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Antimicrobial susceptibility of the pathogens of bacteraemia in the UK and Ireland 2001–2002: the BSAC Bacteraemia Resistance Surveillance Programme

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***Objectives*: To describe the current patterns of antimicrobial resistance in the major pathogens of bacteraemia in the UK and Ireland, to highlight any unexpected resistance patterns and to act as a reference baseline for future studies.**

***Methods*: In 2001 and 2002, 5092 blood culture isolates were collected by 29 laboratories distributed across the UK and Ireland. A single central laboratory re-identified the isolates and measured MICs by the BSAC agar dilution method.**

***Results*: Oxacillin resistance was found in 42% of *Staphylococcus aureus* and 76% of coagulase-negative staphylococci. Streptococci were generally susceptible to β-lactams, but tetracycline resistance was common (except in *Streptococcus pneumoniae*) and particularly common among group B isolates (82% resistant). Nine percent of *S. pneumoniae* had reduced susceptibility to penicillin (MICs 0.12–1 mg/L), but none required ≥2 mg/L for inhibition. High-level gentamicin resistance was seen in 43% of *Enterococcus faecalis*, often in combination with raised ciprofloxacin MICs (≥32 mg/L), but these isolates remained susceptible to ampicillin and imipenem. Only linezolid and tigecycline showed *in vitro* potency against a large proportion of *Enterococcus faecium*. Vancomycin resistance was restricted to enterococci (20% of *E. faecium*, 3% of *E. faecalis*) and a single isolate of coagulase-negative staphylococci (0.2%, MIC of 8 mg/L). *Escherichia coli* isolates were commonly resistant to amoxicillin (56%) and tetracycline (88%) but remained susceptible to ceftazidime, piperacillin/tazobactam and imipenem. Extended-spectrum β-lactamases were detected in 2% of *E. coli* (none in 2001, 3.2% in 2002), 5% of *Klebsiella* spp. and 8% of *Enterobacter* spp. Resistance rates of *Pseudomonas aeruginosa* to ciprofloxacin, ceftazidime, gentamicin, imipenem and piperacillin/tazobactam were between 4% and 7%. Among the newly licensed and developmental agents, there was no resistance to linezolid in Gram-positive organisms. Ertapenem had a wide spectrum, covering Enterobacteriaceae, streptococci and oxacillin-susceptible staphylococci. MICs of tigecycline were low for Gram-positive species and Enterobacteriaceae except Proteeae and *Enterobacter* spp.**

***Conclusion*: Antimicrobial resistance among major bloodstream pathogens to those antimicrobials often selected for empirical therapy was relatively uncommon in 2001–2002, usually <10%. An important exception was oxacillin resistance in *S. aureus*.**

Keywords: bloodstream infections, resistance epidemiology, British Isles, antibacterials

Introduction

Clinically significant bacteraemia is a serious consequence of a wide variety of initially localized infections, including those of the urinary tract, respiratory tract, surgical sites and indwelling devices such as central lines. Treatment is often urgent and may have to be undertaken without definitive identification of the organisms involved and their antimicrobial susceptibilities. Many studies[1–4] have found that inadequate empirical therapy of bacteraemic infections is associated with adverse outcomes, including increased mortality, although this

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finding is not universal.[5] Antimicrobial resistance is a common reason for inadequate therapy. In this situation, knowledge of the most likely causative organisms and their expected resistance patterns can increase the probability of selecting an effective antimicrobial for empirical treatment. Timely surveillance studies can contribute reliable information to this knowledge base at national or regional level, although knowledge of local variations, at the level of individual hospital units, is an invaluable extension.[6] Appropriate surveillance is also essential to monitor resistance trends and help to identify the factors that may be driving them. Such knowledge is a prerequisite to implementing rational measures to tackle the resistance problem.[7]

Bacteraemia provides a particularly good setting for resistance surveillance. Indeed, the reporting of methicillin resistance for *Staphylococcus aureus* bacteraemia was made mandatory in England from April 2001 precisely because it was seen as a marker of the prevalence of MRSA infection, which in turn was seen as a marker of infection control practice and rates of hospital-acquired infection.[8] Unlike the situation in other infections, such as respiratory tract infections in community practice, there is little doubt that samples are taken from nearly all patients, so the scope for sampling bias is considerably reduced. The range of pathogens involved is wide, and the information collected on blood isolates of these organisms can also illuminate their capabilities in other contexts, for example in skin, soft-tissue and surgical site infections, or in endocarditis. The collection of additional information, such as the presumed focus of infection and the therapeutic specialty caring for the patient, enhances the usefulness of the microbiological data.

The BSAC Bacteraemia Resistance Surveillance Programme is designed to meet the need, in the UK and Ireland, for detailed surveillance using consistent methodology. Surveillance began in 2001, is ongoing, and is intended to continue long-term. Each year, the programme collects isolates and related patient information from 25 laboratories distributed across the UK and Ireland. The isolates are re-identified and tested centrally against a wide range of antimicrobials, including recently developed and investigational compounds. In addition to publication of pooled data at national level, results from the BSAC Bacteraemia Resistance Surveillance Programme are fed back to individual collecting laboratories where they may contribute to clinical thinking, quality assessment and standardization of laboratory testing.

Comparison between results from this programme and others will clarify whether, and to what extent, the theoretical weaknesses of different surveillance systems really affect the reliability of the results obtained. The results reported here for the first 2 years of the programme will also provide a baseline for reference as resistance continues to evolve in the future.

Materials and methods

Isolates

Twenty-five clinical laboratories in the UK and Ireland contributed isolates in each of the years 2001 and 2002, with 29 laboratories (see Acknowledgements) contributing in total. The laboratories were selected to give wide geographical coverage, serving urban and rural areas with a range of social deprivation scores, and were attached to hospitals of varying sizes. Twenty predominantly served teaching hospitals and nine exclusively served non-teaching hospitals. Each was asked to collect up to 10 consecutive isolates per year of each of the following 12 groups of organisms: *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., Proteeae, *Pseudomonas* spp., and other Gram-negative bacteria (excluding *Salmonella* spp. and *Neisseria* spp.), *S. aureus*, coagulase-negative staphylococci, enterococci, β-haemolytic streptococci, *Streptococcus pneumoniae*, and other α- and non-haemolytic streptococci. The 'other Gram-negative' group was split into Enterobacteriaceae and non-fermenting Gram-negative bacteria for testing and reporting purposes (see Results).

The isolates were cultured from blood samples routinely collected for clinical testing, and were considered by the responsible medical microbiologist in the collecting laboratory to be clinically significant. Repeat isolates of the same species within 1 week were considered to represent the same infection episode and were excluded.

Isolates were sent on an agar chosen to maintain the viability of the organisms to a central laboratory (Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL), Health Protection Agency, Colindale, London) for further testing. The Respiratory and Systemic Infection Laboratory (RSIL) (Health Protection Agency, London) undertook the species identification of streptococci and typing of pneumococci.

Isolates were subcultured on appropriate agar to confirm purity. Their identities were confirmed, in most cases to species level, by colony morphology, Gram stain and further tests as follows:

Enterobacteriaceae, with API20E strips (bioMérieux, Marcy l'Étoile, France).

Non-fermenting Gram-negative bacteria, with API20NE strips (bioMérieux).

Staphylococci, by coagulase tests and, for coagulase-negative staphylococci, with PCR.[9] Coagulase-negative staphylococci remaining unspeciated after all rounds of PCR were recorded as unspeciated.

S. pneumoniae, by optochin susceptibility, and by serotyping with slide agglutination using serum from the Statens Serum Institute. Non-typeable organisms were confirmed as *S. pneumoniae* by bile solubility and recorded as untyped.

α- and non-haemolytic streptococci, with ID RAPID 32 STREP kits (bioMérieux). Further speciation was according to the scheme described by Beighton, Hardy & Wiley.[10]

β-Haemolytic streptococci, by Lancefield group.

Enterococci, by PCR of ddI.[11,12] Enterococci remaining unspeciated after all rounds of species-specific PCR were confirmed as Lancefield group D and recorded as unspeciated enterococci.

Antimicrobial susceptibility testing

MICs were measured by the BSAC agar dilution method.[13,14] Iso-Sensitest agar was supplemented with 5% defibrinated whole horse blood for streptococci and *Haemophilus influenzae*, with 20 mg/L NAD for *H. influenzae* only, and with 50 g/L PNPG (*p*-nitrophenylglycerol) for Proteeae to prevent swarming. Columbia agar supplemented with 2% sodium chloride was used for testing staphylococci with oxacillin. The incubation atmosphere was air for all species except *H. influenzae*, *S. pneumoniae* and other α- and non-haemolytic streptococci, for which air plus 4%–6% CO_2 was used. The incubation temperature was 35–37°C for all species except staphylococci with oxacillin, for which it was 30°C. The inoculum size was 10^4 cfu/spot except in the case of staphylococci with penicillin for which it was increased to 10^6 cfu/spot.

