meropenen	826	0

* Any of cefotaxime, ceftazidime, cefpodoxime or ceftriaxone; †defined as reduced or non-susceptibility

Table 4c. Multi-drug antimicrobial testing and non-susceptibility among isolates of bacteraemia due to *Citrobacter* spp., England, 2016

Organism	Antimicrobial combinations	No. tested	% resistant†
Citrobacter spp.	Gentamicin and ciprofloxacin	961	1
	Gentamicin and 3rd-generation cephalosporin*	968	1
	Ciprofloxacin and 3rd generation cephalosporin*	950	1
	Gentamicin, ciprofloxacin and 3rd generation cephalosporin*	943	<1
	Gentamicin, ciprofloxacin, 3rd generation cephalosporin*and meropenen	826	0

* Any of cefotaxime, ceftazidime, cefpodoxime or ceftriaxone; †defined as reduced or non-susceptibility

Microbiology Services

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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References

1. Office for National Statistics (ONS). Mid-year population estimates for England, Wales and Northern Ireland
2. PHE (2017). Polymicrobial bacteraemia and fungaemia in England, Wales and Northern Ireland: 2016. *HPR* **11**(12): Infection Report
3. Leclercq R, Cantón R, Brown DFJ *et al* (2013). EUCAST expert rules in antimicrobial susceptibility testing. *Clin Microbiol Infect* **19**(2): 141-160
4. European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for interpretation of MICs and Zone Diameters, Version 1.3, 2011
5. European Committee on Antimicrobial Susceptibility Testing. Breakpoint Tables for interpretation of MICs and Zone Diameters, Version 5.0, 2015
6. Pitout JD, Laupland KB (2008). Extended-spectrum β-lactamase–producing *Enterobacteriaceae:* an emerging public health concern. *Lancet Infect Dis*. **8**:159–66
7. Nordmann P, Naas T, Poirel L (2011). Global spread of carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis*. **17**(10):1791–8
8. PHE (2013). Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae
9. PHE (2013). Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae
10. PHE (2015). Electronic reporting system. Enhanced surveillance of of carbapenamase-producing Gram-negative bacteria. NHS Trust and microbiology laboratory user guide
11. PHE. Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI).
12. Mycology Reference Laboratory (MRL) Bristol.

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