Finding a strategy: the case for co-operative research on resistance epidemiology

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Progress on rational intervention to prevent increasing antibiotic resistance has been slow. We suggest that this is because the science of resistance epidemiology has received little attention, and that a systematic, co-operative investigation of this area might yield a relevant knowledge base, analogous to the basis for effective public health intervention in infectious disease given by infection epidemiology. The steps required to progress this approach in the UK are discussed, along with a summary of what is known and speculation on what might emerge.

Keywords: antibiotic resistance, surveillance of antibiotic resistance, resistance epidemiology

The resistance problem and epidemiology

Increasing antibiotic resistance has become the subject of concern1–5 and many reviews,6–10 but our knowledge of the processes contributing to this problem remains an unbalanced patchwork. A massive clinical literature outlines resistance in individual infections. However, it is largely anecdotal, with local efforts to assemble advice based on aggregated raw microbiological data, but little international effort to achieve a synthesis of generalized principles to optimize therapy and minimize resistance. At the opposite end of the spectrum, documentation of the in vitro biochemistry and genetics of resistance mechanisms is detailed and comprehensive. However, the work on genetic transfer mechanisms has not been extended beyond the test tube in any systematic way, and we have little knowledge of their performance in natural conditions. Between these two areas lies the field of resistance epidemiology. This has the potential to bridge the gap between the in vitro studies and the clinical observations, resolving complex natural interactions into a comprehensible set of generalized and specific rules. Essentially, resistance epidemiology could provide a rational framework for effective intervention in resistance, just as infection epidemiology has provided an effective rational framework of public health intervention in infection.11–15

Unfortunately, resistance epidemiology has been grossly neglected. Although some antibiotic or infection journals kindly host papers, the subject has no dedicated journal and there are few relevant papers and no systematic approach. Consequently, the many interventions that have been suggested for the resistance problem are almost entirely based on conjecture and unproven assumptions. Basic questions that might indicate a rational strategy, such as which factors affect the incidence of resistant infection, remain unanswered. Rational targets for the extent of reduction in antimicrobial usage have not been formulated, and we have no idea of the likely time-scale and extent of intervention effects. The functional knowledge base supporting intervention is only a little better than that for infectious disease in the mid-18th century.

Worse still, the major potential data source for such studies—routine diagnostic susceptibilities—has never been subjected to detailed critical validation studies for epidemiological use, and is regarded by many as subject to a host of potential biasing factors. Our all-Wales studies demonstrate that one of the most widely believed contentions of bias, inclusion of duplicate isolates,16 produces comparatively trivial effects, whereas another factor that has been largely ignored—laboratory testing policy—produces much more significant effects.17 The belief structure that moulds the current view on resistance surveillance is based on assumptions, rather than proven facts. Current attitudes have proven singularly ineffective in providing answers to the many critical questions that are required to produce a rational intervention strategy.8–10

The path to resistance epidemiology—data

Without data, and rigorous analysis to determine facts, interventions will continue to be based on unproven assumptions. The main reason for using routine data is to obtain sufficient isolate numbers for rigorous statistical analysis. In a 5 year all-Wales community survey,16 the number of isolates for any individual pathogen was small for all but the most common pathogens (urinary coliforms and Staphylococcus aureus). Extended study periods are an option. However, time becomes a complex confounding variable affecting many factors, and studies become excessively long. Further, laboratory systems automatically cull records to conserve limited storage, leaving recovery of past data problematic.
data a minefield of hidden problems. Similar difficulties may affect data for potentially resistance-associated variables.

It is unlikely that studies confined to the most common pathogens—*Escherichia coli*, MSSA and MRSA—will provide an adequate picture of resistance epidemiology that can be applied across the full range of pathogens and antibiotics (see below). For many important pathogens, collection of resistance data on adequate numbers of isolates for rigorous statistical analysis, over a reasonable time period, requires data collection on a UK national basis. It would be sensible, rather than repeatedly restructuring national data collection for individual investigations, to institute an ongoing national resistance surveillance scheme for all organisms.

