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Antibiotic resistance surveillance: action for international studies

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Introduction

Ten years ago O'Brien *et al.*[1] described the position on antibiotic resistance surveillance as follows: 'There are no reliable data in this area—simply fragments of information and anecdotes that we use to draw an overall picture'. Recent reviews on this topic point to much activity but suggest that in many areas little has changed.[2–7] At the start of the 21st century one of the most pressing medical problems is the rise of antimicrobial resistance, and surveillance is generally seen as being a principal weapon in the global response to this threat. However, if surveillance is to make such a contribution it needs to resolve its organizational and scientific difficulties. Recent definitions of surveillance in public health[8] and antimicrobial resistance[9] settings have failed to address these and have ignored the essential aspect of drug usage. Although much contemporary work has focused on international programmes, antimicrobial resistance surveillance remains peppered with numerous disparate local as well as multinational studies. This paper will review how such efforts can be improved and a better fit obtained to serve the key purpose of surveillance in controlling the evolution and spread of resistance.

Surveillance programme problems

Some of the traditional shortcomings of early surveillance studies have been corrected in the current programmes.[6,7] It is recognized that small studies are inappropriate and that there must be standardization of the definitions used for both collection and the methods employed to test isolates. The greatest benefit rests in longitudinal investigations that permit subtle trends to be detected. Although many projects use a central laboratory to ensure consistency of results, there are benefits to local testing, including rapid and meaningful result production with ownership of the aims and outcomes of the scheme. For such an approach to meet equivalent standards to central laboratory testing, these schemes must include robust external quality assessment distribution panels of both the organisms and resistance patterns being sought in the study, e.g. the MYSTIC[5] 2001 programme. Simple quality control included in the susceptibility testing panels does not meet this need.

Duplicates

The inclusion of duplicate data is recognized to be one of the major flaws in many of the early surveillance reports. However, there remains confusion and controversy over the definition of a duplicate isolate, although this is clearly fundamental in terms of the numerator on which study results will be calculated. Some studies have adopted the absolute practice (but simple) of allowing only a single isolate per species per patient.[10] However, this limits the ability to monitor the dynamic position in patients who may be at particular risk of acquiring antimicrobial resistant strains through cross-infection or the development of resistance during antibiotic treatment. Other approaches to avoiding duplication have been based on linking one isolate to one patient in a variety of ways, e.g. by time between isolates, by specimen type, by the antibiogram of the organism or by molecular typing. Although a study using pulse gel electrophoresis showed a dramatic effect in this regard, such methods are not applicable for routine use.[11] It is likely that there is no one correct approach to this issue and that different steps will be required according to the scheme in question. Four separate algorithms for removal of duplicates are offered in the WHONET software.[10] There is a real need to establish which model is most appropriate in any given situation, and in the meantime in each study the methods deployed must be clear, rational, sustained and auditable.

There is a corresponding obligation on surveillance studies to be absolutely clear on the definition of the denominator against which results are being placed. This means accurate and unambiguous specification of the population under study in terms of its demographic and clinical background. The true impact of resistance is not in terms of the organisms or specimens studied, often the data used in surveillance work, but in the context of patient outcomes.

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Presentation of susceptibility data

Whereas in the world of surveillance there are masses of data this is not accompanied by the same amount of useful information. One problem at the heart of this issue is how surveillance data are presented. Although it is well recognized that one final stage in the surveillance loop is to apply the data to control resistance development, little consideration has been formally given as to how the information should be best presented to achieve this end. Surveillance programmes now focus properly on quantitative results and generally present their data as either absolute or continuous findings. No surveillance studies now produce categorical data with findings recorded over-simplistically and uselessly in this context as sensitive, intermediate or resistant.

Absolute data are usually presented as MIC_{50} or MIC_{90}. Information presented in this manner has the advantage of being understood in medical journals and reduces the need for large tables of printed material. However, such data only provide a point figure or rate and have to be repeated to detect a change in resistance. Subtle shifts in antimicrobial resistance may be difficult to detect in this form and the data may appear to lack clinical relevance. Surveillance programmes providing continuous data have the advantage of providing clinically relevant information. The data can be interpreted over time in longitudinal studies and are comparable year on year and, potentially, to other studies undertaken with the same methodology. Subtle changes in resistance patterns can be detected before interpretable categories have been breached.[12] Continuous data provided in surveillance studies are not restricted to interpretation by criteria set down at any particular national level or by international organizations. Therefore the data are truly international. In addition, continuous data provide antibiotic susceptibility information on organisms for which breakpoints are not available.

Continuous data are most commonly presented as cumulative percentages of susceptible organisms at each dilution, e.g. in the MYSTIC surveillance programme.[5] Alternatively, the total number of susceptible organisms at each dilution is calculated when the findings can be summated and presented graphically, e.g. in the form of 'Finland-o-grams'.[5,12] Information presented in this last manner is preferable to extensive tables since, by capturing and simplifying large volumes of data, the results can be easily interpreted at a headline level. This approach lends itself to the comparison of results between centres, geographical areas or programmes.

Surveillance programmes, whether using continuous or absolute data, can still be subject to bias. Surveillance data do not give the infection status but rather the burden of bacterial resistance in the population included in the study. Specialized areas may contribute more to surveillance projects through simple influences, such as their greater tendency to investigate infection leading to under-representation of the position at smaller hospitals and in the community. Also, hospitalized patients contribute more isolates, leading to misrepresentation of the picture for the whole population. Therefore, the issue must be how accurate is the measure of susceptibility? In many cases it is probably reasonable to achieve an accurate estimate of the extent of the problem to permit valid comparisons. What is essential is that this estimate must be transparent both in terms of its status and derivation.

