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Non-susceptibility trends among staphylococci from bacteraemias in the UK and Ireland, 2001–06

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***Objectives*: Investigation of the antibiotic susceptibilities and trends for staphylococci collected from bacteraemia cases in the UK and Ireland, from 2001 to 2006, as part of the British Society for Antimicrobial Chemotherapy's Bacteraemia Surveillance Programme.**

***Methods*: Twenty-five hospitals from the UK and Ireland each collected up to 10 consecutive isolates of both *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) per year from 2001 to 2006. MIC determination and identification to species level were carried out centrally. *mecA* and also *mupA* alleles were sought by PCR in *S. aureus* and CoNS from 2005 and 2006, respectively.**

***Results*: One thousand four hundred and forty-eight *S. aureus* and 1214 CoNS were collected. The overall prevalence of methicillin resistance was 42% (with $\leq$6% annual fluctuation) for *S. aureus* and 67% (range 54% to 80%) for CoNS. Resistance to aminoglycosides, macrolides, quinolones and tetracyclines was strongly associated with methicillin resistance in both species groups. Many (20.8%) CoNS and three (0.2%) *S. aureus* isolates were non-susceptible to teicoplanin, but there was no vancomycin non-susceptibility found in *S. aureus* and only one vancomycin-intermediate CoNS isolate. There was little evidence of susceptibility trends over time for any antibiotic, with the surveillance period preceding the recent fall in methicillin-resistant *S. aureus* (MRSA) prevalence indicated by the mandatory surveillance of MRSA bacteraemia in England. The newer antibiotics, ceftobiprole, daptomycin, linezolid, telavancin and tigecycline, all had excellent activity against staphylococci.**

***Conclusions*: Multiresistant staphylococci remain abundant in the UK and Ireland but many new antimicrobials are becoming available and these may prove effective alternatives to glycopeptides.**

Keywords: Prevalence, MRSA, surveillance

Introduction

Staphylococcus aureus is the bacterial pathogen of which the British public are most aware, owing to the prolific media coverage of methicillin-resistant *S. aureus* (MRSA). MRSA is not only a UK problem; internationally, it poses a very substantial heathcare threat, and in some countries, including the UK, epidemic MRSA strains have become endemic in many hospitals.[1–6]

S. aureus was the most commonly isolated pathogen from bacteraemias in the UK in the first few years of this century but has now been overtaken by *Escherichia coli*. On admission to hospital in the UK, one in three patients is already colonized with *S. aureus*; a significant fraction of care-home residents and readmissions may already carry MRSA.[7] Alternatively, patients may be infected from others, often by staff acting as vectors, and infections due to MRSA are often used as a marker by those evaluating infection control programmes. *S. aureus* infection often involves these organisms taking advantage of vulnerabilities in host defence caused by mechanical damage, such as the insertion of lines or surgery. Antimicrobial use may affect the skin microflora; quinolones, for instance, are excreted in sweat, favouring colonization by MRSA, as MRSA is often resistant to quinolones.[8] Coagulase-negative staphylococci (CoNS), too, take advantage of breaches in host defence, causing opportunistic line-associated bacteraemias. Unlike with *S. aureus*, however, CoNS bacteraemias tend to be transient, often resolving naturally once the source of the infection has been removed, for example, following removal of a contaminated line.[9]

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The British Society for Antimicrobial Chemotherapy (BSAC) Bacteraemia Surveillance Programme aims to provide high-quality microbiological data, with molecular investigation of unusual strains. In this report, the data for staphylococci collected between 2001 and 2006 are reviewed and compared with the findings of other surveillance programmes, including the UK Health Protection Agency (HPA) voluntary bacteraemia surveillance,[10] the national mandatory system for monitoring of MRSA bacteraemias and the European Antimicrobial Resistance Surveillance System (EARSS).[2] These are more wide-ranging than the BSAC programme, but do not collect bacteria for central investigation, with the exception of UK EARSS MRSA and pneumococci isolates, which do have their results centrally verified.

Materials and methods

The collection, testing and statistical methods used in the BSAC Bacteraemia Programme are detailed elsewhere in this Supplement.[11] Until 2005/06, resistance to methicillin was inferred from oxacillin resistance, with cefoxitin also tested in 2004/05 only. Subsequently, *mecA* and also *mupA* alleles were sought in *S. aureus* and CoNS from 2005 and 2006, respectively, by PCR, using methods detailed previously.[12,13] Isolates were deemed to be methicillin-resistant if *mecA* was detected, regardless of the results of phenotypic testing.

Results

Sources of S. aureus and MRSA

One thousand four hundred and forty-eight *S. aureus* isolates were submitted from 2001 to 2006. Table 1 shows the age distribution of the patients from whom the isolates were obtained. Sixty percent of these were from patients over 60 years of age, with a male:female ratio of 3:2. The majority (61%) of the isolates were from patients admitted to hospital for >48 h, but 37% of them were from out/community patients (5.7%) or those admitted for ≤48 h (31%). The top three specialties associated with *S. aureus* were general medicine, surgery and nephrology, accounting for 25%, 17% and 14% of submissions, respectively.

