Antimicrobial resistance in the UK and Ireland

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After the dramatic expansion of extended-spectrum β-lactamase (ESBL)-producing Escherichia coli and Klebsiella in the UK and Ireland from 2001 onwards, the situation appears to have stabilized, with similar ESBL prevalence detected in 2007 as in 2006. Equally dramatic, but more welcome, is the sharp reduction since 2005 in the number of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemias in England, and the reduction in prevalence of MRSA as a proportion of all S. aureus bacteraemias. These two trends dominate the information from the major resistance surveillance schemes in the UK and Ireland, but a wealth of further detail is available from these rich information sources.

Resistance rates vary between hospitals, between specialties within hospitals and between patients within specialties depending on their characteristics such as age. In addition, resistance varies over time as new genetic mechanisms appear in clinically relevant bacteria, and spread or retreat under the pressures of competition and changing patterns of antibiotic use. Up-to-date information is required, not only at a national level for research and policy purposes, but at a very local level to inform day-to-day clinical decisions.

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Introduction

Antimicrobial resistance is a fluid and constantly evolving challenge. Ongoing surveillance is needed to provide the current information that can help clinicians make good treatment decisions before microbiological tests provide individual results. Choosing an antimicrobial to which the infecting organism is susceptible means a shorter delay in starting effective treatment and a lower risk of poor clinical outcomes and prolonged hospital stays, with their associated costs.1 Surveillance also has an important role in providing the information required to identify new resistance threats, assess the overall impact of interventions aimed at controlling resistance and inform related decisions on health policy.

Resistance surveillance schemes

The UK and Ireland are covered by a patchwork of surveillance schemes. Table 1 summarizes the scope and main features of three of the most prominent of them. The longest running is the voluntary reporting of cases of bacteraemia (together with the susceptibility of the infecting pathogens) by hospital microbiology laboratories to the Health Protection Agency (HPA), with the data being stored in a national database (LabBase). This surveillance programme now includes some 90% of clinical laboratories in England, Wales and Northern Ireland, and is estimated to receive data on ~75% of all clinically significant bacteraemias.2,3 The mandatory MRSA Bacteraemia Surveillance was established in 2001 and requires participation from all acute health trusts in England.4,5 The BSAC Resistance Surveillance Project6,7 (www.bsacsurv.org) has separate programmes in bacteraemia and community-acquired respiratory infection; it covers the UK and Ireland.8–13 It is the only one of the three to use centralized testing, and to provide full MIC results instead of collecting laboratories’ own susceptible/ intermediate/resistant categorization.

Dissemination of information is a vital aspect of resistance surveillance. Results from the HPA voluntary scheme are published at regular intervals in the weekly Health Protection Report and are collated in annual reports, both available from the HPA website (www.hpa.org.uk). The mandatory MRSA Bacteraemia Surveillance also uses the HPA website, where its data are updated quarterly. The BSAC Resistance Surveillance Project has a dedicated website (www.bsacsurv.org) where its data can be accessed in various user-chosen formats, e.g. MIC distributions, MIC summary measures and percentage susceptible/intermediate/resistant. Data from the BSAC Project’s first eight seasons of respiratory and first 6 years of bacteraemia surveillance have also recently been summarized and interpreted in a Supplement to this Journal.1,6–14

Bacteraemia is a relatively uncommon form of infection, compared with respiratory, urinary or skin and soft tissue infections, but its prominence in surveillance schemes is quite rational. Using blood as a source of isolates for surveillance reduces the risk of selection bias, as it is highly likely that
a patient with suspected bacteraemia will have a blood sample sent for microbiological investigation. The same is not true of respiratory or urinary tract infection where, particularly in the community, samples may only be taken routinely from patients who fail initial therapy.

Bacteraemia represents severe infection so, excluding samples contaminated by normal skin flora during collection, the organisms concerned are clinically significant and not mere colonists. It also provides a window onto a very wide variety of clinically relevant bacterial species, as bacteria can invade the bloodstream whatever the original site of infection. Information from bacteraemia surveillance may reasonably be extrapolated to support treatment of infections at other sites, but with some caution. Not all episodes of infection will lead to bacteraemia and those that do may be a selected population, probably over-representing severe infections and patients with greater underlying morbidity, and possibly over-representing resistant organisms responsible for treatment failure at the original site.

In addition, the prevalence of resistance detected in bacteraemia represents an average from diverse original sources of infection, which can each have quite different resistance patterns.

Finally, of course, bacteraemia is a serious clinical condition in itself, almost always warranting empirical therapy, so prior knowledge of the likely infecting organisms and their resistance profiles, obtained through surveillance, is important to increase the chances of selecting appropriate treatment before individual laboratory results are available.

The current picture of antimicrobial resistance

Some key trends in antimicrobial resistance since 2000 are summarized in Figure 1.

