The worldwide threat of antimicrobial resistance

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Antibiotics have undoubtedly made a major contribution to improvements in both human and animal health and welfare. The recent years have brought an alarming rise in the prevalence of resistance to some agents among certain groups of bacteria. Concern is growing that therapeutic options will become increasingly limited if resistance rates continue to rise. There is widespread agreement that action is required to reverse or at least slow down this process. Necessary steps to manage the situation include better surveillance to assess accurately the extent of the problems, more prudent use of the available antibiotics to conserve valuable therapeutic resources and improved infection control to limit the spread of resistant organisms. Achieving these goals will not be possible without the government, medical professionals and public being better informed and educated. Regulatory bodies and the pharmaceutical industry need to work together to ensure a steady supply of new antimicrobials. Our understanding of the processes driving resistance at both the molecular and population levels is advancing. However, the relative contributions of the various uses of antimicrobials to the resistance problem and which will be the most effective containment measures are still hotly debated. Progress is being made, but continued concerted action is necessary if the usefulness of this most important group of therapeutic agents is to be preserved. Developing countries have an important role to play...eventually the non-prescription availability of agents will have to be addressed.

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OVER the past half a century, not only have the major bacterial infections been controlled, but far more technologically advanced medicine has been practiced with the aid of antibiotics. Food animals can now be reared more intensively (hence cheaply) with the use of growth promoters and herd/flock therapy. However, major risks to public health are now emerging.

Antimicrobial resistance has been recognized since the earliest days of chemotherapy. This now involves almost all the genera of bacteria associated with disease in animals and man. The problems appear to be accelerating, accumulating and worldwide. Not only are antibacterials involved but anti-fungals, anti-virals and anti-parasitic agents (Box 1). The impact of resistance on animal health is often little appreciated by the medical profession, for example, many species of nematodes of sheep and horse are resistant to anthelmintics: resistance of the common sheep liver fluke to benzimidazoles and avermectins has seriously curtailed sheep farming in Australia and resistance in Parascaris equorum (an ascarid of horses) has been reported in the Netherlands.

It would therefore seem that the profligacy of man is endangering the vital resource that antimicrobials bring mankind. What are the risks to man and what can be done to stabilize or even reverse this situation? These are major issues of public health and the answers are far from clear. The developing countries also pose their own issues with their own prescribing problems and resistance issues. This article will attempt to address some of these concerns.

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Box 1.

Anti-virals (HIV, neuraminidase inhibs.), anti-fungals and anti-parasitic agents, for example:

Many species of nematodes of sheep and horse resistant to anthelmintics.

In Australia, resistance to benzimidazoles and avermectins has affected sheep farming and multidrug resistance is common in horses.

Resistance of Parascaris equorum (an ascarid) of horses to macrocyclic lactones has been reported from the Netherlands. The common liver fluke (Fasciola hepatica) has been reported to be resistant to triclabendazole in Australia.
concentrating on antibacterials. It is based on a paper published in the *Journal of Antimicrobial Chemotherapy*.

**The bacteria**

To bacteria, antibacterials are, by definition, a threat. So much of our knowledge to date can be simply explained according to Darwinian principles, popularly described as ‘survival of the fittest’ (Figure 1). Jones, in his update points to three properties which favour natural selection in any population. First, a large number of individuals, a condition undoubtedly true for bacteria, which so vastly outnumber all other life forms combined. Jones has calculated that man is exposed to bacteria in excess of $10^{14}$ and this excludes those in the soil and sea. Secondly, bacteria exhibit a variety of mechanisms to alter or exchange genetic information, including mutation, transformation and especially conjugation which can be mediated rapidly and efficiently by plasmids and transposons. Additionally, the observation of hypermutation and its contribution to the acquisition of antimicrobial resistance is yet another fascinating insight into the ability of bacteria to adapt to new environments. Mankind, on the other hand, has more limited and slower abilities to adapt to changing environments. Thirdly, natural selection is favoured by the intensity of selection pressure and exposure to any, in this context, antimicrobial use. It is difficult to judge the total global antimicrobial production, but it is probably 100–200 million tonnes per annum at a conservative estimate. Developing world use, which is often ill-controlled, is extraordinarily difficult to assess as is global animal use.

