

**National Glycopeptide-Resistant Enterococcal  
Bacteraemia Surveillance Working Group**

**Report to the Department of Health**

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## Abbreviations

A&E	Accident and Emergency
APACHE	Acute Physiology and Chronic Health Evaluation
ARMRL	Antibiotic Resistance Monitoring and Reference Laboratory, HPA
BSAC	British Society for Antimicrobial Chemotherapy
CAPD	Continuous Ambulatory Peritoneal Dialysis
CDC	Centres for Disease Control and Prevention, USA
CDSC	Communicable Disease Surveillance Centre, HPA
CMO	Chief Medical Officer, Department of Health
COSURV	CDSC computerised reporting system for epidemiological surveillance
DOH	Department of Health
EARSS	European Antimicrobial Resistance Surveillance System
FCE	Finished Consultant Episodes
GRE	Glycopeptide-resistant enterococci
HAISSG	Healthcare-associated Infection Surveillance Steering Group
HCAI & AMR	Healthcare-Associated Infection and Antimicrobial Resistance
HIS	Hospital Infection Society
HPA	Health Protection Agency
ICNA	Infection Control Nurses Association
ICU	Intensive Care Unit
ITU	Intensive Therapy Unit
LARS	Local and Regional Services, HPA
LHCAI	Laboratory of HealthCare Associated Infection, HPA
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
NHS	National Health Service
NCCLS	National Committee for Clinical Laboratory Standards
NEQAS	National External Quality Assessment Scheme
PICU	Paediatric Intensive Care Unit
QAL	Quality Assurance Laboratory
RE	Regional Epidemiologist, HPA
SCBU	Special Care Baby Unit
SLA	Service Level Agreement
SRMD	Specialist and Reference Microbiology Division, HPA
VanA, B, C etc	Vancomycin resistance types (see section 5.3)

## Summary

1. From September 2003 acute NHS Trusts in England have been required by the DOH to undertake mandatory surveillance of bacteraemias caused by glycopeptide-resistant enterococci.
2. Four thousand, eight hundred and fifty-five enterococcal bacteraemias (including 256 reports of "Group D streptococci") were reported through the voluntary reporting system to CDSC in England and Wales in 2002, and 8.9% of the reports that contained information on vancomycin susceptibility indicated that the isolate was resistant to vancomycin. Most hospitals reported fewer than five GRE bacteraemias per year to CDSC, only 13 reporting more than five per year, although there is undoubtedly an element of under-reporting.
3. This Working Group was established to review the methods used to identify and test the susceptibility of enterococci to glycopeptides and to make recommendations on the reporting of GRE bacteraemias, as there were indications that current methods would not provide a suitable basis for this surveillance.
4. A review of methods was undertaken, including a national questionnaire on methods, approaches to testing and risk factors for GRE bacteraemia. This, together with data from routine laboratory reports and special surveys, revealed that:
  - A significant proportion of enterococci are not identified to species level.
  - There are problems with identification of enterococci. The commercially available kits do not identify some enterococcal species reliably.
  - Not all laboratories test vancomycin susceptibility of enterococci from bacteraemia. This does not allow a robust assessment of GRE bacteraemia rates, because the prevalence of glycopeptide resistance will be underestimated if laboratories test only teicoplanin or no glycopeptide against enterococci.
  - There are technical difficulties in detecting non-VanA resistance in enterococci and this will also contribute to under-reporting of glycopeptide resistance.
5. Clinically significant GRE infection is associated with a worse prognosis than infection with susceptible strains, but this factor has not been clearly separated from the possible influence of co-morbidities and antibiotic usage.
6. GRE bacteraemia occurs mainly on specialist units, particularly transplantation, renal, haematological malignancy and intensive care units. Hospitals with such units will inevitably have a higher risk of featuring prominently in surveillance studies. Hence, meaningful denominators for surveillance of GRE bacteraemia are required.

## Recommendations for GRE bacteraemia surveillance

1. As the mandatory surveillance of GRE bacteraemias has already started, this report recommends a phased approach to some of the developments, such as using meaningful denominators for the bacteraemia rates.
2. Rates of GRE bacteraemias in Trusts should not be used as a performance indicator, because the numbers are too small for valid analysis in this way.
3. GRE bacteraemias as a proportion of all clinically significant bacteraemias in the Trust should be measured as an indicator of changing trends.
4. Since most GRE are likely to be associated with specialist units, reports of GRE bacteraemia should indicate the specialty in which the patient acquired the infection.
5. Data on clinical activity in the Trust special units where patients acquired GRE bacteraemias should be obtained from Trusts with more than five GRE bacteraemias in a year.
6. The significance of blood cultures containing GRE should be assessed clinically. If the bacteraemia which includes GRE is deemed clinically significant (according to the case definitions for bacteraemia), whether mono- or polymicrobial, it should be reported as a GRE bacteraemia.
7. Enterococci from blood cultures should be identified to species level to provide data on resistance rates in different species.
8. Biochemical identification should be augmented by antimicrobial susceptibility patterns. The identification is suspect if *E. faecalis* appears ampicillin resistant and/or quinupristin/dalfopristin susceptible, or if *E. faecium* appears ampicillin susceptible and/or quinupristin/dalfopristin resistant. The identification and susceptibility of such isolates should be checked and, if confirmed, the isolate should be sent to a reference laboratory for further investigation.
9. Enterococci from blood cultures should be tested for susceptibility to vancomycin. Teicoplanin is not an acceptable alternative to vancomycin for these purposes.
10. Standardised methods should be used for glycopeptide susceptibility testing of enterococci and the technical requirements of the methods must be adhered to.
11. The situation should be reviewed after a year and the methodology subsequently amended as appropriate.

## **Recommendations for further research**

1. A group should be established to explore methods of data collection for global and individual risk factors for GRE bacteraemia.
2. Further studies on the performance of commercial identification kits with a range of enterococcal species are necessary.
3. Further studies to improve the reliability of susceptibility testing methods for detection of GRE are necessary.

## 1 Introduction

- 1.1 The Minister of Health gave an undertaking in October 2000 that all Trusts in England would monitor levels of hospital acquired infection and that this compulsory monitoring would be developed to cover certain blood stream infections.<sup>1</sup> The first phase of this initiative was the implementation of mandatory surveillance of *Staphylococcus aureus* (including MRSA) bacteraemias from April 2001. The extension of this to include the surveillance of glycopeptide-resistant enterococcal bacteraemias from September 2003 was announced on the 9<sup>th</sup> June 2003.<sup>2</sup> These initiatives form part of the healthcare associated infection developments referred to in the Chief Medical Officer's strategy to combat infectious disease, *Getting Ahead of the Curve*.<sup>3</sup>
- 1.2 Under the terms of a Service Level Agreement with the Department of Health, the Public Health Laboratory Service was required to implement these initiatives. This responsibility was transferred to the Health Protection Agency, which includes part of the former Public Health Laboratory Service. This SLA is largely derived from the recommendations of the Healthcare-associated Infection Surveillance Steering Group of the DOH. The Communicable Disease Surveillance Centre, via its Department of Healthcare-associated Infection & Antimicrobial Resistance, together with the Regional Epidemiology Service, has been charged with the delivery of the major part of the SLA. The letter from the Chief Medical Officer<sup>2</sup> stated that reporting should be through the routine laboratory reporting system to the Communicable Disease Surveillance Centre and that Trusts need to ensure that microbiology laboratory systems are able to download and electronically export their surveillance information automatically by December 2003.
- 1.3 A national group was established to examine issues related to surveillance of GRE, as there were indications that current methods would not provide a suitable basis for this surveillance. The membership of the group is given in Appendix 1.

## **2 Remit of the GRE Bacteraemia Surveillance Working Group**

- 2.1 To review technical problems associated with detection and reporting of GRE.
- 2.2 To establish the current approaches to detection of GRE.
- 2.3 To review the significance and reliability of reports of GRE bacteraemia and the comparability of data from different hospitals.
- 2.4 To make recommendations on the characterisation, susceptibility testing and reporting of enterococcal bacteraemias to inform the national surveillance system for GRE bacteraemia.

### **3 National questionnaire on methods, approaches to testing and risk factors**

- 3.1 In order to provide reliable background data, and as part of an educative exercise for laboratories aimed at supporting the objective of reliable GRE bacteraemia surveillance data, a questionnaire was distributed in June 2003 via Regional Epidemiologists to laboratories in their regions. The questionnaire responses are given in Appendix 2 and were taken into account when preparing this report.
- 3.2 The questionnaire was returned by 169 (82%) of 205 laboratories. Four of the returned questionnaires were not completed, giving 165 assessable returns.
- 3.3 Thirty-four percent of questionnaire respondents reported enterococcal bacteraemias to CDSC in 2002 (question 12). Notably, 33% of the bacteraemias were not reported to CDSC via the routine reporting system. Only 16 (30%) of the 55 laboratories reporting GRE bacteraemic episodes indicated that they detected more than five in the year.

