



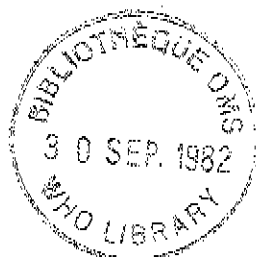
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## ANTIMICROBIAL RESISTANCE

Report of a Scientific Working Group  
Geneva, 23-27 November 1981





ANTIMICROBIAL RESISTANCE REPORT OF SCIENTIFIC WORKING GROUP

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*Drug resistance, Microbial -  
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A WHO Scientific Working Group on antimicrobial resistance met in Geneva from 23-27 November 1981. Dr I. D. Ladnyi, Assistant Director-General of the World Health Organization, opened the meeting on behalf of the Director-General.

## 1. INTRODUCTION

The constant exposure of the body flora of man and animals to antibiotics<sup>a</sup> has led to the selection and wide dissemination of antibiotic-resistant bacteria, and the transfer of resistance genes between strains in a selective environment has widened the range of bacteria in which resistances are prevalent.

This exposure to antibiotics is a consequence of their use (1) in human and veterinary medicine for the treatment or prevention of disease (2) in animal husbandry for the promotion of growth or (3) in various other ways for disease control in agriculture. The use of antibiotics other than in human medicine has been reviewed in previous WHO publications, 1, 2, 3 and various proposals were made to limit its impact on bacteria pathogenic for man. It was accepted in these publications that the administration of antibiotics to the human population was a major cause of the accumulation of resistant bacteria in its flora, but measures designed to limit this usage were not discussed in detail.

The Working Group decided, therefore, to concentrate its attention on the use of antibiotics in human medicine, and to (1) consider what types of antibiotic use were inappropriate, (2) provide general guidelines for the appropriate use of antibiotics, and (3) suggest measures to improve the quality of antibiotic treatment. The Group also decided to review briefly the operation of restriction on the use of antibiotics in animal husbandry and veterinary medicine and to suggest improvements in their clinical use in animals.

## 2. ANTIBIOTIC RESISTANCE IN BACTERIA PATHOGENIC FOR MAN

### 2.1 Historical background

The first clinically serious consequences of antibiotic resistance to attract widespread 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- ( $\beta$ -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 coded 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 attributable to their spread from patient to patient in populations exposed to several of the antibiotics to which they were resistant.

In the early 1950s it was also observed<sup>4</sup> that certain gram-negative organisms, notably strains of Klebsiella, Proteus and Pseudomonas aeruginosa that were naturally insusceptible to currently available antibiotics, were assuming a great 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 R plasmids that coded for resistance to several unrelated antibiotics and which

<sup>a</sup> This term is used to include both antibiotics and synthetic chemicals with a similar selective antibacterial activity.

could be easily transferred as a single genetic event between bacterial strains and (2) 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, the gram-negative bacilli had by the early 1970s 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 had become rather uncommon.<sup>5</sup>

The serious clinical consequences of antibiotic resistance became apparent considerably later in the general population than in hospitals. 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 "overflow" of exceptionally virulent hospital strains in the years 1955-1960, 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,<sup>3</sup> including the agents of choice for the treatment of these infections. In 1974, a plasmid-determined  $\beta$ -lactamase (TEM 1) identical with that found in many enterobacteria appeared in Haemophilus influenzae.<sup>6,7,8</sup> In 1976 plasmid borne enzyme-mediated chloramphenicol resistance in H. influenzae was discovered<sup>9</sup> and emergence of multiple resistant strains carrying resistance to ampicillin, chloramphenicol and tetracycline (antibiotics of first choice for the therapy of of infections) have been reported since.<sup>10,11</sup>

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 select for resistance. With tubercle bacilli, and until recently gonococci, the situation is different: clinically infected persons are the main source of the organism, and high-case finding rates and the elimination of treatment-failure 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  $\beta$ -lactamase appeared in gonococci,<sup>12,13,14,15</sup> which then exhibited total resistance to penicillin. (For reviews of the development of resistance in gonococci, see references 16,17,18.)

