Clinical implications of antimicrobial resistance: how big is the problem?

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This presentation addresses the question of the size of the antimicrobial resistance problem by examining the monitoring of antimicrobial use and resistance. It focuses on the main sources of information, possible pitfalls of the data and the susceptibility of the main pathogens responsible for bacteraemias in England and Wales. It addresses some of the difficulties in establishing the link between antimicrobial resistance and antimicrobial prescribing and concludes with some thoughts on necessary developments.

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The remit of this paper was to address the size of the antimicrobial resistance problem; clearly an impossible task. However, by defining some parameters, an attempt will be made to address this question with regard to potentially life-threatening infections caused by common bacterial pathogens in England and Wales.

SURVEILLANCE OF ANTIMICROBIAL USE AND RESISTANCE

Measuring the size of the problem is dependent on surveillance activities around antimicrobial resistance. This has two facets: surveillance of the prevalence and levels of resistance and surveillance of antimicrobial use, which might contribute to increasing resistance in potential pathogens. These two aspects contribute to individual patient care and the wider public health in slightly different ways.

Surveillance of antimicrobial resistance

The surveillance of antimicrobial resistance allows decisions to be made on the appropriate treatment of individual patients and, on the wider scale, on the development of prescribing policies in the hospital and community. In addition to these measures, it monitors changing patterns of resistance, in particular signalling emerging problems. This allows prevention and control measures to be targeted appropriately and subsequently evaluated, while areas for further research, especially with regard to the development of new antimicrobial agents, are identified.

Surveillance of antimicrobial use

Surveillance of antimicrobial use provides insight into the other side of the coin, allowing the exploration of the relationship between antimicrobial use and antimicrobial resistance and interpretation of trends and variations in antimicrobial resistance rates.

Sources of information on antimicrobial resistance

The main sources of information contributing to knowledge on antimicrobial resistance in England and Wales are:

1. routine laboratory reports to the Communicable Disease Surveillance Centre (CDSC) of the Public Health Laboratory Service (PHLS);
2. information on isolates referred to the national reference laboratories of the PHLS;
3. prescribing analyses and cost data from the Prescription Pricing Authority;
4. hospital activity statistics;
5. information from ad hoc studies or surveys.

SURVEILLANCE: BIASES AND CAVEATS

Whenever surveillance data is being examined and interpreted, it is important to recognize that there are usually many caveats. Variations in practice account for inherent biases in antimicrobial resistance rates; for instance, a general practitioner consultation does not necessarily reflect the severity of a patient’s illness but is more closely allied to their normal behaviour in consulting their doctor. Whether this consultation then results in a specimen being taken is also dependent on a variety of factors: mid-stream urine specimens are not only taken for suspected urinary tract infections, but also when patients present with many other different problems, such as backache. The inverse of this is that about 50% of prescribing in the community is related to respiratory tract infections, but sputum specimens are rarely sent for microbiological investigation in these circumstances. Specimens sent to the laboratory may

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Figure 1. Ampicillin resistance in *Escherichia coli* from blood and cerebrospinal fluid samples in England and Wales, 1990-1999. Source: routine laboratory reports to Public Health Laboratory Service/Communicable Disease Surveillance Centre.

BACTERAEMIA SURVEILLANCE

Given these biases in the data, this paper focuses on the more prevalent pathogens causing bacteraemias in England and Wales. Bacteraemias tend to provide more robust data, as they indicate serious, potentially life-threatening infections, where the diagnosis of infection is usually more clear-cut than in other infections. Much of this data comes from voluntary reporting of clinically significant isolates by microbiologists in England and Wales to the PHLS Communicable Disease Surveillance Centre. There is good coverage across England and Wales, 91% of 229 laboratories identified in 1998 reporting bacteraemias through this system.

