Antimicrobial resistance: bacteria on the defence

Resistance stems from misguided efforts to try to sterilise our environment

Bacterial resistance to multiple antibiotics characterises the present decade. Finding organisms insensitive to over 10 different antibiotics is not unusual. Although most of the hardier organisms are present in hospitals, strains of multidrug resistant bacteria, such as *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Escherichia coli*, also cause serious community acquired infections. Moreover, resistant bacteria from hospitals can be introduced into the community via the estimated 5% of patients discharged for continued treatment at home—taking with them multidrug resistant *Staphylococcus aureus* and vancomycin resistant enterococci. Since about half of antibiotic usage in the developed world (and perhaps more in the developing world) is inappropriate, there is a certain optimism that we can reverse the resistance problem if we improve use and thus return to an environment populated with susceptible strains.

To understand resistance, imagine being a bacterium in a world bombarded with antimicrobials. Living in a human, you would face antibiotics being taken for routine infections and for non-threatening conditions like acne. As a susceptible strain you have to acquire a survival mechanism. This is not too difficult, as your resistant counterparts, though less common, are very willing to share their antibiotic fighting strategies with you. Armed with their donated plasmids and transposons, you survive the continuous onslaught of antimicrobials. You may sustain a mutation, rendering the antibiotic target within you resistant. Your progeny bearing the mutation survive along with you, while your sensitive counterparts succumb and diminish or vanish. With any one or more of these new defence mechanisms, you are equipped to survive when introduced to new human hosts.

Should you happen to live in an animal host you face the same onslaught since antibiotics are used heavily in animal husbandry, both as growth enhancers and in treatment—and under this chronic selection pressure you enhance your resistance capabilities. In the United States you may readily become resistant to the ubiquitously used penicillins and tetracyclines. Elsewhere you will probably be confronted with growth promoters unique to the farm, such as avoparcin or virginiamycin.[1] These drugs, though not used in humans, are closely related to human therapeutic drug families, such as vancomycin and streptogramins. You might face fluoroquinolones used to treat animals, a practice which has led to the emergence of quinolone resistance in organisms like *E coli, Salmonella* spp, and *Campylobacter* spp.[1 2] As you make your way through the food chain back to a human host you carry the trademark of your journey through the animal host—multidrug resistance.

Or perhaps you have come into the home by way of a food crop. In that environment, too, you have undergone the selective grooming afforded by copious amounts of antimicrobials applied as pesticides. Now in the home, along with the myriad other natural flora found there, you encounter the subtle inhibitory effects exerted by antimicrobials impregnated into soaps, lotions, dishwashing liquids, plastics, and other products.[3] These agents, along with disinfectants, exert their own subtle effects to further mould hardy "survivors" into a population that far outnumbers its defenceless predecessors.

You may perhaps find yourself living in yet another hostile environment—the hospital. Armed with your multidefence mechanisms derived from human, animal, or foodcrop hosts, you are not only well equipped to ward off the attacks of newer and more powerful drugs, but may also share your well developed arsenal with other unarmed, potentially infectious, travelling companions. As such, you have helped create some of today's most resistant and feared pathogens.

The above scenario portrays the multiple and cumulative impacts of antimicrobial agents on the bacterial world. The message is clear—we are using too many antimicrobial drugs for the wrong reasons. Each use can contribute to an altered microbial ecology.

Studies of newly emerging resistance show that resistance in bacteria, as in cancer, arises in steps progressing from low level to high level, unless a plasmid is acquired on which full blown resistance is already present. The initial penicillin resistant pneumococci appeared with slightly decreased susceptibility to the antibiotic but over time evolved high level resistance. Penicillin and tetracycline resistance among gonococci emerged in a similar way. The phenomenon has also been observed with quinolone resistant *E coli*, where multiple steps are required to reach a clinically relevant level of resistance.[4] Currently, we are witnessing the same phenomenon with chromosomally mediated resistance to vancomycin in *S aureus*.[5] Decreased drug susceptibility should be a warning to change antibiotic use to diminish selection for resistance.