## 2.2 The present situation

The Working Group reviewed the prevalence of antibiotic resistance in man since the last WHO Report on this subject.<sup>3</sup> In this report it was noted that information about its distribution was patchy; it was particularly deficient in developing countries and was often difficult to interpret because the methods used for testing susceptibility to antibiotics were often not standardized. The present Working Group considered the information now available, and 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 members of the gram-negative bacilli. There was, however, recent evidence from Britain, the USA and Australia of an increasing number of local outbreaks of infection caused by staphylococcal strains with a very broad spectrum of resistance to antibiotics, including

methicillin and aminoglycosides.<sup>19, 20, 21, 22, 23, 24</sup> Some reports from developing countries indicated that strains of *S. aureus* resistant to locally available antibiotics were 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  $\beta$ -lactamase, and that an additional type of  $\beta$ -lactamase had been reported in *H. influenzae*,<sup>25</sup> that multiple antibiotic resistant strains of the latter organism had been found,<sup>26, 27</sup> and that *H. influenzae* type b resistant to both ampicillin and chloramphenicol had caused an outbreak of meningitis with three deaths in an orphanage in Thailand.<sup>28</sup> Clinical failure in the treatment of meningitis caused by *H. influenzae* with ampicillin has now been reported with considerable frequency. In recent years, penicillinase-forming gonococci have shown considerable spread worldwide,<sup>29, 30, 31</sup> and several different  $\beta$ -lactamase plasmids have been identified among them.<sup>32</sup> A penicillinase-producing gonococcus with a high level of resistance to spectinomycin has been described,<sup>33, 34</sup> but such strains appear to be still uncommon. Decreased susceptibility to the newer cephalosporins has also been described.<sup>35</sup> Penicillin resistant strains of pneumococci had become locally prevalent in South Africa,<sup>36</sup> 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<sup>37</sup> and had been found occasionally elsewhere. Antibiotic resistance in *Bacteroides* has been on the increase for some years, and a transferable R factor for clindamycin had now been reported.<sup>38</sup> 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 Tanzania<sup>39</sup> and Bangladesh<sup>40</sup> in which an initially sensitive strain became predominantly resistant within a few months; the R factors responsible for this specified resistance for 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.<sup>41</sup> 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.<sup>42</sup> 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  $\beta$ -lactamases in enterobacteria from developing countries revealed a correspondingly greater variety of types, and of instances of multiple  $\beta$ -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.

### 2.3 Consequences of widespread antibiotic resistance

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

2. 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.

3. 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.

### 3. 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.

#### 3.1 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.<sup>43</sup> 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, encourage 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,<sup>44</sup> 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.

#### 3.2 The misuse of antibiotics

##### 3.2.1 In hospital practice

Recent surveys in North America and Britain indicate that about one-quarter of all patients receive one or more courses of antibiotic whilst in hospital,<sup>45,46,47,48,49,50</sup> though the rates vary somewhat between hospitals and even more between hospital departments. In Britain, some 20% of all patients in general hospitals on any one day are receiving antibiotics. About one-third of all courses of antibiotic are given for prophylaxis.<sup>50</sup> 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%.<sup>45,46,47,51,52,53</sup> In a retrospective Canadian survey in 1976,<sup>46</sup> only 41% of all courses of antibiotics were considered to be "rational"; 38% were "irrational", and 22% were "questionable".

### 3.2.1.1 Antibiotic treatment

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

An example of the analysis of antibiotic use for treatment is shown in the investigation carried out in a London hospital provided with a well run laboratory service. Antibiotic use was monitored at the time of administration by an independent team of experts; it was concluded<sup>51</sup> that in this hospital the most frequent form of therapeutic misuse was giving unnecessary courses of antibiotics. The most common reasons for giving antibiotic treatment were infections and 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 was: (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 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 often gave inappropriate treatment.

