Resistance surveillance studies—comparability of results and quality assurance of methods

Gunnar Kahlmeter1* and Derek F. J. Brown2

1Department of Clinical Microbiology, Central Hospital, S-351 85 Växjö, Sweden; 2Clinical Microbiology and Public Health Laboratory, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QW, UK

Keywords: surveillance, EARSS, antimicrobial, resistance

Surveillance of antimicrobial resistance currently has a high profile. One surveillance system with wide representation in Europe is the European Antimicrobial Resistance Surveillance System (EARSS). The paper by Bronzwaer et al.1 describes an external quality assessment (EQA) exercise undertaken as part of the EARSS programme and prompts comment on comparability of susceptibility testing methods and breakpoints and quality assurance of resistance surveillance studies in general.

Surveillance of antimicrobial resistance is generally considered to be necessary for providing local data for selection of empirical therapy, for assessing the scale of the resistance problem at a local, national or international level, for monitoring changes in resistance rates, for detecting the emergence and spread of new resistances, and for providing a measure of the effectiveness of any interventions aimed at reducing resistance.2–6 It can also provide an opportunity for improving the quality of susceptibility testing among those taking part in the surveillance.7,8 The potential limitations of resistance surveillance studies have been highlighted,4–6,9 and of particular concern are bias and error related to the populations sampled, and differences in susceptibility test methods and breakpoints that make it difficult to compare different geographical regions and different published studies.

The most effective way to overcome differences between methods, or differences in the same method performed in different laboratories, is to collect isolates and perform all tests in one centre. This is the approach taken in several major surveillance programmes.5,10–13 The centralized approach should ensure that organism collection, storage and transportation are standardized as well as the susceptibility testing method. Internationally recognized quantitative methods of testing are used in such studies and the range of agents tested can be extensive. An additional advantage of the centralized approach is that the organisms are available for further studies of resistance mechanisms and for epidemiological typing. The main limitations of centralized studies are the restricted throughput in terms of numbers of isolates and the possibility that the small numbers of laboratories in some studies may not be representative. There may also be sampling bias with regard to variation in which patients have samples sent for microbiological analysis. In centralized studies, quality control of methods is generally based on performance with control strains. Although it is rarely used, an element of external quality assurance can be applied to centralized surveillance studies by testing of strains supplied by an external reference laboratory with the susceptibility of strains undisclosed at the time of testing.

Surveillance based on routine susceptibility testing exploits extensive data that are already being collected and could include all clinical laboratories as long as software solutions are available to collect the data.7,8 However, the limitations of sampling bias, with regard to variation in which patients have samples sent for microbiological analysis, still apply. In addition, routine susceptibility testing methods differ within and between countries, both in technical detail and with some agents, MIC breakpoints distinguishing categories of susceptibility. Even when it is claimed that a standardized method is in use there may be significant user modification of the method.14 There is a tendency for laboratories to claim that they are using recognized standardized methods because of the associated scientific respectability, but practice frequently does not meet the requirements of the standardized method. Although user modification of methods may be difficult to control, there are surveillance studies based on use of data from routine testing, with participation restricted to laboratories using specific standardized methods and an element of rule-based result checking applied before data are accepted.8,15 Any surveillance system based on susceptibility tests performed by the participating laboratories needs to include quality assurance tests to detect differences that might relate to methods and breakpoints rather than to true differences in resistance.

*Corresponding author. Tel: +46-470-587-477; Fax: +46-470-587-455; E-mail: gunnar.kahlmeter@ltkronoberg.se

© 2002 The British Society for Antimicrobial Chemotherapy
The EARSS is based on methods used routinely in clinical laboratories all over Europe. The laboratories, or a reference laboratory, are expected to confirm and quantify important genotypic resistance such as penicillin resistance in Streptococcus pneumoniae and methicillin resistance in Staphylococcus aureus. This system may confirm suspected resistance but will not identify failure of routine methods to detect resistance. While it would be ideal for all participating laboratories to use the same routine method this is far from the reality in Europe. Among laboratories participating in the EARSS programme the NCCLS guidelines are the most widely employed, with 61% of 433 laboratories from 19 countries stating that they follow these guidelines. However, it is not clear which techniques were actually used, as 25% of laboratories used a variety of automated systems and those using MIC methods were not distinguished from those using disc diffusion. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is a committee of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). EUCAST has the objective of harmonization of the results of susceptibility tests in different countries but has pragmatically recognized that there are currently different approaches to susceptibility testing, particularly with regard to routine testing methods. The routine methods include disc diffusion methods, home-produced and commercial versions of both agar and broth dilution MIC methods, restricted range versions of MIC methods including breakpoint methods and automated systems. Individual laboratories, and particularly national organizations that have developed their own methods, are reluctant to change to another method just for the sake of standardization, particularly when other methods have not been shown to be any more reliable than their own or there are disagreements over MIC breakpoints. The NCCLS methods are the most widely used internationally, but the EARSS EQA exercise does not show the NCCLS methods to be more reliable than other methods used.

