Public Health England

Health Protection Report
weekly report

Infection report

Volume 11 Number 15 Published on: **21 April 2017**

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

These analyses are based on data relating to the diagnosis of blood stream infections by *Enterococcus* spp. bacteraemia between 2009 and 2016. Data for England were extracted from the Public Health England (PHE) voluntary surveillance database, SGSS (Second Generation Surveillance System) on 15 March 2017. Data for Wales and Northern Ireland were extracted separately (DataStore on 9 March and CoSurv on 15 February 2017, respectively) and are included in the geographical and species analyses only.

SGSS comprises a communicable disease module (CDR, formerly CoSurv/LabBase2) and a separate comprehensive antimicrobial resistance module (AMR; formerly AmSurv). The majority of analyses presented are based on data from the CDR module of SGSS. The exceptions are the analyses of resistance to more than one antibiotic among *Enterococcus spp.* bacteraemia, these are based on data from the AMR module. This module captures more comprehensive antibiogram data allowing more robust evaluation of multi-drug resistance rates. However, these data cannot be used for trend analysis due to the addition of this data collection being relatively recent.

Rates of bacteraemia laboratory reports were calculated using mid-year resident population estimates for the respective year and geography with the exception of 2016 rates, which were based on 2015 population estimates as population estimates for 2016 were not available at the time of producing this report [1,2]. Geographical analyses were based on residential postcode, 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 the trends, age and sex distribution and geographical distribution, of cases of *Enterococcus* spp. bacteraemia in England, Wales and Northern

Ireland. Antimicrobial susceptibility five-year trends for England and Northern Ireland have been included in the report. In addition, details of relevant recent antimicrobial resistance alerts and microbiological services guidance concerning enterococcal isolates are provided. A web appendix is available featuring the findings of this report including only data submitted via SGSS from laboratories in England.

The data presented here may differ in some instances from data in earlier publications due to the change in surveillance systems and the inclusion of late reports.

Key points

- the overall incidence rate of *Enterococcus* spp. bacteraemia in England, Wales and Northern Ireland was 12.6 per 100,000 population in 2016
- in 2016, the *Enterococcus* spp. bacteraemia rates in England, Northern Ireland and Wales were 12.4, 13.1 and 15.4 per 100,000 population, respectively
- within England, the South West PHE centre (PHEC) reported the highest rate (14.8/100,000 population) of *Enterococcus* spp. bacteraemia and Yorkshire and Humber the lowest (9.0/100,000 population) in 2016; all PHECs reported an increase between 2012 and 2016 in absolute terms.
- 85% of enterococcal bacteraemia isolates were reported to species level in 2016
- the two most frequently isolated species within the genus in 2016 were *Enterococcus faecalis*, and *Enterococcus faecium*, representing 42% and 33% respectively; the primacy of each varied by country
- the incidence rate of *Enterococcus* spp. bacteraemia was highest among the elderly (≥75 years; 56.1/100,000) and infants (<1 year old; 40.4); and higher among males than females (15.4 and 9.8/100,000 respectively) in 2016
- there was a relatively low rate of *E. faecium* bacteraemia in infants (aged <1 year) compared with *E. faecalis* bacteraemia (2.6 compared with 31.2/100,000)
- in England, 77% of infant enterococcal bacteraemias occurred in the first four weeks of life
- the percentage of *Enterococcus* spp. from England and Northern Ireland resistant to vancomycin reduced from 17% in 2015 to 15% in 2016 following annual increases in the preceding four years
- in 2016, the proportion of isolates of *E. faecium* resistant to ampicillin/amoxicillin, vancomycin, teicoplanin and linezolid was higher than the corresponding proportion seen with *E. faecalis*.