Thus almost all bacteria seem to express resistance to antibacterials and different environments generate particular problems. Until recently, it was considered that the hospitals, and especially the intensive care units (ICUs) were the major source of bacterial resistance, with many reporting problems worldwide with *Ps. aeruginosa*, *Acinetobacter baumannii*, Enterobacteriaceae and staphylococci. The reasons for this are, of course, well known.

Antibacterials are used intensively, and opportunists and cross-infection are all too common.

I believe that the effects of community resistance are already evident. Examples include the continuing problems of penicillin and macrolide-resistant *Streptococcus pneumoniae*, now compounded by fluoroquinolone resistance in this organism – this profoundly alters the therapeutic approach to community-acquired pneumonia and meningitis in some countries (Figures 2 and 3).

While methicillin-resistant *Staphylococcus aureus* (MRSA) was considered a hospital pathogen, it is now increasingly recognized as a community problem, whether it is the hospital endemic strains found in vulnerable patients such as the elderly in care homes, or the more recently described cases with the Panton Valentine leucocidin virulence gene which are often community-acquired. Another example of profound change is the expanding problem of extended spectrum β-lactamases (ESBL) (Figure 4) found in the community for some time in France and more recently in UK hospitals. Perhaps ESBL-mediated resistance will become the ‘norm’ just as TEM-mediated resistance to ampicillin amongst many Gram-negative genera (Figure 5). The increasing resistance of *N. gonorrhoeae* to fluoroquinolones is yet another example and is having a major impact on therapy.

Why are we seeing this change from hospital to community? Again, a possible explanation lies in Darwinian principles. The UK House of Lords Report estimated that about 90–95% of all antimicrobial use in the UK is...
within the community, as opposed to hospitals. In addition, changes in society such as day-care centres for children, homes for the elderly and communities of other groups such as drug abusers, all create fertile grounds for microbial transmission.

**Solutions to the problems**

The tools to manage the problems of antibacterial resistance are remarkably few. As discussed below, novel agents active against new bacterial targets (as opposed to modifications of existing antibacterials) are likely to be few in the foreseeable future. The three remaining interventions, reducing selection pressure (that is reducing antibiotic prescribing), cross-infection control and the increased use of vaccines all need to be assessed and monitored.

**Surveillance**

Although the best definition of surveillance is information for action, very few, if any, measures of bacterial resistance provide such data. The vast majority of data is passively acquired, i.e. it is derived from samples received in hospital laboratories, with little knowledge of why it was sent in the first place and how representative any bacteria isolated are of such strains in the general population. Hence, the main weakness is lack of meaningful denominator data. Without this such surveillance could be positively misleading. For example, does the *Escherichia coli* reported from urine over- or underestimate the resistance in *E. coli* at large? There is some suggestions that such data over-estimate the problem in this example. Without such knowledge it is difficult to devise realistic guidance for clinicians.

The Seventh Report of the House of Lords Science and Technology Committee stressed upon the importance of surveillance and also reflected on its piecemeal development in the UK (and elsewhere). Changes are taking place and in the UK, mandatory reporting of MRSA bacteremia and vancomycin-resistant enterococci (and *C. difficile*) is an important development, but still sheds little light on the ‘drivers’ of resistance. There are a number of important issues which need to be addressed.

**Laboratory:** These include: (i) Accurate identification of strains. For example, identifying only to the level of ‘coliform’ should be abandoned as far as possible. (ii) Often too few antimicrobials are tested. (iii) Consistency of methodology is required, and is being addressed by the BSAC Working Party Report. (iv) Molecular characterization of resistance will give greater insights.