## 4 Clinical significance of GRE bacteraemia

- 4.1 GRE are undoubtedly significant pathogens. Although there is variability among results from different studies, with some indicating that glycopeptide resistance may not be an independent marker for mortality (e.g. Lautenbach *et al*, 1999<sup>4</sup>), significantly greater rates of clinical treatment failure (60% vs. 40%) and all-cause mortality (52% vs. 27%) have been reported recently with glycopeptide-resistant compared with glycopeptide-susceptible enterococcal bacteraemia in a multivariate analysis.<sup>5</sup> Furthermore, in a recent comparative but historically-controlled cohort study from a university tertiary referral hospital in the USA, there was a 27.7% attributable excess mortality rate of GRE bacteraemia compared with that of glycopeptide-susceptible strains in matched patients, while excess length of stay was 17 days and excess costs per patient of approximately \$81,000.<sup>6</sup> However, it is appreciated that costs in the UK would be significantly less than this.
- 4.2 Most clinical isolates of *Enterococcus* spp., whether glycopeptide-susceptible or resistant, represent colonisation rather than infection, which is typically endogenous (i.e. the patient is infected with enterococci with which they were already colonised). In addition, about 50% enterococcal bacteraemias are mixed (polymicrobial) and the role of the enterococci may be difficult to assess. However, if multiple organisms including GRE are isolated from a blood culture that is regarded as clinically significant, we believe that the GRE should be reported. In the questionnaire 99% of laboratories indicated that they could provide data on whether GRE were isolated from mixed infections (question 11). The current system of reporting to CDSC has no built-in mechanism for capturing data on polymicrobial bacteraemias. This can be done through complicated matching procedures but would be aided by the use of patients' NHS numbers.
- 4.3 There are caveats, however, in that enterococci from blood cultures are more commonly assessed as contaminants than are *S. aureus* isolates. For example, Weinstein *et al* (1997)<sup>7</sup> assessed 87.2% of 204 *S. aureus* bacteraemias as clinically significant, but only 69.9% of 93 enterococcal bacteraemias. Such assessments require considerable contemporary clinical knowledge and are based on a wide range of information that is not standardised or currently routinely recorded within clinical microbiology computer systems or reported via COSURV. Microbiological measures of significance (e.g. requiring that enterococci be isolated from more than one bottle of a blood culture set, or from more than one blood culture set) are difficult to apply because of the large number of likely-significant isolates that would be excluded.
- 4.4 Device-related information is of limited value in assessing the significance of enterococcal bacteraemia because of the high prevalence of intravascular and other devices used in the types of patient at risk, the lack of routine collection of information on the presence of such devices, and the difficulties of defining true clinical infection in the presence of the devices. In the questionnaire only 69% of laboratories said they could provide data on whether lines were *in situ* at the time of bacteraemia (question 11).

- 4.5 Antimicrobial treatment given to cover GRE isolated from blood cultures might be taken as an indicator of the perceived clinical assessment of a likely significant infection, but device-related infection may be managed by removal of the device without antimicrobial therapy. Only 81% in the questionnaire said that they could provide information on whether antibiotic treatment was given to treat GRE (question 11).
- 4.6 Recommendations
- 4.6.1 The significance of GRE bacteraemia must be assessed clinically taking into account all relevant factors. If a bacteraemia with GRE is judged to be clinically significant, whether mono- or poly-microbial, the GRE should be reported. A proposed case definition is given in Appendix 4.

## 5 Identification of enterococci

- 5.1 The genus *Enterococcus* includes over 20 species<sup>8</sup> but most enterococcal bacteraemias are caused by *E. faecalis*, with *E. faecium* the second most common (Table 1). Other species are infrequent pathogens.

Table 1: Enterococci reported from bacteraemia in England and Wales in 2002 (HCAI & AMR Division, CDSC, London)

Species	Number of reports	Percent isolates
<i>E. faecalis</i>	2046	42.1
<i>E. faecium</i>	783	16.1
<i>E. gallinarum</i>	89	1.8
<i>E. durans</i>	32	0.7
<i>E. avium</i>	23	0.5
<i>E. casseliflavus</i>	20	0.4
<i>E. hirae</i>	5	0.1
<i>E. raffinosus</i>	2	<0.1
<i>Enterococcus</i> species	1599	32.9
Group D streptococcus	256	5.3
TOTAL	4855	

- 5.2 Some clinical microbiologists do not identify all enterococci from blood cultures to species level because it is perceived to be of limited clinical relevance, expensive and time-consuming. Furthermore, because of technical difficulties, the accuracy of identification of enterococci in clinical laboratories is often suspect.
- 5.3 There were 4855 reports to the CDSC of enterococcal bacteraemia in England and Wales in 2002 and 1855 (38%) of the isolates were not identified to species level (Table 1). Similarly, of the 297 isolates which were found to be vancomycin resistant, about 37% were not identified to species level. In addition, it is almost certain that in the UK a significant number of *E. faecalis* are incorrectly identified because 15% of *E. faecalis* bacteraemia isolates were reported as resistant to ampicillin/amoxicillin during 1990-1998<sup>9</sup> and 12% were reported resistant in 2000.<sup>10</sup> It is likely that the ampicillin/amoxicillin-resistant *E. faecalis* isolates were actually *E. faecium* since *E. faecium* are commonly ampicillin/amoxicillin resistant, there have been no confirmed cases of ampicillin/amoxicillin resistance in *E. faecalis* in the UK and they are very rare or have never been reported in other countries.
- 5.4 In the British Society for Antimicrobial Chemotherapy bacteraemia resistance surveillance project in 2002, 7% of isolates reported as *E. faecalis* were *E. faecium*, 12% reported as *E. faecium* were *E. faecalis* and 43% were not identified to species level (Table 2; D. Livermore, unpublished observations). Identification methods used in the participating laboratories were not known.

Table 2: Identification of 222 enterococci submitted to ARMRL as part of the BSAC bacteraemia resistance surveillance programme.

Organism	Number identified in original laboratory	Number identified at ARMRL				
		<i>faecalis</i>	<i>faecium</i>	<i>durans</i>	<i>casseliflavus</i>	Not speciated
<i>E faecalis</i>	81	74	6		1	
<i>E faecium</i>	40	5	33			2
<i>E gallinarum</i>	2		2			
<i>E casseliflavus</i>	0					
<i>E durans</i>	3	1	1	1		
<i>Enterococcus</i> species	86	65	21			
Enterococcus Gp D	3		2	1		
Streptococcus Group D	7	4	3			
Total	222	151	67	1	1	2

- 5.5 Responses to the questionnaire indicated that 84% of respondents routinely identified isolates to the species level (question 1).
- 5.6 In the European Antimicrobial Resistance Surveillance System (EARSS) quality assessment exercise in 2001,<sup>11</sup> 8.6% of 546 laboratories in Europe incorrectly reported the identification of an *E. faecium* (16 *E. faecalis*, 8 *E. gallinarum*, 4 *E. casseliflavus*, 16 *Enterococcus* sp. and 3 non-enterococci). There were fewer errors with *E. faecalis* (4 *E. faecium*, 1 *E. gallinarum*, 1 *E. avium*, 17 *Enterococcus* sp. and 4 non-enterococci). In another EARSS quality assessment exercise in 2002, 13% laboratories in Europe (17% of 24 in UK) misidentified an *E. faecium* but the reported identifications were not published.<sup>12</sup>
- 5.7 As vancomycin resistance is currently more common in *E faecium* than *E. faecalis*, incorrect identification may also lead to errors in reported resistance rates for individual species. Accurate identification is required to determine whether changes in resistance rates reflect the dissemination of resistance determinants among enterococci in general or a rise in the relative importance of *E. faecium*, which is the species where glycopeptide resistance is most common.<sup>13</sup>
- 5.8 Identification that relies only on detection of Lancefield Group D antigen will lead to errors because it is found within some non-enterococcal species including *Streptococcus bovis*. Also, *Pediococcus* spp. may react with Group D antigen and these are intrinsically resistant to vancomycin.
- 5.9 The HPA Standard Method for blood cultures<sup>14</sup> includes identification to species level but in the HPA Standard Method for identification of enterococci<sup>15</sup> there is no specific recommended method for achieving this other than by use of "a commercial kit". Kits commonly used in the UK include API 20 Strep (bioMérieux, Basingstoke, UK), API Rapid ID 32 Strep (bioMérieux), BBL Crystal Gram Positive (Becton Dickinson, Oxford, UK), and BBL Crystal Rapid Gram Positive (Becton Dickinson). Ninety-one percent of laboratories in the questionnaire used one or more of these kits. Vitek (bioMérieux) and Phoenix (Becton Dickinson) automated systems for identification and antimicrobial

