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Antimicrobial resistance*

WHO SCIENTIFIC WORKING GROUP[1]

The development of antimicrobial drugs, and particularly of antibiotics, has played a considerable role in substantially reducing the morbidity and mortality rates of many infectious diseases. However, the fact that bacteria can develop resistance to antibiotics has produced a situation where antimicrobial agents are losing their effectiveness because of the spread and persistence of drug-resistant organisms. To combat this, more and more antibiotics with increased therapeutic and prophylactic action will need to be developed.

This article is concerned with antibiotic resistance in bacteria which are pathogenic to man and animals. The historical background is given, as well as some information on the present situation and trends of antibiotic resistance to certain bacteria in different parts of the world. Considerable concern is raised over the use of antibiotics in man and animals. It is stated that antibiotic resistance in human pathogens is widely attributed to the "misuse" of antibiotics for treatment and prophylaxis in man and to the administration of antibiotics to animals for a variety of purposes (growth promotion, prophylaxis, or therapy), leading to the accumulation of resistant bacteria in their flora. Factors favouring the development of resistance are discussed.

Constant exposure of the bacterial flora in man and animals to antibiotics[a] has favoured the selection of antibiotic-resistant organisms and their wide dissemination in the human population, and the transfer of resistance genes between bacterial strains has widened the range of resistant organisms. This exposure is due to the use of antibiotics in human and veterinary medicine for the treatment or prevention of infections, in animal husbandry for the promotion of growth, and in various other ways for disease control in agriculture. The use of antibiotics in fields other than human medicine has been reviewed in previous WHO publications (*1-3*), and various proposals were made to limit the impact on bacteria pathogenic for man. It was accepted in these reports that the administration of antibiotics to the human population was a major cause for the accumulation of resistant bacteria, but measures to limit this usage were not discussed in detail.

The Scientific Working Group therefore concentrated its attention on the use of antibiotics in human medicine, and (1) considered what types of antibiotic use were inappropriate, (2) provided general guidelines for the appropriate use of antibiotics, and (3) suggested measures to improve the quality of antibiotic treatment. The Group also reviewed briefly the operation of restrictions on the use of antibiotics in animal husbandry and veterinary medicine and suggested improvements in their clinical use in animals.[b]

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[1] This article is based on part of the report of the WHO Scientific Working Group on Antimicrobial Resistance, which met in Geneva from 23 to 27 November 1981. The remainder of this report appears as a Memorandum on pages 423-433. The participants at this meeting are listed on page 392. A French translation of this article will appear in a later issue of the *Bulletin*.

[a] This term is used to include both antibiotics and synthetic chemicals with a similar selective antibacterial activity.

[b] The present article describes the historical background and present situation of antibiotic resistance in bacteria pathogenic to man, and the use and misuse of antibiotics in man and animals. The remaining topics from the Scientific Working Group's report appear in the Memorandum on pages 423-433.

ANTIBIOTIC RESISTANCE IN BACTERIA PATHOGENIC FOR MAN

Historical background

The first clinically serious consequence of antibiotic resistance to attract considerable attention was the wide dissemination in hospitals of strains of *Staphylococcus aureus* that were resistant to penicillin by virtue of their ability to form an antibiotic-destroying enzyme, penicillinase-(β-lactamase), and subsequently acquired resistance to several other chemically unrelated antibiotics. Some but by no means all of these other resistances were also mediated by the production of antibiotic-destroying enzymes. From the early 1950s onwards, these so-called "multiple-antibiotic resistant" staphylococci became endemically established in most hospitals throughout the world and were for some years the main cause of hospital-acquired septic infection. Many of the genetic determinants for resistance in these strains of *S. aureus* were extrachromosomal pieces of DNA, called plasmids (R factors), most of which carried the code for resistance to only one antibiotic or group of related antibiotics; multiple-antibiotic resistance had thus arisen as a result of several genetic events. The wide dissemination of multiple-antibiotic resistant strains was due to their spread from patient to patient in populations exposed to several of the antibiotics to which these strains were resistant.