Collection of bulk routine data from computerized laboratory reporting systems is no longer a technical problem. Microbiology DataStore, developed in NPHS Wales, provides robust automated transfer of bacteriology and virology reports (negative and positive) from a wide variety of laboratory systems into an inexpensive industry-standard database system. The design provides clear advantages to participating laboratories. There is local ownership of the system, long-term continuity of records through system changes and facilities for rapid, flexible analysis of local data. For the most part, difficulties of varied proprietary reporting systems, local variation of result coding, patient confidentiality and automated transfer of results for regional analysis have been resolved. Institution of regional and national collection of data in the UK is now largely a matter of will, organization and comparatively minor finance.

One problem with national collection of routine diagnostic results is doubt on the validity of the data. Enthusiasm in this area seems to centre on advancing hypothetical criticism outside refereed journals, rather than on publication of a structured, detailed and critical examination of real data that aims for a consensus approach to discovery and elimination of confounding factors. A systematic co-operative effort to achieve a consensus pre-processing strategy for elimination of confounding and biasing factors is an essential first step.

Collection of validated bulk data is merely an intermediate (though essential) step in attacking the resistance problem. In our view, the primary purpose of national resistance surveillance is to provide data for a systematic analysis of resistance epidemiology. Provision of figures outlining geographical variation in resistance, current local levels and trends are an important immediate by-product. The longer-term goals for real public health impact are the resolution of the factors and mechanisms involved in the spread of resistance, and the formulation of rational interventions, with realistic targets and expectations. Clarity and constancy of purpose are essential to achieve these long-term goals in the face of a host of immediate, but minor and ephemeral requirements.

Close co-operation with other agencies, to obtain data on the factors that may influence resistance, is another essential aspect of this approach. Antibiotic consumption, including age-sex demographics, is the most obvious input, but access to data on other potential intervention factors, such as the psychology of the patient and practitioner in prescribing, social deprivation or infection control activity, would be crucial. Access to the growing number of relevant computerized data sources, such as the Welsh Medusa system for hospital pharmaceutical consumption and National Census data, requires commitment to co-operation, high levels of computer expertise, and a clear knowledge of the evolving range of information sources.

### Resistance epidemiology, what is known and what might be found

Resistance epidemiology may prove to be as varied as infection epidemiology. As examples: staphylococcal resistance to fusidic acid reflects frequent mutation with clonal spread and little genetic transmission; whereas gentamicin resistance in Enterobacteriaceae reflects a negligible mutation rate to effective resistance, with inter- and intra-species transmission contributing to spread. It is likely that differing balances between clonal proliferation and genetic transmission will produce distinct epidemiology. Small differences in transmissibility, vigour costs of resistance, and efficiency of expression could have marked effects on the epidemiology of the same resistance genes in distinct species. It may be that, for some antibiotics, these varied individual characteristics may impact on optimal strategies for intervention.

Co-resistance—genetically linked multi-resistance—may also have effects via co-selection processes. Ampicillin–trimethoprim co-resistance is common in community urinary *E. coli*, so trimethoprim usage would be expected to select for ampicillin resistance and vice versa. Clear cross-associations between resistance and usage have been demonstrated for these antibiotics. Surveillance of multiple linked resistances is minimal, leaving a critical gap in our knowledge. The impact of resistance to a single agent on treatment is minor; multi-resistant strains present the major therapeutic problems. Surveillance schemes must monitor known associations between resistance to appropriate agents and seek evolving associations, in view of the therapeutic implications and likely impact on epidemiology.

Cross-over effects are also found between species. Therapy may be targeted on the infecting organism, but the effects spill into the general commensal flora of the patients, their contacts and the environment. For example, most community UK ampicillin/amoxicillin prescribing is for respiratory infection, yet this usage is clearly associated with ampicillin/amoxicillin resistance of distinct organisms affecting another site—urinary coliform isolates.