A key denominator for result presentation is the clinical source of the isolate. Stratification of samples into origin of specimen has demonstrated different patterns of resistance in different tissues. North American data from the SENTRY project show higher levels of penicillin-resistant isolates of *Streptococcus pneumoniae* in bloodstream compared with respiratory tract infections.[4,13] This influence can be demonstrated even further if isolates are considered according to the clinical area of the hospital from which they arise. There is a significant stepwise improvement in antibiotic susceptibility from intensive care patients to non-intensive care and out-patients for most clinical isolates.[3,14] However, there are exceptions. The ICARE project demonstrated a higher prevalence of ciprofloxacin-resistant strains of *Pseudomonas aeruginosa* in the community than in hospital. It was thought that the increased consumption of oral fluoroquinolones in the former setting might be responsible.[3]

National and international surveillance programmes

The international nature of antimicrobial resistance has seen an international response with global surveillance programmes.[6] Previous international surveillance studies, such as the World Health Organization programme into tuberculosis,[15] which concentrate on a specific organism, have generated epidemiological data of value in public health control. National or international studies, which target an individual organism, can demonstrate resistance outbreaks and dissemination of the resistant strain. However, they are unable to monitor either the spread of resistance between species or the broader emergence of resistance.

More recent international studies have tried to link resistance with antibiotic prescribing data, e.g. MYSTIC, and in this way set out to monitor the geographical spread and selection pressure resulting from antibiotic usage.[2,5] Resistant isolates can then be typed and resistance mechanisms explored. However, not all surveillance programmes are set up to achieve this.[6] The rates of antibiotic resistance for specific organisms are often significantly different from country to country,[16] and debate has centred on the potential implications of recognized diversities in antimicrobial utilization, both in terms of volume and routes of administration. Unfortunately these debates have not previously been informed by robust evidence, as this is an area where

surveillance has contributed little in the past. The Alexander Project, which limited surveillance of antibiotic resistance to community-acquired pneumonia, included antibiotic prescribing data[17] and showed that countries with the highest per capita consumption of antibiotics demonstrated the greatest resistances rates. However, in countries with high antibiotic consumption *S. pneumoniae* isolates were found to have a progression in penicillin resistance from susceptible through to resistance that was not directly related to penicillin consumption. Rather it was related to the aminopenicillin:cephalosporin usage ratio, i.e. when the consumption of cephalosporins increased in relation to aminopenicillins there was an acceleration in the emergence of resistance. In contradistinction, the same pattern was not seen in Italy where there was a low rate of penicillin-resistant *S. pneumoniae* compared with France but a higher level of cephalosporin prescribing.[2,17]

On the other hand, large global studies may not have the ability to detect subtle or confounding factors that lead to resistance. Globally, antibiotic resistance is seen to be associated with antibiotic usage but at a local level this may not hold true. The ICARE project showed that, despite the similar use of the methicillin group of antibiotics in all hospital areas, the level of methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci was higher in intensive care units than elsewhere.[3]

These data demonstrate that there are complex dynamics that are not fully appreciated surrounding the association and inter-relationships between different antibiotic class prescribing and how this influences the emergence of resistance.[18,19] Global surveillance systems might inform where resistance has occurred and its mechanism, but regional surveillance programmes are perhaps best placed to explain why the problem has arisen. Melding these differences into a complete picture demands the integration of large global studies with regional surveillance. Only by understanding the amount of antibiotic use at the appropriate level of unit, institution, local and international level with international susceptibility surveillance results can the necessary insights be achieved.

Laboratories or hospitals that provide data for global surveillance schemes in a standardized manner often use a different set of standards and methods for regional or local schemes. Not only can this waste time and effort but it also compromises particularly the local standing and utility of the data. Ideally the information provided for international surveillance should be produced to the same standards and methods as that used at local level, and international schemes should themselves adopt a single methodology. Presently there is no convention for international surveillance programme laboratory methods, although most of the major ones, e.g. MYSTIC, SENTRY and the Alexander Project, now work to NCCLS recommendations.[20] This trend towards standardization is to be encouraged.

The vindication of surveillance has to be that it generates data that lead to initiatives to control the development of antimicrobial resistance. To date there are only a limited number of studies to link surveillance with a reduction in antibiotic resistance, most of which relate to effective antibiotic policy implementation,[21,22] and therefore the benefits of surveillance still have to be questioned both clinically and financially. Notwithstanding this relative lack of hard evidence, surveillance for antibiotic resistance is an important part of modern clinical microbiology, and it should not be overlooked that much has been learnt from previous efforts. However, design changes are needed to improve and target studies more accurately at delivering benefits, and this should be seen as part of the evolution of existing schemes where flexibility must be built into the programmes. Clearly identified organism stratification according to infection site and clinical service must be linked to antibiotic usage information. The effective integration of regional schemes with standardized global surveillance will lead to better understanding of the progress of resistance at the local level whilst tracking its worldwide implications, so allowing prevention and control measures to be put in place. Only by addressing the weaknesses of the present schemes can the full potential of surveillance be achieved and its cost benefits, and therefore its future, established.

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