In the early 1950s it was also observed (*4*) that certain Gram-negative organisms, notably strains of *Klebsiella*, *Proteus* and *Pseudomonas aeruginosa* that were naturally insusceptible to currently available antibiotics, were assuming a greater importance as causes of septic infections in hospitals. This process continued into the 1960s, by which time a number of other Gram-negative organisms—some of them derived from the natural environment—had been added to the list of important "hospital" pathogens, and the established Gram-negative pathogens were acquiring additional resistances to more recently introduced antibiotics. Resistance in Gram-negative organisms differed from that in *S. aureus* in that (1) it was in many cases determined by resistance (R) plasmids that coded for resistance to several unrelated antibiotics which could be easily transferred as a single genetic event between bacterial strains, and (2) the R plasmids were transferable not only between members of a single species but also between members of many genera of Gram-negative bacilli and cocci.

As a result of these changes, by the early 1970s the Gram-negative bacilli replaced *S. aureus* as the most important cause of hospital-acquired septic infections and, at least in a number of developed countries, widespread endemic prevalences of multiple-antibiotic resistant strains of *S. aureus* became uncommon (*5*).

The serious clinical consequences of antibiotic resistance appeared considerably later in the general population. Penicillin resistance in *S. aureus*, which had become common in hospital-acquired strains by 1950, did not reach a similar frequency in the outside population for another ten years or more; and, apart from some spread of exceptionally virulent hospital strains in the years 1955–60, multiple-antibiotic resistant strains have seldom been very prevalent in the general population. Multiple-antibiotic resistant strains of group-A streptococci became very common in some countries in the 1960s, but the clinical significance was limited by their continued sensitivity to penicillin.

A more serious situation developed when antibiotic resistance became a common cause of treatment failure in diarrhoeal and enteric diseases. Plasmid-determined transferable resistance was detected with increasing frequency among shigellae and salmonellae during the 1960s, and a few years later there were widespread epidemics of severe bacillary dysentery and of typhoid fever caused by strains that were resistant to several antibiotics (*3*), including the agents of choice for the treatment of these infections. In 1974, a plasmid-determined β-lactamase (TEM 1), identical with that found in many enterobacteria,

appeared in *Haemophilus influenzae* (*6–8*). In 1976 plasmid-borne, enzyme-mediated chloramphenicol resistance in *H. influenzae* was discovered (*9*) and the emergence of multiple-resistant strains carrying resistance to ampicillin, chloramphenicol and tetracycline (antibiotics of first choice for the treatment of infections) has been reported more recently (*10*, *11*).

For most of the organisms so far discussed, the number of carriers greatly exceeds the number of clinical infections, so that exposure of the whole population to antibiotics might be expected to favour the development of resistance. With tubercle bacilli, and until recently gonococci, the situation has been different: clinically infected persons are the main source of the organism, and high case-finding rates and the elimination of treatment failures thus assume exceptional importance in controlling resistance. The resistance of gonococci to penicillin increased slowly over many years, but treatment failure could be prevented by suitably increased doses of penicillin. This resistance was chromosomal and non-enzymic; in 1976, however, plasmids determining the production of the TEM 1 β-lactamase appeared in gonococci (*12–15*), which then exhibited total resistance to penicillin. (For reviews of the development of resistance in gonococci, see references *16–18*).

The present situation

The Working Group reviewed the prevalence of antibiotic resistance in man since the last WHO report on this subject (*3*). In this report it was noted that information about the distribution of such prevalence was patchy, being particularly deficient in the developing countries and often difficult to interpret because the methods used for testing the susceptibility to antibiotics were often not standardized. The present Working Group, after studying the information now available, concluded that, although the frequency of resistance in individual pathogens and the patterns of multiple resistance varied considerably between countries and often in different parts of the same country, the situation had in a number of respects worsened in the last few years.