Co-amoxiclav was tested in a 2:1 ratio (amoxicillin/clavulanic acid) and piperacillin/tazobactam was tested with a fixed concentration of 4 mg/L of tazobactam; the reported MICs refer to the concentrations of amoxicillin or piperacillin, respectively. The antimicrobial agents tested are listed in the results tables and were obtained from suppliers as follows:

Aventis (West Malling, Kent, UK) supplied cefotaxime and teicoplanin. Bayer (Newbury, Berkshire, UK) supplied ciprofloxacin. GlaxoSmithKline (Welwyn Garden City, Hertfordshire, UK) supplied

ceftazidime and clavulanic acid. Merck, Sharp & Dohme (Hoddesdon, Hertfordshire, UK) supplied cefoxitin, ertapenem and imipenem. Pharmacia (Milton Keynes, Buckinghamshire, UK) supplied clindamycin and linezolid. Sigma (Poole, Dorset, UK) supplied amoxicillin, ampicillin, cefuroxime, clindamycin, erythromycin, gentamicin, oxacillin, penicillin, tetracycline, trimethoprim and vancomycin. Wyeth (Maidenhead, UK) supplied piperacillin and tazobactam. Wyeth-Ayerst (New York, USA) supplied minocycline and tigecycline.

Detection of extended-spectrum β-lactamases

Enterobacteriaceae (excluding *Serratia* spp.) collected in 2001 were screened with ceftazidime. Resistant isolates with MICs ≥ 4 mg/L (or, in the case of *Klebsiella*, those with MICs ≥ 2 mg/L) were further tested by agar dilution with ceftazidime and cefotaxime ± 4 mg/L clavulanic acid. Isolates requiring MICs ≥ 8-fold lower in the presence of clavulanate (for either cephalosporin) were inferred to have ESBLs.[15] This level of testing was customary and generally considered adequate at that time. However, in response to concerns about the emergence of CTX-M enzymes, the screening and testing were upgraded for isolates collected in 2002. From 2002, Enterobacteriaceae (excluding *Serratia* spp.) were screened with both ceftazidime and cefotaxime. Isolates resistant to cefotaxime at 1 mg/L and those with ceftazidime MICs ≥ 4 mg/L (and *Klebsiella* with ceftazidime MICs ≥ 2 mg/L) were further tested with ceftazidime, cefotaxime and cefepime ± 4 mg/L clavulanic acid. Isolates requiring MICs ≥ 8-fold lower in the presence of clavulanate (for any of these cephalosporins) were inferred to have ESBLs. The criterion of ≥8-fold potentiation gives some false-positive results (with cefotaxime/clavulanate and cefepime/clavulanate only) for *Klebsiella oxytoca* isolates, with phenotypes implying hyperproduction of K1 enzymes i.e. highly resistant to piperacillin/tazobactam and cefuroxime but not to cefotaxime and ceftazidime.[16] Such cases were excluded from the count of likely ESBL producers, after confirming that they gave a negative result in cefpodoxime/cefpodoxime+clavulanate combination disc tests (Oxoid).

Statistical methods

Isolates were classified as susceptible, intermediate or resistant according to the most recently available BSAC breakpoints.[17,18] Ninety-five percent confidence intervals for percentages were calculated by the exact Binomial method.

Associations between pairs of categorical variables were assessed using chi-squared (χ^2) tests or Fisher's exact tests, as appropriate. Where multiple tests were performed, a Bonferroni correction was applied to the *P* values. Age groups of 0–4, 5–24, 25–49, 50–74 and ≥75 were used to test for association between patient age and other factors; patients of unknown age were excluded from these tests. Patients of unknown sex were excluded from tests for association with sex. Categories of care setting considered were community and outpatients; patients in hospital for <48 h at the time of isolate collection; patients in hospital for >48 h at the time of isolate collection; other and unknown. For referring specialty, the categories considered were intensive care; haematology/oncology; surgery; general medicine; care of the elderly; paediatrics; nephrology; cardiology; other and unknown. The categories for focus of infection were lines and devices (excluding urinary catheters); genitourinary tract (including urinary catheters); respiratory tract; gastrointestinal tract; skin, soft tissue and surgical sites; endocarditis; other and unknown.

Results

MIC summary measures and resistance rates are shown in Tables 1–5.

Isolates and patient characteristics

A total of 5092 isolates was collected, 2522 in 2001 and 2570 in 2002, 68.5% of them from England and the remainder divided approximately equally between Ireland, Northern Ireland, Scotland and Wales. Male patients contributed 56.7% of isolates (based on 5058 isolates), and 52.0% of patients had been in hospital >48 h when samples were taken (based on 4620 isolates). The mean age of patients was 58.5 years (based on 5038 isolates); >70% were aged 50 or over, and 30% were aged 75 or over.

Associations between demographic factors and organism group

There were highly significant associations between organism group and each of the demographic indicators (adjusted $P < 0.0001$ in each case).

Sex. E. coli was strongly associated with females, as might be expected given the prevalence of *E. coli* in urinary tract infection: 58% of *E. coli* isolates were from females, compared with 38% for all other organisms in this (selected) collection.

Age. E. coli and Proteeae were associated with older age groups, with patients aged 75 years and more contributing 41% and 48% of these groups, respectively. Coagulase-negative staphylococci and β-haemolytic streptococci were less commonly isolated from older patients.

Care setting. There was a strong association between *S. pneumoniae* and patients in hospital <48 h. *E. coli* and β-haemolytic streptococci showed similar but less pronounced associations. *Enterobacter* spp., *Enterococcus* spp. and coagulase-negative staphylococci were less likely to be from patients in hospital for less than 48 h.

Referring specialty. Coagulase-negative staphylococci were associated with referrals from haematology/oncology and paediatrics. *S. aureus* were associated with nephrology, *S. pneumoniae* with general medicine, and β-haemolytic streptococci with accident and emergency, other and unknown specialities.

Focus of infection. S. pneumoniae isolates were overwhelmingly associated with prior respiratory tract infections: 73% of *S. pneumoniae* blood isolates were attributed to respiratory sources, compared with 9% for all other organism groups. Seventy percent of the coagulase-negative staphylococci were attributed to lines and devices, compared with 19% for all other organism groups. β-Haemolytic streptococci were associated with skin, soft tissue and surgical site infections, whereas α- and non-haemolytic streptococci were associated with endocarditis. *E. coli* and Proteeae were associated with genitourinary tract infections.

Associations between patient factors

Most associations between sex and other patient factors were weak or insignificant. However, there was a very strong association between sex and age (predictably), and also in each of the six possible pairwise combinations of age, care setting, specialty and focus (adjusted $P < 0.0001$ in all cases).

Age. Females comprised 49% of patients aged ≥75 years, compared with 41% of patients in younger age groups.

Patients in the oldest age group were more likely than expected to have been admitted to hospital <48 h before isolate collection, and less likely to have unknown care setting.

Table 1. Staphylococci: resistance (%, with 95% confidence limits), breakpoints and MIC summary values (mg/L)

