The need for a global response to antimicrobial resistance


Summary
Antimicrobial resistance is a major public health threat that no country is exempt from. The problem is complex and is influenced by many interconnected factors such as poverty, self-medication and misdiagnosis (World Health Organization 2001). A global response is essential and urgent.

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The scale of the problem
For many antimicrobials, the development of resistance in several pathogens now limits their effectiveness (WHPA 2001). This is a serious public health concern with global economic, social and political implications. The primary economic implication of resistance is the need to rely on more expensive drugs that may be practically unaffordable for most primary healthcare programmes (WHO 2001). Multidrug-resistant tuberculosis (MDR-TB) is no longer confined to any one country or to those co-infected with the human immunodeficiency virus (HIV), but has appeared in locations as diverse as Eastern Europe, Africa and Asia among healthcare workers and in the general population (WHO 2001, WHPA 2001).

The cost of treating one patient with MDR-TB can be as much as treating 100 patients with tuberculosis (WHPA 2001). Penicillin-resistant pneumococci are likewise spreading rapidly, while resistant malaria is on the increase, disabling and killing millions of children and adults each year. In some areas of the world – notably South East Asia – 98% of gonorrhoea frequently fatal (WHO 2002b). Following their 20th century success in human medicine, antimicrobials have also been used increasingly for the treatment of bacterial disease in animals, fish and plants. They also became an important element of intense animal husbandry because of an observed growth-enhancing effect when added in sub-therapeutic doses to animal feed. Antimicrobials are also used in industry, for example, to eliminate bacterial growth on the inside of pipelines (WHO 2002a). They might also be required against biological weapons, such as anthrax (Hart and Beeching 2001).
infections are multidrug-resistant. Managing sexually transmitted infections (STIs) is a key strategy in HIV prevention because STIs increase individuals’ susceptibility to HIV and their infectiousness with it. The behaviours that put individuals at risk of STIs also put them at risk of HIV (Family Health International 2001). In the industrialised world, as many as 60% of hospital-acquired infections are caused by drug-resistant microbes. These infections, the most recent of which are glycopeptide-resistant Enterococcus and meticillin-resistant Staphylococcus aureus (MRSA), are no longer confined to wards but are also evident in the community (WHO 2001).

**Healthcare-associated infection in the UK**

In the 19th century hospitals were hazardous environments. The situation improved dramatically in the UK with increased understanding of the link between basic hygiene and infection. Further improvements were associated with the discovery of the value of antisepsis during surgery. Healthcare-associated infections (HCAIs) were resurgent in the last three decades of the 20th century and are now a major problem for the NHS.

Initiatives have taken place in the UK to address these issues, such as the development of the Healthcare Commission which has a mandate to work on HCAIs (Healthcare Commission 2006) and the development of the Health Act 2006 which is a code of practice for the prevention and control of HCAIs.

**Antimicrobial resistance**

The emergence and spread of antimicrobial resistance are complex problems caused by numerous interconnected factors, many of which are linked to the misuse of antimicrobials and are therefore amenable to change. In turn, antimicrobial use is influenced by an interplay of the knowledge, expectations and interactions of prescribers and patients, economic incentives, characteristics of a country’s health system and regulatory environment (WHO 2002b). Inadequate health services, inadequate drug supplies, non-adherence to treatment strategies and dubious drug quality all favour the emergence of resistance (WHO 2001).

**Environment and society** Forty years ago physicians in industrialised nations believed that infectious diseases were a scourge of the past. Major drug manufacturers turned away from intensive antibacterial research, and focused their energies on seeking cures for chronic diseases, such as heart disease and Alzheimer’s disease. This further reduced research into new drugs designed to combat bacterial infections (WHO 2001). Numerous new classes of antimicrobials were discovered in the 1950s and 1960s, and the 1980s and 1990s yielded only minor improvements within these classes. During the past ten years, micro-organisms have developed resistance to antimicrobials, and therapeutic options are narrowing (DH 1998).