### 3.2.1.2 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 certain types of surgical operation, notably those of the intestinal or urogenital tract,<sup>54</sup> 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 selects resistant organisms. Guidelines for the appropriate prophylactic use of antibiotics are given in the Annex.

### 3.2.2 In primary health care

There is little quantitative information about antibiotic-prescribing habits in primary health care, and this mainly concerns practice in developed countries. It suggests considerable misuse in the treatment of mild upper-respiratory-tract infections, febrile episodes and diarrhoea. In one survey in the USA,<sup>55</sup> 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.<sup>56,57</sup> Tetracycline was also widely used for respiratory-tract infections in children.<sup>58</sup> There has

been considerable overuse of tetracycline in Britain for many years; treatment of relapses in chronic bronchitis with this drug, in which it is now believed to be ineffective, accounted for much of this. There are now few common diseases in non-tropical areas in which tetracycline is the drug of first choice<sup>59</sup> but it continues to be widely used in family practice in Britain. Richmond & Linton<sup>60</sup> concluded that this was the main cause of 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 of Bristol.

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<sup>61,62,63</sup> appears to have had little impact yet in primary health care.

In highly affluent countries there has been a recent 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 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 habitually taken without medical advice. The unexpected finding of widespread trimethoprim resistance in E. coli strains in Mexico is a probable consequence of uncontrolled use.<sup>64</sup> 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 overgrowth of resistant organisms 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.

#### 4. 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 each of these purposes over many years and it is difficult to separate the contribution made by each to the pool of resistant organisms in animals. The importance of this pool to man are (1) that antibiotic resistant pathogens common to animals and man may reach man by cross-infection and (2) that antibiotic resistant, non-pathogenic organisms in the animal may be passed to and colonize man, thereby carrying R plasmids into the human environment. These R plasmids may be transferred subsequently to human pathogens or to his indigenous flora.

##### 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 spp. and/or 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. Where strains of antibiotic-resistant salmonellae arise in animals, they eventually reach man.<sup>65,66,67</sup>

The frequency of antibiotic resistance in various salmonella serotypes from animals varies from country to country. A survey of isolates in the United Kingdom from 1958-1979<sup>68</sup> revealed that whilst 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<sup>69</sup> and, since 1977, principally in phage types 193 and 204.<sup>66,70</sup> 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 must 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 by the movement of infected calves as frequently occurs in the calf industry and human infections followed.

Higher levels of antibiotic resistance have been experienced in the United States of America. A survey of animal salmonellae in the Northeastern United States of America<sup>71</sup> revealed that the majority of S. typhimurium, S. saint-paul, and S. heidelberg were resistant to three or more antibiotics; these included resistance to ampicillin, kanamycin and tetracycline, in addition to sulfonamides and streptomycin. Several authors<sup>65</sup> attribute this, 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 United States of America at levels considerably higher than those recommended under EEC legislation for growth promotion.

The level of multiple resistance of salmonellae in the Netherlands falls between that experienced in the United Kingdom and the United States of America. 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 suggested strongly that the use of tetracycline for growth promotion played a part in the emergence of drug resistant salmonellae in pigs and their subsequent transfer to humans in that country.<sup>72,73,74</sup>

Thus it is clear that marked differences in antibiotic resistance has been experienced in animal salmonellae in different countries. These may reflect the difference 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 (a common route for therapy, prophylaxis and growth promotion) invariably selects for a resistant strain 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 Escherichia coli. The highest incidence of antibiotic resistant E. coli are found in calves,<sup>75</sup> pigs<sup>76</sup> and poultry<sup>77</sup> species in which 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.<sup>77,78,79</sup> These strains reach the kitchen on meat and meat products,<sup>77</sup> subsequently colonize the gut of man<sup>80</sup> and may be detected in 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 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, once a common practice, is now much less widespread because the frequency of antibiotic resistance in contaminating organisms limits its efficacy. It is probably no longer an important consideration.