Another interesting aspect is the contrast between the contribution of antibiotic usage to risk of resistant infection for individual treated patients, with its contribution to increased risk for the general population. There is an increased risk of resistant infection for individual patients post-antibiotic treatment. The risk is associated with use of the specific antibiotic and other antibiotics, i.e. trimethoprim resistance in urinary tract infection is associated with prior trimethoprim treatment, and prior treatment with other antibiotics. It is large initially, but decreases to an insignificant level after 6 months. This ‘individual risk’ will probably dominate short-term epidemiological effects for usage of many antibiotics.

However, the population affected by treatment is not the individual patients, but their pathogen and commensal flora, and there is no doubt that the affected organisms will be transmitted between hosts. The clonal spread of MRSA in hospitals and into the community provides a clear example of the existence of a real ecological effect, and there are many similar instances. Resistance genes often show close sequence similarity between
and within species, demonstrating ecological spread by genetic transmission, and inter-species spread of resistance genes has been implicated in hospital outbreaks. Equally, antibiotics spread from the patient to the environment, and may well select for resistance in the ubiquitous microbial ecology. A ‘population effect’ due to clonal or genetic spread of resistance between hosts may be undetectable in short-term studies, but there are good reasons to believe that it exists, and that it may have more significant long-term effects than ‘individual risk’.

Resistance to an antibiotic generally follows an S-shaped curve with time from introduction (Figure 1). This is not compatible with a model based solely on individual risk. In particular, the early slow rise phase of this curve does not correspond to a plausible pattern of antibiotic usage, which usually rises much more rapidly to a plateau. The change in UK incidence of penicillin-resistant *Streptococcus pneumoniae* in 1976 was not due to any concurrent change in penicillin prescribing, but probably to the introduction of a resistant clone into the ecology via international travel.

The underlying processes that contribute to the long-term problem are also incompatible with a purely ‘individual-risk’ model. For most antibiotics, establishment of effective resistance has been a prolonged process involving a chain of low probability events, some of which have occurred in non-pathogenic species. These comprise: accumulation of a mosaic of point mutations to produce resistance; integration into a favourable genetic environment; mobilization into transmissible elements and transmission to other species. If one postulates that each step produces a tiny but cumulative risk of resistant infection at the population level, then the early phases of the S-shaped trend curve are readily explained. Large effects that ultimately derive from events with extremely low probabilities are likely to be a key theme in resistance epidemiology.

The key arguments are that long-term trends in resistance and known fundamental mechanisms for generation of resistance indicate a slow cumulative effect. The ‘individual risk’ effect is not cumulative; it decays rapidly, and so cannot be maintained or amplified in a host population where most individuals receive less than one antibiotic prescription per annum, as in the UK. Further, there is a real ecology—clonal and genetic-transmission spread of resistance between hosts is a well-established fact and a known key factor in the epidemiology of, for example, MRSA.

There are clear associations between resistant infection and patient age and gender. Resistance tends to decrease from age 1 to 15 years, plateau, and then increase beyond age 65 for many pathogens and antibiotics. Age emerged as a significant risk factor, independent of individual patient prescribing, for trimethoprim resistance in community urinary *E. coli* infection. This indicates that other factors may be involved in age differences. Increased inter-host transmission in child and geriatric-care facilities, and possible differences in colonization-susceptibility are clear candidates. A small but significant excess of resistance in males is commonly found, with the exception of trimethoprim resistance in community urinary *E. coli*, where excess resistance occurs in females. The causes of excess resistance in males are obscure. Overall UK antibiotic prescribing is higher in females, which supports a non-usages-associated effect. Unpicking this puzzle may prove difficult.