- susceptibility testing are used for identification in 6% and 1% laboratories respectively in the questionnaire (question 2).
- 5.10 In earlier evaluations of commercial kits performance in speciation of enterococci was reasonable, but the studies often included multiple genera and a relatively small number of enterococci, predominantly *E. faecalis*.<sup>16-18</sup>
- 5.11 With collections of selected isolates, e.g. glycopeptide-resistant isolates or those with a high proportion of non-*faecalis* and non-*faecium* isolates, the performance of the API systems has been poorer than in earlier studies. Reed *et al.* found that the API 20 Strep identified only 60% of 42 isolates correctly, 38 of which were *E. faecalis*.<sup>19</sup> In a study of the API 20 Strep with 369 nosocomial enterococcal strains,<sup>20</sup> 20% of 125 *E. faecalis* were mis-identified, the majority as *E. faecium*, 9% of 215 *E. faecium* were mis-identified and nine of the 12 *E. gallinarum* isolates were identified as *E. faecium*. The predictive value of the species identification for the API 20 Strep was 95% for *E. faecalis*, 84% for *E. faecium* and 55% for non-*faecalis* and non-*faecium* enterococci. The authors noted that the API 20 Strep kit was modified by the manufacturer subsequent to their study.
- 5.12 A study comparing genotypic and phenotypic methods with 28 enterococcal isolates showed the API 32 Rapid Strep to perform better than the API 20 Strep, mis-identifying 14% and 29% of isolates respectively.<sup>21</sup> Both kits failed to differentiate *E. gallinarum* from *E. faecium* and vice versa. However, in a study comparing the ability of the BBL Crystal and API systems to identify 28 *E. faecium* isolates,<sup>22</sup> only 2 (7%) were correctly identified by the API Rapid 32 Strep while 16 (57%) were correctly identified by the API 20 Strep. *E. faecium* was often identified as *E. gallinarum* or *E. casseliflavus*. In this report the BBL Crystal Gram Positive and Rapid Gram Positive kits identified 93% and 96% of the isolates correctly.
- 5.13 Antimicrobial susceptibility can be a useful check on identity of enterococci. At present in the UK, *E. faecalis* are susceptible to ampicillin/amoxicillin and *E. faecium* are mostly resistant. Conversely, *E. faecium* are usually susceptible to quinupristin/dalfopristin and *E. faecalis* are commonly resistant.<sup>23</sup>
- 5.14 Recommendations
- 5.14.1 Accurate identification of enterococci to species level is required for GRE bacteraemia surveillance.
- 5.14.2 Identification should be based on use of commercial kits although accuracy is currently suspect, particularly with species other than *faecalis* and *faecium*. Molecular techniques are the reference methods but are not currently practical for routine use in clinical laboratories.
- 5.14.3 Further studies on the performance of kits with a range of enterococcal species are necessary.
- 5.14.4 A quality control check on identification by biochemical tests would be that any ampicillin resistant and/or quinupristin/dalfopristin susceptible *E. faecalis*, and ampicillin susceptible and/or quinupristin/dalfopristin resistant *E. faecium* is likely to indicate an error. Such strains should be sent to a reference laboratory (e.g. ARMRL) for checking.

## 6 Glycopeptide agents tested in clinical laboratories

- 6.1 Two glycopeptide antibiotics, vancomycin and teicoplanin, are licensed in the UK. A new glycopeptide, oritavancin, which is active against glycopeptide-resistant enterococci, is in Phase III trials.<sup>24</sup> Dalbavancin, another glycopeptide in Phase III trials, also has activity against glycopeptide-susceptible and some glycopeptide-resistant enterococci, although not against strains with the VanA type (see paragraph 6.3) resistance.<sup>25</sup>
- 6.2 Currently, there is no national agreement on which glycopeptide to test routinely in diagnostic laboratories. In most laboratories either vancomycin or teicoplanin are tested, according to clinical preference. HPA LabBase2 data for 2002 indicate that among 4855 *Enterococcus* spp. (including Group D streptococci) reported from bacteraemias in England and Wales, 1617 (35.7%) were tested against vancomycin as the only glycopeptide, 108 (2.2%) against teicoplanin only, and 1735 (35.7%) against both agents. Susceptibility to either glycopeptide was not reported for 1395 (28.7%) enterococci from bacteraemias (HCAI & AMR Division, CDSC). In the questionnaire, 92% of respondents said they tested all isolates against vancomycin and 72% tested all against teicoplanin (question 3).
- 6.3 Six types of glycopeptide resistance have been identified in enterococci.<sup>25</sup> The predominant acquired types are VanA (approximately 80% isolates) and VanB (approximately 20% isolates). Other acquired types (VanD, VanE and VanG) have not been reported in the UK. VanC resistance is an intrinsic characteristic of *E. gallinarum* and *E. casseliflavus/flavescens*.
- 6.4 Enterococci expressing VanA type resistance display high-level resistance to vancomycin and cross-resistance (not always at high-level) to teicoplanin. Isolates with other types usually display resistance only to vancomycin, with this at a lower level than in VanA isolates. There are exceptions to these generalisations, but they are rare at present.
- 6.5 There are no confirmed reports of enterococci displaying resistance to teicoplanin while remaining vancomycin susceptible (though artefactual results of this type may arise in disc tests because glycopeptides are large hydrophobic molecule that diffuse poorly; see paragraph 7.4). Any isolates genuinely showing this phenotype must be rigorously investigated.
- 6.6 If laboratories test only teicoplanin against enterococci, the prevalence of glycopeptide resistance will be underestimated because non-VanA isolates will be missed. If vancomycin is tested (either alone or as well as teicoplanin), the sensitivity of screening would be improved as all glycopeptide-resistant enterococci could theoretically be detected (but see paragraphs 7.6 to 7.8).
- 6.7 Recommendations
- 6.7.1 All laboratories should test vancomycin against enterococci from blood cultures.
- 6.7.2 Teicoplanin susceptibility, if tested, should only be tested in addition to vancomycin susceptibility. It must not be considered as an alternative to vancomycin for surveillance purposes, even if it is the hospital's preferred glycopeptide for therapeutic purposes.

## 7. Glycopeptide susceptibility testing

- 7.1 Most UK diagnostic laboratories assess antimicrobial susceptibility (including to glycopeptides) by disc diffusion testing (91% in the questionnaire, question 5), a few use breakpoint methodologies (4% in the questionnaire), and some use automated systems (10% in the questionnaire). It was notable that 20% of laboratories routinely used more than one method (question 5). An increasing number of laboratories supplement these protocols with additional tests for confirmation of resistance (88% in questionnaire, question 6), most commonly the Etest (84% of those confirming resistance in the questionnaire, question 7).
- 7.2 As noted in paragraph 6.4, vancomycin resistance in VanA enterococci is generally high-level and its detection presents no problem for diagnostic laboratories. In recent distributions from the UK National External Quality Assessment Service (NEQAS), >99% of participating UK laboratories detected vancomycin resistance in two isolates with the VanA phenotype (V. James, QAL, personal communication).
- 7.3 Teicoplanin resistance in isolates with the VanA phenotype may be expressed at lower levels and is detected less reliably; rates of reporting resistance in the same NEQAS distributions as in paragraph 7.2 were 79-91% despite unequivocal resistance being shown in reference laboratories (teicoplanin MICs 32–64 mg/L; V. James, QAL, personal communication).
- 7.4 Paragraphs 6.6 and 7.3 illustrate the potential for under-reporting of resistance if only teicoplanin is tested. Paradoxically, there is also a potential for laboratories to over-report teicoplanin resistance in enterococci. With the BSAC disc diffusion method, teicoplanin zone diameters for susceptible strains are commonly close to the interpretative zone diameter breakpoint, which can lead to poor reproducibility of tests and glycopeptide susceptible isolates being incorrectly reported as teicoplanin-resistant, vancomycin-susceptible - see paragraph 6.5.<sup>26</sup> Performance of other standardised methods has not been examined in the same way.
- 7.5 The difficulties of teicoplanin susceptibility testing outlined in paragraphs 7.3 and 7.4 further underscore our recommendation that vancomycin should be used to screen all enterococci for glycopeptide resistance in any mandatory surveillance programme (see paragraph 6.7).
- 7.6 Vancomycin is also the only glycopeptide appropriate for detecting non-VanA type resistance (see paragraphs 6.4 and 6.6). However, as enterococci with VanB and VanC resistance often display much lower levels of vancomycin resistance than VanA isolates, detection of their resistance in diagnostic laboratories is not always reliable.<sup>27,28</sup> In particular, laboratories frequently do not incubate tests for the full 24 h (not “overnight”) as required,<sup>29</sup> and plates are not closely examined to detect small colonies within zones, leading to under-reporting. It may be that re-reading plates after 48 h incubation would assist in distinguishing resistance in strains that appear borderline after 24 h incubation, but this has not been validated.