#### 4.1 Antibiotic usage for growth promotion

The Working Group noted that an earlier WHO Report<sup>1</sup> had recommended that no antibiotic that was of therapeutic value in man, or showed cross-resistance with such an antibiotic, should be used for growth-promotion. It was the opinion 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.

#### 4.2 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 section 7.5).

### 5. MEASURES TO CONTROL THE PREVALENCE OF ANTIBIOTIC-RESISTANT BACTERIA

#### 5.1 Surveillance of antibiotic resistance

##### 5.1.1 The need for surveillance

Without reliable information about the susceptibility to antibiotics of important human pathogens it is impossible to find solutions to the problems created by antibiotic resistance. Surveillance is necessary at several levels.

- (1) To improve the quality of antibiotic prescribing for the individual patient; information obtained in the course of routine investigations of patients can be used as a guide for the treatment of other patients with severe infections from whom the causative organism has not yet been isolated.
- (2) To influence the pattern of antibiotic usage in the individual hospital.
- (3) To assist national governments and international organizations in the formulation of policy for the supply of antibiotics and their use in man and animals; and to encourage responsible action by antibiotic manufacturers in the marketing and promotion of their products in individual countries.

In countries with well developed laboratory facilities a great deal of valuable information about antibiotic susceptibility accumulates in hospital records. In some hospitals this is analysed periodically for local use, and in a few countries a comprehensive scheme of surveillance, based on hospital-laboratory data, is in operation. At least one informal international collaborative study has been made of resistance in a range of important human pathogens.<sup>81</sup> To these sources of information must be added several special schemes for the surveillance of resistance in individual pathogens, notably enteric pathogens and gonococci, by WHO reference centres.

Information from these sources, though valuable, is far from comprehensive. Earlier WHO reports have urged the establishment of national and regional centres for the surveillance of resistance. The Working Group is of the opinion that such a scheme to cover a wide range of important human pathogens is now required.

## 5.1.2 Requirements for surveillance

### 5.1.2.1 Surveillance of resistance in human pathogens

The primary objective of this is to provide information about resistance in bacteria that are responsible for infection. The most readily available source of these is the clinical microbiology laboratory. There is thus a very strong case for basing a surveillance scheme on the selection of routine isolates from this source. Considerable advantages would be gained if the results of routine sensitivity tests performed in the local laboratories were made use of in this scheme. The role of the national centre would be (1) to organize the selection by participating laboratories of strains to be included in the surveillance, and (2) to ensure that laboratory testing is performed reliably and by a standard method. This arrangement would keep the work-load of the national centre within reasonable limits and would tend to upgrade the quality of routine sensitivity testing in local laboratories.

The scheme for selecting test results for inclusion in the surveillance would be standardized internationally. Sampling should be designed to include adequate numbers of each important pathogen from a series of specified clinical sources (e.g. blood, pus, faeces, significant urinary-tract infection) in each participating laboratory in an agreed period of time. Participating laboratories should be those in which standard methods are employed and are monitored, and are as representative as possible of major geographical regions of the country.

The national centre would specify acceptable methods for sensitivity testing according to the guidelines given in requirements for antimicrobial susceptibility tests<sup>a</sup> and would monitor their performance in participating laboratories regularly by a system of external quality control. It should also evaluate commercially available reagents (antibiotic discs, sensitivity-test media), and if necessary specify locally produced alternatives, and provide standard cultures for use in internal quality-control tests.

National centres would, in collaboration with WHO, specify which pathogenic bacteria should be tested and with which antibiotics. In the first instance it would be wise to limit surveillance to common and easily identifiable pathogens. Later, consideration might be given to extending surveillance to other organisms for which special testing methods are required.

The national laboratory centre should be prepared also to examine "problem" cultures from local laboratories, including strains thought to exhibit "new" resistances. It is not envisaged that such centres would undertake advanced research on the biochemical basis of resistance or on genetics; this should be left to academic centres in the same or other countries. However, they would be expected to make use of simple procedures for the recognition and characterization of R plasmids. They would have an important role in providing bacterial strains suspected of containing new or unusual R factors to specialized laboratories for further study.