**Hospital surveillance:** (i) Improved information on hospital prescribing is central to our understanding of resistance in this setting; (ii) Improved information technology; (iii) Strategies for monitoring must be coordinated with infection control/antibiotic prescribing control measures. The development of ‘antibiotic pharmacists’ in England is an important step in achieving this.

**Community surveillance:** (i) Attempting to overcome the bias in samples sent to laboratories; (ii) Lack of population denominators; (iii) Need for primary care prescribing data; (iv) Need to understand where resistance is initiated – in hospitals with spread to community or vice versa; (v) Appropriate IT which can report on both prescribing, resistance and clinical outcomes.

**Information technology:** Central to all the above is the need to achieve the following linked datasets: Hospital prescribing – by clinical indication; Hospital resistance – by site and organisms and similarly in the community.

To achieve the above is going to take time and investment. A first step is to undertake this by setting up sentinel studies in the community and in hospitals where the ‘antibiotic pharmacist’ can play a central coordinating and information-collecting role.

The lessons we have failed to learn about in antibacterial use and resistance should not be repeated in antiviral therapy. There are now about 30 antiviral drugs available and resistance is an issue, especially in anti-retroviral therapy. Again, there is a major need to have denomina-
tor studies of clinical failure rates, the prevalence and nature of antiviral resistance, standardization of laboratory methodology and national (or at least sentinel) databases of the above. The extent and pace of anti-retroviral resistance in sub-Saharan Africa is so alarming that if the investment and hopes in this therapy are not to come to nought, then such surveillance is an immediate priority.

Most developed countries do undertake antibacterial resistance surveillance but, by and large it is, as indicated, of a poor calibre. At best it sheds little light on the problems and at worst, it can be misleading. As an example of the latter, Harbarth and colleagues\textsuperscript{18} have shown the difference between the use of aggregated data (on imipenem use and resistance), where there was little or no relationship between the number of defined daily doses used and susceptibility data. Yet when individual cases were analysed, the risk of imipenem resistance to an individual had a marked relationship to exposure to the antimicrobial.

**Infection control**

It is not the purpose of this article to examine infection control measures that can reduce the spread of resistant bacteria, although it is axiomatic that there is a major role for improvements in this area and the impact it will have. In hospitals, certainly in circumscribed units, such as intensive care units (ITUs), enhancement of infection-control procedures can have a major impact. Both in the ITU and more widely in a hospital, the interplay between antimicrobial use and the spread of infection is complicated. It is stated that hospital-acquired infection costs the UK £1 billion per year and leads to some 5000 deaths\textsuperscript{19}, yet there are poor provisions in hospitals to contain the problem (for example, sufficient single rooms), too many patient movements from one ward to another, lack of trained staff and unclear lines of responsibility (Box 2).

As already mentioned, there is a trend for multi-resistant pathogens, such as MRSA and ESBL to be spreading in the community. There is a major need to understand the drivers of this new phenomenon, so that concerted and informed action can occur.

Further information is required on the impact of two modern developments in society. As mentioned above, at both extremes of life the traditional role of care is changing.

The very young are now coming together in child-care centres and the elderly in care homes. The role of both of these settings in the spread of resistant bacteria must be considerable. Far more research is required to understand these issues. To change attitudes will be difficult, but, for example, requiring children who are receiving antimicrobials not to attend such centres would have a major socioeconomic impact. The greater role of immunization of both groups is promising\textsuperscript{20}, and needs further exploration. Certainly, raising the levels of public awareness about the importance of hygiene is central to control.

In the UK, the government is attempting to increase both the public and the medical profession’s concerns by the publication of advice\textsuperscript{21} and a national plan reviewing the current state of play on healthcare-associated infections and setting out action necessary for their control. Central to this is, of course, the need to reduce the reservoirs of infection, maintaining high standards of hygiene, the prudent use of antimicrobials and the necessary management arrangements to ensure that this occurs. There will be no rapid responses, but this is a long road which must be followed.