Antimicrobial		OXA	PEN	TZP	IPM	ETP[a]	GEN	CIP	TMP	ERY	CLI	VAN	TEC	LZD	TET	MIN[a]	TGC[a]
Low breakpoint: S ≤		2	0.12	2	4	n/a	1	1	0.5	0.5	0.5	4	4	4	1	0.5	n/a
High breakpoint: R ≥		4	0.25	4	8	n/a	2	2	1	1	1	8	8	8	2	1	n/a
Oxacillin-susceptible	minimum	≤0.5	≤0.015	≤0.5	≤0.06	0.06	0.06	0.25	≤0.25	0.25	0.125	≤0.5	≤0.5	≤0.5	0.125	0.03	0.125
S. aureus $n = 280$ (145[a])	MIC_{50}	≤0.5	32	1	≤0.06	0.125	0.5	0.5	0.5	0.5	0.125	1	1	2	0.5	0.125	0.25
	MIC_{90}	≤0.5	≥128	2	≤0.06	0.25	1	1	1	1	0.125	1	1	4	1	0.125	0.25
	maximum	2	≥128	4	0.125	0.5	32	≥256	≥256	≥256	≥256	2	4	4	128	4	0.5
	1st mode	≤0.5	≥128	≤0.5	≤0.06	0.125	0.5	0.5	0.5	0.5	0.125	1	1	2	0.5	0.125	0.25
	(2nd mode)		(0.06)	(≤0.5)				(128)	(≥256)	(16)	(≥256)				(64)	(4)	
	% R	0	82.5	1.8	0	n/a	2.9	5.0	31.4	13.6	0.4	0	0	0	4.3	0.7	n/a
	95% CI	n/a	77.5–86.8	0.6–4.1	0–1.1	n/a	1.2–5.6	2.7–8.2	26.0–37.2	9.8–18.2	0–2	0–1.1	0–1.1	0–1.1	2.2–7.4	0–3.8	n/a
Oxacillin-resistant	minimum	4	2	1	≤0.06	0.125	0.06	0.25	≤0.25	0.25	0.125	≤0.5	≤0.5	≤0.5	0.125	0.03	0.125
S. aureus $n = 203$ (100[a])	MIC_{50}	≥256	≥128	128	4	≥32	0.5	128	0.5	≥256	0.25	1	1	2	0.5	0.125	0.25
	MIC_{90}	≥256	≥128	128	≥32	≥32	1	≥256	16	≥256	≥256	1	1	4	1	0.125	0.5
	maximum	≥256	≥128	≥256	≥32	≥32	128	≥256	≥256	≥256	≥256	2	4	4	≥256	0.25	1
	1st mode	≥256	≥128	128	4	≥32	0.5	128	0.5	≥256	0.125	1	1	2	0.5	0.125	0.25
	(2nd mode)			(1)	(≥32)	(0.5)	(64)	(0.5)	(128)	(0.5)	(≥256)				(64)		
	% R	100	100[b]	100[b]	100[b]	100[b]	9.9	94.6	29.6	83.7	22.7	0	0	0	1.5	0.0	n/a
	95% CI	n/a	n/a	n/a	n/a	n/a	6.1–14.8	90.5–97.3	23.4–36.4	77.9–88.5	17.1–29.0	0–1.5	0–1.5	0–1.5	0.3–4.3	0–3.0	n/a
Oxacillin-susceptible coagulase-negative staphylococci $n = 98$ (56[a])	minimum	≤0.125	≤0.015	≤0.5	≤0.06	0.06	≤0.25	0.125	≤0.25	≤0.125	0.125	≤0.5	0.125	≤0.5	≤0.06	≤0.015	0.06
	MIC_{50}	0.25	4	≤0.5	≤0.06	0.25	≤0.25	0.25	1	0.5	0.125	1	2	1	0.5	0.125	0.25
	MIC_{90}	2	64	1	≤0.06	0.5	16	32	≥256	≥256	0.25	2	8	2	16	0.5	1
	maximum	2	≥128	2	0.125	1	≥256	≥256	≥256	≥256	≥256	4	≥32	4	128	1	1
	1st mode	0.25	8	≤0.5	≤0.06	0.25	≤0.25	0.25	0.5	0.25	0.125	1	2	1	0.25	0.06	0.25
	(2nd mode)	(2)	(0.03)	(≥256)			(8)	(64)	(≥256)	(≥256)	(≥256)				(64)		
	% R	0.0	75.5	0.0	0.0	n/a	21.4	18.4	52.0	37.8	6.1	0.0	22.4	0.0	32.7	3.6	n/a
	95% CI	n/a	65.9–83.6	0–3.0	0–3.0	n/a	13.8–30.9	11.3–27.5	41.7–62.2	28.2–48.1	2.3–12.9	0–3.0	14.6–32.0	0–3.0	23.5–42.9	0.4–12.3	n/a
Oxacillin-resistant coagulase-negative staphylococci $n = 311$ (144[a])	minimum	4	≤0.015	≤0.5	≤0.06	0.06	≤0.25	≤0.03	≤0.25	≤0.125	0.125	≤0.5	0.125	≤0.5	0.125	0.06	0.125
	MIC_{50}	128	64	2	0.25	4	16	8	≥256	≥256	0.125	2	4	1	2	0.25	0.5
	MIC_{90}	≥256	≥128	128	≥32	≥32	128	128	≥256	≥256	≥256	2	8	2	128	0.5	1
	maximum	≥256	≥128	≥256	≥32	≥32	≥256	≥256	≥256	≥256	≥256	8	≥32	4	≥256	32	4
	1st mode	≥256	≥128	1	≤0.06	≥32	64	0.25	≥256	≥256	0.125	2	8	1	2	0.25	0.5
	(2nd mode)			(≥256)	(≥32)	(4)	(≤0.25)	(64)	(0.5)	(0.25)	(≥256)				(128)	(4)	
	% R	100	100[b]	100[b]	100[b]	100[b]	74.3	59.2	82.3	72.7	30.9	0.3	35.0	0.0	60.8	9.7	n/a
	95% CI	n/a	n/a	n/a	n/a	n/a	69.0–79.0	53.5–64.7	77.6–86.4	67.4–77.5	25.8–36.3	0.0–1.8	29.7–40.6	0–1.0	55.1–66.2	5.4–15.8	n/a

MICs and breakpoints in mg/L; S, susceptible; R, resistant; 95% CI, 95% confidence interval (exact binomial calculation) for % R; n/a: not available or not applicable; CIP, ciprofloxacin; CLI, clindamycin; ERY, erythromycin; GEN, gentamicin; IPM, imipenem; LZD, linezolid; OXA, oxacillin; MIN, minocycline; PEN, penicillin; TZP, piperacillin/tazobactam; TEC, teicoplanin; TET, tetracycline; TGC, tigecycline; TMP, trimethoprim; VAN, vancomycin; ETP, ertapenem.

If more than one population peak is clearly visible on the MIC distribution, the 1st mode is reported as the mode MIC of the largest sub-population and the 2nd mode is reported as the mode MIC of the second largest sub-population.

[a]ETP, TGC and MIN were tested only in 2002 so there were fewer results than for other agents.

[b]100: edited value—staphylococci showing resistance to oxacillin are regarded as resistant to other penicillins, cephalosporins, carbapenems and combinations of β-lactams and β-lactamase inhibitors.

Table 2. Streptococci: resistance (%, with 95% confidence limits) and intermediate susceptibility (%), breakpoints and MIC summary values (mg/L)

Antimicrobial		PEN[a]	AMX	TZP	CTX	IPM	ETP[a,b]	GEN	CIP[a]	ERY	CLI	VAN	TEC	LZD	TET	MIN[b]	TGC[b]
Low breakpoint: S≤		0.12	1	2	1	4	2	1	1	0.5	0.5	4	4	4	1	0.5	n/a
(for *S. pneumoniae*[a])		(0.06)					(0.03)	2	(n/a)								n/a
High breakpoint: R≥		0.25	2	4	2	8	4		2	1	1	8	8	8	2	1	
(for *S. pneumoniae*[a])		(2)					(2)		(4)								
S. pneumoniae[a] *n* = 447 (220[b])	minimum	≤0.03	≤0.015	≤0.03	≤0.015	≤0.015	≤0.015	8	0.5	0.06	0.03	0.25	0.125	0.5	≤0.125	0.03	0.03
	MIC_{50}	0.06	≤0.015	≤0.03	≤0.015	≤0.015	≤0.015	64	2	0.125	0.125	0.5	0.125	1	0.25	0.125	0.125
	MIC_{90}	0.06	0.06	0.125	0.125	≤0.015	0.03	64	4	32	0.25	0.5	0.125	2	0.25	0.25	0.25
	maximum	1	1	4	1	0.125	0.5	128	64	≥256	≥256	1	0.5	2	64	16	0.25
	1st mode	≤0.03	≤0.015	≤0.03	≤0.015	≤0.015	≤0.015	64	2	0.125	0.125	0.5	0.125	1	0.25	0.06	0.125
	(2nd mode)	(0.5)	(1)	(2)	(0.25)	(0.125)	(0.5)			(32)	(≥256)				(32)	(4)	
	%R	0	0	2.0	0	0	0	100	24.2	16.8	2.2	0	0	0	4.3	4.5	n/a
	(%I)	(8.5)					(9.5)		(75.8)								
	95% CI	0–0.7	0–0.7	0.9–3.8	0–0.7	0–0.7	0–1.3	99.3–100	20.3–28.4	13.4–20.6	1.1–4.1	0–0.7	0–0.7	0–0.7	2.6–6.6	2.2–8.2	n/a
Other α- and non-haemolytic streptococci[c] *n* = 334 (173[b])	minimum	≤0.03	≤0.015	≤0.03	≤0.015	≤0.015	≤0.015	0.5	0.5	≤0.06	≤0.015	0.25	0.125	≤0.25	≤0.125	0.03	0.03
	MIC_{50}	0.06	0.125	0.125	0.06	≤0.015	0.125	16	4	0.125	0.125	0.5	0.125	1	0.5	0.125	0.25
	MIC_{90}	0.5	0.5	1	0.25	0.06	0.5	64	8	8	0.25	1	0.25	2	64	16	0.5
	maximum	8	16	≥32	≥8	0.5	2	128	128	≥256	≥256	1	1	2	≥256	32	1
	1st mode	≤0.03	0.125	0.125	0.125	≤0.015	0.125	16	2	0.125	0.125	0.5	0.125	1	0.5	0.125	0.125
	(2nd mode)		(4)							(8)	(≥256)				(64)	(16)	
β-Haemolytic streptococci group A *n* = 167 (76[b])	minimum	≤0.008	≤0.004	0.015	≤0.015	≤0.008	≤0.015	0.25	0.25	≤0.06	≤0.06	0.125	0.125	1	0.125	0.03	0.06
	MIC_{50}	≤0.008	0.015	0.06	≤0.015	≤0.008	≤0.015	8	1	≤0.06	≤0.06	0.5	0.125	2	0.5	0.125	0.125
	MIC_{90}	0.015	0.03	0.125	≤0.015	≤0.008	≤0.015	8	1	0.125	0.125	0.5	0.125	2	64	16	0.25
	maximum	0.125	0.125	0.25	1	0.015	0.125	32	4	≥256	≥256	1	0.5	4	128	32	0.5
	1st mode	≤0.008	0.015	0.06	≤0.015	≤0.008	≤0.015	8	1	≤0.06	≤0.06	0.5	0.125	2	0.5	0.125	0.125
	(2nd mode)									(8)	(≥256)				(64)	(16)	
	%R	0	0	0	0	0	0	94.6	4.8	6.6	0.6	0	0	0	21.6	21.1	n/a
	95% CI	0–1.8	0–1.8	0–1.8	0–1.8	0–1.8	0–3.9	90.0–97.5	2.1–9.2	3.3–11.5	0–3.3	0–1.8	0–1.8	0–1.8	15.6–28.6	12.5–31.9	n/a
β-Haemolytic streptococci group B *n* = 137 (70[b])	minimum	≤0.008	≤0.004	0.03	≤0.015	≤0.008	0.03	4	0.5	≤0.06	≤0.06	0.5	0.125	0.5	0.25	0.125	0.125
	MIC_{50}	0.03	0.06	0.25	0.06	0.015	0.06	16	1	≤0.06	0.125	0.5	0.25	2	64	32	0.125
	MIC_{90}	0.06	0.125	0.25	0.06	0.015	0.06	32	2	0.25	0.125	0.5	0.5	2	64	32	0.25
	maximum	0.125	0.125	1	0.125	0.06	0.125	128	64	≥256	≥256	1	0.5	2	128	32	0.5
	1st mode	0.03	0.06	0.25	0.06	0.015	0.06	8	1	≤0.06	0.125	0.5	0.25	2	64	32	0.125
	(2nd mode)									(4)	(≥256)				(0.5)	(0.25)	
	%R	0	0	0	0	0	0	100	44.5	8.8	2.2	0	0	0	81.8	80.0	n/a
	95% CI	0–2.2	0–2.2	0–2.2	0–2.2	0–2.2	0–4.2	97.8–100	36.0–53.3	4.6–14.8	0.5–6.3	0–2.2	0–2.2	0–2.2	74.3–87.8	68.7–88.6	n/a
β-Haemolytic streptococci group G *n* = 101 (52[b])	minimum	≤0.008	≤0.004	0.015	≤0.015	≤0.008	≤0.015	1	0.5	≤0.06	≤0.06	0.25	0.125	0.5	0.125	0.06	0.06
	MIC_{50}	≤0.008	0.015	0.06	≤0.015	≤0.008	≤0.015	4	1	0.125	0.125	0.5	0.125	2	8	0.25	0.25
	MIC_{90}	0.015	0.03	0.125	0.03	≤0.008	0.03	8	1	4	0.125	0.5	0.125	2	64	32	0.5
	maximum	0.125	0.125	0.25	≥2	0.015	0.125	32	64	≥256	≥256	1	0.25	2	128	32	0.5
	1st mode	≤0.008	0.015	0.06	≤0.015	≤0.008	<0.015	4	1	0.125	0.125	0.5	0.125	2	64	0.125	0.25
	(2nd mode)				(≥2)				(64)	(4)	(≥256)				(0.5)	(16)	
	%R	0	0	0	1.0	0	0	98.0	8.9	15.8	5.0	0	0	0	66.3	40.4	n/a
	95% CI	0–2.9	0–2.9	0–2.9	0–5.4	0–2.9	0–5.6	93.0–99.8	4.2–16.2	9.3–24.5	1.6–11.2	0–2.9	0–2.9	0–2.9	56.3–75.4	27.0–54.9	n/a