- 7.7 In recent NEQAS distributions, 20-30% of participating laboratories in the UK failed to detect vancomycin resistance in VanB enterococci (V. James, personal communication). Similarly, in the 2002 EARSS distribution,<sup>12</sup> 50% of 24 participating laboratories in the UK failed to detect VanB glycopeptide resistance in *E. faecium*. Some laboratories consistently fail to detect low-level vancomycin resistance. In recent NEQAS distributions, only 25% of 266 laboratories detected low-level vancomycin resistance in all of five strains of enterococci, and 6% of laboratories failed to detect vancomycin resistance in any of these strains (V. James, personal communication).
- 7.8 Based on current experience, it is estimated that data generated in the mandatory surveillance programme will have an inherent error (under-reporting of glycopeptide resistance – see above) of at least 5% if the screening is undertaken with vancomycin. This figure is based on the likely failure of diagnostic laboratories to detect vancomycin resistance in at least 25% of non-VanA isolates, which account for ca. 20% of GRE from bacteraemias.
- 7.9 Recommendations
- 7.9.1 Laboratories should follow details of standardised methods as specified.
- 7.9.2 A brief guidance note (Appendix 3) advising laboratories on vancomycin susceptibility testing should be distributed.
- 7.9.3 Modification of routine testing methods to improve the reliability of detection of VanB resistance should be investigated.

## 8 Risk Factors for GRE bacteraemia

- 8.1 In hospitals the reservoir of enterococci is the bowel of patients. Cross-infection and clusters of infection occur and resistant strains (glycopeptide-resistant or high-level aminoglycoside-resistant) have been transmitted via staff hands and occasionally the environment.<sup>30-33</sup> As with outbreaks of many other antimicrobial resistant organisms, colonisation is more frequent than true infection.
- 8.2 The emergence of enterococci with acquired glycopeptide resistance is mainly the result of the appearance and spread of transposons encoding *VanA* and *VanB* genes. This usually occurs within environments where there is heavy usage of glycopeptides and/or cephalosporins, for example in renal,<sup>34,35</sup> liver,<sup>36</sup> haematology,<sup>37</sup> oncology,<sup>38-41</sup> transplant<sup>36</sup> and intensive care units.<sup>42,43</sup> The emergence of GRE in the mid 1980s coincided with an increase in the global usage of glycopeptides<sup>44</sup> for the treatment of methicillin resistant *S. aureus*, coagulase-negative staphylococci and *Clostridium difficile* diarrhoea. However, the role of increasing glycopeptide usage in GRE selection and spread is not clear (see 8.3) and other antimicrobials, such as cephalosporins and fluoroquinolones, have also been implicated.<sup>37,38,41,45-52</sup> In a study of 50 ICUs in the USA there was a fall in the incidence of GRE in units that reduced vancomycin usage, compared with a rise in those that did not (mean decrease of 7.5% compared with mean increase of 5.7% respectively,  $P < 0.001$ ).<sup>53</sup> In contrast, another study showed no reduction in infection or colonisation with GRE despite significant reduction in the use of vancomycin.<sup>45</sup>
- 8.3 The CDC reported that the percentage of GRE implicated in nosocomial infections in ICUs in the USA increased from 0.4% in 1989 to 7.2% in 1997.<sup>54</sup> A recent study of blood isolates in England and Wales has shown that vancomycin resistance in *E. faecium* increased from 6.3% in 1993 to 24% in 1998, whereas in *E. faecalis* it increased from approximately 3% in 1996 to 5% in 1998.<sup>9</sup> These increases probably reflect the coincidence of risk factors including severe illness and antimicrobial therapy.<sup>46,55,56</sup> Cephalosporin and vancomycin therapy are the most cited antimicrobial risk factors for GRE colonization or infection,<sup>43,49,51,52,55-58</sup> although a meta-analysis of multiple studies, a carefully-controlled observational study and a systematic review failed to confirm the independent effect of vancomycin therapy.<sup>51,59,60</sup> Preceding therapy with agents active against anaerobes have also been implicated.<sup>50,61</sup> Tokars *et al.*<sup>62</sup> have shown a stepwise increase in GRE prevalence with increasing total antimicrobial-days per patient, a factor that may be as important as the risk associated with specific agents themselves.<sup>62,63</sup>
- 8.4 Risk of acquisition of GRE is proportional to the length of hospital stay; Montecalvo *et al.*<sup>64</sup> noted that patients with GRE bloodstream infection had been in-patients for a median of 26 days. However, hospitalisation may not be a strongly independent risk factor in high-risk groups when analyses are controlled for antimicrobial use.<sup>65</sup> GRE are encountered more frequently in teaching hospitals and in hospitals with a higher complement of beds: a 1993 survey conducted by the CDC showed a GRE prevalence of 3.6% of enterococci in hospitals with >500 beds, 1.8% in those with 200-500 beds, and 0% in hospitals with <200 beds.<sup>66</sup> Presumably the higher occurrence of GRE in larger hospitals is related to their more complex case-mix.

- 8.5 Apart from receipt of antimicrobial agents, and inpatient care on particular units (especially those where other GRE-positive patients are being nursed), other risk factors for GRE colonisation and infection identified in a number of studies include malignancy, receipt of enteral feeding, gastric acid suppression, possession of central venous lines, increased morbidity as measured by increased Acute Physiology and Chronic Health Evaluation (APACHE) score, renal failure, mechanical ventilation, neutropenia, organ transplantation and haematological malignancy.<sup>4,5,13,50,67,68</sup> In general, the risk factors for GRE colonisation have not been studied separately from those for clinically-significant infection, although treatment of GRE carriers in oncological populations with vancomycin have been found to increase risks of GRE bacteraemia,<sup>41</sup> and severe mucositis may also be a predisposing factor.<sup>69</sup> The questionnaire indicated that most hospitals did not consider GRE carriage of sufficient clinical significance to warrant routine faecal screening for GRE even among at-risk patient groups (question 9).
- 8.6 In Europe, GRE (particularly those with the VanA phenotype) are found in the bowels of normal people in the community, in frozen meats and animal carcasses, and in the bowels of animals fed the glycopeptide avoparcin as a food supplement.<sup>70</sup> Although the scientific evidence is far from conclusive, it is generally accepted that the use of avoparcin as an ergotropic agent in animal husbandry is associated with the emergence of GRE in animal faeces. At least some of these strains then enter the food chain and colonise humans.<sup>71</sup> Administration of glycopeptides may result in the subsequent emergence of GRE following hospital admission.<sup>72</sup> GRE may also spread by cross-infection between hospital patients<sup>42,43,45,46,56,73-75</sup> and, presumably, within community cohorts. In addition, transposons encoding glycopeptide resistance probably transfer between commensal enterococci in animal and human gut.<sup>76-78</sup> However, avoparcin has not been used as an ergotrope in the USA: GRE are therefore thought not to have entered the food chain and colonised the general population.<sup>79</sup> Nevertheless, nosocomial GRE colonisation and infection appear to be much more frequent in the USA than in Europe.<sup>80</sup> The use of avoparcin in food animals in EU member states and Switzerland was banned in April 1997 and this was followed by declines in glycopeptide resistance in enterococci recovered from poultry or poultry products.<sup>81</sup>
- 8.7 Detectable GRE colonisation of the human bowel can be prolonged: often for months and sometimes for years.<sup>82,83</sup>
- 8.8 The main routes of transmission between patients and health care workers are probably via hands, fomites and/or environmental contamination. Enterococci may contaminate the environment around a patient and survive there for several days<sup>56,74,84</sup> and environmental contamination is increased when patients have diarrhoea.<sup>56</sup> Surfaces or fomites (including medical instruments and equipment) that come into contact with staff hands may also become contaminated.<sup>42,85</sup> These environmental sites are potentially secondary sources for cross-infection. However, several studies<sup>43,63,86,87</sup> have failed to find epidemic strains of enterococci in the hospital environment and the recovery of environmental isolates is dependent on culture methods; environmental screens must therefore be interpreted with care.<sup>88</sup> Strains of GRE originating in the community are

usually of multiple types,<sup>72</sup> whereas hospital associated outbreaks may involve single<sup>42,43,56,73,75</sup> or multiple strains.<sup>45,46,74</sup>