### 5.1.2.2 Surveillance of resistance determinants in the general population

The Working Group considered that information about the prevalence of R plasmids in the bacterial flora of the general population would be of great assistance in forecasting future changes in the resistance of pathogens. A programme should therefore be initiated for national centres to monitor periodically the R factors in coliform bacteria in the faecal flora of healthy persons. Faecal samples would be plated by a serial-dilution method on, for example, MacConkey's medium. Replication on to plates of the same medium each containing one of a series of clinically important antibiotics would be used to enumerate colonies resistant to one or more antibiotics, and simple methods would be used to examine selected colonies for plasmid DNA.

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<sup>a</sup> Document WHO/BS/81.1337 Rev.1.

Information about the prevalence of R plasmids in the faecal flora is already available in many countries. The value of the proposed surveillance would therefore be greatest in countries - mainly in the developing world - in which this sort of information is otherwise unlikely to be obtained. However, information about the prevalence of R plasmids in faecal coliform bacteria is unlikely to be of much use unless the current situation in clinically important pathogens is also known.

#### 5.1.2.3 Analysis of surveillance data

The methods of analysis of the results of surveillance should be so chosen that they can conveniently be applied successively at each level - local, national and global. Hand or simple mechanical sorting may be appropriate to give early information locally but computer assistance will be essential for analysis of national and global data. Regional cooperation in the use of computer facilities might help to meet deficiencies in individual countries.

### 5.2 Control of antibiotic use in hospitals

#### 5.2.1 Hospital antibiotic policy

The decision to administer an antibiotic to a patient is taken by the doctor responsible for his care. In many hospitals, however, attempts have been made to influence such decisions by the development of an antibiotic policy, agreed upon by the heads of the main clinical departments in collaboration with the microbiologist. This policy may be given official status by the Hospital Infection Control Committee or Committee of Consultants. It may conveniently be codified in a booklet issued to all medical members of the staff. This booklet may begin by setting out basic information about the action of common antibiotics, dosage schedules, etc., but its main purpose is to outline agreed principles for the rational use of antibiotics (see Annex). It should not seek to establish rigid rules because (1) the ultimate right of the doctor to decide upon the treatment appropriate for his patient must be preserved; (2) alternative courses of action may be acceptable in the present state of knowledge, and (3) changing circumstances, e.g. increasing resistance in an important pathogen, introduction of a new antibiotic, may from time to time dictate modifications. Thus, the antibiotic policy should seek only to define limits within which antibiotic prescribing is justifiable and appropriate. The heads of individual departments may establish more precise rules, within these guidelines, to which junior doctors are expected to adhere.

##### 5.2.1.1 General strategy

The following is an outline of the general advice to be given in an antibiotic policy, which can be elaborated, with suitable examples, according to local circumstances. Antibiotic treatment should be based on precise clinical diagnosis of the nature of the infective process. It is directed against specific pathogens identified by culture or, when this is not practicable, inferred from the site and nature of the infection. The antibiotic is chosen, whenever possible, in accordance with results of susceptibility tests (with advice from the laboratory); when immediate treatment is deemed necessary, this should be reviewed when the test results become available. When no pathogens are isolated, a suitable antibiotic for the inferred pathogen should be chosen with reference to the known susceptibility of recent local isolates of the species. In all cases, an effective antibiotic with the narrowest possible spectrum of activity should be chosen. (For an elaboration of this strategy, and for indications for the prophylactic use of antibiotics see the Annex.)