Table 1. Age distribution of patients with bacteraemia caused by *S. aureus* ($n = 1448$)

Age (years)	Percentage of patients
0–4	3.4
5–19	2.7
20–39	12.1
40–49	7.5
50–59	12
60–69	17.6
70–79	23.3
80+	20.7

Some data fields were incomplete, and hence percentages do not always total 100%.

The origin of the *S. aureus* bacteraemias remained unknown in 33% of cases, while lines, skin or soft tissue and the respiratory tract comprised the three highest-ranked known sources, accounting for 25%, 16% and 9% of the cases, respectively. Of the 1448 isolates, 613 (42%) were MRSA. The prevalence varied between years from 36% to 48% without any discernible year-on-year trend in proportion, at least until 2006. The proportion of MRSA increased with age, rising to 51% for patients ≥70 years of age, independent of the patient's sex. Among patients who had been admitted to hospital for >48 h before their *S. aureus* bacteraemia was first identified, 50.5% had MRSA, compared with 28.4% among those whose bacteraemia was identified within ≤48 h of admission or who were from the community or outpatients. Many of these latter patients may have had recent hospital contact and the data do not challenge the view that MRSA largely remains a hospital-acquired pathogen in the UK and Ireland. The prevalence of MRSA was highest in intensive care units (ICUs) (63.5%), care of the elderly (58%) and surgery (50.8%).

Antibiotic resistance and trends in S. aureus

Antibiotic resistance in *S. aureus* is discussed here in terms of methicillin-susceptible *S. aureus* (MSSA) and MRSA, as multi-resistance (resistance to two or more classes of antibiotic) was strongly associated with methicillin resistance.

Table 2 summarizes the susceptibilities of MSSA isolates. Non-susceptibility rates were highest for penicillin, erythromycin and cefoxitin, at 82%, 28% and 19% respectively. Cefoxitin 'resistance' in 24 MSSA is perplexing as the trait is viewed as an indicator for *mecA*-mediated resistance.[14] These isolates were all oxacillin-susceptible (MIC ≤ 2 mg/L with a mode of 0.5 mg/L) and were confirmed *mecA*-negative by PCR. They all required cefoxitin MICs of 8 mg/L, which is one doubling dilution above both the breakpoint and the modal cefoxitin MIC for MSSA based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distribution.[15] In contrast, cefoxitin MICs for genuine MRSA isolates ranged from 16 to >128 mg/L, meaning that discrimination between MSSA and MRSA remained good, but with a breakpoint of 16 mg/L rather than 4 mg/L.

Although erythromycin resistance was observed frequently in MSSA, the levels of resistance were quite different from those in MRSA; erythromycin resistance in MRSA was often high, with 93% of the resistant isolates having MICs ≥ 128 mg/L. Among MSSA, only 25% of the resistant isolates had MICs at this level, whereas 48% required MICs of 1 mg/L, corresponding to only one dilution above the susceptible breakpoint.

Methicillin resistance (Table 3) was strongly associated with other resistances in *S. aureus*. For several drugs, the difference in the proportion of resistance between MRSA and MSSA was highly significant ($P < 0.00001$), e.g. 95.9% of MRSA were resistant to ciprofloxacin, whereas for MSSA this was only 9.1%. The pattern of high-level ciprofloxacin resistance is typical of the EMRSA-15 and -16 clones that dominate MRSA in the UK. Curiously, one MRSA isolate was susceptible to oxacillin; this isolate poorly expressed the *mecA* gene *in vitro*. The only established drugs where there was no significantly greater prevalence of non-susceptibility in MRSA than MSSA were fusidic acid, minocycline and tetracycline.

Table 2. MIC distributions and susceptibilities of MSSA isolates from the BSAC Bacteraemia Surveillance Programme

	MIC (mg/L)[a]																			Susceptibilities (%)		
Antimicrobial agent	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Isolates tested	*S*	*I*	*R*
Cefoxitin											**102**	24							126	81.0	0	19.0
Ceftobiprole							56	**410**	89										555			
Ciprofloxacin						10	92	**375**	282	34	8	2	6	7	5	12	2[b]		835	90.9	0	9.1
Clindamycin						**790**[b]	37	3		1							4[b]		835	99.4	0	0.6
Daptomycin							74	**294**	61										429	100	0	0
Erythromycin							57	**544**	113	4	42	3	6	5	3	2	56[b]		835	72.0	0	28.0
Fusidic acid				4	150	**321**	29		3	5	16	15	7	1	1		1	2[b]	555	91.4	0	8.6
Gentamicin				1[b]	2	47	296	**345**	123	17	3			1					835	97.5	0	2.5
Linezolid								1[b]	16	**734**	84								835	100	0	0
Minocycline				1	11	**576**	106	2			4[b]								700	99.4	0	0.6
Oxacillin								**756**[b]	48	31									835	100	0	0
Penicillin			3[b]	65	69	10	7	8	15	23	37	33	86	104	85	**290**[b]			835	17.6	0	82.4
Rifampicin	134[b]	**200**	193	26							2[b]								555	99.6	0	0.4
Teicoplanin								156[b]	**524**	148	6	1							835	99.9	0.1	0
Telavancin						19	**212**	58											289			
Tetracycline						4	17	**682**	98	1	4	1	1	13	10	3	1[b]		835	95.9	0	4.1
Tigecycline					1	185	**504**	10											700	100	0	0
Trimethoprim							121[b]	**519**	163	12		1	3	3			13[b]		835	96.2	0	3.8
Vancomycin								38[b]	**477**	320									835	100	0	0