## 8.9 Recommendations

8.9.1 GRE bacteraemia surveillance data should be related to known risk factors.

8.9.2 Methods of data collection for global and individual risk factors should be explored.

## 9 Denominators for GRE bacteraemia surveillance

- 9.1 Currently GRE bacteraemias are an infrequent occurrence in most hospitals in England and Wales: there were 297 reports to CDSC of vancomycin-resistant enterococcal bacteraemias in 2002, only 13 hospitals reporting more than 5 per year; of these, 8 hospitals reported more than 10. Similarly, among 163 laboratories responding to the survey questionnaire (question 12), 16 indicated that they had more than five GRE bacteraemias in a year (only 67% of 55 laboratories with GRE bacteraemias reported all GRE bacteraemias to CDSC so CDSC 2002 data are an underestimate). GRE bacteraemias are generally concentrated in particular specialties within a hospital. Given this situation it would not be appropriate to use hospital-wide activity figures as the denominator for GRE bacteraemias, as is done for the mandatory *S. aureus* bacteraemia surveillance data.
- 9.2 GRE bacteraemia, unlike MRSA, is strongly associated with inpatient stays on only a few special units and with only a few predisposing clinical factors. Hospitals vary widely in whether they have such high-risk patient groups (questionnaire, question 8). Given these risk factors, the most appropriate denominators for GRE bacteraemia surveillance would take into account whether a hospital contains those units where GRE prevalence has been reported to be high, and some representation of activity on these units. Such data are required for meaningful assessment and comparison of individual hospitals' rates of GRE bacteraemia. Failure to relate data to these risk factors in individual hospitals will introduce major bias into any national surveillance scheme.
- 9.3 Obtaining exact numbers of patients in the high risk groups clearly presents major problems for a large proportion of hospitals (questionnaire, question 10). High risk patients are not confined to specialist units, and even if numbers of patients on specialist units were available, the data would be limited by the fact that use of beds on specialist units is not protected. In addition, specialist units with patients at-risk for significant GRE infections may have long term (e.g. renal units), medium term (e.g. haematological malignancy) or short term (e.g. ICU) endogenous populations. Furthermore, a renal unit may be divided into acute haemodialysis, chronic haemodialysis, home-based peritoneal dialysis, and other moderately ill patients. Epidemiological representation of denominators per unit time would be different for each type of unit and it is likely that necessary data would not be immediately available but require special collection.
- 9.4 Recommendations
- 9.4.1 GRE bacteraemia surveillance should be related to risk factors represented by particular units as data will be highly misleading without such information. However, it is highly unlikely that collection of detailed information on all relevant risk factors will be practical for the majority of hospitals at present.
- 9.4.2 As numbers of GRE bacteraemias are small in most English Trusts currently, the collection of specialty-based activity information from all Trusts is not warranted, particularly given the difficulties obtaining this data. It is therefore recommended that, in the first instance, specialty-

based denominator information is obtained only from Trusts with more than five GRE bacteraemias in a year.

- 9.4.3 Rates of GRE bacteraemias in Trusts should not be used as a performance indicator, as the numbers are too small for valid analysis in this way.
- 9.4.4 The usefulness of monitoring GRE bacteraemia lies in detecting changing trends. In order to detect such changes, it is recommended that GRE bacteraemias are analysed as a proportion of all clinical bacteraemias in the Trust. This could utilise the data on bacteraemias already collected for the mandatory *S. aureus* bacteraemia surveillance. GRE bacteraemias should also be analysed as a proportion of enterococcal bacteraemias for *E. faecalis*, *E. faecium* and for other species combined. These results would form the basis for further investigation as necessary.
- 9.4.5 The situation should be reviewed after a year and the methodology subsequently amended as appropriate.

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## Appendix 2: Questionnaire on methods and risk factors

### Review of methods, approaches to testing and risk factors for GRE bacteraemia

In July 2003 questionnaires were sent to 205 laboratories in England. The survey was undertaken to provide detailed knowledge on practice with regard to identification and glycopeptide susceptibility testing of enterococci, and to examine the practicality of collecting information to associate risk factors with GRE bacteraemia rates.

#### Response rate:

The questionnaire was returned by 169 laboratories (82%).

Region	Percent return
East of England	90
East Midlands	100
London	70
North East	100
South East	52
North West	97
South West	100
West Midlands	90
Yorkshire and Humber	86
National total	82

#### Denominators:

Three laboratories submitted null returns as they do not process blood cultures, and one did not complete the form on the grounds that they rarely see this type of infection. Hence the total denominator value for laboratory questions is 165. If a question was not answered by a laboratory the denominator was reduced accordingly.

There were data entries for 165 laboratories that are associated with 153 trusts. Thus the trust denominator value is 153.

#### Relationships between laboratories and Trusts:

	Percent laboratories
For 165 laboratories associated with Trusts:	
Laboratories serving one Trust	93
Laboratories serving two Trusts	5
Laboratories serving three Trusts	2
Laboratories serving more than one Trust	7

For 153 Trusts associated with laboratories:	Percent Trusts
Trusts served by 1 laboratory	84
Trusts served by 2 laboratories	13
Trusts served by 3 laboratories	2
Trusts served by 4 laboratories	1
Trusts served by more than 1 laboratory	16

### Questionnaire responses:

In each question n values are given for the denominator. Percentages are given to the nearest whole number so in some analyses they total slightly over 100%.

- Q1. *Glycopeptide resistance rates differ in different species so identification to species level is desirable. To what extent are enterococci from blood cultures routinely identified in your laboratory? (n=165):*

Level of identification	Percent laboratories
Genus only	5
Species only	62
Lancefield group D only	2
Genus and Lancefield group D	3
Species and Lancefield group D	22
Other (11 responses)	7
Main points:	
Level of identification is dependent on the antibiotic susceptibility of the isolate (if displays resistance will be identified to species level).	
Speciated if deemed clinically relevant.	
Speciated if specifically requested by the clinician or microbiologist.	
Unclear or "identified" by susceptibility only.	

- Q2. *There are problems with the identification of enterococci which would lead to errors in glycopeptide resistance rates. How are enterococci from blood cultures routinely identified in your laboratory? (n=163):*

Identification test/method*	Percent laboratories
Colonial morphology	82
Gram stain	80
bioMérieux API Rapid ID 32 Strep	63
Lancefield grouping	56
Catalase	50
Aesculin hydrolysis	40
bioMérieux API Rapid ID 20 Strep	21
PyrA	9
BBL Crystal Gram-positive ID kit	6
Vitek	4
Antibiotic resistance phenotype	3
Vitek2	2
Biostat rapid strep/Rapid structure system for biochem ID	2
BBL Crystal Rapid Gram-positive ID kit	1
Tellurite	1
Reference lab	1
Phoenix	1

\*Multiple tests/methods commonly used.

- Q3. *If vancomycin is not tested non-vanA-mediated resistance will be missed. Which glycopeptide agents are tested on enterococci from bacteraemias in your laboratory? (n=163):*

Glycopeptide tested	Percent laboratories
Vancomycin (total)	98
Vancomycin on all isolates	92
Vancomycin on specified isolates (n=10): (multiple selection criteria in some laboratories so total >6%)	6
as requested by medical staff	2
if resistant to ampicillin or amoxicillin	3
if resistant to first line antibiotics	1
if indicated on clinical grounds	1

Glycopeptide tested	Percent laboratories
Teicoplanin (total)	86
Teicoplanin on all isolates	72
Teicoplanin on specified isolates (n=23) (multiple selection criteria for some laboratories so total >14%)	14
As requested by medical staff	3
If resistant to ampicillin or amoxicillin	5
If vancomycin resistant	6
If patient is receiving teicoplanin	2
If patient has renal impairment	1
If patient is from a specialist unit (ICU, SCBU, oncology, haematology)	2
Clinical indication	2
Endocarditis	1

## Additional comments:

- 1 Problems of checking for vancomycin resistance (the only glycopeptide we check) are substantial. At the moment they are out of proportion to the problem at our hospital.

Q4. *There may be problems with direct susceptibility tests from blood cultures. Do you do direct susceptibility tests from blood cultures? (n=163):*

Yes 94%

*If yes, are all enterococcal susceptibilities repeated on pure cultures? (n=154):*

Yes 45%

## Additional comments:

- 1 Yes but only if the direct test inoculum is too heavy or not pure.
- 2 Repeat if inoculum heavy/light/doesn't conform to BSAC, if extra sensitivities required or Etest for confirmation.
- 3 Yes if not pure or inoculum incorrect.
- 4 In our experience problems regarding the use of direct susceptibility testing for blood culture only relates to purity in a very small number of cases. It is more likely that doubt is cast on the validity of the result because of the difficulty of standardising the inoculum and obtaining the correct weight of growth. In these instances tests would be repeated.

Q5. *There may be differences in the reliability of different methods of testing for glycopeptide resistance. Which method is used for **routine** glycopeptide susceptibility testing of enterococci from blood cultures in your laboratory? (n=162):*

Method used	Percent laboratories
Disc diffusion by BSAC standardised method	59
Disc diffusion by NCCLS	1
Disc diffusion by Stokes (or other comparative)	31
Breakpoint: (n=6)	4
Breakpoints: 4 mg/L (n=5)	
Not stated (n=1)	
Vitek	5
Vitek2	4
MIC Etest	15
Mini API ATB Enterococci	1
Phoenix	1
Combinations:	
1 method	81
2 methods	19
BSAC and Etest	6
BSAC and Vitek	2
BSAC and Vitek2	2
BSAC and Stokes	2
BSAC and breakpoint	1
BSAC and Mini API ATB Enterococci	1
Stokes and Etest	2
Stokes and Vitek	1
Stokes and Vitek2	1
Stokes and breakpoint	1
NCCLS and Phoenix	1
3 methods	1
BSAC, Vitek2 and Etest	1

Additional comments:

- 1 We note that BSAC teicoplanin disc testing gives frequent false positives, - false resistant results.
- 2 Reduced zones are not inoculum dependent. When the vancomycin disc test result is sensitive, to date the Etest is always sensitive.
- 3 There is a need for specification of the preferred method for sensitivity testing.
- 4 We appreciate that we might miss some GREs perhaps because the disc diffusion is not read at +2 days. We are addressing this. Neither API nor Vitek give reliable identification.