In most developed countries, endemic hospital infection caused by multiple-antibiotic resistant strains of *S. aureus* continued to present less urgent problems than infections with certain Gram-negative bacilli. There was, however, recent evidence from Australia, the United Kingdom, and the USA of an increasing number of local outbreaks of infection caused by staphylococcal strains with a very broad spectrum of resistance to antibiotics, including meticillin and the aminoglycosides (*19–24*). Some reports from developing countries also indicate that strains of *S. aureus* resistant to locally available antibiotics are still a major cause of serious infections in hospitals.

The Working Group noted that there had been a further dissemination of strains of gonococci and of *H. influenzae* that possessed the TEM 1 β-lactamase, and that an additional type of β-lactamase had been reported in *H. influenzae* (*25*), that multiple-antibiotic resistant strains of the latter organism had been found (*26*, *27*), and that *H. influenzae* type b resistant to both ampicillin and chloramphenicol caused an outbreak of meningitis with three deaths in an orphanage in Thailand (*28*). Clinical failure in the ampicillin treatment of meningitis (caused by *H. influenzae*) has now been reported with considerable frequency. In recent years, penicillinase-forming gonococci have shown considerable spread worldwide (*29–31*), and several different β-lactamase plasmids have been identified among them (*32*). A penicillinase-producing gonococcus with a high level of resistance to spectinomycin has been described (*33*, *34*), but such strains appear to be still uncommon. Decreased susceptibility to the newer cephalosporins has also been described (*35*). Penicillin-resistant strains of pneumococci had become locally prevalent in South Africa (*36*), where they caused treatment failure and the death of infants. This resistance was non-

enzymatic and chromosomally determined, and was often accompanied by resistance to other antibiotics, including chloramphenicol and tetracycline. Pneumococci with clinically significant levels of penicillin resistance were also common in Papua New Guinea (*37*) and had been found occasionally elsewhere. Antibiotic resistance in *Bacteroides* had been on the increase for some years, and a transferable R factor for clindamycin had now been reported (*38*). Until quite recently cholera vibrios with R factors coding for multiple-antibiotic resistance were seen infrequently. Extensive epidemics of cholera have now been reported from the United Republic of Tanzania (*39*) and Bangladesh (*40*), in which an initially sensitive strain became predominantly resistant within a few months; the R factors responsible for this indicated resistance to several antibiotics, including tetracycline, the current drug of first choice for treatment.

Clinically significant resistances may be mediated by antibiotic-inactivating enzymes or by other resistance mechanisms; and they may be determined genetically on a plasmid or on the chromosome. Multiple-antibiotic resistance may be specified by a single plasmid or by a number of distinct resistance genes, some on plasmids and others on the chromosome. Evidence continues to accumulate of the genetic adaptability of many of the R plasmids (*41*). They may be self-transferable or may be accompanied by other plasmids that mobilize them for transfer. Many of them can move as distinct genetic elements called "transposons" from a plasmid to the chromosome, or to a phage. This permits modification of the pattern of resistance conferred, and the bringing together of resistance determinants and transfer mechanisms appropriate for a fresh host bacterium. Transposition may also lead to the association on the same plasmid of resistance determinants and genes for colonization, toxin production and other so-called "virulence factors".

When an infection is treated with an antibiotic to which the causal agent is initially susceptible, resistance may appear as a result of the transfer of an R plasmid or its transposable resistance determinant from another organism in the patient's flora (*42*). Numerous instances have been reported in which an R plasmid, after being introduced into a hospital in one Gram-negative organism, is subsequently transferred to another strain of the same or a different species, which then spreads extensively among the patients.