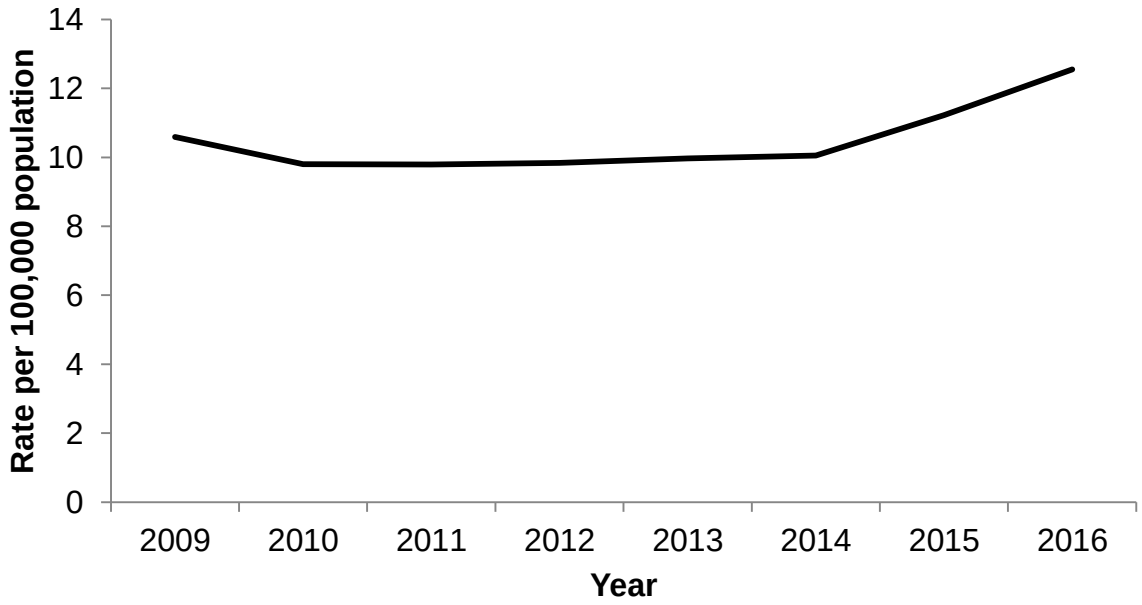
Trends

Between 2009 and 2016 there has been an overall increase in the incidence rate of bacteraemia caused by *Enterococcus* spp., climbing from 10.6 to 12.6 per 100,000 population in England, Wales, and Northern Ireland (figure 1). However, the incidence rate has fluctuated over the time period, with a decrease between 2009 and 2010, followed by a relatively stable period (around 9.5/100,000 population) until 2014. Between 2014 and 2016 an absolute increase of 24.8% in the rate of enterococcal bacteraemia infection was reported (10.1 per 100,000 to 12.6, respectively).

The observed increase in *Enterococcus* spp. bacteraemia reports observed between 2014 and 2016 may be partly due to more extensive laboratory reporting to PHE following the switch from LabBase2 to SGSS in October 2014. Other relevant and potentially contributory laboratory changes included the widespread adoption of MALDI-TOF, changes in PCR testing in a number of laboratories, and national policy changes and public health interventions resulting in an increase in blood cultures being taken [3,4]

Enterococcus faecalis was the eighth most commonly identified organism reported in mono-microbial bacteraemias/fungaemias in 2016, comprising 1.9% of such infections. In addition, *Enterococcus faecalis* and *E. faecium* were the fifth and seventh most common organisms in poly-microbial bacteraemias/fungaemias (4.3% and 2.8% of such infections), respectively [5].