**Figure 1.** A hypothetical curve illustrating the dynamics of increasing resistance [reproduced with permission from Magee, J. T. (2001). Antibiotic resistance and prescribing in the community. *Reviews in Medical Microbiology* 12, 87–96]. The points show resistance to ampicillin/amoxicillin in urinary *E. coli* taken from various UK surveys. The table below speculates on the relative importance of various resistance growth mechanisms through the phases of the curve.
Associations between social deprivation and resistance may also be important. Examples include: penicillin-resistant pneumococcal carriage, MRSA infection, and resistance in community urinary tract infection. These associations seem to be independent of the high antibiotic usage found in deprived communities. It may be that behavioural and environmental patterns associated with community deprivation provide pathways favouring transmission of resistant organisms in these communities. It would be interesting to dissect the details of such effects, and determine whether analogous factors influence resistance in hospitals.

Finally, there have been growing efforts to produce mathematical models of the resistance problem, a welcome input of external expertise that will be essential to progress. The models hypothecate a set of assumptions on the laws governing resistance, and predict the behaviour of resistance from these assumptions and their interactions. The next step in this approach is to test the predictions against many real datasets, to determine which of the assumptions are universally applicable, which are true, but only in special cases, and which are incorrect. The major problem is the lack of large, validated observational datasets to compare with the predictions, a deficiency that might be cured by the measures outlined below. This cyclic process of hypothesis, observation, and revision of hypotheses has been essential in producing sets of well-tested universal laws in other sciences. However, it has rarely been exploited in biology, and its adoption here might encourage a more general attempt to deduce generalized laws from the vast bulk of purely observational biological data. It would be particularly informative to explore a model of ‘individual risk’ effects at prescribing rates above 2–3 prescriptions per patient per annum. These high rates are encountered in some countries, care homes or hospital wards, and could lead to self-amplifying effects.

Specific recommendations

1. A UK discussion forum for resistance epidemiology should be instituted. The initial aims would be: to gather together UK (and international) research groups for an exchange of views; to lobby for support and resources; to produce an outline plan for an infrastructure suited to cooperative research, exchange of ideas, data and publication; and to recruit a broad inter-disciplinary pool of expertise.

2. A new peer-reviewed journal specializing in resistance epidemiology is required to cope with the growing interest and increasing numbers of research papers.

3. A thorough systematic investigation of confounding and biasing effects in resistance surveillance from routine diagnostic data is essential to progress. Regional (and international) variation in practice may well affect these issues, so confirmatory studies in a variety of settings are essential.

4. A UK-wide infrastructure for collection of routine diagnostic resistance data is required for adequate surveillance and input to epidemiological research. All issues on data validity (point 3 above), and patient/laboratory anonymity must be resolved, and the system should offer clear advantages to the individual participating laboratories, while minimizing any additional local workload.

5. This surveillance system must be staffed adequately. Provision of maintenance and support to the participating laboratories; local, regional and nationwide analyses and recommendations; and surveillance of multiple resistance are essential aspects, requiring staff with a firm, broadly-based experience of laboratory practice and computer expertise. These are rare in the UK, a more general training issue at technical and medical level that must be addressed. Above all, the purpose of this infrastructure must be to provide valid resistance data for epidemiological research, and to facilitate access of associated information on prescribing, deprivation, etc.

Conclusions

The need for a rational, convincing intervention strategy to limit the antibiotic resistance problem is clear. Effective infection prophylaxis and treatment is a keystone of modern hospital (particularly, surgical) treatment, but this ability is slipping away with increasing resistance. Our long-term capability to produce an ongoing stream of effective new antibiotics is in doubt. Current interventions have been notably unsuccessful in preventing spread of, for example, EMRSA. We must search for effective interventions, and these are most likely to emerge from a new science of resistance epidemiology. The route to this science is through national (and international) data collection, detailed validation of routine diagnostic results as a data source, and a clear and unyielding commitment to a systematic investigation of resistance epidemiology. Does the UK have the will, organization and finance to carry this forward?

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References


47. McHugh, C. G. & Riley, L. W. (2004). Risk factors and costs associated with methicillin-resistant *Staphylococcus aureus* blood-