Globally we need to look at how antibiotics are used and where resistant strains reside, since these organisms can move easily between countries. As importantly, we need to look at the ecology in general—the kinds of resistances in so called reservoirs, the commensal or non-clinical bacteria. They will tell us where the next resistance problem will arise and also where antibiotic selection pressure for resistance is high. Importantly, it may not be the antibiotic itself, but other compounds, that exert the selective force. Heavy metals, disinfectants, antibacterials, and antimicrobials—all can select for different kinds of bacteria, including those resistant to lifesaving antibiotics.[3 6]

If a single point can be derived from our understanding of antibiotic resistance, it is the ecological nature of the problem. To this can be added the genetic fluidity of the bacteria. The difficulties we face today derive from misguided efforts to try to sterilise our environment by indiscriminately destroying bacteria when we should reserve our killing capabilities for cases when health is threatened by infectious strains. We should act now to restore and maintain the healthy

BMJ 1998;317:612–3

balanced microbiology of the pre-antibiotic era—that is, one populated by a predominantly susceptible flora.

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Control of antimicrobial resistance: time for action

The essentials of control are already well known

Until recently the medical community world wide has seemed incapable of reacting to the imminent crisis of antibiotic resistance. Several explanations exist for this lack of action, including the complex interaction between doctors, patients, and parents over antibiotic use[1 2] and the fact that the pharmaceutical industry has so far succeeded in developing new antibiotics when resistance to existing ones has emerged. Although we still need a better understanding of the factors involved in the emergence and spread of antibiotic resistance, action cannot wait until all the answers are available. The essentials of better control of antibiotic resistance are already well known.

Surveillance of bacterial resistance is a key element in understanding the size of the problem. The large number of existing networks for resistance surveillance need to be coordinated and the results made available.[3] To help doctors choose appropriate antibiotics and to detect local epidemics of resistant bacteria surveillance at local level is necessary. Good quality local data provide a basis for national and international surveillance.

There are two ways of fighting the development and spread of resistant bacteria. The first is to reduce the use of antimicrobial agents to decrease selection of resistant bacteria. About 85-90% of antibacterial drugs are used in the community, and up to 80% of these are used to treat respiratory tract infections. Thus, major efforts have to be targeted on diagnosis and treatment of respiratory tract infections in the community.[4 5] Sales of antibiotics over the counter should be stopped. Statistics on the use of antimicrobial agents (including sales over the counter) are of key importance for changing prescription patterns but at present are available only in some countries. We also need to know the patterns of prescription of antibacterial agents in different infections to identify where clinical practice needs to be improved.[4]

To reduce antibiotic consumption we need a multifaceted approach that includes education of doctors; widely accepted recommendations for good clinical diagnosis and treatment; and follow up of compliance with such guidelines. Evidence exists that changing the way general practitioners are paid can change their prescribing behaviour.[6] Measures to improve the public's knowledge about the risks and benefits of antimicrobial therapy are also important. A free return visit for patients not prescribed antibiotics at the first consultation for a respiratory tract infection has been used as one way of changing patients' expectations.[7] Restriction policies such as the requirement for written justification or automatic stop orders may be useful in hospital settings. Integrated strategies have reduced antibiotic use or curtailed antimicrobial resistance.[7–10]

The second major way to tackle resistance is by improving hygienic measures to prevent the spread of resistant bacteria. Only 40-50 years ago hygienic measures were the most important means of preventing the spread of transmissible diseases. Indeed, during this century Western societies have been transformed by major investments in preventing the spread of pathogenic bacteria: tap water and sewerage, as well as our kitchens with all their equipment. The question is simple: how much are we ready to pay to prevent the spread of resistant bacteria?

In hospitals effective prevention of cross infection and the development of strict antibiotic policies should be in the hands of experts.[11] Each hospital thus needs an infection control team with infectious disease specialists, clinical microbiologists, and infection control nurses and sufficient resources and a mandate to run the programme. One urgent practical question is how to raise the standard of hand hygiene in hospitals: at best hand disinfection is achieved on fewer than half the occasions it is required.[12]

Research is also a cornerstone in the fight against bacterial resistance. We have to improve our understanding of bacterial flora, the evolution of resistance, and the mechanisms of transmissibility of resistant bacteria. New diagnostic technologies to enable rapid identification of viral and bacterial infections are also necessary: for too long it has been easier for clinicians to prescribe an antibiotic than to make a specific diagnosis.

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