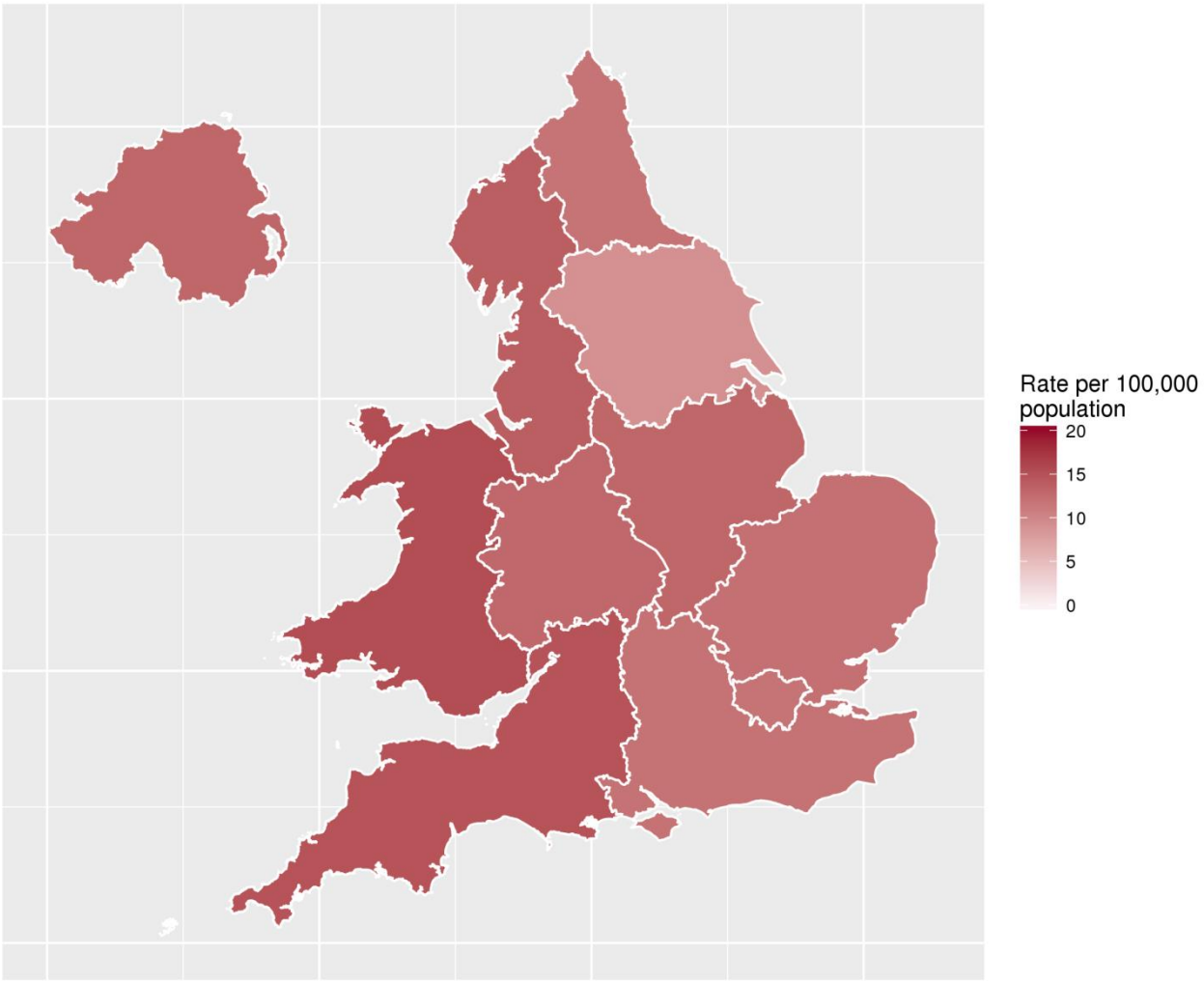
Figure 1. *Enterococcus* spp. bacteraemia per 100,000 population (England, Wales and Northern Ireland): 2009 to 2016



Geographic distribution

The overall rates of *Enterococcus* spp. bacteraemia in England, Wales and Northern Ireland in 2016 were 12.4, 15.4 and 13.1 per 100,000 population, respectively (figure 2). In England and Northern Ireland, there are links from the different laboratories to SGSS/CoSurv that report clinically significant isolates. Data from Wales is collected by extraction from a single laboratory information system used by all microbiology laboratories, where all positive blood cultures are extracted from all laboratories, including those not thought to be clinically significant.