Q6. *It may be useful to do additional tests to confirm resistance in some isolates. Do you use additional methods to confirm resistance? (n=163):*

Yes 88%

*If yes, are all GRE confirmed? (n=144)*

Confirmation of GRE	Percent laboratories
All GRE confirmed	85
Confirmed only if*:	
Borderline susceptibility	9
VanB phenotype	3
High Etest value	1
Result in doubt	1
VanA phenotype	1
At request of Medical Microbiologist	1

\* Several laboratories indicated more than one criterion

Q7. *Different methods are available for confirmation of resistance. If additional methods are used to confirm resistance, indicate which (n=143):*

Method for confirmation of GRE	Percent laboratories
Etest	84
PCR	1
Breakpoint	1
Not specified	1
Isolate sent to reference laboratory	64
Combinations:	
1 method	50
2 methods	48
Etest and reference laboratory	47
Etest and PCR	1
Etest and breakpoint	1
3 methods	2
Etest, PCR and reference laboratory	1
Etest, breakpoint and reference laboratory	1

Additional comments:

- 1 Send to reference laboratory if result still in doubt or if typing required to detect cluster.
- 2 None isolated to date but all would be confirmed given the situation.

- Q8. *GRE infection is associated with particular risk factors. Which of the acute hospital Trusts served by your laboratory has these units? (n=142):*

Unit	Percent Trusts
Adult ICU	96
Leukaemic ward (adult or paediatric)	71
Dialysis unit	51

*Which of the acute hospital Trusts served by your laboratory performs these transplants? (n=142):*

Transplant	Percent Trusts
Liver	5
Renal	17
Bone marrow / stem cell	24

- Q9. *Colonisation of the gut with GRE is an additional risk factor for GRE infection. For different units, indicate whether you routinely screen patients' faeces for GRE (n=denominator values from Q8):*

Unit	Percent Trusts
Adult ICU (n=136)	4
Renal transplantation (n=24)	8
Liver transplantation (n=7)	14
Bone marrow or stem cell transplantation (n=34)	18
Leukaemic ward (adult or paediatric) (n=101)	10
Dialysis unit (n=73)	3
Other: (6 responses)	
PICU (n=1)	
All oncology patients, and heart and lung transplants (n=2)	
Ward or patient group not stated (n=3)	

Additional comments:

- 1 Surveillance based on stool culture did not provide useful clinical information on a bone marrow transplant patient where I worked before.
- 2 We currently screen faeces from patients with diarrhoea for GRE on ITU, renal, haematology wards.

Q10. *As GRE infection is associated with particular risk factors it is desirable to use appropriate denominators for GRE infection rates. If required, could you provide annual data on the following? (It may be that other data would be more accessible or appropriate e.g. bed occupancy):*

For parts a-f:

Denominator values are from the relevant part of question 8.

Numerator values are from those who answered yes to both relevant parts of question 8 and question 10 (i.e. they have this type of ward and could provide data on it).

For parts g and h:

Denominators are the total numbers of laboratories (n=165).

Numerator values are the number of trusts who could provide these data mapped back to their associated laboratories.

Data item	Percent laboratories
a. Number of beds on adult ICU	88
b. Number of patients on renal dialysis	67
c. Number of liver transplant patients for whom inpatient care is provided	57
d. Number of renal transplant patients for whom inpatient care is provided	58
e. Number of bone marrow or stem cell transplant patients for whom inpatient care is provided	74
f. Number of leukaemic patients (adult or paediatric)	63
g. Total numbers of bacteraemias (episodes) on different units	87
h. Total numbers of enterococcal bacteraemias (episodes) on different units	95

Additional comments:

- 1 Bed Occupancy as recorded on KH03 returns is readily available on the DOH website.
- 2 Other than ITU, the main problem is that of case mix on wards not being specifically one speciality or another, e.g. haematology ward. This would require searching on consultant name, but these may be spread around medical wards in Trust.
- 3 Many blood cultures are taken in A&E, so there is no relationship to wards to which they are admitted unless they become the source of GRE to others on the ward.
- 4 ? interpretation re e.g. leukaemic patient numbers. ? no. of inpatients. ? total size of 'unit'. Accurate data may be difficult to obtain.
- 5 "Different units" is not always straightforward. ITU is easy, but on other wards there are always so many outliers that it can be difficult to know.
- 6 Denominator data should include risk status of Trust to compensate for high risk units present on site i.e. performance should be risk stratified.
- 7 By the very nature and set up of this hospital beds are multipurpose.

- 8 Even the oncology unit (which includes any leukaemic admissions) has to take other medical patients so there is no such thing as a "specialist" unit. There are insufficient beds so no beds are protected. Patients returning here after transplants will be in a side room wherever it is available, therefore we cannot specify how many beds there are for that. This means that bacteraemia episodes on specific units cannot be calculated if you really mean to assess episodes in leukaemic patients or renal dialysis patients. The computer systems will not be able to break it down to this extent. It will be able to pick up the bacteraemias and the enterococcal bacteraemias for the hospital but manual work will have to be done to break it down further (The MRSA screening does not require this and the figures are produced quarterly but this has its problems too).
- 9 Numbers of blood cultures are OK to compute back.
- 10 The data not ticked may be available from other parts of the Trust e.g. Information Department, but we could undertake to collect it ourselves.
- 11 Basic data is fairly easy to obtain, bed occupancy on ITU (e.g.) is possible but more time consuming.
- 12 Re Q10B, only data regarding the dialysis patients in the satellite unit we cover.
- 13 We do not have a dialysis unit as such but ITU do have facilities to carry out haemofiltration. We also have patients admitted to various wards on CAPD. Are these to be included in the figures as it would be very difficult to find out this information?
- 14 While it would be possible to report positive bacteraemias by unit given the very low numbers at present this would have to be collected manually and would not be viable with increased numbers.
- 15 You must clarify the definitions of question 11 in order to produce accurate data. Do you mean such patients currently under care or any that have had at least 1 admission/transplant in the subject period, admission any time post-transplant i.e. in six months post Tx. Bed occupancy at midnight (KHO3) is useless and should not be used for any infection surveillance. It does not represent the population at risk. Possible to use FCEs as a simple baseline (or provider spells if concerned about varying episode/spell ratios between trusts, so long as strongly weighted by six risk factor categories mentioned.) The FCEs would have to be carefully specified. Can nobody see that comparing trusts is IMPOSSIBLE and UNFAIR! Our trust has looked into denominator difficulties in detail because of the MRSA bacteraemia rates and we would be more than pleased to advise further on finer details if needed.
- 16 Giving data on the number of bone marrow transplants or leukaemia patients at any one time is obtainable but is difficult to obtain. Bed occupancy may be easier.
- 17 We could get denominator data but it might prove very difficult, i.e. almost impossible.

Q11. *Clinical significance of GRE bacteraemia can be difficult to assess. If required, could you provide the following for all GRE bacteraemias? (n=157):*

Data item	Percent laboratories
Other organisms present if mixed infections	99
Line in situ at time of bacteraemia	69
Antibiotic treatment given to cover GRE	81

Additional comments:

- 1 Clinical information would be easier to provide prospectively rather than retrospectively.
- 2 CVC line status would be difficult to provide retrospectively.
- 3 For enterococcal isolates it is often very difficult to assess whether they are clinically significant or not. Many blood cultures have contaminants and if an enterococcus is mixed with a coagulase-negative staphylococcus it is often very difficult to predict the likely significance of the isolates, especially in ICU patients.
- 4 Although we could provide all 3 options if required it would be with some difficulty.
- 5 Details of clinical state may be available in some but would require notes for others. It is very difficult to provide anything other than laboratory data. Clinical information cannot be reported unless the information is supplied for requesting clinicians. Many of the categories in question 11 cannot be provided.
- 6 Line in situ at time of bacteraemia could be provided but not by a computer list. Antibiotic treatment given to cover GRE - Yes but not by a computer list.
- 7 Both the Line In situ and antibiotic treatment would require additional surveillance.
- 8 We don't routinely collect data re lines and antibiotic cover but could put a system in place to do so.
- 9 Line in situ at time of bacteraemia, we can usually supply this information, but it is not always recorded consistently. The answers I have given to Q11. depend on the availability of staff resources to write some of the queries required – sadly this cannot always be guaranteed! One of the things I noticed when eyeballing the data was the large number of episodes of enterococcal bacteraemia that were recurrent over a period of time. Whether these were truly 'new' episodes or simply reflected continuous or intermittent bacteraemia that was only detected when blood cultures were taken is debatable. At present we would report them as separate episodes if they are a month or more apart. This needs careful definition if reporting is to be consistent. The clinical significance of enterococcal bacteraemia is not always easy to assess. This is one of the reasons why some of our episodes of bacteraemia are not reported, although others appear to have been missed due to human error.
- 10 Can be done but it would take considerable staff time in non-teaching hospitals like this one.

- 11 Line in situ - "yes - manual data collection only". Antibiotic treatment to cover GRE - "yes - manual data collection only"
- 12 Line in situ "No - Yes if prospective study".
- 13 Information re lines and antibiotic therapy could not be called from laboratory data and would require microbiologist to go through patient notes.
- 14 Clinical criteria for significant cultures very important.