*Staphylococcus aureus*

*Staphylococcus aureus* is one of the most common agents of bacteraemia, and has a very high public profile as well as true clinical significance. Reducing the burden of methicillin-resistant *S. aureus* (MRSA) infection has been a political imperative in the UK over several years. From 2006, data from mandatory surveillance in England have shown a sustained and rapid fall in the total number of MRSA bacteraemias, from an average of 3650 per 6 months between April 2001 and September 2006 to 1562 in the 6 months April–September 2008.15 The HPA’s voluntary surveillance system also showed a drop, but not to such a great extent.

Both LabBase and the BSAC Bacteraemia Programme have also found that the proportion of MRSA among *S. aureus* bacteraemias has fallen in line with the drop in the total number of MRSA bacteraemias. The LabBase estimates here are more precise than those of the BSAC Surveillance Project, and show a fall from 40% to 42% between 2001 and 2005 down to 31% in 2007.15 This indicates that the number of methicillin-susceptible *S. aureus* (MSSA) bacteraemias has not fallen in the same way as MRSA, and that the interventions that appear to have had a beneficial impact on MRSA have had a differential effect, even on different forms of the same species of bacteria. This should not be unexpected considering that the interventions are hospital focussed and that, for example, MRSA infections are more commonly clearly hospital acquired (occurring after 48 h stay) than...
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- Increased prevalence of multi-resistant ESBL-producing *E. coli* and *Klebsiella* from 2001 to 2006, perhaps now stabilized
- Increased prevalence of ciprofloxacin resistance in ESBL-non-producing Enterobacteriaceae
- MRSA prevalence of ~40%–42% from 2000 to 2005 now falling (31% in 2007)
- Stable and relatively low prevalence of resistance in community-acquired respiratory infections

Figure 1. Resistance highlights 2000–2007.

are MSSA (73% compared with 53%, in BSAC bacteraemia data 2001–07).

The BSAC Resistance Surveillance Project, which reports full MICs, has not reported ‘creep’ in geometric mean vancomycin MICs for *S. aureus* over time. Re-testing of isolates from all years simultaneously would be required to gain definitive information about subtle shifts in MICs, as experimental variation from year to year could give a misleading impression of creep if contemporaneous data are analysed simplistically.

*S. aureus* gives a good example of how resistance can vary in the same organism depending on the site of infection and other factors. The mandatory surveillance of surgical site infections for 2003–07 found 64% of *S. aureus* to be MRSA, compared with 38% of MRSA in *S. aureus* from blood reported through the voluntary LabBase system in the same period. Within the BSAC Bacteremia Resistance Surveillance Programme, MRSA rates in blood isolates varied both by specialty and presumed origin of infection, e.g. 35% in haematology/oncology compared with 62% in intensive care, and 22% for isolates thought to originate from endocarditis compared with 56% for those with a respiratory origin. Interestingly though, the apparent differences between the various sites of origin were largely explained by differences in the age of the patients concerned, older patients being more likely than younger patients to have MRSA.

**Enterococci**

Vancomycin resistance has been a concern in enterococci since the 1980s. In 2007, 12% of *Enterococcus* spp. from the BSAC bacteraemia study were vancomycin resistant, although interspecies variation was apparent, with 27% of *Enterococcus faecium* and 3% of *Enterococcus faecalis* showing resistance. As in LabBase, there was no distinct trend over time. Vancomycin-resistant enterococci (VRE) had a particularly clustered distribution, with 3 out of 29 collecting centres accounting for 35% of the VRE collected from 2001 to 2007, emphasizing the importance of local knowledge for clinical purposes, in addition to national surveillance.

**Enterobacteriaceae**

While the number of *S. aureus* bacteraemias has fallen over recent years, the number of *Escherichia coli* bacteraemias reported to LabBase has continued to rise faster than the general increase in the number of bacteraemia reports received, and *E. coli* has regained its position as the leading cause of bacteraemia in the UK. At the same time, a powerful resistance mechanism—CTX-M extended-spectrum β-lactamases (ESBLs)—has become established in the species. These enzymes hydrolyse third-generation cephalosporins. The prevalence of ESBL production in *E. coli* rose from none in 2001 to 12% in 2006 in the BSAC bacteraemia dataset, but was no higher (at 9%) in 2007. The larger LabBase dataset does not contain information on ESBLs, but showed a similar rise and subsequent plateau in the prevalence of cefotaxime resistance. The ESBL producers are very commonly multiresistant, with 83% showing ciprofloxacin non-susceptibility and 40% gentamicin non-susceptibility in *E. coli* (BSAC bacteraemia data, 2001–07).

Separately from the rise of ESBL-related multiresistance in *E. coli* from blood, fluoroquinolone and gentamicin resistance has also increased in ESBL-negative isolates, with ciprofloxacin non-susceptibility up from 8% in 2001 to 16% and 17% in 2006 and 2007 in BSAC data, and gentamicin non-susceptibility rising from 5% to 8%. By 2007, 24% of *E. coli* overall were non-susceptible to ciprofloxacin and 11% to gentamicin.