Figure 2. Geographical distribution of *Enterococcus* spp. bacteraemia per 100,000 population (England, Wales and Northern Ireland): 2016



Between 2012 and 2016, the reported *Enterococcus* spp. bacteraemia rates increased by 31.7% in England (9.4 to 12.4/100,000 population; table 1) and 5.9% in Northern Ireland (12.3 to 13.1/100,000 population), with a 3.8% decrease reported in Wales (16.0 to 15.4/100,000 population).

Within England, incidence rates of *Enterococcus* spp. bacteraemia varied greatly in 2016, from 9.0 per 100,000 population in the Yorkshire and Humber PHEC to 14.8 per 100,000 in the South West PHEC (table 1).

All PHECs in England reported increased rates of *Enterococcus* spp. bacteraemia between 2012 and 2016. No single PHEC in England continuously reported the highest (or lowest) rates.

Table 1. *Enterococcus* spp. bacteraemia per 100,000 population by region (England, Wales and Northern Ireland): 2012 to 2016

		Rate per 100,000 population				
Region	**PHE Centre**	**2012**	**2013**	**2014**	**2015**	**2016**
North of England	North East	8.1	8.6	8.0	8.6	11.8
	Yorkshire and Humber	7.4	6.4	6.7	9.3	9.0
	North West	11.1	11.6	11.5	11.9	13.8
Midlands and East of England	West Midlands	8.9	11.7	12.0	12.1	12.9
	East Midlands	9.3	9.3	8.9	11.8	13.0
	East of England	9.4	8.8	9.9	10.3	12.1
London	London	10.1	9.6	10.2	10.3	11.8
South of England	South West	10.6	10.3	11.0	13.7	14.8
	South East	8.3	8.0	7.9	9.7	11.9
England		9.4	9.4	9.7	10.9	12.4
Northern Ireland		12.3	13.4	12.1	12.5	13.1
Wales		16.0	17.2	15.2	16.2	15.4
England, Wales & Northern Ireland		**9.8**	**10.0**	**10.1**	**11.2**	**12.6**

Species distribution

In 2016, 85% of *Enterococcus* spp. bacteraemia reports were identified to species level in England, Wales and Northern Ireland, an increase from 82% reported to species level in 2012. There was variation by country with 84%, 96% and 99% of *Enterococcus* spp. bacteraemia reports identified to species level in England, Wales and Northern Ireland, respectively, in 2016.

Across England, Wales and Northern Ireland, 42% of *Enterococcus* spp. bacteraemia reports were identified as *E. faecalis* in 2016 (n=3,177/7,501). *E. faecium* was the second most frequently identified *Enterococcus* spp. (33%; n=2,871/7,501). Over the past five years, the proportion of *Enterococcus* spp. bacteraemia caused by *E. faecium* has increased from 34% in 2012 to 38% in 2016; the proportion of *Enterococcus* spp. bacteraemia caused by *E. faecalis* has remained stable.

Of note within other enterococcal bacteraemia species; the number of *E. raffinosus* bacteraemia reports increased from 24 in 2012 to 48 in 2016. However, the proportion of *Enterococcus* spp. bacteraemia caused by *E. raffinosus* remained low. There was also a sustained decrease in the number of *E. gallinarum* bacteraemia reports, from 127 in 2012 to 95 in 2016.

The changes in distribution of less common species of *Enterococcus* may in part be due to the increasing use of MALDI-ToF analysis in hospitals, which allows for better species identification and also a greater reporting of minor species not previously recognised in most clinical laboratories.