I, intermediate; AMX, amoxicillin; CTX, cefotaxime.
[a]Note different breakpoints (shown in brackets) for *S. pneumoniae*.
[b]ETP, TGC and MIN were tested only in 2002 so there were fewer results than for other agents.
[c]Percent resistant not shown for other α- and non-haemolytic streptococci as there are no currently agreed BSAC breakpoints for them.
Other abbreviations and notes as Table 1.

Associations between age and referring specialty remained significant even after excluding paediatrics and care of the elderly. Patients aged 75 and over were under-represented in referrals from haematology/oncology, and were positively associated with general medicine. Young patients between 5 and 24 years were more likely to have been referred by haematology/oncology. The youngest patients (0–4 years) were more likely to have been referred by intensive care units.

Patients aged 5–24 and 24–49 were more likely than others to contribute isolates from line-related bacteraemias, whereas isolates from patients of 75 and older were more likely to have a genitourinary source.

Care setting. Community- and outpatients were more likely to have unknown referring specialty, probably simply because the defined specialties are hospital-based.

Hospital stay of >48 h was positively associated with line-related bacteraemia. A genitourinary or respiratory focus of infection was more likely among patients in hospital for <48 h. Patients for whom care setting was unknown were more likely to have bacteraemias of unrecorded origin.

Speciality. Haematology/oncology and nephrology were more likely than other specialties to refer line-related infections, and these were less commonly referred by general medicine. Surgery was more likely to refer isolates derived from the gastrointestinal tract.

Staphylococcus aureus

Oxacillin resistance was seen in 203 of 483 *S. aureus* isolates, giving a resistance rate of 42.0% (95% CI 37.6–46.6%). Oxacillin-resistant *S. aureus* showed a high prevalence of resistance to ciprofloxacin (95%) and erythromycin (84%) as is typical of the EMRSA types 15 and 16 predominant in the UK;[19] 23% were resistant to clindamycin, implying that the MLS_B resistance remained inducible in the remaining three-quarters of resistant isolates. There was some resistance to gentamicin (10%, mostly with MICs of 64 mg/L) but little to tetracycline (<2%), and none to vancomycin, teicoplanin or linezolid. The 60 isolates (30%) resistant to trimethoprim included 27 requiring MICs of only 1 mg/L, just one doubling dilution above the breakpoint for susceptibility.

The 280 oxacillin-susceptible *S. aureus* isolates were more diverse. There was much penicillin resistance (83%). There was also considerable erythromycin resistance (14%), which appeared inducible in almost all cases as only one of these 38 isolates was resistant to clindamycin. Other resistance rates were 5% or below, except for trimethoprim where 88 isolates (31%) were classified as resistant, though only 11 of these required more than 1 mg/L for inhibition.

Coagulase-negative staphylococci

The two most frequently isolated coagulase-negative species were *Staphylococcus epidermidis* (58%) and *Staphylococcus haemolyticus* (14%). Resistance rates were similar in these two species. Other isolates were mainly *Staphylococcus hominis* (10%), *Staphylococcus capitis* (5%) and unspeciated (see Methods, 10%).

Oxacillin resistance was very common in coagulase-negative staphylococci, occurring in 311 of 409 isolates (76.0%, 95% CI 71.6–80.1%). All these oxacillin-resistant isolates remained susceptible to linezolid. One isolate was resistant to vancomycin (MIC 8 mg/L) and 35% were resistant to teicoplanin, 30% requiring an MIC of 8 mg/L. Resistance to all other tested agents except minocycline was very widespread; breakpoints were not available to assess resistance to tigecycline. In contrast to oxacillin-resistant *S. aureus*, trimethoprim resistance, seen in 82% of these oxacillin-susceptible isolates, was mostly high-level, with the large majority of MICs at or above 64 mg/L.

Three-quarters of the oxacillin-susceptible coagulase-negative staphylococci (n = 98) were resistant to penicillin. Resistance to ciprofloxacin (18%), gentamicin (21%), tetracycline (33%), erythromycin (38%), trimethoprim (52%) and teicoplanin (22%) also remained common, although only 6% were resistant to clindamycin and none was resistant to imipenem, piperacillin/tazobactam, vancomycin or linezolid. The majority (55%) of trimethoprim resistance remained high-level.

Streptococcus pneumoniae

None of 447 *S. pneumoniae* isolates showed resistance to penicillin (MIC ≥ 2 mg/L), and intermediate susceptibility (MICs of 0.12–1 mg/L) was seen in only 8.5%. A similar proportion required raised MICs to other β-lactams including imipenem and ertapenem, although no more than 2% were actually resistant. Tetracycline resistance was found in 4% of the isolates. These tetracycline-resistant isolates were cross-resistant to minocycline, but tigecycline MICs were not raised. Seventeen percent were resistant to erythromycin. Gentamicin MICs were in the range 8–128 mg/L, consistent with inherent resistance. There were 39 different serotypes represented in the collection. The seven commonest serotypes together accounted for 57% of the isolates; these were 14, 9V, 8, 23F, 6B, 19F, and 3, contributing, respectively, 78, 44, 32, 31, 25, 23 and 23 of the 447 isolates. Twenty-one serotypes occurred only occasionally, each representing <1% and collectively representing only 9% of the isolates.

Other α- and non-haemolytic streptococci

Fourteen species of other α- and non-haemolytic streptococci were collected, with six species contributing 81% of the 334 isolates; these six were *Streptococcus oralis* (84 isolates), *Streptococcus anginosus* (63), *Streptococcus sanguis* (37), *Streptococcus bovis* II (32), *Streptococcus parasanguis* (27) and *Streptococcus mitis* (26). Breakpoints were not available to assess resistance in these species.

The mode MICs of ciprofloxacin (2–4 mg/L) and gentamicin (16 mg/L) were as expected given the inherent resistance of this group. Fifteen percent of the isolates required penicillin MICs ≥ 0.25 mg/L. The MIC distribution for erythromycin was clearly trimodal: the majority of isolates were distributed around a mode MIC of 0.12 mg/L but ~17% of isolates formed a sub-population around a mode of 8 mg/L, and a further 7% grouped around a mode of ≥256 mg/L. Tetracycline also produced a strikingly bimodal MIC distribution, with a first peak around 0.5 mg/L, and ~28% of isolates in an upper peak around a mode of 64 mg/L. Most isolates with raised tetracycline MICs (≥8 mg/L) also required higher MICs of minocycline (≥2 mg/L), again giving a bimodal MIC distribution. MICs of tigecycline were not raised for the tetracycline- and minocycline-resistant organisms.