Q12. *Current reporting of bacteraemias to CDSC may not be complete. Did you see any glycopeptide resistant enterococcal bacteraemias in 2002? (n=163):*

Yes 34%

*If yes, were all reported to CDSC? (n=55)*

Yes 67%

*How many GRE bacteraemias (episodes) were seen:*

Number of bacteraemias	Percent laboratories
No value entered	4
0	15
1 to 5	53
6 to 10	13
11 to 15	2
16 to 20	7
22	2
40	2
55	2
120 (provisional number)	2

Additional comments:

1. Less than 10 but would have to check figures.
2. Unknown if reported or how many.

Q13 *Any additional comments?*

- 1 Where is all the extra man (woman) power needed to fill in questionnaires? We are being measured to death! No time for real work.
- 2 A lot of data which are likely to be required for GRE surveillance e.g. number of bed days, denominator blood culture figures, are already provided with current MRSA surveillance data. We hope there will not be duplication of this work.
- 3 The MRSA bacteraemia scheme is held up as a measure of hospital acquired infection, when in reality all it is identifying is the number of MRSA positive cases detected by microbiology laboratories – as in 2 above, they may not relate to being as a result of hospital acquired

infection (unless specific case auditing is done). This should not be used as a measure of HAI, but a measure of the PRESSURE exerted on hospital wards and other clinical areas! (which is what the MRSA bacteraemia should have been used as!)

We note that the ever increasing requirements for surveillance data has not been accompanied by any increase in resources for microbiologists. In contrast, the hospital pharmacy initiative for promoting prudent hospital antibiotic use (PL/CMO/2003/3) has been supported by a £12 million allocation to pharmacists. Where is the fairness in that? How will surveillance lead to reduced numbers of cases, since risk factors in terms of antibiotic selection are unknown.

4 Are VanCs to be included?

5 GRE bacteraemia in district general hospitals not as prevalent as tertiary referral centres. We see about 2-3 GRE bacteraemias per year. Faecal surveillance may identify a few more from ITU and leukaemia units. But what is the significance?

6 I think it is more of a marker of an ill patient rather than poor infection control practice, so what does it measure? How many really ill patients there are?

7 If GRE identified in an ITU patient:

Strict infection control procedures followed.

Patients in the unit are screened.

Faecal screening carried out.

Patients in the unit are screened.

8 I'm not at all convinced that this data will be either useful or interesting.

9 It is extremely rare for us to identify a GRE, which I don't think is incompetence!

10 Numbers currently small so should not be a big problem to collect the data if similar to MRSA bacteraemias. (Additional information may be more problematic). However, some recognition of the time and resources needed to do this extra work would have been appreciated (We got none for MRSA bacteraemia). This contrasts starkly to the £12 million on offer to pharmacists.

11 Please be aware that I neither have time nor have I sophisticated computer systems to generate detailed epidemiological data. It is essential for you to realise that with the current number of infection control personnel (2 nurses and 1/3 infection control doctor) we do not have time to collect the data you require.

12 We do not undertake routine surveillance - as yet we have not had a GRE from blood cultures on any patient.

13 GRE are extremely rare here at the moment.

14 The current trend of increasing demand for infection rates and other data is placing great demands on laboratories who are not properly funded to take up this additional work.

15 The data required should be kept to a minimum and must be recovered from LIMS.

16 The government should be paying if they want labs to collect this data.

17 We have only seen 2 patients in 3 years-transferred from other hospitals.

18 There is a need for specification of the preferred method for sensitivity testing.

- 19 We have a massive reservoir of chronic carriers for MRSA, VRE, gentamicin resistant Enterobacteriaceae due to our speciality patient mix length of stay etc. Coupled with rates of CVC use we expect to have some of the highest rates of "Bacteraemias".  
Significant resource diversion will be requested to give the kind of breakdown of information suggested above, which will likely impact on the delivery of an infection control service. Experience locally re: MRSA bacteraemias has been negative so far as the factors that affect ascertainment of the HAI are concerned, e.g. whether sample is line culture or peripheral stab (early on all our cultures are single sample from lines and are often contaminants or mixed), whether community acquired has been overlooked during the design of the surveillance. This compromises the validity of data which I am sure would not stand up to peer review!
- 20 We currently report all of our clinically significant bacteraemias via Cosurv - this should include VRE.

### Appendix 3: Guidelines on vancomycin susceptibility testing of enterococci

- 1 There is no single method which has proved outstandingly reliable. PCR is the reference method for detection of known resistance genes, but is not currently practical for routine clinical laboratory use.
- 2 If a disc diffusion method is used a standardised method, such as the BSAC<sup>1</sup> or NCCLS<sup>2</sup> methods, is preferable:
  - 2.1 Follow the method guidelines exactly as specified. In particular, the BSAC and NCCLS methods require plates to be incubated for a full 24 h (not just 'overnight'), and for zones to be examined closely for small colonies within zones.
  - 2.2 An additional useful indicator is that susceptible strains usually have sharp zone edges whereas vanB enterococci often have "fuzzy" edges. Enterococci with the vanA phenotype usually show no zone of inhibition around vancomycin discs.
  - 2.3 Use vanB enterococcal strains distributed by NEQAS as educational exercises to demonstrate to all staff the appearance of zones.
  - 2.4 Confirm borderline or equivocal results with an additional test such as PCR or the Etest.
- 3 With "Stokes" disc diffusion method, there are multiple variables as the method is not defined, but the following will improve reliability:
  - 3.1 Use a 5µg vancomycin disc.
  - 3.2 Use *E. faecalis* ATCC 29212 as the control strain.
  - 3.3 Interpret any test zone size smaller than the control as resistant.
  - 3.4 Points 2.1-2.4 also apply to Stokes' Method.
- 4 For Etests follow exactly the instructions of the manufacturer (AB Biodisk). An acceptable variation is that IsoSensitest agar may be used in place of Brain Heart Infusion agar. As with disc diffusion tests it is important to examine zones carefully for the presence of small colonies, which must not be ignored.

#### References

- 1 Andrews, J. M. for the BSAC Working Party on Susceptibility Testing. BSAC standardized disc susceptibility testing method (version 3). *J Antimicrob Chemother* 2004; 53: 713-28.
- 2 National Committee for Clinical Laboratory Standards (2003) Performance standards for antimicrobial disc susceptibility tests - Eighth edition; Approved Standard M2-A8. NCCLS, Wayne, PA, USA.

## Appendix 4: Definition of bacteraemia:

**Bacteraemia** (including fungaemia) must meet **one** of the following **criteria**:

### **Criterion 1:**

One or more **recognised pathogens** that are not common skin flora\* isolated from one or more blood cultures.

\* **Common skin flora**, e.g. *Bacillus spp.*, coagulase-negative staphylococci, diphtheroids, micrococci, or *Propionibacterium spp.*

### **Criterion 2:**

At least **one of the following clinical signs or symptoms\*\*** of infection within 24 hours of a positive blood culture being taken:

fever (skin temperature  $\geq 38^{\circ}\text{C}$ ),  
chills,  
rigors,  
hypotension (systolic blood pressure  $< 90\text{mm Hg}$ )

**and** an organism that is isolated from:

a. two or more blood cultures taken on separate occasions from new venepuncture sites

or

b. one blood culture taken from a venepuncture site **and** an intravascular catheter tip culture, both positive for the same organism

or

c. one blood culture from a patient with an intravascular device **and** there is resolution of clinical signs and symptoms after removal of the intravascular device, or following appropriate antimicrobial therapy

or

d. one blood culture from a patient with neutropenia ( $\leq 500$  neutrophils/ $\text{mm}^3$ ), which is considered clinically significant by the attending physician.

\*\* **For children < 1 year of age**, at least one of the following: fever (skin temperature  $\geq 38^{\circ}\text{C}$ ), hypothermia (skin temperature  $< 36.5^{\circ}\text{C}$ ), apnoea, or bradycardia.

### **Individual patient episodes**

Multiple clinically significant bacteraemias in one patient should only be counted once in any two week period.

**Hospital-acquired bacteraemia** must meet **one** of the following **criteria**:

**Criterion 1:** Bacteraemia, as defined above, that is acquired during hospitalisation, and was not present or incubating at the time of hospital admission. (This is usually taken as infection acquired more than 48h after admission)

**Criterion 2:** Patients re-admitted to hospital with a newly established bacteraemia resulting from previous hospitalisation. (This would include patients in some GRE risk groups, eg dialysis patients, renal transplant patients, who have an ongoing relationship with the hospital even if they are not strictly inpatients. Infections would be likely to be hospital acquired rather than community acquired)

## Appendix 5: Comments on the draft report and working group responses to comments

Page numbers refer to pages in the draft issued for consultation in February 2004. The report has been modified to take account of comments as indicated in the responses.