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

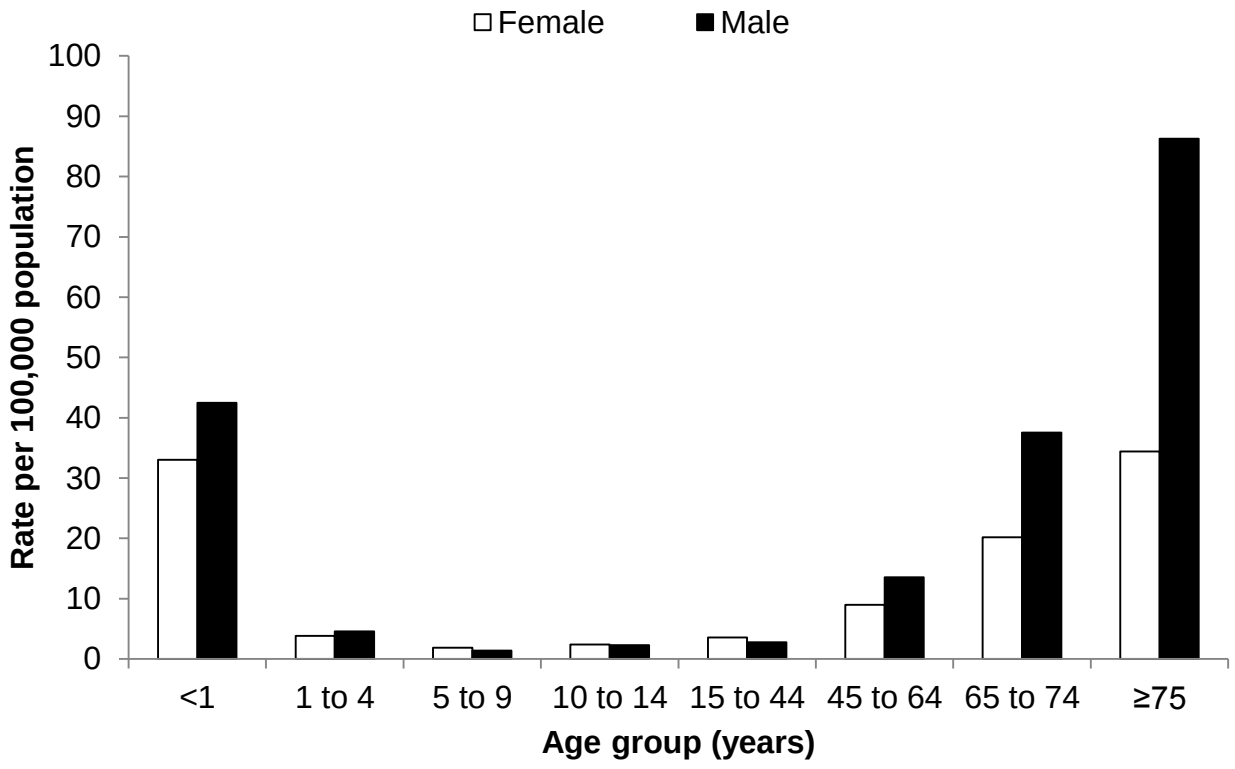
	2012		2013		2012		2015		2016	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
***Enterococcus* spp.**	5,747	100	5,864	100	5,964	100	6,709	100	7,501	100
E. avium	55	1	50	1	55	1	65	1	53	1
E. casseliflavus	34	1	42	1	57	1	54	1	71	1
E. durans	25	<1	23	<1	20	<1	20	<1	20	<1
E. faecalis	2,406	42	2,429	41	2,453	41	2,768	41	3,177	42
E. faecium	1,973	34	2,094	36	2,238	38	2,512	37	2,871	38
E. gallinarum	127	2	111	2	85	1	88	1	95	1
E. gilvus	0	<1	0	<1	0	<1	0	<1	1	<1
E. hirae	4	<1	1	<1	5	<1	5	<1	6	<1
E. malodoratus	0	<1	0	<1	0	<1	0	<1	1	<1
E. raffinosus	24	<1	40	1	35	1	54	1	48	1
Enterococcus spp., other named	63	1	40	1	58	1	38	1	33	<1
Enterococcus spp., species not recorded	1,036	18	1,034	18	958	16	1,105	16	1,125	15

Age and sex distribution

In line with previous reports, the highest rates of *Enterococcus* spp. bacteraemia in England, Northern Ireland and Wales in 2016 were observed in those aged 75 years or older (56.1/100,000 population) and those aged less than one year (40.4/100,000 population) [6].

