The relentless problem of antimicrobial resistance

R Wise and Lord Soulsby

The past twelve months have seen the emergence of considerable global concern about antibiotic resistance. The House of Lords Select Committee on Science and Technology issued its report *Resistance to antibiotics*, the Department of Health published *The path of least resistance*; the European Chief Medical Officers of Health met in Copenhagen and later published *The Copenhagen recommendations*; the UK Government recently responded to the House of Lords report, and in September 1998 an issue of the *British Medical Journal* was devoted to antimicrobial resistance. In the US the Institute of Medicine published a workshop report, *Antimicrobial resistance: issues and options*.

In addition, there is concern over antibiotic use in animal husbandry, out of which have arisen two WHO meetings. More locally, the matter was raised at a British Veterinary Association Congress and consequently a code of practice is being developed on the use of antibiotics in animals. Most recently, the European Union has banned the use of four antibiotics for growth promotion in animals. Are these activities justified; and are the underlying problems, as the House of Lords suggested, 'a major threat to public health'?

The threat

Over the last fifty years effective agents have been developed for use against common bacteria (including *Mycobacteria*) but only more recently have safe and useful drugs to treat fungal and viral pathogens become available. However, antimicrobial resistance is occurring across the whole range of micro-organisms pathogenic to man and animals. This resistance is almost universal, one exception being *Streptococcus pyogenes* to penicillin. Resistance is not confined to bacteria but includes viruses: this is especially true in regards to the new antiviral agents. The high replication rate of many viruses means that genetic variants that are resistant to therapeutic compounds already exist in untreated infected patients, a depressing fact which implies that such patients will require therapy with multiple agents. Therefore, it is inevitable that antimicrobial use generates antimicrobial resistance. Indeed, antibiotic resistance is fundamentally a natural phenomenon whereby microbes (eg bacteria) safeguard themselves against competing organisms.

The major clinical threats well illustrate various mechanisms that pathogens have developed to circumvent antimicrobials. Drug destruction or inactivation is a common mechanism and is shown by the ubiquitous Gram negative bacteria encountered in hospital practice. *E. coli*, *Klebsiella* sp and *Pseudomonas aeruginosa* have all developed β-lactamases that can hydrolyse the penicillins, cephalosporins and carbapenems (such as imipenem and meropenem). These enzymes are genetically coded on mobile elements, such as plasmids and transposons, and therefore there is the potential for spread not only to other organisms of the same genus but across bacterial genera. In a recent European study, 23% of hospital isolates of klebsiellae were resistant to broad spectrum cephalosporins because of this mechanism. Similarly, aminoglycosides can be inactivated by enzymes common in Gram negative bacteria. It is of particular importance that the genetic information for these and other resistance mechanisms can be linked and exchanged as described above, favouring the spread of multiple resistant bacteria.

The resistance of *Streptococcus pneumoniae* to penicillin (and the other β-lactams) illustrates how the antibiotic target site alters so that it is no longer susceptible to these agents. Resistance is now widespread globally and localised areas of considerable resistance have recently been described: in the UK, for example, 45% of patients in one Belfast hospital were penicillin resistant; similarly, there is currently an epidemic of methicillin resistant *Staphylococcus aureus* (MRSA), caused by organisms whose target sites have been altered.

Target site mutation is the common mechanism of fluoroquinolone resistance, which is of considerable concern. In some parts of Europe resistance in *E. coli* to this important family of agents is now high and increasing. Resistance in *Salmonella typhi* in Asia means that the fluoroquinolones, which had previously shown considerable clinical promise, are being significantly compromised.

An antimicrobial may fail to gain entrance to a bacterium (impermeability) or may be rapidly pumped out (efflux) so that it cannot reach the target site. The resistance of *Pseudomonas aeruginosa* to carbapenems, and of *Streptococcus pneumoniae* to the fluoroquinolones, comprises these mechanisms.

Bacteria have thus produced a wide range of strategies for combating antimicrobials and sophisticated means of exchanging genetic information to aid their spread. The difficulty of implementing rigorous infection control procedures (in turn related to economic pressures in hospitals),

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together with the fact that no new classes of antimicrobials have been introduced for many years, implies that microorganisms are currently winning the battle against infectious diseases.

The major threats to antimicrobials are summarised in Table 1. One significant change over recent years is that therapeutic options for treating some of the common pathogens associated with community-acquired infections are becoming limited. The most relevant example is *Strept. pneumoniae*, which as already mentioned is now increasingly resistant to the penicillins. Whereas chest infections caused by these pathogens may still respond to high dose amoxicillin, more serious infections (such as meningitis) may not. The acquisition of β-lactamases in *H. influenzae* (resistance rates may be as high as 35% in the US) means that agents such as amoxicillin are no longer effective. It is likely that the increasing use of cephalosporins for chest and other infections is related to the increasing incidence of pseudomembranous colitis due to *C. difficile*.