[a]Modal values in bold.
[b]These isolates should be considered to require less than or equal to or more than or equal to the listed MIC dependent upon whether they are at the bottom or top of the MIC range.

Table 3. MIC distributions and susceptibilities of MRSA isolates from the BSAC Bacteraemia Surveillance Programme

	MIC (mg/L)[a]																		Susceptibilities (%)		
Antimicrobial agent	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Isolates tested	*S*	*I*	*R*
Cefoxitin													3	47	**50**	10	8[b]		118	0	0	100
Ceftobiprole							1	9	107	**290**	3								410			
Ciprofloxacin							3	15	7	1		7	31	35	113	**282**	119[b]		613	4.1	0	95.9
Clindamycin						**361**[b]	130	7								1	**114**[b]		613	81.2	0	18.8
Daptomycin						1	40	**200**	51										292	100	0	0
Erythromycin							10	102	9	1	5	1	3	4	11	1	**466**[b]		613	18.3	0	81.7
Fusidic acid				6	129	**214**	20	1	2	2	13	7	6		1	1		8[b]	410	90.7	0	9.3
Gentamicin					3	65	**270**	193	27			1	3	18	28	4	1[b]		613	91.0	0	9.0
Linezolid								2[b]	15	**540**	56								613	100	0	0
Minocycline				1	9	**417**	74	3		1	5[b]								510	98.8	0	1.2
Oxacillin								1[b]			6	6	6	7	21	101	**465**[b]		613	0.2	0	99.8
Penicillin					1			1		2	2	1	2	15	112	**477**[b]			613	0.2	0	99.8
Rifampicin	**149**[b]	148	101	3							9[b]								410	97.8	0	2.2
Teicoplanin								229[b]	**318**	58	6	1	1						613	99.7	0.2	0.2
Telavancin						17	**152**	28											197			
Tetracycline						3	8	**473**	110	2			1	5	6	4	1[b]		613	96.9	0	3.1
Tigecycline						34	**401**	73	2										510	99.6	0	0.4
Trimethoprim							167[b]	**268**	54	6	12	16	22	17	7	21	23[b]		613	79.8	0	20.2
Vancomycin								56[b]	**390**	166	1								613	100	0	0

[a]Modal values in bold.
[b]These isolates should be considered to require less than or equal to or more than or equal to the listed MIC dependent upon whether they are at the bottom or top of the MIC range.

Hospital acquisition of infection, specialty (particularly ICU) and age group were significant independent predictors of *S. aureus* bacteraemia being caused by MRSA, generally with its associated resistances to other antimicrobials. In addition, age group was a significant predictor of ciprofloxacin resistance in MSSA and MRSA separately. In MSSA, the prevalence of ciprofloxacin resistance increased with age, being 3.9%, 9.5%, 6.3% and 16.4% in age groups 0–19, 20–59, 60–79 and ≥80 years, respectively. In contrast, the prevalence of ciprofloxacin resistance in MRSA was >90% in all age groups over the age of 4 years (mean 96.9%, $n = 604$), but was strikingly lower in children up to the age of 4 years (17%, $n = 6$). This may reflect the dominance of the same few MRSA lineages across most age groups while different clones tend to infect the very young. There are reports of ciprofloxacin-susceptible 'paediatric' MRSA clones in France, Japan, Portugal and Brazil, but as yet no occurrence of this clone in the UK paediatric patients has been reported, although it has been found in the adult population, and ciprofloxacin-susceptible MRSA strains have been reported in UK paediatric patients.[5,16–18]

Seven *S. aureus* isolates in 2006 carried the *mupA* gene, which confers high-level resistance to mupirocin. All of these isolates except one were also *mecA*-positive. There was no non-susceptibility to linezolid or vancomycin, and only three teicoplanin non-susceptible isolates (one MSSA and two MRSA).

Among the newest antibiotics with anti-*S. aureus* activity, ceftobiprole, daptomycin, tigecycline and telavancin all performed well. EUCAST has assigned MIC breakpoints for tigecycline ($S \leq 0.5$; $R > 0.5$ mg/L) and daptomycin ($S \leq 1$; $R > 1$ mg/L). Only two isolates were resistant to tigecycline on these criteria, both with borderline MICs of 1 mg/L while no resistance was found to daptomycin. Ceftobiprole MICs for staphylococci were all ≤4 mg/L, ranging from 0.25 to 4 mg/L (mode 2 mg/L) for MRSA and 0.25 to 1 mg/L (mode 0.5 mg/L) for MSSA. Telavancin MICs for both MRSA and MSSA were all in the range of 0.12–0.5 mg/L.