Preliminary evidence from surveillance data presented to the Working Group indicated that serious consequences of antibiotic resistance were no longer confined to urban hospitals but were being encountered increasingly in the general population. It also showed a greater prevalence in developing countries of resistance to easily available antibiotics, such as ampicillin, tetracycline, chloramphenicol and sulfonamides, than is known to occur in developed countries. Surveys of β-lactamases in enterobacteria from developing countries revealed a correspondingly greater variety of types, and of instances of multiple β-lactamases in the same isolate. Patients in developing countries were thus in a situation in which only the cheaper antibiotics were available to them and these agents were becoming progressively less effective. In the absence of local laboratory support and of up-to-date information about the prevalence of resistance, the choice of an appropriate antibiotic was becoming a gamble against worsening odds. It was clear that the uncontrolled importation of the expensive "new" antibiotics now available in developed countries, even if economically feasible, would cause only a temporary improvement in the situation.

Consequences of widespread antibiotic resistance

Antibiotic resistance limits the therapeutic efficacy of antibiotics against pathogens that are initially resistant to them or that acquire a transferable resistance from another organism in the patient's flora during treatment.

Widespread use of antibiotics encourages the overgrowth of other resistant bacteria in the flora of the treated patient. This process ("superinfection") may have important

clinical consequences, especially in hospital patients, many of whom have an increased susceptibility to infection by organisms that seldom invade healthy persons. In such patients these organisms are frequently responsible for respiratory or septicaemic complications that may be a greater hazard than the infection for which antibiotic treatment was given.

Wide spectra of antibiotic resistance in prevalent bacteria seriously limit the possibility of controlling the further spread of resistant organisms by the selective use of antibiotics.

THE USE OF ANTIBIOTICS IN MAN

Antibiotic resistance in human pathogens is widely attributed to the misuse of antibiotics for treatment or prophylaxis in man. Before making proposals for the more rational use of antibiotics, the Working Group considered the nature and extent of this misuse.

Social pressures favouring the excessive or inappropriate use of antibiotics

The decision to use an antibiotic may be influenced by social pressures that outweigh the medical indications (*43*). When antibiotics are available on the open market, the attitude of the patient and his family is decisive. The desire to do the best for the patient in a situation of fear and anxiety, coupled with public ignorance about the efficacy of antibiotics in particular diseases, encourages unnecessary and sometimes damaging treatment. Poor choice of antibiotics is encouraged by the bewildering multiplicity of names under which they are marketed, by the promotion in developing countries of antibiotics that are obsolete or in other ways inappropriate (*44*), notably unjustified fixed combinations of drugs, and by misleading advertising material.

Even when the physician is the only or the preferred source of antibiotics, he may find it difficult to resist pressure from the patient or the family. He is also motivated to do the best for the patient; unless he has a good knowledge of the management of microbial infections, of antibiotic action, and of the current local state of susceptibility of pathogens to antibiotics, he may be tempted to give unnecessary treatment. He may feel that even if an antibiotic is unlikely to do good it will do no harm, or he may attempt to ensure the efficacy of treatment by giving larger doses or more prolonged treatment than is necessary. For similar reasons he may employ broad-spectrum agents or antibiotic combinations as a routine to cover the possibility of infection by unusual organisms. All of these practices will be particularly difficult to resist if laboratory and other diagnostic support are not available.

The misuse of antibiotics

In hospital practice

Recent surveys in North America and the United Kingdom indicate that about one-quarter of all patients receive one or more courses of antibiotic while in hospital (*45–51*), though the rates vary somewhat between hospitals and even more between hospital departments. In the United Kingdom, some 20% of all patients in general hospitals on any one day are receiving antibiotics; about one-third of all antibiotic courses are given for prophylaxis (*50*). A similar situation exists in many other advanced countries.

Several workers have claimed that the administration of antibiotics was irrational or inappropriate in a considerable proportion of patients, variously estimated at 38–66% (*45–47, 51–53*). In a retrospective Canadian survey in 1976 (*46*), only 41% of all courses of antibiotics were considered to be "rational", 38% were "irrational", and 22% were "questionable".