The spectre of vancomycin resistant staphylococci is alarming. The organism has been found in Japan, the UK and several European countries, but as yet remains rare. Similarly, the spread of vancomycin resistant enterococci (which in the UK is only a problem in certain specialised units, yet in the US is more widespread), has significant therapeutic implications.

**The cause**

Antibiotic use is both the cause of the problem (in selecting resistant variants) and the reason behind its accumulation and acceleration. At least 75% of the antibiotics used in humans are consumed in the community outside hospitals – some put the figure at over 95%. Most of these antimicrobials are used in respiratory tract infections. The majority of upper airway infections, acute bronchitis and many cases of the acute exacerbations of chronic bronchitis are viral diseases, in the treatment of which antibiotics have been found to be of little use. One of the most potent influences on prescription is the expectation of the patient and, in turn, the general practitioner’s perception of his patient’s expectation.

Although less than one quarter of human antibiotic use takes place in hospitals, there is a greater ability to select resistant mutants, and to transfer these resistant strains between bacteria and between patients when infection control is ineffective. Inappropriately prolonged therapy or surgical prophylaxis favour the emergence of resistant pathogens.

According to US figures (and EU figures are probably similar) about half of all antibiotics are used in animals and 80% of these are for the purely commercial purpose of growth promotion (that is, to make mainly pigs and poultry gain weight more rapidly). The House of Lords and WHO

### Key Points

**Antimicrobial resistance is an increasing and accumulating problem**

**Antimicrobial resistance is now considered a major threat to public health**

**Resistance is related to over-use**

**Major changes in clinical practice will have to occur in order to combat the problem**

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**Table 1. The common bacterial pathogens and their resistance to the important classes of antimicrobials.**

| Bacteria                       | Antimicrobial agents       | Mechanisms of resistance                      |
|-------------------------------|---------------------------|-----------------------------------------------|
| **Community pathogens**       |                           |                                               |
| *Haemophilus influenzae*      | Amoxicillin               | β-lactamase                                   |
|                               | Amoxicillin & cephalosporins | Target site alteration                       |
| *Streptococcus pneumoniae*    | Penicillins & cephalosporins | Target site alteration                       |
|                               | Fluoroquinolones          | Efflux and target site alteration             |
|                               | Macrolides                | Enzymatic modification                        |
| *Streptococcus pyogenes*      | Macrolides                | Enzymatic modification                        |
| **Hospital pathogens**        |                           |                                               |
| Enterobacteriaceae (eg E. coli, Klebsiella etc) | Cephalosporins          | β-lactamases                                 |
| *Pseudomonas aeruginosa*      | Aminoglycosides           | Enzymatic modification                        |
|                               | Fluoroquinolones          | Target site alteration                        |
|                               | Carbapenems               | β-lactamases and impermeability               |
| *Staphylococcus aureus*       | β-lactams                 | β-lactamases and target site alteration (MRSA) |
| Enterococci                   | Vancomycin                | Target site alteration                        |
| Mycobacterium tuberculosis    | All agents                | Various                                       |
amongst others suggest imprudent use of antibiotics in livestock to be an abuse of a precious resource, as there is evidence that it can lead to resistance in man. Examples of this are the gastro-intestinal pathogens campylobacter, Salmonella spp and E. coli, where fluoroquinolone use has led to resistant strains in man. Similarly, avoparcin (closely related to vancomycin) use in animals has been implicated in increasing enterococcal resistance in man.

Solutions

The recent House of Lords report1 suggested a number of strategies to address this difficult problem. They can be summarised as follows:

- Better education of doctors. The Royal Colleges were urged to increase ‘the attention paid to antimicrobial therapy in their programmes of postgraduate education and vocational training’
- Enhanced public education. A campaign targeted at young mothers was recommended
- Accurate and timely surveillance of resistance
- Enhanced infection control with more attention given to community issues (such as the problems of day and elderly care institutions)
- More prudent use of antibiotics in animals
- Encouragement of funding of both fundamental and applied research by government and charities
- Prioritisation of new drug development by the pharmaceutical industry.

Some of these aims are more readily achievable than others. Antibiotic animal growth promoters could be phased out, as they have been in Sweden13. Educating doctors and their patients will require major long-term commitment on many fronts11. Doing nothing is not an option, unless we wish to return to the days before antibiotics. The UK government has stated its desire to address the problem4; let us hope that resources are made available for the long battle ahead.

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