Some new antimicrobials have been developed, for example, new beta-lactams, the streptogramins, linezolid, the protease inhibitors and monoclonals (British National Formulary (BNF) 2006); however, initially they will be too expensive for many in developing countries. Drug and vaccine research is a crucial issue for all nations given the emergence of antimicrobial resistance among human pathogens. The fact that there are currently several novel antimicrobial agents and vaccines in clinical trials reflects the industry’s awareness of the problems of antimicrobial resistance and the enormous investment by some companies in anti-infective drug development (WHO 2001).

At the same time, however, there are concerns in the industry that efforts to encourage more appropriate use of antimicrobials may have a negative impact on sales (WHO 2001).

**Microbiology** Antimicrobial use exerts an inevitable Darwinian selection for resistance, that is, ‘survival of the fittest’. Once selected, resistant bacteria spread or transfer their resistances to other bacteria. The result has been erosion of antimicrobial efficacy (DH 1998). A bacterium may develop resistance either by chromosomal mutation and selection, or by plasmid transfer. Mutation involves a chance change in the genetic code of the chromosome, leading to the formation of an abnormal protein. If this new protein protects the bacterium from a particular antibiotic, the bacterium is resistant (Kelly 2001). Antimicrobials kill susceptible bacteria but resistant ones survive to infect other patients. At the same time, advances in medicine enlarge the pool of patients susceptible to infection by organisms that historically were harmless, but which are adept at developing resistance (DH 1998). Disease and, therefore, resistance, also thrive in conditions of civil unrest, poverty, mass migration and environmental degradation – where large numbers of people are exposed to infectious diseases with little basic health care (WHO 2001).

**Drug access and resistance** More than any other issue, poverty and inadequate access to drugs continue to be a major force in the development of resistance (WHO 2001). Self-medication occurs in many countries with lax laws and
In Uganda, patients are regularly prescribed chloroquine which has a high resistance to malaria. The second-line treatment for malaria sulphafoxine-pyrimethamine is showing clinical failure rates of 50% in East Africa but it is still prescribed by some health workers (Allan 2001). Treatment with second and third-line drugs is generally more costly (WHO 2001).

**Misdagnosis and resistance**
Misdagnosis is another symptom of weak public health systems in industrialised and developing nations. Busy and ill-equipped clinics inevitably lead to defensive and unnecessary prescribing as a means of forestalling potential complications. A lack of laboratories in poorer nations means healthcare workers are forced to engage in the kind of symptom-based guesswork that often leads to misdiagnosis and the increased likelihood of prescribing the wrong medication (WHO 2001). In Uganda, it is not unusual for a patient to take a sick child to a clinic and be given a list of five drugs (for example, aspirin as an analgesic which should not be given to children under 12 years, antibiotics and various vitamins) that they need to buy, when the child may have an upper respiratory tract viral infection.

As an example a non-health worker colleague took his 18-month-old daughter to the government-run Kawempe Health Centre, as she was coughing at night. She did not receive a clinical examination and no laboratory tests were carried out. She was prescribed chloroquine injection as well as amoxicillin tablets, salbutamol and aminophylline syrup and a cough medicine. As her father had limited money on the day of consultation he had to choose which drugs to buy as he could not afford them all. This is not an unfamiliar scenario.

**Dubious pay-offs and high-priced prescriptions**
Owing to fears of resistance, many health workers avoid prescribing narrow-spectrum drugs that treat specific complaints in favour of broader-spectrum antibiotics that have wider applications, such as augmentin or ciprofloxacin. In countries where healthcare providers earn only subsistence wages, pharmaceutical companies sometimes pay a commission for recommending more expensive broader-spectrum medications when cheaper narrow-spectrum alternatives would suffice. This results in a smaller, more highly-priced pool of antimicrobials combating a larger number of infectious diseases (WHO 2001).

**Advertising**
Patient demand for antimicrobials – sometimes the result of television, internet, magazine or newspaper advertising – also increases the development of resistance (WHO 2001).