Antibiotic treatment. Antibiotic therapy is inappropriate if it is unnecessary, or if the agent is unsuitable or given in the wrong dosage. This may be attributable in varying degrees to (1) poor clinical decision-taking, (2) absence of or failure to make use of laboratory support, (3) ignorance of the types of bacteria most likely to cause particular infections, (4) inadequate information about the current susceptibility of the suspected causal agent to antibiotics, and (5) ignorance about the pharmacokinetic properties of particular antibiotics.

An example of the analysis of antibiotic use for treatment is shown in an investigation carried out in a London hospital which had a well run laboratory service. Antibiotic use was monitored at the time of administration by an independent team of experts; it was concluded (*51*) that in this hospital the most frequent form of therapeutic misuse was the giving of unnecessary courses of antibiotics. The most common reasons for antibiotic treatment were infections or suspected infections of the lower respiratory tract (39%) and of the urinary tract (20%). Reconsideration of the clinical, bacteriological and radiological findings led to the conclusion that there was no significant evidence of pneumonia in 40% of the patients treated for this disease. Nearly 40% of all patients aged more than 80 years who were admitted to the hospital received antibiotics for "chest infection". In patients given antibiotics for suspected infection of the urinary tract, no justification could be found for the treatment in 49%. Irrational treatment occurred by (1) giving an antibiotic, or failing to stop treatment, when the initial urine specimen showed no evidence of bacteriuria (33%), and (2) treating bacteriuria in the absence of relevant symptoms in patients on continuous catheterization or when the only evidence of infection was a "significant" number of bacteria reported in a single routine midstream urine specimen (16%). There was thus very considerable overuse of antibiotics attributable to poor clinical decision-taking, notably inadequate diagnostic criteria for infection and uncritical interpretation of chest X-ray films and laboratory reports. In this hospital the choice of antibiotics for infections confirmed by laboratory examination was in general good, but there was disturbing evidence that, in the absence of a significant laboratory report, physicians had little idea of the most likely microbial cause of an infection and its probable susceptibility to antibiotics, and so they often gave inappropriate treatment.

Antibiotic prophylaxis. The widespread use of antibiotics prophylactically has undoubtedly contributed greatly to the spread of resistant organisms in hospitals. On the other hand, antibiotic prophylaxis significantly reduces the risk of infection after certain types of surgical operation, notably those of the intestinal or urogenital tract (*54*), and its use in these circumstances must be considered justifiable. Misuse can be defined as using prophylaxis when there is no clear evidence that this will prevent serious clinical infection, or using a prophylactic regimen that unnecessarily favours the selection of resistant organisms. Guidelines for the appropriate prophylactic use of antibiotics are given in the Annex of the second part of this report, which is published as a Memorandum (see pages 432–433).

In primary health care

There is little quantitative information about antibiotic-prescribing habits in primary health care. What is available comes from the developed countries and suggests consider-

able misuse in the treatment of mild upper-respiratory-tract infections, febrile episodes, and diarrhoea. In one survey in the USA (*55*), nearly 60% of physicians used antibiotics to treat the common cold. Until quite recently, considerable quantities of chloramphenicol continued to be used mainly by older physicians and in rural areas for the treatment of infections of the upper respiratory tract, despite repeated official condemnation of the practice (*56*, *57*). Tetracycline was also widely used for respiratory-tract infections in children (*58*). There has been considerable overuse of tetracycline in the United Kingdom for many years; treatment of patients with relapses of chronic bronchitis using this drug, which is now believed to be ineffective in such cases, accounted for much of this abuse. There are now few common diseases in non-tropical areas in which tetracycline is the drug of first choice (*59*), but it continues to be widely used in general practice in the United Kingdom. This wide use of tetracycline has been identified as the main cause for the prevalence of tetracycline-resistant strains of *Escherichia coli*, many of which were also ampicillin resistant, in the faeces of members of the general population in Bristol (*60*).