Resistance rates in the other major groups of Enterobacteriaceae, *Klebsiella* and *Enterobacter*, also rose in the early 2000s but appear to have stabilized slightly before those of *E. coli*. The most recent figures from the BSAC bacteraemia surveillance (2007, www.bsacsurv.org) show the prevalence of ESBL production and non-susceptibility to ciprofloxacin and gentamicin at 12%, 18% and 11%, respectively, in *Klebsiella* and 10%, 17% and 6% in *Enterobacter*; a further 23% of *Enterobacter* had cephalosporin resistance due to derepressed AmpC enzymes. ESBL production remains rare in Proteae.

Carbapenems are the agent of choice for infections caused by ESBL-producing Enterobacteriaceae, so the development of widespread carbapenem resistance in this group would be a serious problem. This has not happened yet, but a small number of resistant isolates have been identified during surveillance, showing the potential for the organisms to carry such resistance mechanisms. The BSAC bacteraemia study has received two separate isolates of non-Proteae Enterobacteriaceae fully resistant to imipenem (MICs > 8 mg/L) since 2001 (out of a total collection of 5570 isolates); both were highly resistant to ciprofloxacin but susceptible to gentamicin. The first was an *Enterobacter* apparently causing two episodes of infection in the same patient in 2003 and 2004 and was the first UK strain with a KPC carbapenemase. The second was an *E. coli* isolated in 2006, which was, rather surprisingly, susceptible to cefotaxime.

**Non-fermenters**

*Pseudomonas aeruginosa* from blood has shown little change in its typical resistance patterns over many years of surveillance through LabBase, resistance to ciprofloxacin being the most
widespread at ~12%. Out of 1424 P. aeruginosa collected over 7 years of BSAC bacteraemia surveillance, just two had broad high-level resistance, one of which expressed a VIM-2 metallo-β-lactamase. The picture is well known to be less benign in P. aeruginosa from the respiratory tract of patients with cystic fibrosis, again emphasizing the need for caution in extrapolating from the results of a bacteraemia surveillance scheme to a specialist therapeutic area.

Acinetobacter baumannii/calcoaceticus is a rare cause of bacteraemia, accounting for only ~1% of all cases reported to LabBase, but it causes concern out of proportion to its numerical importance because of its propensity for multiresistance and its ability to cause outbreaks amongst vulnerable patients in settings such as intensive care units. As in Enterobacteriaceae, carbapenem resistance is a particular concern. Out of 139 A. baumannii/calcoaceticus collected from blood for the BSAC survey up to 2007, four were clearly resistant to imipenem (MIC >8 mg/L); the most recent, from 2007, was also clearly resistant to ciprofloxacin, gentamicin and tigecycline.

Respiratory pathogens

Resistance rates in Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis from community-acquired lower respiratory infection in the UK and Ireland have been relatively stable over nine winter seasons of surveillance by the BSAC respiratory programme. Penicillin non-susceptibility in S. pneumoniae in 2007/08 was found in 4.7% of isolates from the UK, in line with the figures reported for invasive isolates to LabBase (3.8%) and to the European Antibiotic Resistance Surveillance Scheme17 (EARSS; 4.0%); most were intermediate and would be considered treatable with high-dose penicillin, with only 0.4% being resistant. Isolates from Ireland were much more likely to be non-susceptible, a difference that has been reported previously18 and that is confirmed by EARSS data for invasive isolates in 2007 (11% intermediate, 6% resistant). Erythromycin and tetracycline non-susceptibility (8.6% and 5.1%, respectively, in the UK) are closely associated with penicillin non-susceptibility and were also higher in Ireland. The UK rates are comparable to those of other northern European countries (for invasive isolates), and lower than those in southern and eastern Europe. High-level resistance to ciprofloxacin (MIC >8 mg/L), which is a marker for resistance to ‘respiratory’ fluoroquinolones, was very uncommon at 0.5%.

β-Lactamase production was found in 16.5% of H. influenzae isolates, giving resistance to ampicillin. Non-susceptibility to tetracycline and ciprofloxacin was even less common at 2.1% and 0.5%, respectively; the species has inherent borderline resistance to erythromycin. Of M. catarrhalis collected in 2007, 93% produced β-lactamase, but resistance to erythromycin, tetracycline and ciprofloxacin was extremely rare at <0.2% over the nine seasons.

The relatively low rates of resistance in bacteria from community respiratory infections are encouraging, but occasional isolates of S. pneumoniae with unusually high penicillin MICs have been found recently. These will be studied further, and results reported in more detail if confirmed.

Discussion

Containing the spread of antibiotic resistance presents a major public health challenge for the future. There are abundant clinical data showing that treatment of bacterial infections with antibiotics to which the infecting pathogen is resistant is associated with increased morbidity, mortality and cost. Hence knowledge of the occurrence and frequency of resistant organisms is central to the formulation of policies for empirical prescribing of antibiotics. Such information is generated by surveillance, thus surveillance will continue to play a central role in the monitoring of both established and newly emerging resistance.

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Transparency declaration

None to declare.

References