Examining bacteraemia reports for the period 1990-98, there was a 61% increase in these reports over the period, from 31,763 in 1990 to 51,232 in 1998. This increased further to 55,917 in 2000 (reports to PHLS/CDSC). There was a year-on-year proportional increase for most of the main pathogens, with the exception of *Haemophilus influenzae*, which declined steeply from 1992 as a result of the vaccination programme. There was a steeper increase in the number of reports from 1996, possibly reflecting improved laboratory reporting following the appointment of regional epidemiologists nationwide. *Escherichia coli*, *Staphylococcus aureus*, coagulase-negative staphylococci, pneumococci and either enterococci or klebsiellae accounted for 60% of reports each year. However, the amount of information on the susceptibility of these organisms has not been
keeping pace with the increased reporting, other than for methicillin in \textit{S. aureus}.\textsuperscript{3}

\textbf{Escherichia coli bacteraemia surveillance: antimicrobial resistance}

Focusing on susceptibility reporting in \textit{Escherichia coli} bacteraemias, the commonest bacteraemias in the period 1990–99, ampicillin resistance has remained at a high level, approximately 55\% of cases, over the period (Figure 1). Gentamicin resistance increased from 1.7\% in 1990 to 3\% in 2000 and ciprofloxacin resistance has been increasing from extremely low levels at the beginning of the period less than 1\%, to 5\% in 2000 (Figure 2).\textsuperscript{1,4} Comparisons with resistance rates in isolates referred to the Laboratory of Enteric Pathogens (LEP) at the Central Public Health Laboratory for further investigations\textsuperscript{5} showed that there was general agreement between the two datasets, indicating that the routine data reported to CDSC are sufficiently robust to be related to prescribing and population data. The proportions of resistant isolates in the two datasets were broadly similar. Resistance to ampicillin and trimethoprim was frequent, while to gentamicin and ciprofloxacin was rare, although gradually increasing. However, the estimated proportional annual increase in resistance was most marked for gentamicin and ciprofloxacin. Differences between the datasets, such as lower rates of gentamicin resistance in the LEP dataset and of ciprofloxacin resistance in the CDSC one, may have arisen as a result of biases in the samples; for instance, only a small proportion of isolates from \textit{E. coli} bacteraemias are referred to LEP for further investigations, while routine laboratory reports to CDSC may not contain full susceptibility information. In addition, some teaching hospitals were not reporting early in the period and will have been under-represented. Variations in the definition of resistance or the use of non-standardized methodology could have also had an effect, distorting gentamicin and ciprofloxacin susceptibility reporting.

\textbf{Staphylococcus aureus bacteraemia surveillance: methicillin resistance}

\textit{Staphylococcus aureus} is the second commonest reported bacteraemia. Resistance to methicillin, which indicates flucloxacillin resistance, has been growing dramatically since the early 1990s. This has resulted in a Governmental requirement for compulsory bacteraemia reporting from all acute National Health Service (NHS) Trusts in England from April 2001, with publication of the data by named Trusts in 2002—a departure for monitoring of hospital-acquired infections in this country.\textsuperscript{6} Methicillin resistance in reported \textit{S. aureus} bacteraemias rose from 1.7 to 3.8\% between 1990 and 1993, then increased steeply to 32\% in 1997 and 42\% in 2000 (Figure 3).\textsuperscript{1,7} The steeper rise in the middle of the decade may have been, in part, related to improved laboratory reporting. This has also been seen in terms of improvements in reporting methicillin susceptibility, where there has been a decrease in the number of reports lacking this information.\textsuperscript{3}

\textbf{Streptococcus pneumoniae bacteraemia surveillance: penicillin and erythromycin resistance}

In the case of another common pathogen in bacteraemias, \textit{Streptococcus pneumoniae}, penicillin resistance has been gradually increasing from less than 1\% in 1990 and 1991 to 3.6\% in 1998.\textsuperscript{1} The picture for invasive pneumococcal isolates in 1999 showed significant regional
variation in penicillin resistance rates, from a low of 3% in the South West of England to a high of 11% in London.\(^8\) Erythromycin resistance is reported more commonly, increasing from 5% in 1990 to about 11% in the mid-1990s. In 1999, reported erythromycin-resistance rates in invasive isolates ranged from 10% to 16%.\(^8\) Putting this in an international context, antimicrobial resistance in \(S.\) pneumoniae is a bigger problem in many other countries;\(^9\) the United States’ Department of Health & Human Services Public Health Action Plan to Combat Antimicrobial Resistance states that in some areas of the USA up to 30% of pneumococci are no longer penicillin susceptible and that multidrug resistance is common.\(^10\)