**Lack of education**
Many drug dispensers in developing countries are under-educated and under-informed. One study in Ghana found that only 8% of drug dispensers (that is, those who are based in pharmacies and can give out medicines) had received formal training in an institution (Ameayaw and Ofori-Adjei 1997). Another study found that drug retailers in seven sub-Saharan African nations often advised consumers to buy non-essential drugs without adequate explanation – and without any suggestion that individuals consult a health worker before their purchase (Bruneton et al 1997). The combination of poverty and ignorance provides an ideal situation for antimicrobial resistance to advance (WHO 2001).

**Resistance and hospitals**
Hospital doctors sometimes prescribe antibiotics inappropriately (WHO 2001). Insufficient training in infectious diseases and antibiotic treatment, difficulty in selecting the appropriate anti-infective drugs, insufficient use of microbiological information, the need for self-reassurance and the fear of litigation are prompting the use of broad-
spectrum drugs (WHO 2001). A study in the UK showed that perceived patient pressure is a strong independent predictor of doctors’ behaviour – including prescribing (Little et al 2004). This can also have a medicalising effect, as it will encourage patients to return for more medication next time (Welschen et al 2004).

Compliance of healthcare staff with basic infection control practices, such as hand washing or disinfection, is incomplete, and the shortage of healthcare staff often makes isolation precautions difficult to implement (Struelens 1998, DH 2002).

Antimicrobial resistance and food
Another source of resistance lies in our food supply and is related to infectious agents that live in food and drink. Currently, only half of all antibiotics produced are for human consumption. The remainder is used to treat sick animals, as growth promoters in livestock and to rid cultivated food of various destructive organisms (Wise et al 1998, WHO 2001). This ongoing and often low-level dosing for growth and prophylaxis inevitably results in the development of resistance in bacteria in or near livestock, and also increases the risk of new resistant strains moving between species (WHO 2001).

Globalisation and resistance
International travel and trade also play a role in the development of antimicrobial resistance. A microbe originating in Africa or South East Asia can arrive in North America within 24 hours. One example occurred in Canada where healthcare authorities traced two outbreaks of MRSA to a small village in Northern India (WHO 2001).

The need for a global response
In September 2001, WHO launched the first global strategy for combating the serious problems caused by the emergence and spread of antimicrobial resistance. Known as the WHO Global Strategy for Containment of Antimicrobial Resistance, it recognises that antimicrobial resistance is a global problem that should be addressed by all countries (WHO 2001). The strategy provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial resistant micro-organisms by (WHO 2001):

- Reducing the disease burden and the spread of infection.
- Improving access to appropriate antimicrobials.

- Improving the use of antimicrobials.
- Strengthening health systems and their surveillance capabilities.
- Enforcing regulations and legislation.
- Encouraging the development of appropriate new drugs and vaccines.

Given the constraints of health systems in some countries and the complex factors involved in promoting antimicrobial resistance, support from the international community should be a priority. Of the 79 countries that are members of the WHO programme for international drug monitoring, six are from sub-Saharan Africa (Couper et al 2006). The global strategy can be used as an advocacy tool to lobby for further support in carrying out the recommendations and raising awareness of the problem. The interventions are organised according to groups of people whose practices and behaviours contribute to resistance, and where changes are judged likely to have a significant impact at both national and international levels (WHO 2002b).

Patients and the community
Education is a key area for containment of antimicrobial resistance. This includes educating patients and the community on the appropriate use of antimicrobials and ways to prevent infection, such as the use of bed nets to prevent malaria, and adequate environmental and personal hygiene measures. Effective hand washing is acknowledged as the most cost-effective intervention in hospitals to reduce infection (Infection Control Nurses Association (ICNA) 1997). It also includes education on seeking appropriate health care as opposed to self-medication, or using unqualified health professionals (WHO 2001). In Tanzania it was proposed to replace drug stores with Accredited Drug Dispensing Outlets for the improvement of malaria treatment. This would include improving malaria diagnosis to reduce over-diagnosis of malaria with clinical assessment alone and training staff to avoid potentially harmful practices, such as the inappropriate use of antibiotics (Kachur et al 2006).

