Regulating the use of antibiotics in the community

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All parties perceive antibiotic resistance as a global threat.[1] We examined the literature on the use of antibiotics in the community to establish how the issue of antibiotic resistance might be managed. We chose illustrative examples from recent important publications.

Costs

The world market for antibiotics in 1997 was $17bn (£10.6bn), of which $12bn was for community use, with about 818 billion prescriptions for respiratory tract infections. Although the value is rising (the 1993 market was $15bn), the number of prescriptions is now static. From 1980 to 1991, however, the overall increase in prescriptions for antibiotics in England was 46%—but still below the rate of growth over the same period in France.[2,3]

Several factors may influence the increase in antibiotic costs.[1,3,4] Recently, two characteristics of antibiotics prescribing—that is, use of doses that are too small or treatments that are too long—have been shown to increase the risk of selection of resistance.[5] The ecological impact of poor compliance or of the use of highly selective agents remains to be established.

Respiratory tract infection accounts for 75% of community prescriptions.[1,4] Most are for tonsillopharyngitis, followed by bronchitis. In both France and Britain about 90% of patients receive antibiotics for tonsillopharyngitis. In France, 9 million prescriptions a year are issued for this indication. In France, however, the consultation rate is more than three times the rate in the United Kingdom.[1,3] A rapid diagnostic test with 90% sensitivity for group A streptococci is available[6] but is not widely used and is not even reimbursed under the French healthcare system. On the assumption that only 35% of patients have been infected with group A streptococci,[7] then theoretically a rapid test may lead to a saving of about 6 million prescriptions for antibiotics. This would substantially reduce the antibiotic burden in France—with an obvious positive short term economic impact—and slow or reduce the rate of macrolide resistant *Streptococcus pneumoniae* or group A streptococci.[8]

Reversing the increasing rate of resistance

How reversible is the increasing rate of resistance among major pathogens involved in infections acquired in the community? When the selective pressure (antibiotic) is removed, sensitive organisms will increase and resistant organisms will decrease. A more formal and mathematical consideration of the population genetics of resistance and experimental studies of the costs of resistance come to a more pessimistic conclusion. Models show that after a slow start the change in the frequency of resistance is sigmoid. After a period of time there is a quick ascent and a slow decline. The maximum rate of change in frequency of resistant organisms is seen when the sensitive and resistant genes are equally frequent.[8,9]

Summary points

Political measures to control costs of antibiotic use generally have had a short term effect without affecting resistance

Although the reversibility of the current situation of resistance is unknown, actions that could decrease the volume of antibiotic use without affecting quality of care should be considered

General practitioners should help to set guidelines for selecting patients to be treated; improved treatment schedules must be researched and put into practice

The clinical evaluation of antibiotics must be improved—to show effectiveness and effects on the ecology of resistance, as well as safety and efficacy

The pharmaceutical industry, microbiology physicians, academia, regulators, policymakers, and healthcare providers should participate in managing the issue of antibiotic resistance

Changing or reducing antibiotic use

To date, concerns over resistance have not led to any legal measures to reduce antibiotic use. However, antibiotic use in the community has been reduced or altered in several countries. What can we learn from them?

In Iceland, after the introduction from Spain of a multiresistant strain of *Streptococcus pneumoniae*, community antibiotics were removed from the list of reimbursable drugs by the government for financial reasons. At the same time a nationwide campaign against inappropriate antibiotic use was started. Subsequently, antibiotic consumption started to decline, and in 1994 pneumococcal resistance started declining (as defined by nasopharyngeal carriage in day care centres).[10] Data are lacking on the clinical impact on patients arising from this changing resistance. In Finland the pattern of erythromycin resistance among group A streptococci during 1991-6 in relation to use of macrolides was studied. A national recommendation in late 1991 resulted in a reduction in their use (erythromycin resistance peaked at 19% in 1993 and then declined to 8.6% in 1996).[11]

In 1996 the Australian Health Insurance Commission, which manages and processes prescribing claims, wrote to 2000 prescribers stating that co-amoxiclav was being prescribed too often and inappropriately and that if co-amoxiclav was prescribed freely, the commission would conduct an audit. The commission assumed that most prescribers would switch to amoxycillin. The use of co-amoxiclav fell dramatically, with substantial increases in sales of two heavily promoted

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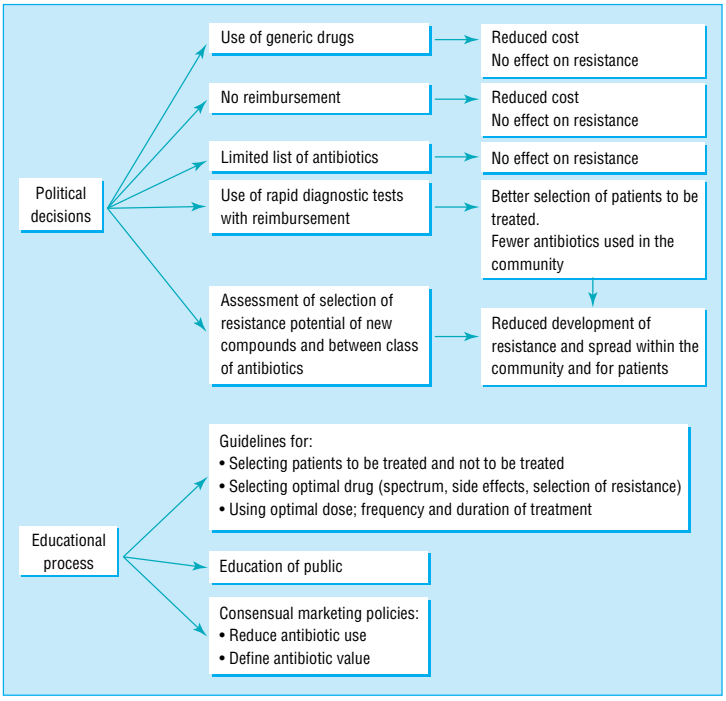

Possible strategies to regulate use of antibiotics. Adapted from Bax[17]

antibiotics, cefaclor and roxithromycin. The clinical impact of these prescribing changes are unknown but are being investigated (J Marley, personal communication). The action taken by the Australian Health Insurance Commission teaches us that reducing the use of a particular antibiotic does not reduce overall costs or the use of other antibiotics and may have a negative impact on clinical outcome.