### Enterococcal bacteraemia surveillance: antimicrobial resistance

The situation with enterococci differs in that there is a growing threat of vancomycin resistance. This is probably mainly a problem in *Enterococcus faecium*, where vancomycin resistance was reported in 24% of reports in 1998, compared to 5% of *E. faecalis* reports, reaching 27% and 11%, respectively, in 2000 (Figure 4).\(^1,\,11\) However, significant numbers of laboratory reports of ampicillin resistance in *E. faecalis* and the converse in *E. faecium* are suggestive of frequent mis-speciation in the laboratory, as results from a sentinel survey suggest that most *E. faecium* spp. are amoxycillin/ampicillin resistant and that over 99% of *E. faecalis* spp. are still susceptible.

### INFORMATION ON ANTIMICROBIAL PRESCRIPTIONS

It is easier to collect, analyse and interpret antimicrobial resistance information from laboratory isolates than it is to examine prescribing data. This hinders efforts to establish the link between prescribing behaviour and antimicrobial resistance. Prescribing data are collected nationally by the Prescription Pricing Authority from prescriptions in general practice, and contain useful comparative information, but have limitations constraining their use.\(^12\) These limitations range from restrictions on what information is available and how widely it can be used (for instance, at regional level and above, data are normally only available by health authority rather than by individual general practitioner or practice); to weightings, which might not be appropriate for antimicrobials as they were developed for other agents (for instance, weightings according to age); to lack of information on the reason for the prescription. The latter, plus the inability to analyse the actual dose, frequency and duration of the prescribed antimicrobial, make it impossible to assess the suitability of the prescription. In addition, information is not available on prescriptions that were not ‘cashed in’ or prescriptions in private practice. These are substantial obstacles to linking antimicrobial resistance to prescribing behaviour, but there are even more insurmountable ones in hospital practice, where prescribing data is not yet collected routinely at district, regional or national level.

### LINKING ANTIMICROBIAL PRESCRIBING TO ANTIMICROBIAL RESISTANCE

To date, much of the emphasis on altering prescribing behaviour has been targeted at general practitioner level through national campaigns\(^13\) but it could be argued that this emphasis is misplaced as the infections seen and treated by general practitioners over the last 30 years or more have not changed significantly and neither have the commonly used antimicrobial agents.\(^14\) The changes in antimicrobial susceptibility of pathogens normally treated in the community in England and Wales have been small compared to the changes in susceptibility to the parenteral penicillins and cephalosporins, beta-lactamase inhibitors, newer beta-lactams, such as imipenem, aminoglycosides and glycopeptides—antimicrobials not normally prescribed in the com-

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Figure 4. Vancomycin resistance in enterococci from blood and cerebrospinal fluid in England and Wales, 1990–2000. Source: routine laboratory reports to Public Health Laboratory Service/Communicable Disease Surveillance Centre.
munity. So maybe it is time to focus on antimicrobial prescribing in hospital practice.

Studies examining prescribing practice have often unearthed interesting prescribing trends, but it is usually difficult to correlate these with antimicrobial resistance patterns, possibly for the reasons outlined above. Thus a study comparing *Escherichia coli* ampicillin and trimethoprim resistance patterns by region with prescribing data found that some regions had consistently lower resistance rates, whereas others had consistently higher ones. Although there was a trend for regions with high total prescribing to have higher rates of ampicillin resistance, and one region stood out for having both low antimicrobial resistance rates and low prescribing, correlations between resistance patterns and prescribing were weak. Analysis of antimicrobial prescribing data by health authority in London indicated district to district variation in prescribing practice within a small geographical region and a notable decrease in antimicrobial prescribing between 1997/98 and 1998/99. This decrease in antibacterial prescribing by general practitioners, possibly allied to the national campaign, has also been seen on a wider scale, falling by 19% in England between the year ending September 1997 and that ending in September 1999.