Distribution of CoNS in bacteraemia

From 2001 to 2006, 1214 CoNS were received (Table 4). The 2001–05 collections ($n = 1011$) were identified to species level as follows: *Staphylococcus epidermidis* ($n = 615$, 60.8%), *Staphylococcus haemolyticus* ($n = 123$, 12.2%), *Staphylococcus hominis* ($n = 107$, 10.6%), unspeciated *Staphylococcus* ($n = 73$, 7.2%), *Staphylococcus capitis* ($n = 72$, 7.1%), *Staphylococcus warneri* ($n = 12$, 1.2%) and *Staphylococcus saprophyticus* ($n = 9$, 0.9%). Species identification was discontinued in 2006. The largest number of isolates (19.4%, $n = 236$) was from patients aged 60–69 and the male:female split was 56%:42%. Sixty-eight percent of the isolates were from patients who had been admitted to hospital for >48 h, the remainder being from community/outpatients (7.3%) or those admitted for ≤48 h (19.3%). The largest number (30%, $n = 365$) of isolates was from haematology/oncology patients followed by nephrology (14%, $n = 67$) and ICU (12% $n = 146$). Intravascular lines accounted for 62% of the cases, with a further 27% noted as being of unknown source.

Table 4. Age distribution of patients with bacteraemia due to CoNS ($n = 1214$)

Age (years)	Percentage of patients
0–4	10.8
5–19	7.8
20–39	12.5
40–49	11.5
50–59	16.6
60–69	19.4
70–79	14.7
80+	5.6

Some data fields incomplete, and hence percentages do not always total 100%.

Antibiotic resistance and trends in CoNS

Tables 5 and 6 summarize the antibiotic susceptibilities and MIC ranges for the CoNS. Species was significantly related to resistance even when other factors, such as source of bacteraemia, age group or referring specialty, were included in the multiple logistic regression model. *S. haemolyticus* was more resistant than the other species with 84% of the isolates non-susceptible to three or more of ciprofloxacin, erythromycin, gentamicin, oxacillin, teicoplanin and tetracycline. This compared with *S. epidermidis* where 70% of the isolates were non-susceptible to three or more of these antibiotics.

There were no smooth year-on-year resistance trends for any antibiotic, but there was some evidence of fluctuation in non-susceptibility between years for oxacillin, erythromycin, clindamycin, teicoplanin, tetracycline and tigecycline. The year-on-year variation for oxacillin, teicoplanin and tetracycline could be due to experimental variation as the breakpoints for these antibiotics lie on, or close to, the MICs of many susceptible isolates, meaning that 2-fold variation in MIC can change the susceptibility category. Apparent differences seen in tigecycline MICs between years were almost wholly due to high MICs seen in 2002; these were probably due to incorrect handling of tigecycline which is susceptible to oxidization during *in vitro* susceptibility testing.[19]

The prevalence of methicillin-resistant CoNS (MRCoNS) among CoNS ranged from 54.2% to 79.9% and was strongly correlated with multiresistance in CoNS [the following figures refer to the percentage resistance to various antibiotics for MRCoNS and methicillin-suceptible CoNS (MSCoNS), respectively], particularly to ciprofloxacin (67.1% versus 24.4%), clindamycin (25.5% versus 6.3%), erythromycin (80.2% versus 55.9%), fusidic acid (58.1% versus 40.1%), gentamicin (73.4% versus 23.2%), penicillin (99.1% versus 80.9%), rifampicin (19.2% versus 4.7%), teicoplanin (26.4% versus 9.1%), tetracycline (61.1% versus 34%) and trimethoprim (77.7% versus 40.1%). Thirty-four (17%) CoNS isolates from 2006 had *mupA* (which was not sought previously); of these, only two lacked *mecA*. No CoNS were found non-susceptible to linezolid and only one isolate was non-susceptible to vancomycin with an MIC of 8 mg/L, thus indicating intermediate resistance at current BSAC breakpoints.[14]

The newer antibiotics, ceftobiprole, daptomycin, tigecycline and telavancin were almost universally active against CoNS, with patterns similar to those for *S. aureus*. For instance, the

Table 5. MIC distributions and susceptibilities of MSCoNS isolates from the BSAC Bacteraemia Surveillance Programme