Strategies for managing antimicrobial resistance

Achieving public health objectives with an antimicrobial resistance strategy may entail legal measures. Strategies to address antimicrobial resistance as a public health and legal challenge must consider the research and development components of public health strategy both nationally and internationally. Antimicrobial resistance is a global problem, and if national reform takes place in only a minority of countries, the sum effect would be small.

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Combinatorial chemistry is a groundbreaking technique for producing new drugs

Whereas microbes move freely around the world unhindered by borders, public health responses must consider national and international law. Effective public health strategies to combat antimicrobial resistance must entail improved surveillance, better use of existing agents to maintain effectiveness of antibiotics, and increased research and development of totally new antibiotics.[12] How are we going to use these products in the future?

The mantra that bacterial resistance is bad, that resistance is caused by antibiotic use and therefore we should reduce antibiotic use is too simplistic and is unlikely to be effective. Interest is increasing in providing evidence based health care and in considering appropriate factors when deciding whether to act on or promote the implementation of research findings. Practitioners often discover that research evidence is biased or otherwise limited. Though we will still need to use imperfect research information, new clinical policies should not be implemented unless clinicians find that a strong evidence of benefit exists.[13]

The figure summarises what can be done, in terms of both political decisions and educational processes. Actions that could reduce the costs (as a short term effect) while providing a positive long term ecological impact should be encouraged, even if the total reversibility of selection of resistance has not yet been fully shown. The rapid spread of multiresistance among bacterial strains responsible for nosocomial infections observed in the past 20 years, as a consequence of uncontrolled use of antibiotics in hospitals, should be kept in mind.

Role of pharmaceutical industry

The pharmaceutical industry is, as a matter of priority, conducting research into totally new classes of antibiotics with new modes of action using bacterial genome sequencing and combinatorial chemistry.[14] The pharmaceutical industry in the United States spent $2.8bn on research in infectious diseases in 1997.[15] In Britain, SmithKline Beecham and Glaxo-Wellcome stated clearly to the House of Lords Select Committee on Science and Technology that if use of their anti-infective products was restricted beyond a certain point then they would move their research investments to other therapeutic areas.[16]

Responsibility for action

The rapid rise in resistance has led to difficult and complex questions. Who decides what to do, and on what evidence does that body base its decision? Who has the responsibility for disseminating information to professionals and the public. What is the nature of the information, who provides it, in what form is it provided, and how are the decisions implemented? These questions must be answered. There is an incomplete understanding of the relation between resistance and clinical and microbiological failure in the community. This makes us unsure of both the urgency of the problem and how to precisely manage the situation.[17] Despite the multiplying problems and the gloomy prospects for their immediate solution, the fourway partnership of a vigorous pharmaceutical industry, physicians, academia, and healthcare providers is the

best hope for the future. Much also depends on the attitude of governments—we must hope that they can foster social, educational, economic, and regulatory environments that encourage innovation in all aspects of control of infectious disease.[18]

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Use of antimicrobial drugs in veterinary practice

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Shortly after antimicrobial drugs were developed they were used in veterinary medicine to treat mastitis in dairy cows.[1 2] Disease is inevitable in all animals, whether farm animals or pets, and healthy animals may also be carriers and asymptomatic excreters of pathogens. The use of antimicrobial drugs varies between species and may be influenced by husbandry and the pattern of trade in a particular class of animal.[3] Antimicrobial drugs are given to animals by injection (intravenously, intramuscularly, and subcutaneously), orally in food or water, topically on the skin, and by intramammary and intrauterine infusions. Antibiotics are easier to give to animals by injection, and the digestive system of ruminants often renders oral antimicrobial drugs ineffective.

Summary points

- Antimicrobial drugs are used by veterinary surgeons for pet and farm animals in their care
- Veterinary use of antimicrobial agents is for therapeutic and prophylactic reasons, and they may be used to promote growth
- Antimicrobial agents are more often given intramuscularly to animals compared with humans
- They are also given to groups of animals in food or water
- Antimicrobial drugs may be given to animals reared for food only if they are licensed for that purpose
- Withdrawal periods are specified for antimicrobial drugs used in animals reared for food, and there is regular monitoring for drug residues

Treatment of farm animals

The prevalence of pathogens on farms depends on many factors, not least the type of husbandry, the environmental pressure on a farm, and the standard of stockmanship. The most commonly used antimicrobial drugs in animals reared for food are from five major classes: β lactams, tetracyclines, aminoglycosides, macrolides, and sulphonamides. In addition, quinolones have been available in some European countries for more than 20 years.[4] The discovery of third generation fluoroquinolones with a broader spectrum of activity has led to interest in their use in animals.[5 6]

Whereas the treatment of bacterial disease in humans and their pet animals is invariably directed at a patient, the treatment of animals reared for food, especially pigs and poultry, is generally directed at groups or herds of animals.[3] The main reasons to use antimicrobial drugs in animals are for treatment and prophylaxis or strategic treatment. In farm animals antimicrobial agents are also used to enhance performance by increasing feed conversion, growth