Variation in rates were also observed by gender, with higher rates noted in men (15.4/100,000 population) than women (9.8/100,000 population) in 2016, exceptions being for those aged between five and 44 years (figure 3). The most striking differences were noted in those aged 75 years and over (males: 86.3/100,000 population; females: 34.4/100,000 population) and to a lesser extent in those aged between 65 and 74 years (males: 37.5/100,000 population; females: 20.2/100,000 population).

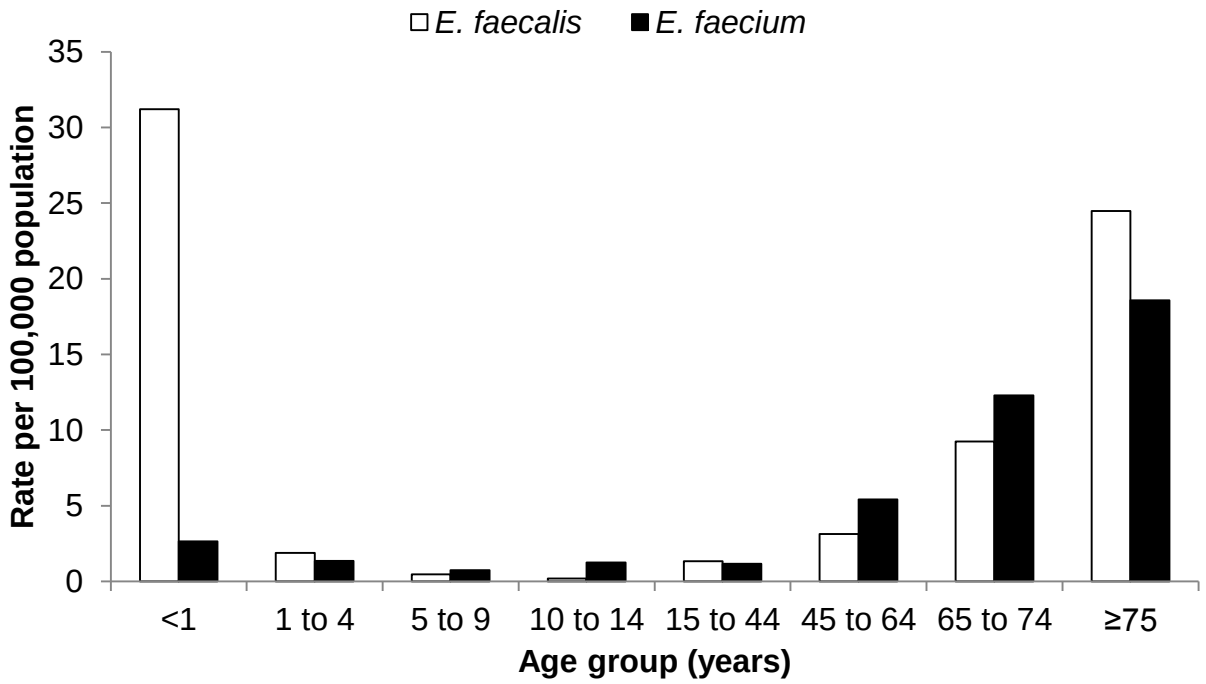
Figure 3. *Enterococcus spp*. bacteraemia rates by age and sex (England, Wales and Northern Ireland): 2016