	MIC (mg/L)[a]																		Susceptibilities (%)		
Antimicrobial agent	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Isolates tested	*S*	*I*	*R*
Cefoxitin				3[b]			1	1	16	**28**	19	16	1	5	3				93			
Ceftobiprole			1	2	6	18	80	**82**	75	33	2								299			
Ciprofloxacin				1[b]	21	89	**106**	70	13	9	13	4	13	17	25	15	1[b]		397	75.6	0	24.4
Clindamycin						**297**[b]	70	5	1	1	1		1				21[b]		397	93.7	0	6.3
Daptomycin					6	18	85	**99**	19	1									228	99.6	0	0.4
Erythromycin						11[b]	107	57	7	22	7	7	10	7	14	24	**124**[b]		397	44.1	0	55.9
Fusidic acid			4[b]	7	**104**	41	23			1	11	21	32	47	5		1	2[b]	299	59.9	0	40.1
Gentamicin							**302**[b]	3		8	11	15	15	23	14	4	2[b]		397	76.8	0	23.2
Linezolid								29[b]	**314**	53	1								397	100	0	0
Minocycline			1[b]	1	84	**135**	67	60	5	2									355	98	0	2
Oxacillin						**145**[b]	87	27	75	63									397	100	0	0
Penicillin			14[b]	35	20	7	12	8	9	25	40	43	42	**71**	39	32[b]			397	19.1	0	80.9
Rifampicin	47[b]	49	**96**	59	34	3					1					2	2	6[b]	299	95.3	0	4.7
Teicoplanin						2	42	59	60	**109**	89	30	5	1[b]					397	90.9	7.6	1.5
Telavancin				2	4	56	**73**	3											138			
Tetracycline					1[b]	5	96	**136**	24	79	16		2	5	21	7	5[b]		397	66	0	34
Tigecycline				1[b]	21	**150**	104	69	9	1									355	97.2	0	2.8
Trimethoprim							**98**[b]	86	54	12	6	2		9	21	17	92[b]		397	59.9	0	40.1
Vancomycin								14[b]	153	**226**	4								397	100	0	0

[a]Modal values in bold.
[b]These isolates should be considered to require less than or equal to or more than or equal to the listed MIC dependent upon whether they are at the bottom or top of the MIC range.

Table 6. MIC distributions and susceptibilities of MRCoNS isolates from the BSAC Bacteraemia Surveillance Programme

	MIC (mg/L)[a]																		Isolates tested	Susceptibilities (%)		
Antimicrobial agent	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512		*S*	*I*	*R*
Cefoxitin									1		3	22	7	**42**	19	8	8[b]		110			
Ceftobiprole		1[b]	1			2	3	32	**230**	154	83								506			
Ciprofloxacin				1[b]	11	55	**107**	79	16	15	41	89	37	59	157	95	55[b]		817	32.9	0	67.1
Clindamycin						**485**[b]	115	9	9	2	1		2	2	1	2	189[b]		817	74.5	0	25.5
Daptomycin				1[b]	2	22	**117**	195	53										390	100	0	0
Erythromycin						18[b]	76	68	9	11	14	5	7	32	36	38	**503**[b]		817	19.8	0	80.2
Fusidic acid				4	122	75	9	2		5	8	61	63	**131**	12		3	11[b]	506	41.9	0	58.1
Gentamicin							**209**[b]	3	5	16	77	91	79	123	144	56	14[b]		817	26.6	0	73.4
Linezolid								64[b]	**573**	175	5								817	100	0	0
Minocycline					73	145	173	**208**	29	8	6	3	2	3					650	92.2	0	7.8
Oxacillin						2[b]	1	4	10	20	86	73	37	96	103	102	**283**[b]		817	4.5	0	95.5
Penicillin			1[b]	1	3	2	5	9	4	11	12	35	79	154	159	**342**[b]			817	0.9	0	99.1
Rifampicin	52[b]	**134**	124	62	37	15	1		5	4	7		1	2		9	8	45[b]	506	80.8	0	19.2
Teicoplanin						3	28	49	68	185	**268**	191	22	3[b]					817	73.6	23.4	3.1
Telavancin					2	72	**185**	9											268			
Tetracycline						9	57	155	97	**253**	72	16	10	20	50	40	38[b]		817	38.9	0	61.1
Tigecycline					8	105	**236**	230	59	10	2								650	89.1	0	10.9
Trimethoprim							66[b]	75	41	19	11	1	4	23	56	62	**459**[b]		817	22.3	0	77.7
Vancomycin								9[b]	177	**604**	26	1							817	99.9	0.1	0

[a]Modal values in bold.
[b]These isolates should be considered to require less than or equal to or more than or equal to the listed MIC dependent upon whether they are at the bottom or top of the MIC range.

ceftobiprole MIC ranges were 0.015–4 mg/L (mode 0.5 mg/L) for MSCoNS and ≤0.008–4 mg/L (mode 1 mg/L) for MRCoNS.