The use of antibiotics to treat suspected infections of the urinary tract in women is certainly excessive. Treatment is commonly given to all women with frequency and dysuria despite the fact that no more than one-half of them have significant bacteriuria. The evidence that very short courses of antibiotic are as effective as longer courses in uncomplicated urinary-tract infection (*61–63*) appears to have had little impact so far in primary health care.

In highly affluent countries there has recently been a tendency to use new high-cost proprietary agents, such as oral cephalosporins and derivatives of ampicillin, though these are seldom more effective than cheaper alternatives.

Evidence from developing countries that was presented to the Working Group indicated that the total consumption of antibiotics was often enormous, but there was little precise information about the purposes for which they had been given. In most such countries, antibiotics are freely available on the open market and are often taken without medical advice. The unexpected finding of widespread trimethoprim resistance in *E. coli* strains in Mexico is a probable consequence of uncontrolled use (*64*). Chloramphenicol is widely used in developing countries for the treatment of diarrhoea, which is often attributed to typhoid fever without bacteriological evidence.

The prophylactic use of antibiotics on individual patients outside hospital does not appear to make a material contribution to total antibiotic usage, and complications attributable to the development of resistant organisms in such patients are infrequent. Mass prophylaxis with narrow-spectrum agents such as penicillin, e.g., for the control of group-A streptococcal infection in institutions, though not always very effective, appears to have had few untoward consequences. On the other hand, mass prophylaxis with broad-spectrum antibiotics, e.g., tetracycline, for the control of diarrhoeal diseases is likely to contribute materially to the spread of resistant strains.

ANTIBIOTIC USAGE IN ANIMALS

It is well recognized that the administration of antibiotics to animals for any purpose (growth promotion, prophylaxis, or therapy) leads to the accumulation of resistant bacteria in their flora. Antibiotics have been used for all these purposes for many years and it is difficult to separate the contribution made by each one to the pool of resistant organisms in animals. The danger of this pool is due to: (1) antibiotic-resistant pathogens common to animals and man may reach man by cross-infection, and (2) antibiotic-resistant, non-pathogenic organisms in an animal may be passed to and colonize man,

thereby carrying R plasmids into the human environment. These R plasmids may subsequently be transferred to human pathogens or to indigenous flora in the human body.

Antibiotic-resistant animal pathogens

Not all animal pathogens cause disease in man. For instance, pathogenic animal staphylococci (in cattle, poultry and dogs) are mainly distinct from those found in man. Antibiotic-resistant strains which occur in animals, e.g., in staphylococcal mastitis of cows, do not therefore present a problem to man. In contrast, many of the enteric Gram-negative organisms (e.g., *Salmonella* species and some strains of *Campylobacter*) infect man as well as animals. The larger proportion of salmonella infections in man are derived from eating contaminated meat and therefore, indirectly, from animal sources. Wherever strains of antibiotic-resistant salmonellae arise in animals, they eventually reach man (*65–67*).

The frequency of antibiotic resistance in various salmonella serotypes varies from country to country. A survey of isolates in the United Kingdom from 1958 to 1979 (*68*) revealed that, while resistance to sulfonamides and streptomycin occurred in up to 50% of isolates, multiple-resistance was rarely experienced in most serotypes. Where this did arise, it occurred almost exclusively in one serotype, namely *Salmonella typhimurium*, and then only in a few phage types. In the 1960s multiple resistance was experienced in *S. typhimurium* phage type 29 (*69*) and, since 1977, principally in phage types 193 and 204 (*66, 70*). Available evidence indicates that the selection of these multiple-resistant phage types was due to the use of antibiotics for treatment rather than for growth promotion. Since epidemics by multiple-resistant strains have been relatively few, it may be deduced that the circumstances precipitating the genetic events leading to multiple resistance must have been rare in the United Kingdom. Nevertheless, once selected, these strains spread rapidly over a wide area as a result of transport of infected calves, which occurs frequently in the calf industry, and human infections then follow.