**New antibacterials**

The sixty years of the ‘antibiotic era’ has been a story of two halves. The first 30 or so years saw the introduction of a multitude of agents; yet in the last 25–30 years only one new family, the oxazolidinones has been introduced.

The past few years have seen the major pharmaceutical companies of Aventis, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline Roche and Wyeth greatly diminish their research into new antibacterials. It would appear that the antibacterial market has lost its appeal to ‘Big Pharma’. The reasons behind this are numerous\textsuperscript{22}. The market size has remained flat, generics are increasing, pressures against unnecessary use is curtailing prescribing, and regulating authorities are increasing the hurdles that new agents have to cross (one wonders if vancomycin or even the aminoglycosides would gain a license today).

It is calculated that a new agent will cost US$ 300–500 million to develop and ‘BigPharma’ requires such an agent to generate sales of US$ 500–800 million\textsuperscript{23}. The great hopes of genomics and combinational chemistry have spectacularly failed to produce new antibacterials. What of the future? It is to be hoped that the smaller biotechnology companies, with their lesser needs for such high returns in development may produce results. The hope must therefore be for a diverse and thriving smaller biotechnology environment; some of the signs are, however, not encouraging. What has happened with the larger pharmaceutical companies (merging and moving their research base to one country – the US) is now occurring with the smaller players. For example, Powderject acquired by

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**Box 2. The consequences of resistance**

- Increased morbidity/mortality
- Increased hospital stay
- Increased antimicrobial costs/toxicity

and paradoxically, less antibacterials being developed (as doctors/patients being asked to be prudent, reduce length of therapy, and resistance may cut down return on investment).
Chiron, Amersham bought by General Electric and Acambis moving its research centre to the US. The UK has only a small percentage of the global biotech revenues (7% as against 73% in the US) and the capital the UK raised was 1/20 that of the US. Hence, in most countries with active pharmaceutical companies, including India, government policy should support and encourage companies to meet the challenges of this all-important field of therapeutics (Box 3).

However, the answer might still come from the major companies if and when political pressures increase from the public-health needs in response to increasing resistance. In other words, far more, possibly high profile failures of therapy due to increasing antibacterial resistance will be needed to generate pressure and incentives from the government before action is seen. Not a pleasing prospect.

The future

As has been discussed, the main option available to decrease resistance is a decrease in antibiotic usage. Whether this is described as ‘more judicial use’ or an increase in ‘prudent prescribing’, the aim is the same – to decrease the selection pressure on bacteria.

In confined areas of use, such as an ITU, it is not difficult to have a major impact upon either the species of bacteria prevalent at a given time and/or the resistance patterns, but as the clinical conditions require treatment, all that occurs in reality is a ‘squeezing of the balloon’ (Figure 6). That is, a new bacteria or one with another resistance pattern soon takes over – a new set of problems emerge. However, it does illustrate that a change in prescribing will have a dramatic impact. As we have seen, majority of the prescribing is in the community and one would expect that any change in antibiotic usage might have a more attenuated impact.

There are encouraging signs. Two countries which share certain similarities have pointed the way. In Iceland, where Streptococcus pneumoniae resistance to penicillin was genetically linked to resistance to trimethoprim/sulfamethoxazole and the macrolides, a modest 10% reduction in resistance to penicillin was followed by an approximate 30% decrease in the use of co-trimoxazole and macrolides. In Finland, erythromycin resistance among Group A streptococci declined from 16.5% in 1992 to 8.6% in 1996, when macrolide consumption declined from 2.4 defined daily doses per 1000 inhabitants in 1991 to 1.38 in 1996 and remained low during the following 5 years. These studies would therefore suggest that a beneficial impact upon the community can be achieved.