Comment	Response
<p>Person A</p> <p>I have read the draft report and congratulate you on the sensible recommendations. I particularly agree that the clinical significance of GRE bacteraemia should be assessed, and only significant infections reported. We frequently see VRE in 1 or 2 bottles from multiple sets taken from BMT/haematology patients. They are often not specifically treated, and repeat cultures are negative. Studies have shown carriage of VRE on the skin, including the antecubital fossa, in such patients and they can clearly be either v. transient bacteraemias of no significance or skin contaminants. I would estimate that 20-30% of blood culture isolates of VRE are deemed not significant in my lab (much higher than MRSA).</p> <p>I would however question the need for identification to species level by biochemical tests. We feel we can reasonably accurately predict the species on the antibiogram, and the species is not really relevant to the clinician. If this is solely for surveillance purposes then I feel we should either a) forward all the isolates to a Ref Lab/HPA lab, or b) have some additional funding for the extra work involved.</p>	<p>No response required</p> <p>Antibiogram alone does not give accurate identification of species although it is a useful indicator. About 10% of <i>E. faecium</i> are ampicillin susceptible and most laboratories do not routinely test quinupristin/dalfopristin, one of the more useful indicators of species.</p> <p>While identification to species level is important for surveillance purposes it is also recommended for all significant blood culture isolates in authoritative texts (eg HPA Standard Methods; Murphy O and Freeman R. In <i>Medical Bacteriology 2<sup>nd</sup> Edn</i>, Ed Hawkey P and Lewis D, Oxford University Press 2004: 27-53) for possible infection control purposes and to assist in assessment of significance. Moreover, unless isolates are identified to species level it is not possible to distinguish whether GRE increase because <i>van</i> genes spread more widely among enterococci as a whole or whether <i>E. faecium</i>, the main host of <i>van</i> genes, accounts for a larger proportion of enterococci.</p>
<p>Person B</p> <p>I found your document interesting and comprehensive. I have one comment, which pertains to the definition of bacteraemia in appendix 4. According to the current wording all enterococcal isolates are evidence of bacteraemia (under criterion 1), when in fact earlier in the document there is much discussion about the need to distinguish significant from non-significant isolates. It would make more sense to me if attempts were NOT made to distil into a short definition the (highly complex) process by</p>	<p>Agree that it is difficult to define bacteraemia in a few words and the requirement to assess clinical significance is emphasised. This definition has been widely used. It is a general definition of bacteraemia and does not exclude enterococci from being contaminants (and conversely does not exclude common skin flora from being significant). As this is a general definition "enterococcal" has been removed from the title.</p>

<p>which we reach conclusions about significance. This is also an opportunity to champion the contribution made by microbiologists to clinical management. Why not accept that an isolate is significant if deemed so 'after careful analysis by a competent practitioner such as a microbiologist'?</p>	
<p>Person C I've had a quick look through this and I have a few minor comments only. Overall it reads well and is clear. You don't mention isolation media - this is understandable as you're concentrating on B/Cs You use ITU &amp; ICU and SCBU &amp; PICU interchangeably</p> <p>p.6 Bactraemia - spelling mistake p.7 \$81,000 - this should be Reference 6 p.10 You switch between API 20 Strep and API 20S Formatting of Reference 45 p.28 spelling of BioMerieux Confusion between use of Rapid ID 20 Strep in Q2 p. 28 and data on p.10 p.33 Q.10 - open parenthesis</p>	<p>GRE screening media are not relevant to blood cultures Agreed for ITU and ICU. All changed to ICU in text but not if in comments made by individuals. SCBU and PICU are not used interchangeably. Typo corrected Typo corrected Corrected to API 20 Strep Typo corrected bioMérieux is correct No inconsistency in data. Clarified that more than one kit used in some laboratories. Typo corrected</p>
<p>Person D I work in the veterinary diagnostic field and am therefore unaware of the politics etc in HPA. I am surprised at the restricted nature of the locations of members of the Group Members - 7 from London, 3 from Cambridge!</p> <p>Questionnaire 3.2 Reasonable return rate but perhaps the non responders could have been "pressed" to complete it.</p> <p>3.3 Noted indiscipline in the reporting of enterococcal bacteraemias.</p> <p>Recommendations for GRE bacteraemia surveillance. Endorse all these i.e. 1-11 which instils discipline with the diagnostic laboratories. How can those labs which did not respond to the questionnaire be included in this. May need extra effort!</p> <p>Recommendation for further research Again endorse these but in 1) need to ensure good representation across HPA so that you get maximum "buy in".</p>	<p>"Politics" were not involved with the work of this Group, which was convened to report to the DOH, not the HPA. Membership was related to experience with GRE, expert knowledge, representatives nominated by BSAC, HIS and ICNA and support for organisation of the questionnaire and consultation exercise. Considerable efforts were made to increase the response rate, and &gt;80% is a good response for a non-mandatory questionnaire</p> <p>No response required</p> <p>All laboratories are included as the reporting of GRE bacteraemia is mandatory.</p> <p>All clinical laboratories, not only HPA laboratories, are involved. Wide representation would undoubtedly be one factor involved in membership of any group examining data collection.</p>
<p>Person E An excellent report! Page 5 Recommendations for further research - the group to explore methods of data collection should be lead by LARS and the NHS labs to ensure that anything proposed is doable.</p>	<p>Agree that LARS and NHS laboratories should have major involvement in this.</p>

<p>Appendix 4 - these look to be the same as the NINSS's bacteraemia module definitions but if not it would be helpful to be consistent to avoid confusion and to enable comparison.</p>	<p>These are the same. The intention was to be consistent.</p>
<p>Page 17 9.4.4 - all clinically significant bacteraemias and the number of blood culture sets positive are not the same.</p>	<p>Agreed. The MRSA data do exclude duplicates and the text has been modified to avoid ambiguity.</p>
<p>Person F My only comment relates to paragraph 8.6 and the growth promoter avoparcin. For completeness, you could add that the use of avoparcin in food animals in EU member states and Switzerland was banned in April 1997 and shortly after that date commercial production of this compound ceased. The banning of avoparcin was followed by declines in glycopeptide resistance in enterococci recovered from poultry or poultry products in both Denmark and Italy. If you wanted to add a ref for these details: Aarestrup FM, (2000) Acta Pathologica, Microbiologica et Immunologica Scandinavica, Supplementum 101, volume 108.</p>	<p>Sentence and reference added.</p>
<p>Person G Section 4.6 This recommendation is that all GRE bacteraemias should be assessed clinically and only the significant ones reported. The proposed case definition in appendix 4 though suggests that any enterococcal bacteraemia will immediately meet criterion 1 and hence be reportable. The definition and recommendation are not compatible with each other. The definition of common skin flora is admittedly only an example but the absence of enterococci in this group suggests they should not be considered as common contaminants. The only other comment is why are we doing this when there are so many other worthy causes. I appreciate that enterococcal surveillance is patchy in the UK but a two year drive to improve this followed by a review to identify if surveillance is worthwhile would be more productive.</p>	<p>See response to Person B.</p> <p>The requirement for mandatory screening for GRE bacteraemia came from the DOH. There has been much discussion about whether this is useful. The objective of this report is to ensure that the limitations of this surveillance are understood so that data collected are meaningful.</p>
<p>Person H The Summary covers some worthwhile points. Certainly we changed at least 12 months ago to always doing an Etest to confirm vancomycin and teicoplanin MICs. We have also done the same for MRSA's as we believe that VISAs would also be difficult to identify by disc testing alone. I agree with the need to identify the enterococci beyond simply calling it by a strep group alone.</p>	<p>No response required</p>
<p>Person I Thank you for producing this document that reinforces a number of the measures that I have introduced into the laboratory to facilitate the recognition and identification of GRE isolates. My only question is regarding the definition of cases and the time period allowed between positive cultures</p>	<p>As mentioned above, we were keen to retain the same definition of bacteraemia as used for MRSA surveillance, but appreciate that the points raised here are significant and would be appropriate for investigation by the proposed group further investigating data collection.</p>

before you recognise a 2nd episode, the guidelines you have produced recommends 2 weeks, is this too short an interval ? My arguments would be:-

-The purpose of surveillance is to recognise new cases of infection.

-Many of the children we pick up as GRE positive will remain colonised for quite some time as there is no effective eradication mechanism.

-They will remain at risk of bacteraemia as although their CV lines may have been removed with that episode (if they have alternative venous access) they will have had to have new lines inserted to continue their treatment (chemotherapy/TPN etc.) and hence may well go on to have further episodes of bacteraemia.

-We try and avoid overlong courses of antibiotics in these children because of the fear about emergence of linezolid-resistant strains of VRE, so if the lines are removed antibiotic therapy is discontinued or only given for 48hrs post removal. The above measures may encourage more prolonged use.

-We know from treatment of enterococcal infection (even non VRE strains) that with more serious infection such as endocarditis there is a risk of relapse following discontinuation of treatment.

In brief, I am concerned that a single patient may account for several "cases" of GRE bacteraemia and that does not necessary reflect bad infection control practice but the natural history of prolonged colonisation of a child with ongoing risk factors for bacteraemia (CV lines). I agree that we should be doing everything we can to prevent other children acquiring GRE and but we should measure "new cases" of GRE bacteraemia rather than treatment failures or re-infections.