EUCAST has taken the view that the responsibility for harmonizing MIC breakpoints and susceptibility testing methods in Europe must lie primarily with the national breakpoint committees. Several national committees have published guidelines, including susceptibility methods and breakpoints, and harmonization requires a collaborative effort between the national committees, for which EUCAST may serve as the coordinator. EUCAST has published a reference agar dilution MIC method and will shortly publish recommendations for a reference broth dilution MIC method. With these, the results obtained with the various national methods can be cross-correlated.

Harmonization of clinical MIC breakpoints in Europe and worldwide has been the subject of much discussion over the years, and although closer agreement on breakpoints for new agents has been possible, there has been no obvious progress with longer established agents. While international agreement on clinical breakpoints may remain elusive it may be more productive for epidemiological purposes to compare resistance rates on the basis of microbiological characteristics of resistance, which do not differ between countries. The wild-type population (which from a clinical view may be designated susceptible or resistant) can be identified in distributions of MICs or inhibition zone diameters by a variety of standardized methods, and deviations from the wild-type populations can be readily identified. EUCAST is currently developing this approach in parallel with the longer term moves towards harmonization of clinical breakpoints.

One of the problems in establishing the equivalence of methods is that comparisons based on routine isolates often do not include rarer resistances and there is no reference to what expected results should be. The inclusion of the recognized control strains is of limited value as most are susceptible to antimicrobial agents. A reference collection of organisms with different resistance mechanisms and different degrees of susceptibility has been proposed by EUCAST. This collection would have MICs established by reference methods and could be used to compare and calibrate other methods.

Quality assurance procedures play an essential role in ensuring the quality of susceptibility tests and thus the validity of antimicrobial resistance surveillance. Quality assurance procedures include the routine use of standard control strains, result validation procedures (which may include the comparison of results for individual antibiotics against probable and impossible outcomes by the use of expert systems), blinded repetition of routine tests, comparison of zone diameter or MIC distribution against reference templates, and EQA. In EQA, organisms with known but undisclosed susceptibility are distributed from a central organizing laboratory, and participating laboratories return results to the central laboratory for analysis. Details of methods used can then be linked to performance. EQA provides an independent assessment of laboratory performance and has additional benefits for the participating laboratories in that they are able to assess their performance in comparison with a wide range of other laboratories. EQA gives credibility to the laboratory as a responsible approach to quality can be demonstrated, it may identify deficiencies to be rectified and it is a stimulus for education of staff. International EQA exercises have the additional benefits of strengthening collaboration between national groups and possibly highlighting limitations of particular national methods.

The EARSS project is the most widely supported resistance surveillance project in Europe. The value of the results is dependent on comparable methods being used by participating laboratories, and EQA has been organized to establish that the required comparability is achieved. Such EQA exercises are inevitably limited by the small numbers of strains distributed, but they can be targeted at particular resistances and they do provide a valuable indication of comparability, as illustrated by the EARSS study. While it is concluded from the EARSS study that the quality of testing overall is good,
Leading article

there are exceptions, and if performance in this study was reflected in routine results there could be some significant differences between countries that might be related to methods used. Differences between laboratories and countries have also been highlighted in previous international EQA studies.18,19

All resistance surveillance studies have limitations. Studies based on centralized testing overcome many of the concerns about comparability of results. Studies based on routine data can be more comprehensive and therefore less likely to be affected by sample bias, but require assessment of the comparability of results from different centres. This is most appropriately provided by EQA, which should be a part of any surveillance system based on results of tests carried out in participating laboratories. It may be possible to cross-validate data from centralized surveillance studies and those based on routine data by comparison of results from the two types of study for similar time periods and geographical areas.9 However, the greatest progress in establishing comparability of data would derive from all laboratories using the same methods. The prospects of this are not good and arguably not desirable, as no one method has been shown to be more reliable than others. A major advance that should be possible is the acceptance of an international reference method and agreement on epidemiological MIC breakpoints to which all other methods can be related.

References