**THE FUTURE: A WAY FORWARD?**

It is clear from the data presented above that, although England and Wales are fortunate in having relatively low resistance rates to many antimicrobial agents compared to the experience in other parts of the world, there is a need to improve antimicrobial prescribing surveillance data, particularly in hospital practice. This is important for the investigation of the relationship between prescribing and resistance, but also to address the appropriateness of antimicrobial prescribing in community and hospital practice. This is necessary to preserve the current enviable situation with regard to susceptibility to many important antimicrobial agents through their prudent use. The continuing rise in the incidence of methicillin-resistant *Staphylococcus aureus* is a notable exception to this situation, but probably reflects control of infection difficulties rather than unsatisfactory antimicrobial prescribing.

**Improving the quality of the data**

Ideally this surveillance of prescribing should be complemented by enhanced clinical observation in certain sentinel general practices and microbiology laboratories, geographically distributed so as to be representative of the general population. These practices would gather more detailed clinical information on patients presenting with infections and undertake appropriate microbiological investigations, according to agreed protocols, to reduce the inherent biases in routine surveillance data.

Apart from the above-mentioned developments to improve information on antimicrobial prescribing, surveillance developments are required in terms of the quality of the data, the necessary supporting information technology, microbiological diagnostic and typing techniques and wider links to veterinary and agricultural practice. Improvements in the quality of the data require contributors to surveillance systems to be using the same language, so that the data are comparable. This means agreeing some basic definitions, such as definitions of infection and resistance, categorization of procedures, as well as categorization of health service facilities and units. This would allow comparisons by casc mix, risk stratification and the use of appropriate denominators for health service activity.

Improvements in the quality of the data also require underpinning modern information technology. This means installing systems that can automatically export data electronically and that are linked up so that patient-based data in one area, say the microbiology laboratory, can be associated with that from other areas, such as the wards, surgical theatres and pharmacy. Ideally unit-based data should also be linked up with data from the human resources department, so that levels of trained to untrained staff in high risk units, such as intensive care units, could be compared when estimating risk factors for spread of infections in hospitals. These information technology systems should also be able to indicate anomalous results, for instance penicillin resistance in Group A streptococci, so that the results can be checked for errors and true unusual isolates referred for further investigation.

**Improving laboratory methods**

In terms of laboratory methods, there is a need for improved speciation of organisms and more quantitative methods of susceptibility testing to ensure early recognition of ‘creeping’ resistance in a particular species. It is also important that there is a transition from surveillance of phenotypic characteristics to genotypic ones and consideration of the mechanisms of resistance rather than merely their expression.

**Links with veterinary and horticultural spheres**

Lastly, there is a need to forge surveillance links to the veterinary and horticultural spheres to identify the relationships between antibiotic use and resistance in farm animals and horticulture with antimicrobial resistance in humans. This surveillance would also be important in terms of tracking human illness associated with food back to the originating farm.

**Recent initiatives**

Is this a tall order? Perhaps, but the impact of accreditation and increasing automation of laboratories
as well as participation in national quality checks and controls. Surveillance programmes have been developed in this direction in England and Wales. The control of antimicrobial resistance, often allied to the control of hospital-acquired infection, has been increasing in priority over the past few years, following various reports,21-23 which culminated in the NHS Executive’s Health Service Circular in 1999 on Resistance to antibiotics and other antimicrobial agents,22 and the National Audit Office report on infection control in acute Trusts.23-25 Subsequent Government initiatives in terms of compulsory methicillin-resistant Staphylococcus aureus bacteraemia surveillance,26 and inspections by the Commission for Health Improvement are also likely to impact on the technology required to undertake surveillance and ensure that infection control has a higher profile in hospital practice. These initiatives build on the pre-existing broad base of voluntary microbiology laboratory and infection control team participation in surveillance schemes in these countries.

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REFERENCES