##### 5.2.1.2 Tactical modifications of antibiotic policy

Decisions to restrict the use of individual antibiotics, for greater or lesser periods of time, have often been employed as elements in a hospital antibiotic policy. The ultimate measure, withdrawal of all or nearly all antibiotics, was successful in controlling one local outbreak of surgical wound infection caused by a multiple-antibiotic resistant klebsiella infection.<sup>82</sup> Less stringent measures of selective restriction have been practised, often for long periods of time. This restriction may be practised to minimize the use of antibiotics

that are useful for the treatment of serious infections, so delaying the appearance of resistance to them ("keeping antibiotics in reserve"). Other justifiable grounds for restricting the use of particular agents include: high cost, particularly if equally effective alternatives exist; frequency of toxic reactions; and a tendency to disturb the natural flora of the patient. Temporary restriction of a single antibiotic, e.g. carbenicillin,<sup>83</sup> has on occasion resulted in the disappearance of organisms resistant to it from a hospital, but such a satisfactory outcome cannot always be expected, particularly when the organism is resistant to other antibiotics that continue to be used.

Restrictive policies can be used effectively only when close surveillance of resistance in the hospital is practised. Provision must also be made for the release of the restricted agents under exceptional circumstances by "requiring justifications"<sup>84</sup> for this to an outside authority, e.g. the infection-control officer or the infectious-disease physician. Another option is the release of the antibiotic if the patient is transferred to an isolation unit.

#### 5.2.1.3 Improving the quality of antibiotic prescribing

It is generally easy to obtain the agreement of senior hospital staff to establish a policy for antibiotic administration; securing general adherence to it presents greater difficulties.

#### 5.2.1.4 Role of the laboratory

The effect of good laboratory reporting on the appropriate choice of antibiotics is likely to be most effective when the medical microbiologist has convinced his clinical colleagues of his competence to advise on antibiotic treatment (see Annex, section 2.2).

#### 5.2.1.5 Role of the pharmacist

The appropriate hospital authority should agree upon a limited formulary comprising the minimum number of antibiotics required for effective treatment. The pharmacist should under normal circumstances dispense antibiotics only from this list, and should operate rules for the automatic substitution of the least expensive and the most effective of a class of suitable agents. The conditions under which he may depart from these rules should be carefully defined by the authority. Generic names should be required to be used in all prescriptions and in labelling. The pharmacist has an important role in monitoring the hospital's policy for the restricted use of individual antibiotics (see section 5.2.1.2).

#### 5.2.1.6 Restriction of contact between pharmaceutical representatives and physicians

The hospital authorities should enforce the following rules: (1) all representatives should report to the pharmacy for registration; (2) they should visit physicians only by appointment, and should not in general enter the patient-care areas of the hospital; (3) they should be permitted to mount displays of their products only for limited times and in designated places; (4) offers to sponsor speakers at scientific meetings and to provide free samples, test kits, etc. should be accepted with caution and only after consultation with senior staff.

#### 5.2.1.7 Education

The hospital authority has a responsibility to organize a continuing programme of postgraduate education for medical staff on all matters concerning antibiotic use. It must be admitted, however, that the relative effect of different types of educational presentation on subsequent practice is not known (see section 5.4).

#### 5.2.1.8 Monitoring antibiotic use

Perhaps the most valuable means of influencing the pattern of antibiotic use is to obtain information retrospectively about antibiotic consumption and use this to stimulate discussion between physicians about their practices.

The simplest and cheapest form of monitoring is one based on pharmacy records. It will produce good information if these records are based on unit doses, if issues to individual wards are identified, and if issues for inpatients and outpatients are recorded separately. It will provide secular trends in the use of particular agents and may identify unusual practices in some departments and stimulate fruitful discussion of these. Comparison of the pattern of antibiotic use in comparable departments in different hospitals are possible if recording methods are standardized.

More elaborate surveys of particular forms of antibiotic use, made by retrospective examination of patients' records, are more expensive but very valuable. These include studies of the use of antibiotics prophylactically for different types of surgical operation by different surgeons, and of therapeutic practice in groups of patients identified by discharge diagnosis.