β-Haemolytic streptococci

Groups A, B and G contributed the majority of the 420 isolates of β-haemolytic streptococci collected, with 167, 137 and 101 isolates, respectively; the remaining 15 isolates were of group C. Inherent gentamicin resistance was expected and found in all groups. β-Haemolytic streptococci were universally susceptible to β-lactams (including penicillin), glycopeptides and linezolid, with the excep-

Table 3. Enterococci: resistance (%, with 95% confidence limits), breakpoints and MIC summary values (mg/L)

Antimicrobial		PEN	AMP	TZP	IPM	ETP[a]	GEN	CIP	ERY	VAN	TEC	LZD	TET[a]	MIN[a]	TGC[a]
Low breakpoint: S ≤		n/a	8	n/a	4	n/a	512	n/a	n/a	4	4	4	n/a	n/a	n/a
High breakpoint: R ≥		n/a	16	n/a	8	n/a	1024	n/a	n/a	8	8	8	n/a	n/a	n/a
E. faecalis	minimum	≤0.5	0.125	≤0.5	≤0.25	2	≤2	0.5	0.06	0.125	≤0.03	≤0.5	0.25	0.06	0.125
n = 301 (149[a])	MIC_{50}	2	1	4	0.5	4	256	32	≥512	1	0.25	2	64	16	0.25
	MIC_{90}	4	2	8	1	16	≥4096	128	≥512	2	0.5	2	64	32	0.25
	maximum	64	64	≥256	128	≥32	≥4096	≥256	≥512	≥256	128	4	256	32	0.5
	1st mode	1	1	2	1	4	≥4096	128	≥512	1	0.25	2	64	16	0.25
	(2nd mode)						(16)	(2)	(2)	(≥256)	(64)		(0.5)	(0.125)	
	% R	n/a	0.3	n/a	0.3	n/a	43.2	n/a	n/a	3.0	2.7	0	n/a	n/a	n/a
	95% CI	n/a	0–1.8	n/a	0–1.8	n/a	37.5–49.0	n/a	n/a	1.4–5.6	1.2–5.2	0–1.0	n/a	n/a	n/a
E. faecium n = 138 (70[a])	minimum	≤0.5	0.125	≤0.5	≤0.25	0.015	≤2	0.25	0.06	0.125	≤0.03	≤0.5	≤0.125	0.03	0.03
	MIC_{50}	128	64	≥256	128	≥32	16	≥256	≥512	1	0.5	2	0.5	0.125	0.125
	MIC_{90}	≥256	128	≥256	≥256	≥32	2048	≥256	≥512	≥256	16	2	128	32	0.25
	maximum	≥256	≥256	≥256	≥256	≥32	≥4096	≥256	≥512	≥256	≥256	4	256	32	0.5
	1st mode	128	128	≥256	128	≥32	8	≥256	≥512	1	0.5	2	0.5	0.06	0.125
	(2nd mode)	(≤0.5)	(1)	(16)	(≤0.25)	(0.25)	(1024)	(2)	(4)	(≥256)	(8)		(128)	(32)	
	% R	n/a	86.2	n/a	89.1	n/a	31.9	n/a	n/a	19.6	15.2	0	n/a	n/a	n/a
	95% CI	n/a	79.3–91.5	n/a	82.7–93.8	n/a	24.2–40.4	n/a	n/a	13.3–27.2	9.7–22.3	0–2.1	n/a	n/a	n/a

AMP, ampicillin.
[a]ETP, TET, MIN and TGC were tested only in 2002 so there were fewer results than for other agents.
Other abbreviations and notes as previous tables.

Table 4. Enterobacteriaceae: resistance (%, with 95% confidence limits), breakpoints and MIC summary values (mg/L)

Antimicrobial		AMX	AMC	TZP	CXM	FOX	CAZ	IPM	ETP[a]	ESBL	GEN	CIP	TET[a]	MIN[a]	TGC[a]	
Low breakpoint: S ≤		16	16	16	8	8	2	4	2	n/a	1	1	1	0.5	n/a	
High breakpoint: R ≥		32	32	32	16	16	4	8	4	n/a	2	2	2	1	n/a	
E. coli $n = 495$ (250[a])	minimum		≤1	≤1	≤0.5	≤0.5	1	≤0.03	≤0.06	0.004	n/a	≤0.125	≤0.03	1	0.25	0.125
	MIC_{50}		≥512	8	4	4	4	0.25	0.125	0.008	n/a	0.5	≤0.03	2	2	0.5
	MIC_{90}		≥512	16	8	8	8	0.5	0.25	0.015	n/a	2	0.25	256	16	1
	maximum		≥512	64	≥512	≥256	≥256	≥512	1	0.125	n/a	256	≥512	≥512	≥64	2
	1st mode		≥512	4	2	4	4	0.125	0.125	0.008	n/a	0.5	≤0.03	2	1	0.25
	(2nd mode)		(4)									(16)	(32)	(256)	(8)	
	% R		56.2	6.1	3.4	9.9	9.1	2.6	0	0	1.6	11.1	7.3	88.4	89.2	n/a
	95% CI		51.7–60.6	4.1–8.5	2.0–5.4	7.4–12.9	6.7–12.0	1.4–4.4	0–0.6	0–1.2	0.7–3.2	8.5–14.2	5.1–9.9	83.8–92.1	84.7–92.8	n/a
Klebsiella spp. $n = 475$ (242[a])	minimum		≤1	≤1	≤0.5	≤0.5	≤1	≤0.03	≤0.06	0.008	n/a	≤0.125	≤0.03	0.5	1	0.5
	MIC_{50}		256	2	4	4	4	0.25	0.25	0.015	n/a	0.5	0.06	2	2	1
	MIC_{90}		≥512	16	16	32	16	1	0.25	0.03	n/a	1	1	16	16	4
	maximum		≥512	64	≥512	≥256	128	≥512	4	0.25	n/a	256	256	≥512	≥64	8
	1st mode		≥512	2	4	4	4	0.125	0.5	0.015	n/a	0.5	≤0.03	2	2	1
	(2nd mode)		(128)		(≥512)	(≥256)		(256)				(64)	(1)	(≥512)		
	% R		98.3	5.9	9.9	19.2	12.0	6.3	0	0	5.3	6.9	7.4	82.6	100	n/a
	95% CI		96.7–99.3	4.0–8.4	7.4–12.9	15.7–23.0	9.2–15.3	4.3–8.9	0–0.6	0–1.2	3.4–7.7	4.8–9.6	5.2–10.1	77.3–87.2	98.8–100	n/a
Enterobacter spp. $n = 386$ (206[a])	minimum		2	≤1	0.25	≤0.5	2	0.06	0.125	0.008	n/a	0.125	≤0.008	1	1	0.25
	MIC_{50}		256	32	4	32	≥256	0.5	0.5	0.06	n/a	0.5	0.03	4	4	1
	MIC_{90}		≥512	≥128	128	≥256	≥256	128	0.25	1	n/a	16	2	8	16	4
	maximum		≥512	≥128	≥512	≥256	≥256	≥512	2	4	n/a	≥512	256	≥256	≥64	16
	1st mode		≥512	32	4	8	≥256	0.25	0.5	0.015	n/a	0.5	0.03	4	4	1
	(2nd mode)				(64)	(≥256)		(64)		(0.25)		(128)		(≥256)		
	% R		92.0	83.4	22.3	71.2	95.9	35.2	0	0.5	7.5	14.2	10.9	95.1	100	n/a
	95% CI		96.7–99.3	79.3–87.0	18.2–26.8	66.5–75.7	93.4–97.6	30.5–40.2	0–0.8	0–2.7	5.1–10.6	10.9–18.1	8.0–14.4	91.3–97.7	98.6–100	n/a
P. mirabilis $n = 307$ (155[a])	minimum		≤1	≤1	≤0.25	≤0.5	0.5	≤0.03	0.125	0.004	n/a	0.125	0.015	4	4	1
	MIC_{50}		≤1	≤1	≤0.25	1	2	≤0.03	2	0.008	n/a	1	0.06	32	32	8
	MIC_{90}		≥512	8	0.5	2	4	0.06	4	0.015	n/a	2	0.25	64	≥64	16
	maximum		≥512	64	2	32	16	1	16	0.03	n/a	128	32	256	≥64	32
	1st mode		≤1	≤1	≤0.25	1	2	≤0.03	2	0.008	n/a	1	0.06	32	32	8
	(2nd mode)		(≥512)	(8)									(4)			
	% R		27.7	1.0	0	0.7	1.0	0	5.9	0	0	21.8	5.2	100	100	n/a
	95% CI		22.8–33.1	0.2–2.8	0–1.0	0.1–2.3	0.2–2.8	0–1.0	3.5–9.1	0–1.9	0–1.0	17.3–26.9	3.0–8.3	98.1–100	98.1–100	n/a
M. morganii $n = 64$ (30[a])	minimum		4	4	≤0.25	4	4	≤0.03	0.5	0.004	n/a	0.25	≤0.008	1	4	2
	MIC_{50}		256	64	≤0.25	32	8	0.06	2	0.015	n/a	1	0.03	16	16	4
	MIC_{90}		≥512	64	0.5	64	16	1	4	0.03	n/a	4	0.125	128	16	4
	maximum		≥512	≥128	1	≥256	16	8	4	0.125	n/a	32	128	256	≥64	8
	1st mode		256	64	≤0.25	32	8	≤0.03	2	0.015	n/a	1	0.03	16	16	4
	(2nd mode)		(4)	(4)				(1)					(128)	(2)	(4)	
	% R		98.4	98.4	0	93.8	12.5	7.8	0	0	0	31.3	3.1	96.7	100	n/a
	95% CI		91.6–100	91.6–100	0–4.6	84.8–98.3	5.6–23.2	2.6–17.3	0–4.6	0–9.5	0–4.6	20.2–44.1	0.4–10.8	82.8–99.9	90.5 100	n/a
Citrobacter spp. $n = 47$ (28[a])	minimum		8	2	1	1	1	0.06	≤0.03	0.008	n/a	0.25	0.015	2	1	0.25
	MIC_{50}		128	32	4	8	64	0.25	0.25	0.015	n/a	0.5	0.03	2	2	0.5
	MIC_{90}		≥512	64	32	≥256	≥256	128	0.5	0.25	n/a	2	2	256	16	1
	maximum		≥512	64	128	≥256	≥256	256	1	0.5	n/a	≥512	32	≥512	32	2
	1st mode		≥512	32	2	4	≥256	0.25	0.25	0.008	n/a	0.5	0.015	2	2	0.5
	(2nd mode)		(128)	(2)		(≥256)	(2)	(64)				(128)		(≥512)		
	% R		93.6	59.6	12.8	42.6	70.2	29.8	0	0	4.3	10.6	12.8	100	100	n/a
	95% CI		82.5–98.7	44.3–73.6	4.8–25.7	28.3–57.8	55.1–82.7	17.3–44.9	0–6.2	0–10.1	0.5–14.5	3.5–23.1	4.8–25.7	89.9–100	89.9–100	n/a

