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Surveillance of antimicrobial resistance

Centralised surveys to validate routine data offer a practical approach

Antibiotic resistance is increasing and significant public health problems are feared. Actions to mitigate the problem include development of new antimicrobials, better infection control, and greater conservation of existing agents. One pressing problem is the paucity of data to measure the impact of resistance on public health or the effect of interventions to prevent its emergence and spread. Moreover, other factors besides clinical prescribing may drive resistance—failure of infection control; institutionalisation of care for the very young and elderly; changing population age structures; agricultural use of antibiotics; and the spread of strains that are effective colonists and which, coincidentally, are resistant.[1] Better surveillance of resistance is needed to understand this interplay as well as to advise on empirical therapy.[2 3] Once relations between use and resistance have been established surveillance data then can serve as "information for action" for initiatives to decrease unnecessary prescribing and prolong the usefulness of existing antibiotics.

Establishing such surveillance presents several problems.[2 3] It is easiest to count resistance rates of bacteria received at laboratories, but these organisms form a biased sample because *(a)* laboratory requesting varies greatly among clinicians; *(b)* some diseases (such as chronic obstructive airways disease) are more likely to generate laboratory specimens than others (such as pneumonia); *(c)* some age groups, particularly the elderly, are more likely to have specimens taken than others; and *(d)* primary care specimens are usually sent only from patients who have failed to respond to empirical treatment or who have comorbidities. Ideally resistance should have a clinical denominator (number of infected patients) not a laboratory one (number of isolates), but this is not easy except in uncommon diseases such as tuberculosis in the United Kingdom.[4]

If surveillance is based on isolates submitted to laboratories either routine susceptibility results can be collected or the isolates can be sent to a central laboratory for testing. Using routine results exploits data that exist already in sufficient quantities for relation to prescribing and population denominators.[3] However, the quality of these data is patchy if, as in Britain, laboratories use different methods and do not routinely speciate many fermentative Gram negative bacilli. Few antibiotics are tested against all isolates, and "second line" antibiotics are tested only against those with an index resistance, giving a very biased sample. Finally, unless the data are analysed with respect to antibiogram phenotypes, anomalies and new mechanisms cannot reliably be recognised.

Centralised testing, or testing to an agreed protocol by sentinel laboratories, allows standardised methods and measurement of levels of resistance. It also allows early detection of those resistances that accrue and can be linked to molecular studies to identify resistance mechanisms and monitor the spread of their encoding genes. However, centralised testing is limited by throughput and the sentinels may form a biased sample.

Both routine data gathering and centralised surveys are undertaken. Programmes using routine data include MicobeBase in Britain[5]; monitoring of blood and cerebrospinal fluid isolates in England and Wales by the Public Health Laboratory Service (PHLS)[6]; and a commercial system, the Surveillance Network.[7] The European antimicrobial resistance surveillance system (see box) aims to follow a similar strategy, collecting high quality routine data for subsets of isolates. International surveys with centralised testing include the Alexander project for respiratory pathogens[8] and SENTRY,[9] which examines blood culture isolates—chosen because they are of clear clinical importance. Many smaller centralised surveys are undertaken on particular pathogen groups or countries, mostly sponsored by the pharmaceutical industry.

What has been lacking is cross testing of the data gathered by different approaches and relating it to prescribing data. Such cross validation is an attractive strategy for comprehensive surveillance: if centralised surveys with high quality microbiology confirm the trends in routine data then greater confidence can be placed in these routine datasets, which are sufficiently large for relating to prescribing data.

A surveillance programme for Britain and Ireland is being established on this rationale by the PHLS, Scottish and Irish colleagues, and the British Society for Antimicrobial Chemotherapy. The PHLS antimicrobial susceptibility surveillance unit will analyse routine susceptibility data from as many hospitals as possible to relate to population and prescribing denominators. The quality of these data should improve as Britain adopts standardised susceptibility testing,

BMJ 1998;317:614–5

based on new recommendations from the British Society for Antimicrobial Chemotherapy. To validate these data and detect new resistance phenotypes, the PHLS antibiotic reference unit will coordinate sentinel laboratory networks undertaking quantitative testing. Additionally, through its working party on antimicrobial resistance surveillance and with pharmaceutical company partners, the society plans a programme of five year surveys, with isolates from selected infection types sent to central laboratories for determining minimum inhibitory concentrations and mechanistic analysis.

As a pilot, we reviewed how existing routine and central datasets could cross validate each other. For *Escherichia coli* from blood and cerebrospinal fluid the same resistance trends to ampicillin, ciprofloxacin, gentamicin, and trimethoprim were apparent in routine results reported for 5000-7000 isolates annually and for the 150-250 isolates from blood cultures tested centrally each year by the laboratory of enteric pathogens. Conversely, *Pseudomonas aeruginosa* isolates that were resistant to β lactams and aminoglycosides on central testing were almost equally likely to be reported as resistant or susceptible at their source hospitals (unpublished data). Such comparisons reveal which routine data are suitable for analysing in relation to prescribing and identify cases where routine methods need to improve.

International cooperation on surveillance of resistance is desirable, not least to determine the extent to which different national prescribing practices translate into different resistance rates. To this end, the World Health Organisation is establishing networks of surveillance networks (see p 651). At the other extreme, and critically, good local surveillance is needed to inform empirical treatment and to help individual hospitals manage their resistance problems.[2]

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A surveillance system for Europe

European nations share a concern about the emergence of antibiotic resistance, but the means to fight it vary. Differences exist in antimicrobial agents tested, samples chosen for testing, susceptibility tests used, and breakpoints adopted. Moreover, epidemiological appraisal of resistance data is often confounded by inappropriate comparisons.

To obtain more comparable and reliable data the European Community has funded the establishment of a European antimicrobial resistance surveillance system (EARSS). This system, in which all EU member states, Iceland, Norway, and Switzerland participate, is coordinated by the Dutch national institute of public health and the environment (RIVM). EARSS collects comparable and quantitative data for assessing antimicrobial resistance to analyse regional differences, relate these differences to risk factors, and facilitate new guidelines for use of antibiotics. EARSS will fit into the antimicrobial resistance monitoring network being established by the World Health Organisation. Quantitative data will be stored in a database at RIVM. Standardisation and quality control will be developed under the umbrella of the European Society of Clinical Microbiology and Infectious Diseases.

EARSS started on 1 April 1998 with an 18 month feasibility study concentrating on *Streptococcus pneumoniae* and *Staphylococcus aureus*; more pathogens will be added after the pilot phase. The system will use routine data from laboratories. Whenever possible minimal inhibitory concentrations will be collected so that subtle quantitative changes in susceptibility can be detected. The participants will gather unbiased samples of isolates by either total or sentinel coverage. The objective for *S pneumoniae* is to collect quantitative susceptibility data on penicillin and cephalosporins, and possibly other drugs, from blood and cerebrospinal fluid from people with community acquired infections. For *S aureus* associated with nosocomial infection, in particular, data on methicillin resistance will be collected from consecutive isolates from blood. For quality assurance, EARSS will provide a set of reference strains, and strains with "special" resistance patterns will be sent to a central facility. The WHONET application is available for data entry, and data will be shared using the electronic interchange network of the European Union. Feedback—summary tables and geographical cards—will be available on the internet.

EARSS will provide unbiased, comparable, and reliable data on a continuous basis for a growing number of pathogens and will thus be of relevance to public health. For more information see the EARSS website (www.earss.rivm.nl) or contact the project coordinator at the RIVM (info.earss@rivm.nl).

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