Of the Enterococcal bacteraemias reported in infants less than one year of age, 77% are identified as *E. faecalis* (225/291) and 7% as *E. faecium* (19/291). The relative age distribution between the two most frequently reported *Enterococcus* spp. bacteraemia species, *E. faecalis* and *E. faecium*, differed in 2016 in England. Infants less than one year had the highest incidence of *E. faecalis* bacteraemia (31.2/100,000 population), followed

by those aged 75 years and over (24.5/100,000 population; figure 4). In comparison, *E. faecium* was far less likely to cause bacteraemia in infants (2.6/100,000 population).

Figure 4. *E. faecalis* and *E. faecium* bacteraemia rates by age (England, Wales and Northern Ireland): 2016



In England, neonatal (<29 days old) reports accounted for 77% of enterococcal bacteraemia in infants (<1 year; n=221/287); with a rate 0.33/1,000 live births in 2016.

Antimicrobial resistance

Glycopeptide (vancomycin/teicoplanin) resistance of *Enterococcus* spp. has been identified by the Department of Health expert Advisory Committee for Antimicrobial Prescribing, Resistance and Healthcare Associated Infections (APRHAI) as a key drug-bug combination and features in the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) annual reports [7,8].

Antimicrobial resistance data were available for England and Northern Ireland only. The proportion of isolates showing vancomycin resistance among all *Enterococcus spp*. from bacteraemia in England and Northern Ireland increased each year from 12% in 2012 to 17% in 2015 before decreasing to 15% in 2016.

A 2016 UK public health resistance alert recommended that laboratories perform linezolid susceptibility tests on all *Enterococcus* spp. isolates from blood (and other sterile sites); however, the level of test reporting in 2016 was only 64%, albeit an increase from 2012, when only 57% of enterococcal bacteraemia episodes had a linezolid result reported. Resistance rates have remained at 1% or lower from 2012 to 2016.

Resistance among *E. faecalis* isolates was rare in 2016, with rates ≤2% for each of ampicillin/amoxicillin, vancomycin, teicoplanin and linezolid (table 3a). Notably, the proportion of *E. faecalis* bacteraemia isolates that were resistant to ampicillin/amoxicillin decreased between 2012 and 2016 from 4.3% to 1.7%. This decline is likely to be as a result of the improved species identification *within Enterococcus spp*., with fewer misidentifications of *E. faecium* as *E. faecalis*. Resistance to ampicillin/amoxicillin is not expected in *E. faecalis* isolates; this fact is commonly used as a distinguishing characteristic to differentiate between *E. faecalis* and *E. faecium* species.

The proportion of isolates of *E. faecium* resistant to each antibiotic was higher than the corresponding proportion seen with *E. faecalis*. In 2016 the proportion of *E. faecium* from blood specimens resistant to ampicillin/amoxicillin was 90.2%, vancomycin 22.2%, teicoplanin 23.4% and linezolid 1.1% (table 3b).

Resistance to ampicillin/amoxicillin and linezolid identified in *E. faecium* specimens has remained stable over the five year period (2012 to 2016), with only slight fluctuations observed. However, a steady increase in the proportion of *E. faecium* bacteraemia isolates resistant to glycopeptides was reported from 2012 to 2015 with a decrease seen in 2016,

the proportion of *E. faecium* isolates resistant to vancomycin or teicoplanin was 22% and 23% respectively.

The prevalent glycopeptide resistance gene systems confer resistance to both vancomycin and teicoplanin (VanA) or to vancomycin without resistance to teicoplanin (VanB). The apparent higher proportion of isolates resistant to teicoplanin (table 3b) most probably reflects differential local testing and reporting preferences for one or other glycopeptide.

Caution is needed in the interpretation of vancomycin resistance in all enterococci rather than by particular species. A number of enterococci have genes encoding intrinsic low-level vancomycin resistance (e.g. *vanC*; found in *E. gallinarum* and *E. casseliflavus*), while other species such as *E. faecalis* and *E. faecium* only manifest resistance following acquisition of *vanA* or *vanB* genes [9].