Discussion

Owing to its high profile, MRSA is now the subject of multiple surveillance programmes in the UK, all concentrating on isolates from bacteraemia. Aside from the BSAC surveillance programme detailed in this report, these include the Department of Health's mandatory MRSA reporting scheme launched in April 2001[20] and coordinated by the HPA, the HPA's continued voluntary reporting under LabBase[10] and the EARSS launched in 1999.[2] These programmes are independent but overlapping and complementary, and Table 7 compares the UK and Irish MRSA prevalence data from the four surveillance programmes. All four studies reported MRSA prevalence rates within the range 36% to 48% throughout the surveillance period. Within the UK, the two sentinel surveys, BSAC and EARSS, both showed higher prevalence of MRSA than either the mandatory reporting or the LabBase programme, which rely on routine laboratory data, perhaps because larger centres, often with more MRSA, are more willing and, owing to higher staffing levels, better able to participate in sentinel surveillance. All studies except the BSAC saw some reduction in the proportion of MRSA from 2001 to 2006, and this was significant in the mandatory, LabBase and EARSS (UK data only) programmes, with *P* values of 0.008, <0.0001 and 0.043, respectively. Since 2006, the mandatory reporting for England has shown a marked reduction in the incidences of MRSA bacteraemia with recently published figures for third quarter of 2007[21] showing a 35% reduction over the same period in 2006. This promising sign of success reflects the efforts of NHS Trusts to control MRSA bacteraemia and the Department of Health's performance management,[22] but has come after the period of the BSAC surveillance reviewed here.

Since April 2006, the mandatory surveillance for England has collected patient characteristics and case information, obtaining age and sex data for 98% of 6264 patients with MRSA bacteraemias from April 2006 to March 2007. As in the BSAC data set, the incidence of MRSA increased with age and there were more cases in men than women. This 'enhanced' mandatory surveillance showed that 65% of the MRSA bacteraemias arose >48 h after admission, agreeing well with the BSAC surveillance which estimated this proportion as 72% over the entire programme and 71% for 2006. The two specialties with the top ranking number for MRSA bacteraemia cases according to the enhanced mandatory surveillance were general medicine (1436) and general surgery (770), and these were also the top-ranking specialties in the BSAC surveillance.

The UK's MRSA problem is dominated by two lineages, EMRSA-15 and -16, both of which are typically resistant to quinolones and macrolides, with EMRSA-16 sometimes also being resistant to gentamicin.[1] The BSAC surveillance did not show any trend among MRSA in relation to resistance in these agents and neither is currently reported by the mandatory surveillance or EARSS. However, non-susceptibility to erythromycin and gentamicin reduced significantly over time in the LabBase MRSA data, falling from 84.9% to 78.6% ($P < 0.0001$) and from 10.9% to 6.8% ($P < 0.0001$) respectively. The only antibacterial for which there was a significant ($P < 0.0001$) increase in non-susceptibility in the LabBase data for MRSA was trimethoprim, with non-susceptibility increasing from 27.3% to 31.9%. It is uncertain whether these changes reflect gradual loss or gain of resistance by EMRSA-15 or -16 or the gradual penetration of other clones.

Table 8 compares the prevalence of resistance among *S. aureus* and CoNS isolates from the BSAC and LabBase programmes. In general, there was a good agreement between the estimated non-susceptible prevalence levels determined by these two surveillance programmes for both *S. aureus* and CoNS. However, there were a number of key discrepancies between the two studies, some of these almost certainly being laboratory routine testing errors. The LabBase data indicated <0.3% non-susceptibility to vancomycin among MRSA isolates, whereas the BSAC study found all MRSA susceptible. Since the reference laboratory requests that all vancomycin non-susceptible *S. aureus* isolates are submitted for confirmatory testing and none have yet been confirmed, we would treat the LabBase proportion with suspicion. In the case of teicoplanin, non-susceptibility was consistently higher in the BSAC study, particularly among CoNS. This discrepancy was most probably due to the underestimation of non-susceptibility by routine disc testing, where the zone diameter for this large, poorly diffusing antibiotic is poorly related to the MIC and disc testing therefore not recommended by BSAC.[14,23] Other differences between the two studies, for

Table 7. MRSA in relation to all *S. aureus* bacteraemias (%), by year, according to the four multicentre surveillance programmes covering Great Britain and Ireland

Surveillance programme	2001	2002	2003	2004	2005	2006	*P* value
BSAC[a]	43.3	40.8	40.4	48.4	36.1	45	0.86
Mandatory MRSA reporting[b]	39.6	39.2	38.8	38.4	38.3	36.6	0.008
LabBase[c]	41.9	42.6	41.5	39.8	39.8	37.9	<0.0001
EARSS[d]	44.4	43.9	43.3	43.7	43.6	42.1	0.043
EARSS[e]	41.7	42.5	42.2	41.4	41.8	42.3	0.98

[a]UK and Ireland.
[b]England only.
[c]England, Wales and Northern Ireland.
[d]UK.
[e]Republic of Ireland.