Higher levels of antibiotic resistance have been experienced in the USA. A survey of animal salmonellae in north-eastern USA (*71*) revealed that the majority of *S. typhimurium*, *S. saint-paul*, and *S. heidelberg* were resistant to three or more antibiotics, including ampicillin, kanamycin and tetracycline, in addition to sulfonamides and streptomycin. Several authors (*65*) attribute this resistance, at least in part, to the continuing widespread use of antibiotics as feed additives, and this may be a significant cause since antibiotics are often used in the USA at levels considerably higher than those recommended under EEC (European Economic Community) legislation for growth promotion.

The level of multiple resistance of salmonellae in the Netherlands falls between those experienced in the United Kingdom and the USA. Multiple resistance is found in a wider range of serotypes than in the United Kingdom, including *S. dublin* and *S. panama*, in addition to *S. typhimurium*. After a ban on the use of tetracycline in animal feeds in 1974, the incidence of tetracycline resistance in *S. typhimurium* of porcine origin dropped from about 90% in 1974 to 34% in 1980. The incidence of resistance in human strains concurrently decreased from about 80% in 1974 to 25% in 1980. These changes suggest strongly that, in the Netherlands, the use of tetracycline for growth promotion in animals played a part in the emergence of drug-resistant salmonellae in pigs and their subsequent transfer to humans (*72–74*).

Thus it is clear that marked differences in antibiotic resistance in salmonellae have been experienced in different countries, which may reflect differences in the use of antibiotics, methods of animal husbandry, density of animal populations, and local topographical factors.

Antibiotic resistance in the normal gut flora of animals

The antibiotic resistance status of the normal gut flora of domestic animals is somewhat different. The oral administration of antibiotics, which is the common route for therapy, prophylaxis and growth promotion, invariably favours the selection of resistant strains, particularly from among the Enterobacteriaceae and other Gram-negative bacilli, which then become predominant.

Evidence is now available confirming that these resistant strains reach man via the food chain. The most definitive work has been done with *E. coli*. The highest incidences of antibiotic-resistant *E. coli* are found in calves (*75*), pigs (*76*) and poultry (*77*) species in situations where antibiotics have been widely used. Under commercial slaughter conditions, contamination of carcasses on the slaughter line regularly occurs with strains of *E. coli* of the same O-serotypes and antibiotic-resistance patterns as those found in the gut of the animals being slaughtered (*77–79*). These strains are present in human food through such meat and meat products (*77*), subsequently colonize the gut of man (*80*) and may be detected among the dominant gut flora for up to 10 days. No evidence has been presented so far to indicate that antibiotic-resistant *E. coli* of animal origin can cause clinical disease in man, such as urinary tract infections, but they obviously form a rich source of R plasmids that are potentially transferable to a range of Gram-negative bacilli, pathogenic for man, which may be present in the gut.

The use of antibiotics to prevent food spoilage, which was once a common practice, is now much less widespread because the high frequency of antibiotic resistance in contaminating organisms limits its efficacy. It is probably no longer an important consideration.

Antibiotic usage for growth promotion

The Working Group noted that an earlier WHO report (*1*) had recommended that no antibiotic that was of therapeutic value in man, or showed cross-resistance with such an antibiotic, should be used for animal growth promotion. It is now felt that the implementation of this policy would have only a limited effect on the prevalence of resistant bacteria, unless the use of the same antibiotic for prophylaxis and treatment in animals was also restricted.

Prophylactic and therapeutic use of antibiotics

It is not practicable to distinguish between the prophylactic and the therapeutic use of antibiotics in current veterinary practice because antibiotics are usually given not only to sick animals but also to their healthy contacts. While recognizing the value of antibiotics for the treatment of bacterial diseases in animals, the Working Group was of the opinion that governments and professional bodies should exert greater control over the circumstances in which certain agents are administered to animals (see second part of this report, page 430).

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