Serratia spp. $n = 115$ (65[a])	minimum	≤1	≤1	≤0.5	1	≤0.5	0.06	≤0.03	0.004	n/a	≤0.125	0.015	0.25	0.125	0.25
	MIC_{50}	128	64	4	128	32	0.25	0.25	0.03	n/a	1	0.125	16	4	1
	MIC_{90}	≥512	≥128	64	≥256	128	2	1	0.125	n/a	2	2	128	8	2
	maximum	≥512	≥128	128	≥256	≥256	32	2	2	n/a	128	32	256	16	8
	1st mode (2nd mode)	≥512	64 (4)	4 (64)	≥256	32	0.25 (16)	0.25	0.03	n/a	1 (32)	0.125 (2)	16	4	1
	% R	86.1	84.3	20.9	96.5	97.4	4.3	0	0	n/a	13.9	20.0	98.5	98.5	n/a
	95% CI	78.4–91.8	76.4–90.5	13.9–29.4	91.3–99.0	92.6–99.5	1.4–9.9	0–2.6	0–4.5	n/a	8.2–21.6	13.1–28.5	91.7–100	91.7–100	n/a

AMC, co-amoxiclav (2:1 ratio; amoxicillin/clavulanate); FOX, cefoxitin; ESBL, extended spectrum β-lactamase (read % R as % positive for ESBL).
[a]ETP, TET, MIN and TGC were tested only in 2002 so there were fewer results than for other agents.
Other abbreviations and notes as previous tables

tion of a single group G isolate requiring >1 mg/L of cefotaxime. Although 81% of isolates appeared susceptible to ciprofloxacin, a large proportion required MICs at the susceptibility breakpoint of 1 mg/L. Overall, 10% were resistant to erythromycin, with 7% requiring MICs of 1–32 mg/L and 2% requiring ≥256 mg/L; the pattern was similar in all groups. Overall, 2% were resistant to clindamycin. The prevalence of tetracycline resistance was remarkable at 22%, 82% and 66% in groups A, B and G, respectively; in all groups the mode MIC for the resistant sub-population was 64 mg/L. Cross-resistance was apparent in 205 isolates tested with both tetracycline and minocycline, 83% of tetracycline-resistant isolates also showing minocycline resistance, but tigecycline MICs were similar (no more than one dilution higher) in tetracycline-resistant compared with -susceptible isolates.

Enterococci

Of 447 enterococci received, 301 (67%) were *Enterococcus faecalis* and 138 (31%) *Enterococcus faecium.*

E. faecalis. High-level gentamicin resistance (MIC ≥ 1024 mg/L) was found in 43% of the *E. faecalis* isolates, and 48% required MICs ≥ 512 mg/L. There was very little resistance (≤3%) to other agents for which breakpoints have been set—ampicillin, imipenem, linezolid, teicoplanin and vancomycin. MIC distributions for penicillin, piperacillin/tazobactam, ertapenem and tigecycline were unimodal with modes of 1, 2, 4 and 0.25 mg/L, respectively. The MIC distributions for erythromycin, tetracycline and ciprofloxacin were all bimodal, with a substantial proportion of isolates showing increased resistance. For erythromycin, 61% of the isolates were in the upper peak of the MIC distribution where they required ≥512 mg/L for inhibition. For tetracycline (tested only in 2002, $n = 149$) the upper peak, with its mode of 64 mg/L, included 82% of the isolates, almost all of which were also in the upper peak for minocycline (MICs ≥ 4 mg/L, mode 16 mg/L). A group of isolates accounting for 50% of the total all required at least 32 mg/L of ciprofloxacin for inhibition and had a mode MIC of 128 mg/L, compared with a mode of 2 mg/L for the remaining isolates. There was a strong association between high-level gentamicin resistance and ciprofloxacin MICs ≥ 32 mg/L: ciprofloxacin MICs ≥ 32 mg/L were required for 121 (93%) of the 130 isolates with high-level gentamicin resistance but for only 30 (18%) of the other 171. This association reflected the dissemination of two multiresistant strains.[20]

E. faecium. The prevalence of high-level gentamicin resistance (MICs ≥ 1024 mg/L) was similar to that in *E. faecalis* at 32% (and 37% with MICs ≥ 512 mg/L), but resistance to other agents except linezolid (0%) was more frequent, at 15% for teicoplanin, 20% for vancomycin and over 85% for ampicillin and imipenem. A smaller proportion (34%) of *E. faecium* than *E. faecalis* were found in the upper peak of the tetracycline MIC distribution; like the corresponding *E. faecalis* isolates, these required higher MICs of minocycline (generally ≥4 mg/L), although the mode MIC of tigecycline was only raised by one dilution to 0.25 mg/L. For all the remaining agents tested (penicillin, piperacillin/tazobactam, ertapenem, ciprofloxacin and erythromycin), the MIC distributions were bimodal and 76%–90% of isolates were found in the upper peak; the mode MICs for both peaks are listed in Table 3. Unlike *E. faecalis*, there was no significant association between high ciprofloxacin MICs and high-level gentamicin resistance in *E. faecium.*

Table 5. Non-fermenting Gram-negative bacteria: resistance (%, with 95% confidence limits) and intermediate susceptibility (%), breakpoints and MIC summary values (mg/L)

Antimicrobial		TZP	CAZ[a]	IPM	GEN[a]	CIP[a]
Low breakpoint: S ≤		16	8	4	1	1
(for *Acinetobacter*[a])			(2)			
High breakpoint: R ≥		32	16	8	8	8
(for *Acinetobacter*[a])			(4)		(2)	(2)
P. aeruginosa $n = 367$	minimum	≤0.5	0.03	0.125	≤0.125	0.015
	MIC_{50}	4	2	1	1	0.25
	MIC_{90}	16	4	4	4	4
	maximum	256	≥512	128	≥512	64
	1st mode	4	2	1	1	0.25
	(2nd mode)				(≥512)	
	% R	5.2	3.8	7.1	6.3	7.4
	(% I)				(37.6)	(6.0)
	95% CI	3.1–8.0	2.1–6.3	4.7–10.2	4.0–9.3	4.9–10.5
S. maltophilia $n = 44$	minimum	4	0.5	16	0.5	0.06
	MIC_{50}	16	1	≥64	8	2
	MIC_{90}	16	2	≥64	128	8
	maximum	≥512	16	≥64	≥512	16
	1st mode	16	1	≥64	2	2
	(2nd mode)	(256)				
	% R	9.1	2.3	100	63.6	25.0
	(% I)				(31.8)	(61.4)
	95% CI	2.5–21.7	0.1–12.0	93.4–100	47.8–77.6	13.2–40.3
Acinetobacter[a] spp. $n = 75$	minimum	≤0.5	0.5	≤0.03	≤0.125	0.03
	MIC_{50}	2	4	0.06	0.5	0.5
	MIC_{90}	32	16	0.25	8	64
	maximum	≥512	64	0.5	256	256
	1st mode	≤0.5	4	0.06	0.5	0.5
	(2nd mode)	(4)				(256)
	% R	13.3	65.3	0	17.3	21.3
	95% CI	6.5–23.2	53.5–76.0	0–3.9	9.6–27.8	12.7–32.3

[a]Note different breakpoints (shown in brackets) for *Acinetobacter*.
Other abbreviations and notes as previous tables.