The major unknown is the magnitude of such an impact. Mathematical modelling can give some insights and generally shows that resistance can develop rapidly and yet decline only slowly after a reduction in use. The extent and rate of decline of antibiotic resistance following a major decrease in use will vary and will depend upon the extent of the decrease in consumption, the epidemiological setting (hospital, community, etc.), the organism and, of considerable importance, as seen in Iceland, genetically linked resistance to other agents (and their own control) (Figure 7).

Antibiotic usage in Europe varies remarkably. For example, penicillin use in France is more than four-fold greater than that in the Netherlands and total antibiotic use in France is more than three times that in the Netherlands and twice that in the UK. I take heart from this knowledge as it suggests that antibiotic use can be reduced in many countries, as there is no suggestion that the population of the Netherlands or the UK has an increased mortality from infections compared with the French (Figure 8).
is some encouragement. In England, there has been some suggestion that penicillin resistance (both intermediate and high) in pneumococci has declined, changing from 7.1% in 1999 to 2.8% in 2003 (http://www.rivm.nl/ears08, 2008). Of interest, this has not been accompanied by any significant change in macrolide resistance (14.8–12.9%).

Conclusion

Antimicrobial resistance is an inevitable accompaniment to the use of these agents. Profligate use will hasten the decline in the benefit to individuals and society from their life-saving potential. There is a major need to strengthen our understanding of the dynamics of use and resistance which must be underpinned by robust and meaningful surveillance. Inevitably society will have to alter its approach to using antimicrobials; trivial infections must no longer be viewed as a reason for their use. The future is not entirely gloomy. A concerted approach will undoubtedly contribute to preserving these most important therapeutic agents (Box 3).

The role of the developing countries is crucial, especially those whose development is rapid, such as India and China. There is a need for the central governments in such countries to first, accept that antimicrobials are indeed different to other therapeutic agents and secondly, to accept that control is necessary. This, of course, entails stopping the ‘over the counter’ availability. I fully accept that this is a major step... but it is necessary.

In the UK there is some encouraging information: there had been a 21% fall in the number of antibiotic prescriptions between 1995 and 2000 in general practice (http://www.ppa.org.uk/news/pact-092002.htm, 2008). This is good news in itself. However, the survey also showed a six-fold variation in the number of prescriptions between different general practitioners. Again this suggests there is a major possibility to reduce prescribing even further. However, it is necessary to view all such data with caution, as it is possible that there may be other reasons for a decline in prescribing other than general practitioner input, such as a decline in, for example, the prevalence of certain common diseases, such as respiratory-tract infections.

The majority of prescribing is indeed for respiratory tract infections (RTI) and these are most commonly encountered in childhood. In England, there has been a remarkable reduction in paediatric antibiotic prescribing, namely a 50% reduction in the use of broad-spectrum penicillins, oral cephalosporins and macrolides since 1993 (Figure 9).

Have these reductions been accompanied by a reduction in the resistance of any important pathogens? As discussed previously, surveillance, especially in the community, is poorly developed and lacks the basic denominator information. The linkage of usage and resistance rates has, therefore, to be viewed with caution. However, there

MEETINGS/SYMPOSIA/SEMINARS

Indo-German Workshop on ‘Molecular Epidemiology of Infectious Diseases’

Date: 28–30 November 2008
Place: Hyderabad, India

Objectives include: Presentation of emerging and re-emerging infectious diseases in Germany and in India; Organizational structures for the survey of infectious diseases; Protocols for molecular typing; Databases, cluster/outbreak detection, and geographical information systems.

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National Symposium on Infectious Diseases (NSID–2008)

Date: 8–9 August 2008
Place: Coimbatore

Technical sessions/sub themes: Skin and subcutaneous infections; Neurological infections; Respiratory infections; Gastrointestinal infections; Urinary tract infections; Sexually transmitted disease; Nosocomial infections and Diagnostic microbiology.

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