Table 8. Comparison between antibiotic non-susceptibilities obtained from BSAC (%) and LabBase (%) surveillance programmes for *S. aureus* and CoNS

	MRSA		MSSA		MRCoNS		MSCoNS	
Antimicrobial agent	LabBase	BSAC	LabBase	BSAC	LabBase	BSAC	LabBase	BSAC
Ciprofloxacin	96.7	95.9	12.4	9.1	62	67.1	15.5	24.4
Clindamycin	37.7	18.8	3.7	0.6	30.7	25.5	7.9	6.3
Erythromycin	82	81.7	10.2	28	79.8	80.2	38.8	55.9
Fusidic acid	8.4	9.3	9.7	8.6	55.2	58.1	37.2	40.1
Gentamicin	8.7	9	1.3	2.5	56.9	73.4	8.3	23.2
Linezolid	0.02	0	0	0	0.2	0	0	0
Tetracycline	4	3.1	4.5	4.1	25.9	61.1	19	34
Methicillin[a]	100	99.8	0	0	100	95.5	0	0
Penicillin	99.3	99.8	84.3	82.4	98.8	99.1	70.7	80.9
Rifampicin	3.5	2.2	1.5	0.4	13.8	19.2	1.6	4.7
Teicoplanin	0.3	0.4	0.07	0.1	9.6	26.5	2.5	9.1
Trimethoprim	28.2	20.2	12.6	3.8	73.9	77.7	37	40.1
Vancomycin	0.2	0	0.1	0	0.2	0.1	0.1	0

[a]Inferred non-susceptibility to methicillin from resistance to any of the following, cefoxitin, flucloxacillin or oxacillin.

example, in estimated susceptibility to clindamycin in *S. aureus*, trimethoprim in MSSA, erythromycin in MSCoNS and MSSA and tetracycline in CoNS, are not so easily explained but are probably caused by differences in sampling strategy and susceptibility determination methods.

The BSAC and LabBase surveillance both confirmed that methicillin resistance was more prevalent among CoNS than among *S. aureus*, as is widely perceived. Nevertheless, the clinical significance of MRCoNS is mitigated somewhat by low pathogenicity. However, it has been suggested that CoNS may act as a reservoir for resistance genes that can disseminate into *S. aureus*.[24] Therefore, continued surveillance of CoNS is justified.

Methicillin- and multiresistant staphylococci are not just a UK problem but a worldwide one, as illustrated by the EARSS 2006 data which show that 12/27 participating countries had MRSA prevalence levels of 25% to 50% in bacteraemia with Romania having >50%, and only 7 had MRSA rates ≤5%. In the USA, the Centers for Disease Control Active Bacterial Core surveillance system operates similarly to the UK LabBase system and, in 2004–05, estimated the percentage of MRSA in the USA at 77% for hospital-associated *S. aureus* bacteraemia and 65% for community-associated bacteraemia. The majority of the cases were caused by the USA100 or USA300 strains, the former largely being hospital-acquired and the latter, while classically considered a community strain, is also moving into hospitals.[3] In the UK, we have yet to see a community MRSA strain establish itself widely as a hospital-acquired pathogen, though the risk must be taken seriously. With its multiple surveillance systems tracking MRSA rates, any emergence of new epidemic clones should be rapidly detected in the UK, allowing control strategies to be brought to bear.

Treatment options for methicillin-resistant staphylococci

The multiresistant nature of many methicillin-resistant staphylococci leads to a significant therapeutic problem, particularly in serious infections such as bacteraemia. Standard first-line treatment of MRSA bacteraemia is with glycopeptides, often in combination with rifampicin or fusidic acid. However, there is growing support for the view that vancomycin therapy is less effective for infections caused by isolates with vancomycin MICs of ≥2 mg/L.[25–28] In this study, 27.2% of MRSA isolates required MICs of ≥2 mg/L. This cannot be compared with other surveillance data, as the BSAC is the only programme to report MICs. Of the newer antibiotics tested here, ceftobiprole, daptomycin, linezolid, telavancin and tigecycline all had excellent activity versus the staphylococci, with no resistance or, in the case of tigecycline, no convincing resistance (some MICs just above the breakpoint). These agents considerably increase the number of therapeutic options available to treat methicillin-resistant staphylococci and could help combat the over-reliance on vancomycin and teicoplanin.

In conclusion, multiresistant *S. aureus* and CoNS remain abundant in the UK and Ireland, but there are hopeful signs: first in the diminished incidence of MRSA seen in the mandatory surveillance data (though not yet in the BSAC surveillance), and secondly in that there are a growing number of treatment options available for infection caused by these bacteria. The newer agents tested here had excellent *in vitro* antimicrobial activity and may well prove to be effective alternatives to glycopeptides. So far, however, only daptomycin has been evaluated clinically in bacteraemia.[29,30]

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publications from the Project, some of which may include parts of the information presented here.

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References

1. Johnson AP, Pearson A, Duckworth G. Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother* 2005; **56**: 455–62.

2. European Antimicrobial Resistance Surveillance System (EARSS). http://www.earss.rivm.nl (8 February 2008, date last accessed).

3. Klevens RM, Morrison MA, Nadle J *et al*. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007; **298**: 1763–71.

4. Richards MJ, Russo PL. Surveillance of hospital-acquired infections in Australia—one nation, many states. *J Hosp Infect* 2007; **65**: 174–81.

5. Vandenesch F, Naimi T, Enright MC *et al*. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton–Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* 2003; **9**: 978–84.