E. coli

There was little resistance to imipenem, ertapenem, ceftazidime or piperacillin/tazobactam. Nine percent and 10% of isolates showed (mostly low-level) resistance to cefoxitin and cefuroxime, respectively; 7% were resistant to both. The presence of ESBL was confirmed in none of 245 isolates collected in 2001 (95% CI 0–1.2%), and in eight of 250 isolates (3.2%, 95% CI 1.4–6.2%) collected in 2002. These latter eight were all ceftazidime-resistant, so their detection did not depend on the improved screening introduced that year. Gentamicin resistance, seen in 11% of isolates, was mostly low-level, with about half of the resistant isolates requiring only 2 mg/L for inhibition. The MIC distributions of amoxicillin, ciprofloxacin and tetracycline were markedly bimodal. For tetracycline (tested only in 2002, $n = 250$), the upper peak, with a mode MIC of 256 mg/L, included 83 isolates (33%), but even the lower peak had its mode at 2 mg/L so most of these isolates were also classified as resistant by BSAC criteria, giving an overall resistance rate of 88%. Similarly, 89% were resistant to minocycline, but the mode MIC of tigecycline was only 0.25 mg/L. Fifty-six percent of the *E. coli* isolates were resistant to amoxicillin, the great majority of these requiring ≥512 mg/L for inhibition; only 6% of isolates remained resistant to amoxicillin in the presence of clavulanate. Thirty-six isolates of *E. coli* (7%) were resistant to ciprofloxacin and all but two of these required MICs between 8 and ≥512 mg/L. Twenty-nine of these 36 were also resistant to amoxicillin, and all 16 of those tested with tetracycline (in 2002) were resistant; ceftazidime, cefotaxime, piperacillin/tazobactam, imipenem and ertapenem, however, retained good activity against most ciprofloxacin-resistant isolates, and tigecycline also performed well with MICs ≤ 1 mg/L.

Klebsiella spp.

Of 475 *Klebsiella* spp. isolates collected, 344 (72%) were *Klebsiella pneumoniae* and 108 (23%) *K. oxytoca*. Gentamicin and ciprofloxacin MIC distributions were similar to those seen in *E. coli*. The rate of resistance to tetracycline (83%) was also similar to that in *E. coli* but a smaller proportion of isolates (8%) were in the upper peak, with MICs ≥ 64 mg/L. All were resistant to minocycline and the mode MIC for tigecycline was 1 mg/L. Predictably, resistance to amoxicillin was extremely widespread, seen in 98% of the isolates. Six

percent to 10% of isolates remained resistant to amoxicillin and piperacillin in the presence of β-lactamase inhibitors. ESBLs were found in 13 of 233 isolates in 2001 (5.6%, 95% CI 3.0–9.4%) and in 12 of 242 isolates in 2002 (5.0%, 95% CI 2.6–8.5%); testing in the latter year was more comprehensive (see Methods). Of the 25 ESBL-positive isolates, 19 were *K. pneumoniae*, two *K. oxytoca* and four unspeciated *Klebsiella*. Twelve of the 25 were resistant (and 13 susceptible) to piperacillin/tazobactam, 15 were resistant to gentamicin and 12 resistant to ciprofloxacin; five were resistant to all three of these agents but none was resistant to imipenem.

Enterobacter spp.

Two species dominated the collection of 386 *Enterobacter* isolates—*Enterobacter cloacae* (78%) and *Enterobacter aerogenes* (11%). Resistance rates were broadly similar in the two species, although somewhat lower in *E. aerogenes* for ciprofloxacin (2% versus 9%), cefuroxime (50% versus 73%) and gentamicin (5% versus 13%). The overall ciprofloxacin, gentamicin and tetracycline resistance rates (11%, 14% and 95%, respectively) were similar to those among *E. coli* and *Klebsiella* spp. isolates, with the pattern of tetracycline resistance being more like that in *Klebsiella* spp. (only 5% with MICs ≥ 64 mg/L). Resistance to amoxicillin (92%), co-amoxiclav (83%) and cefoxitin (96%) was widespread, as expected; 22% were also resistant to piperacillin/tazobactam and 35% to ceftazidime. There was no imipenem resistance, but one isolate of *E. cloacae* was resistant to ertapenem, with an MIC of 4 mg/L. Although susceptible to gentamicin, ciprofloxacin and imipenem (MIC 0.5 mg/L), this isolate, which was not an ESBL producer, was also resistant to all the other tested penicillins and cephalosporins, including piperacillin/tazobactam. Most ceftazidime-resistant isolates did not produce ESBLs and were presumed to be AmpC hyperproducers. However, ESBLs were inferred in a surprisingly high proportion of *Enterobacter* isolates. Based on limited screening with ceftazidime and subsequent tests with ceftazidime/clavulanate and cefotaxime/clavulanate, ESBL production was inferred in 11 of 180 isolates in 2001 (6.1%, 95% CI 3.1–10.7%) and, based on more extensive testing, including cefepime/clavulanate synergy (which is less prone to interference from inducible AmpC than ceftazidime/clavulanate and cefotaxime/clavulanate), in 18 of 206 isolates in 2002 (8.7%, 95% CI 5.3–13.5%). Of these 29 ESBL-positive isolates, 22 were *E. cloacae*, none *E. aerogenes* and seven were other species. Only eight of the 29 were resistant to piperacillin/tazobactam, but five were resistant to all three of piperacillin/tazobactam, gentamicin and ciprofloxacin as well as to ceftazidime.

Proteeae

Proteus mirabilis was the largest single contributor (76%) to the collection of 405 Proteeae isolates, followed by *Morganella morganii* (16%). *P. mirabilis* showed little resistance to antimicrobials other than tetracyclines (to which Proteeae are inherently resistant), amoxicillin (28% resistant) and gentamicin (22% resistant, two-thirds of which required MICs of only 2 mg/L). As expected, in addition to resistance to tetracycline, *M. morganii* showed resistance to cefuroxime and to amoxicillin with or without clavulanate. Although 31% were gentamicin-resistant, about one-third of these isolates were inhibited by gentamicin at 2 mg/L. Ciprofloxacin resistance was uncommon at 3%. No ESBLs were detected among the Proteeae.

Other Enterobacteriaceae

Among the great variety of Enterobacteriaceae species collected under the umbrella of 'other Gram-negative bacteria', only *Citrobacter* spp. and *Serratia* spp. were numerous enough for discussion, with 47 and 115 isolates, respectively. Twenty percent of *Serratia* isolates were resistant to ciprofloxacin. Thirty percent of *Citrobacter* isolates were resistant to ceftazidime, a similar proportion to *Enterobacter* spp., and two isolates (4%, both *Citrobacter freundii*) were inferred to produce ESBLs.

Pseudomonas aeruginosa

P. aeruginosa were tested against ciprofloxacin, ceftazidime, gentamicin, imipenem and piperacillin/tazobactam, and the resistance rates for all these antimicrobials were between 3.8% and 7.4%. Of 367 isolates in the collection, four were resistant to all five agents. One of these had outstandingly high MICs for ceftazidime (≥512 mg/L) and imipenem (128 mg/L) and was identified as producing a VIM metallo-β-lactamase.[21]

Other non-fermenting Gram-negative bacteria

The 'other Gram-negative bacteria' group contributed non-fermenters as well as Enterobacteriaceae to the collection, the most numerous being *Stenotrophomonas maltophilia* (44 isolates) and *Acinetobacter* spp. (75 isolates). These were tested against the same panel of antimicrobials as *P. aeruginosa*. Resistance to ciprofloxacin, gentamicin and imipenem was widespread among *S. maltophilia* and, whereas only 9% of the isolates were strictly resistant to piperacillin/tazobactam under BSAC test conditions, a further 59% required MICs of 16 mg/L. Among *Acinetobacter* spp., resistance to ceftazidime was very common (65%), but only 13% of isolates were resistant to piperacillin/tazobactam and none was resistant to imipenem.

Discussion

Since 1989, diagnostic laboratories in England and Wales have reported their own identification and susceptibility data for clinical blood culture isolates voluntarily to the Health Protection Agency (formerly the Public Health Laboratory Service), where records are now maintained in the LabBase system. Over 90% of laboratories now participate, giving a clear picture of the relative contribution of different pathogens.[22,23] The two largest single contributors, by a long way, are *S. aureus* at 22% and *E. coli* at 20% (in 2000); *S. aureus* has only recently overtaken *E. coli* as the leading agent of bacteraemia. The remaining Gram-positive groups included in the BSAC study contribute between 3% (α- and non-haemolytic streptococci other than *S. pneumoniae*) and 8% (coagulase-negative staphylococci), while the remaining Gram-negative groups contribute between 3% (*Enterobacter* spp.) and 6% (*Klebsiella* spp.). Altogether, the bacterial groups studied here account for ~90% of all cases of bacteraemia in England and Wales.

Bacteraemia reports to the Health Protection Agency documented a rapid rise in methicillin resistance in *S. aureus* during the 1990s, from under 1.7% of *S. aureus* isolates in 1990, through 4% in 1993, 21% in 1996 and 34% in 1998 to reach 42% in England and Wales in 2000.[22–25] The most recent figures—42% in 2001 and 43% in 2002—suggest that the trend may now have levelled out.[26,27] Sentinel data from the European Antimicrobial Resistance Surveillance System (EARSS, http://www.earss.rivm.nl) also report a steady level (44%) of methicillin resistance in the UK in 2001 and 2002. Our results

agree closely with all of these, showing an oxacillin resistance rate of 42% in 2001–2002 and little variation between the years (43% in 2001, 41% in 2002). Although occasional isolates of *S. aureus* with reduced susceptibility to vancomycin have been reported in the UK in recent years,[28,29] none was identified in this study.