A similar study in Kenya showed that training private drug retailers can improve early treatment of malaria at home. It was found that as well as providing important health benefits improvements in the early home care of malaria could support overstretched public health resources, reduce household economic costs and potentially play a role in reducing the rate of development of drug resistance for over-the-counter anti-malarial medications (Marsh et al 1999).

Health professionals
Health professionals should be educated on appropriate antimicrobial
use, educating patients, adherence to treatment and disease prevention. A study from developing countries has shown that to meet the needs of nurses’ expanding roles in a developing country context, the curriculum content in areas such as pharmacology and microbiology needs to be increased (Kyriacos et al 2001). Resources can be made available, such as the Nursing Standard cards on antibacterial drugs (Knight and Jordan 2004). These have been distributed free in developing countries through Teaching-aids at Low Cost (TALC) (2006).

Despite this, disseminating resources to support health workers remains a problem in developing countries. Many staff work in isolation in their communities. Because of low staffing levels, if workers are regularly called to district level meetings for training health facilities are left unattended by trained personnel. The development of distance learning training methodologies is important and should be further explored. Supervision and support for health professionals are essential as is the audit of practice (WHO 2001).

The governments in developed countries such as the UK should take up their commitments made in Report of the Commission for Africa. They recommended that donors and African governments should urgently invest in training and retention to ensure that there are an additional one million health workers by 2015 (Commission for Africa 2005).

Hospitals and other health facilities

Hospitals and other health facilities should have an effective infection control programme. Antimicrobial usage should be monitored (WHPA 2001).

Governments, industry and the World Health Organization

Much of the responsibility for containing resistance rests with governments who legislate and develop policies about the development, licensing, distribution and sale of antimicrobial agents (WHO 2001, WHO 2002b). Governments should ensure that there is

References


a national essential drugs programme. Essential medicines are defined as those that satisfy the priority healthcare needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness' (WHO 2004).

In addition, the need for active surveillance systems to monitor antimicrobial resistance is important, including bacteria from farm animals and food from animal origin (WHO 2001, WHO 2002a). Surveillance of antimicrobial resistance requires laboratory facilities and information networks which are currently beyond the capacity of many countries and thus require considerable strengthening (Williams and Ryan 1998). WHO recommends that all opportunities are taken to reduce the use of antimicrobials outside human medicine (WHO 2002a). WHO has developed global principles for the containment of antimicrobial resistance in animals intended for food (WHO 2000).

Likewise the development of drugs for developing countries requires further input, in terms of funding provision for the research and development of new drugs for non-profitable infectious diseases. Drug development is done almost exclusively by the Western-based pharmaceutical industry, whose activities are directed by profits rather than health needs (Trouiller et al 2002). Various strategies have been proposed to address, for example, advance price or purchase commitments from a third party such as WHO (Towse and Kettler 2005), development of drugs by focusing on indigenous medicinal plants in developing countries (Reichert and Milne 2006), the development of an international pharmaceutical policy for all neglected diseases and a legal framework to redress the imbalance between rights and obligations in the current patent system (Trouiller et al 2002).

Conclusion

Antimicrobial use is a key factor in antimicrobial resistance. Given the complexity of antimicrobial resistance the focus should be on prevention of infections through good environmental and personal hygiene. A WHO strategy has been developed with recommendations aimed at the main groups of people whose practices and behaviours contribute to resistance and where a change in such practices can reduce antimicrobial resistance. These include: consumers, prescribers and dispensers, veterinarians, hospital managers and diagnostic laboratories as well as national governments, the pharmaceutical industry, professional societies and international agencies (WHO 2002b). Both prescriptive and persuasive methods of prescribing should be explored (Davey et al 2006), as well as innovative ways of conducting appropriate training. Ways of reducing the number of health workers who are able to prescribe should be discussed. The UK could also share some of its success with governments in developing countries to address this global problem. Implementing the global strategy is urgent NS.


Teaching- aids at Low Cost (2006) CD-Rom Number 8. TALC, St Albans.