It is important to identify enterococcal bacteraemia episodes to species level and perform all relevant antimicrobial relevant susceptibility tests; this knowledge would be especially important for infection control and the limitation of potential outbreaks, the concern being that acquired resistance is transferable between organisms [10]. Patients yielding linezolid-resistant enterococci should be isolated, as a precaution, to prevent onward transmission

Table 3a. Antimicrobial susceptibility for *E. faecalis* bacteraemia (England and Northern Ireland); 2012 to 2016

Antimicrobial agent	2012		2013		2014		2015		2016	
	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*
Ampicillin/Amoxicillin	1,954	4	1,961	3	1,862	3	2,102	2	2,479	2
Vancomycin	1,878	1	1,875	1	1,810	2	2,084	1	2,459	1
Teicoplanin	1,467	1	1,471	1	1,462	2	1,663	2	1,968	2
Linezolid	1,196	<1	1,338	<1	1,285	<1	1,520	<1	1,839	<1
Total *E. faecalis* bacteraemia reports	**2,176**		**2,203**		**2,233**		**2,530**		**2,921**	

*defined as reduced- or non-susceptibility

Table 3b. Antimicrobial susceptibility for *E. faecium* bacteraemia (England and Northern Ireland); 2012 to 2016

Antimicrobial agent	2012		2013		2014		2015		2016	
	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*	No. tested	% resistant*
Ampicillin/Amoxicillin	1,620	92	1,680	92	1,666	91	1,883	92	2,275	90
Vancomycin	1,619	20	1,678	24	1,696	24	1,951	26	2,276	22
Teicoplanin	1,358	20	1,378	24	1,402	25	1,616	28	1,970	23
Linezolid	1,195	1	1,311	1	1,302	2	1,534	1	1,848	1
Total *E. faecium* bacteraemia reports	**1,806**		**1,882**		**2,049**		**2,307**		**2,691**	

*defined as reduced- or non-susceptibility

Microbiology services

In 2016, the proportion of reports of enterococcal bacteraemia in which the organism was not fully identified decreased slightly to 15%. Precise species identification of isolates would improve the monitoring of trends in emerging enterococci in particular, in addition to assisting with instigating appropriate treatment and control mechanisms locally [11].

A UK Public Health Resistance Alert was cascaded in June 2016 highlighting that potentially transferable oxalidinone (linezolid and tedizolid) resistance mediated by the *optrA* gene has been detected in *E. faecalis* in the UK and Republic of Ireland. Laboratories are recommended to screen enterococci and staphylococci from sterile sites for resistance to linezolid. Any isolates classified as linezolid-resistant (using the EUCAST criteria) should be referred to PHE's Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (AMRHAI) for confirmation [12]. Welsh laboratories should refer any linezolid-resistant isolates to the Specialist Antimicrobial Chemotherapy Unit (SACU), which will confirm resistance to linezolid before referring on to PHE's AMRHAI [13].

Laboratories are requested to send any enterococcal isolates with suspected linezolid or tigecycline resistance, as well as isolates which show resistance to teicoplanin but not vancomycin to AMRHAI for further investigation (amrhai@phe.gov.uk) [14]. AMRHAI will also examine isolates with suspected high level daptomycin MICs, though it should be noted (i) that there are no EUCAST breakpoints and (ii) that MICs for *E. faecium* typically are 2-4 mg/L. For advice on treatment of antibiotic-resistant infections due to these opportunistic pathogens, laboratories should contact the Medical Microbiologists at PHE's Bacteriology Reference Department at Colindale on colindalemedmicro@phe.gov.uk.

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, the PHE AMRHAI Reference Unit, Public Health Wales and HSC Public Health Agency (Northern Ireland), 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.

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