Like methicillin resistance in *S. aureus*, penicillin non-susceptibility in *S. pneumoniae* increased during the 1990s—from 0.3% in 1989 to 3.7% in 1996 and 7% in 2000 according to routine reports (including isolates from meningitis) for England and Wales.[22,30–33] The 8.5% prevalence recorded here in the BSAC study in 2001–2002 is influenced by the inclusion of isolates from Ireland, where there is known to be a higher rate of penicillin resistance, at least in isolates obtained from respiratory sources.[34] The regional and national rates among the present bacteraemia isolates were 6.5% (95% CI 4.1%–9.7%, $n = 336$) non-susceptible in England and Wales as against 16% in the island of Ireland (95% CI 8.6%–26.3%, $n = 75$). The figure for England and Wales, along with the observation that the overall rate was similar in both years, suggests that the previous rise in penicillin non-susceptibility has not continued between 2000 and 2002. Data from EARSS (http://www.earss.rivm.nl) hint at a reduction in non-susceptibility in the UK from 6.2% in 2000 to 4.7% in 2002, and this is supported by the routine data reported to the Health Protection Agency's LabBase system. Erythromycin resistance reported from routine testing increased similarly from 3.3% in 1989 to stabilize at about 11% during 1993–1998.[22,31]
The resistance rate rose again, to 15%, by 2000[33] and this is very similar to the rate of 17% observed in the present study.

The serotype distribution in *S. pneumoniae* was not unlike that seen in 1999 and 2000 in England and Wales,[33,35] with the same six serotypes occurring most commonly. The estimated coverage of these isolates by current vaccines was also very similar to that estimated for 1999 and 2000. In our collection, 52% (61%) of isolates were in serotypes (serogroups) represented in the 7-valent conjugate vaccine,[36] compared with 54% (56%) in 1999 and 56% (66%) in 2000. Among isolates from children under 5 years old ($n = 45$), the proportion belonging to serotypes (serogroups) covered by the 7-valent vaccine in our collection in 2001–2002 was 78% (87%), compared with 74% and 75% (86% and 82%) in 1999 and 2000, respectively. Assuming cross-protection within serogroups, the 23-valent polysaccharide vaccine[37] would have covered 96% of all our pneumococcal isolates, the same as in 1999 and 2000.

The absence of penicillin resistance among β-haemolytic streptococci was confirmed by LabBase reports in 2001 and 2002.[38,39] Erythromycin resistance in the present isolates (7%, 9% and 16% in groups A, B and G, respectively) was reasonably similar to the levels seen in LabBase reports for the same years (~3%–4%, 5%–7% and 14%–15%). The prevalence of tetracycline resistance among β-haemolytic streptococci was startling at 22%, 82% and 66% in groups A, B and G, respectively, and higher than for routinely reported isolates in the same years (10%–12%, 70% and 43%–49%). Many resistant isolates were from infants under the age of 1 year: fully 43 (93%) of 46 group B isolates from this age group were resistant to tetracycline. Considering that neither infants nor their mothers should be treated with tetracyclines, it is not apparent what is selecting and conserving such high levels of resistance in this group. The presence of cross-resistance to minocycline suggests that the likely resistance mechanism is *tetM*, commonly carried on transposon Tn*916*. The contribution to bacterial survival and virulence of genes linked to those for tetracycline resistance remains to be investigated.

In the absence of MIC breakpoints, it was not possible to compare antimicrobial susceptibilities for α- and non-haemolytic streptococci other than *S. pneumoniae* as the routine reports are restricted to susceptible and resistant categories. However, raised MICs of tetracycline were surprisingly prevalent in this group, too, with 28% of isolates forming a distinct sub-population requiring ≥8 mg/L.

Ciprofloxacin is poorly active against streptococci, and therefore a high prevalence of low-level resistance is not of particular concern. However, we should be alert to rising MICs. Lim *et al*.[40] have highlighted the danger of first-step mutations accumulating in *S. pneumoniae*, with concomitant increases in MICs but without increases in resistance rates defined by certain breakpoints. Already, among the α- and non-haemolytic streptococci collected in this study, 23% required ciprofloxacin MICs ≥ 8 mg/L. The same was true for only 6% of *S. pneumoniae* and less than 1% of β-haemolytic streptococci. Fluoroquinolone resistance in streptococci does not yet appear to be a major problem in the UK and Ireland, but the emergence of a resistant strain of *S. pneumoniae* in England has been reported recently[41] and it will be sensible to continue monitoring not only the apparent resistance rates but also the MICs of the isolates.

Vancomycin resistance in enterococci is another key resistance that increased very markedly through the 1990s, reaching 5% in *E. faecalis* and 24% in *E. faecium* by 1998.[22] The resistance rate we found for ampicillin in *E. faecalis* (0.3%) was considerably lower than that in the routinely reported data for 2001 and 2002 (9% and 6%, respectively), although the vancomycin resistance rates were similar in the two datasets at around 3% in both years.[42,43] The ampicillin difference has been noted before[22] and is commonly attributed to misidentification (of *E. faecium* as *E. faecalis*) by the methods used in diagnostic laboratories, rather than the PCR technique used in the central laboratory for this study. A misidentification rate of 13% for *E. faecium* was also recorded in a quality assessment exercise for the European Antimicrobial Resistance Surveillance System.[44] The observed association between high-level gentamicin resistance and raised ciprofloxacin MICs in *E. faecalis* was found to reflect the presence of two widely disseminated strains.[20] In *E. faecium*, the ampicillin resistance rate seen in this study was similar to that for routinely reported data for the same two years (86% versus 85%), as was the vancomycin resistance rate (20% versus 19%).

In *E. coli*, there was good agreement between our results and those reported routinely in 2001 and 2002 for ampicillin and ciprofloxacin.[45,46] Our study found resistance to gentamicin rather more frequently (11%) than the routine reports (3%–5%); the position of the breakpoint on the shoulder of the main peak in the MIC distribution probably contributed to this apparent difference. For *Klebsiella*, *Enterobacter* and *Serratia* spp., the rates of resistance to ceftazidime, ciprofloxacin and gentamicin noted in this BSAC survey were in good general agreement with those reported from routine data in 2001 and 2002.[45,46] A single *Enterobacter* isolate was found resistant to ertapenem; its susceptibility profile was consistent with a combination of impermeability and AmpC enzyme hyper-production. Such isolates, while uncommon, have been reported previously.[47]

The overall prevalence of extended-spectrum β-lactamases in the Enterobacteriaceae was 1.6% in *E. coli*, 5% in *Klebsiella* spp. and 8% in *Enterobacter* spp. The overall rate in *E. coli* was closely comparable with that found in Spain in 2001,[48] but the much more important point is that all the ESBL-producing *E. coli* in the BSAC survey were isolated in 2002. This represents a sharp rise from 0% to 3.2% between 2001 and 2002 and is unlikely to be due simply to sampling variation ($P < 0.01$); it is also unlikely to be due to a failure to detect ESBL in 2001 as all the ESBL producers identified in 2002 were ceftazidime-resistant. It is notable that this shift coincides with the period when CTX-M β-lactamase began to emerge in the UK (HPA, unpublished

data). For *Klebsiella* and *Enterobacter* spp., there was no significant difference between the two years. Few of the ESBL producers detected in 2002 were ceftazidime-susceptible (2/12 *Klebsiella* and 2/18 *Enterobacter*), suggesting that few would have escaped detection in 2001 (before the introduction of enhanced screening). The prevalence of ESBL production in *Klebsiella* spp. was, unsurprisingly, considerably lower than the 25% seen in isolates from intensive care units in other parts of Europe.[49] It is interesting that the observed prevalence of ESBL was greater among *Enterobacter* than among *E. coli* and *Klebsiella* spp. The latter species have traditionally been considered the likeliest sources of ESBL, but the situation may be changing again with the emergence of CTX-M enzymes. The prevalence of ESBLs in *Enterobacter* spp. was surprising as most cephalosporin resistance in this genus is generally attributed to de-repression of AmpC; nevertheless, for 2002, at least, this prevalence was confirmed by cefepime/clavulanate synergy tests. ESBL production should continue to be monitored closely in view of the frequent multiple resistance found among such isolates.

The resistance rates found for *P. aeruginosa* were very similar to those found by routine testing in 2001 and 2002.[50,51] They confirm that all five agents tested here were still active against a high proportion of isolates. The most notable observation among the *P. aeruginosa* was the single isolate collected in 2001 that was highly resistant to all five tested antimicrobials. This was later identified as a producer of a VIM metallo-β-lactamase, the first of several such confirmed *P. aeruginosa* isolates in the UK and a worrying development.[21]

The results reported here from the first 2 years of the BSAC Bacteraemia Resistance Surveillance Programme show that resistance rates deduced from sentinel and routine data are concordant in most organism–agent combinations, although discrepancies remain for some, such as *E. faecalis* and vancomycin. The trend to increasing resistance seen throughout the 1990s appears to have slowed in some cases, such as oxacillin resistance in *S. aureus* and penicillin resistance in *S. pneumoniae*. However, other resistances continue to arise or increase in prevalence, such as ESBLs in *E. coli* and *Enterobacter* spp. and metallo-β-lactamase production in *P. aeruginosa*.

The greater value of the study will accrue in the future when, providing that the surveillance can be maintained in the same form, trend analysis will become possible within one large consistent dataset. The availability of baseline information for linezolid, ertapenem and tigecycline may be of particular interest as these antimicrobials are new: linezolid was introduced to the UK market only in January 2001 and ertapenem in October 2002; tigecycline is still under development. If resistance to these agents is to emerge in the future, it will be possible to track its development from the outset. Multivariate analysis of potential predictive factors such as patient age, therapeutic specialty and hospital size will also become possible as the number of isolates studied increases.

Isolates from the BSAC Bacteraemia Resistance Surveillance Programme can be made available to other workers for further investigations. Investigators can also access and analyse the data in detail through the BSAC website at http://www.bsac.org.uk.

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