6. Wijaya L, Hsu LY, Kurup A. Community-associated methicillin-resistant *Staphylococcus aureus*: overview and local situation. *Ann Acad Med Singapore* 2006; **35**: 479–86.

7. Cooper BS, Medley GF, Stone SP *et al*. Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: stealth dynamics and control catastrophes. *Proc Natl Acad Sci* 2004; **101**: 10223–8.

8. Hoiby N, Jarlov JO, Kemp M *et al*. Excretion of ciprofloxacin in sweat and multiresistant *Staphylococcus epidermidis*. *Lancet* 1997; **349**: 167–9.

9. Coyle VM, McMullan R, Morris TCM *et al*. Catheter-related bloodstream infection in adult haematology patients: catheter removal practice and outcome. *J Hosp Infect* 2004; **57**: 325–31.

10. Reacher MH, Shah A, Livermore DM *et al*. Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* 2000; **320**: 213–6.

11. Reynolds R, Williams L. Survey, laboratory, and statistical methods for the BSAC Resistance Surveillance Programmes. *J Antimicrob Chemother* 2008; **62** Suppl 2: ii15–28.

12. Bignardi GE, Woodford N, Chapman A *et al*. Detection of the *mecA* gene and phenotypic detection of resistance in *Staphylococcus aureus* isolates with borderline or low-level methicillin resistance. *J Antimicrob Chemother* 1996; **37**: 53–63.

13. Woodford N, Watson AP, Patel S *et al*. Heterogeneous location of the mupA high-level mupirocin resistance gene in *Staphylococcus aureus*. *J Med Microbiol* 1998; **47**: 829–35.

14. Andrews JM on behalf of the BSAC Working Party on Susceptibility Testing. *BSAC Standardized Disc Susceptibility Testing Method (Version 6.1)*. http://www.bsac.org.uk/_db/_documents/version_6.1.pdf (15 December 2007, date last accessed).

15. The European Committee on Antimicrobial Susceptibility Testing (EUCAST). http://www.escmid.org (21 July 2008, date last accessed).

16. David MD, Kearns AM, Gossain S *et al*. Community-associated meticillin-resistant *Staphylococcus aureus*: nosocomial transmission in a neonatal unit. *J Hosp Infect* 2006; **64**: 244–50.

17. Otter JA, Klein JL, Watts TL *et al*. Identification and control of an outbreak of ciprofloxacin-susceptible EMRSA-15 on a neonatal unit. *J Hosp Infect* 2007; **67**: 232–9.

18. Sa-Leao R, Santos Sanches I, Dias D *et al*. Detection of an archaic clone of *Staphylococcus aureus* with low-level resistance to methicillin in a pediatric hospital in Portugal and in international samples: relics of a formerly widely disseminated strain? *J Clin Microbiol* 1999; **37**: 1913–20.

19. Hope R, Warner M, Mushtaq S *et al*. Effect of medium type, age and aeration on the MICs of tigecycline and classical tetracyclines. *J Antimicrob Chemother* 2005; **56**: 1042–6.

20. Health Protection Agency. *Department of Health's Mandatory MRSA Reporting Scheme*. http://www.hpa.org.uk/infections/topics_az/staphylo/staphylo_mandatory_surveillance.htm (15 March 2008, date last accessed).

21. Health Protection Agency. *Commentary for MRSA Bacteraemia*. http://www.hpa.org.uk/infections/topics_az/hai/Tables_for_website/MRSA_Commentary.pdf (10 November 2007, date last accessed).

22. *Saving Lives: A Delivery Programme to Reduce Healthcare Associated Infection (HCAI) Including MRSA*. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_4113193 (15 June 2008, date last accessed).

23. Charlesworth R, Warner M, Livermore DM *et al*. Comparison of four methods for detection of teicoplanin resistance in methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 2006; **58**: 186–9.

24. Hanssen AM, Kjeldsen G, Sollid JUE. Local variants of staphylococcal cassette chromosome mec in sporadic methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative staphylococci: evidence of horizontal gene transfer? *Antimicrob Agents Chemother* 2004; **48**: 285–96.

25. Wootton M, Walsh TR, MacGowan AP. Evidence for reduction in breakpoints used to determine vancomycin susceptibility in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2005; **49**: 3982–3.

26. Tenover FC, Moellering RC Jr. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. *Clin Infect Dis* 2007; **44**: 1208–15.

27. Moise-Broder PA, Sakoulas G, Forrest A *et al*. Vancomycin *in vitro* bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2007; **42**: 2398–402.

28. Gould IM. The problem with glycopeptides. *Int J Antimicrob Agents* 2007; **30**: 1–3.

29. Fowler VG Jr, Boucher HW, Corey GR *et al*. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med* 2006; **355**: 653–65.

30. Falagas ME, Giannopoulou KP, Ntziora F *et al*. Daptomycin for endocarditis and/or bacteraemia: a systematic review of the experimental and clinical evidence. *J Antimicrob Chemother* 2007; **60**: 7–19.