Collaborative schemes for monitoring the effects of treatment in relation to the in vitro susceptibility of the causative organism for example, in gonococcal infection, have contributed materially to preventing the spread of resistant strains.<sup>85,86</sup>

The value of retrospective monitoring depends on the use made of the results. The concept of "peer assessment" of their practices by groups of physicians or surgeons must first be accepted; the potentiality for profitable "feed-back" to practice and to the education programme is very great.

#### 5.2.2 Hospital hygiene and antibiotic resistance

The very high frequency of antibiotic-resistant pathogens in the bacterial flora of hospital patients is attributable not only to frequent exposure to antibiotics but also to the many opportunities that exist in hospital for the transmission of bacteria between patients. However successful we are in controlling antibiotic misuse, the amount of antibiotic used in hospitals will continue to be considerable, particularly in some departments. For example, Casewell and his colleagues<sup>87</sup> concluded from a careful study in a urological ward that 24% of all the patients admitted had received courses of antibiotics that had been prescribed on strictly rational grounds. There is little doubt that the use of antibiotics on such a scale would lead to serious antibiotic-resistance troubles unless the highest standards of hygiene are maintained. Thus an active programme for the control of hospital-acquired infection can be looked upon as an important element in "antibiotic policy". The provision of adequate facilities for the isolation of patients,<sup>88</sup> and sufficient trained staff to work in them, are particularly relevant to controlling the spread of resistant organisms in parts of the hospital where antibiotic usage is heavy. Source isolation is needed to accommodate patients who are heavy dispersers of resistant organisms, and protective isolation for uninfected patients in whom the prolonged administration of broad-spectrum antibiotics is considered to be justifiable.

Close epidemiological surveillance of the spread of identifiable strains of resistant pathogens in the hospital is an important part of the work of the Infection-Control Team,<sup>89</sup> who should advise about special measures needed to deal with individual incidents, whether or not these have yet resulted in clinical infections. These measures may include the detection and elimination of hygienic lapses, the transfer of patients to isolation accommodation, and tactical changes in antibiotic policy.

#### 5.3 Alternatives to the use of antibiotics

The prevention of disease by means other than the use of antibiotics is an important means of reducing antibiotic consumption. Improved hygienic conditions, notably in the quality of drinking water in developing countries, would lessen the use of antibiotics for treatment and reduce pressure for their prophylactic use. Many other examples could be quoted. Certain more specific measures might be expected to have a similar effect.

### 5.3.1 Immunoprophylaxis

Immunization in the general population would in some instances reduce antibiotic consumption, e.g. the use of meningococcal vaccines in high-incidence areas. The development of really effective vaccines against enteric bacterial pathogens, and their widespread employment, would also reduce one of the major uses of antibiotics in developing countries.

Opportunities for the successful deployment of immunoprophylaxis to protect hospital patients at special risk of infection are unfortunately less common. In many cases the increased susceptibility of the patient is of acute onset, and there is insufficient time for active immunity to develop before the infection appears. The proven efficacy of pseudomonas vaccine when given after burning in preventing invasive infection by Pseudomonas aeruginosa is an almost unique exception to this, and certainly lessens the justification for broad-spectrum antibiotic prophylaxis in burned patients.

If the onset of susceptibility can be predicted, as in pregnant women and their babies, there may be time for the development of active immunity. There is evidence that giving staphylococcal vaccines to pregnant women reduces somewhat the frequency of puerperal mastitis and neonatal skin sepsis, but the present infrequency of these conditions in most countries hardly justifies the practice. A similar procedure for preventing neonatal group-B streptococcal infection by means of a polysaccharide vaccine is under investigation.

Acute immunization may be of value in protecting certain categories of patients with an established susceptibility to a single bacterial pathogen, e.g. to the pneumococcus in asplenic persons. However, some other patients with a similar susceptibility may give a poor response to the vaccine, and caution should therefore be exercised in abandoning long-term antibiotic prophylaxis in favour of vaccination.

### 5.3.2 The use of chemical disinfectants

The topical application of relatively non-toxic disinfectants such as chlorhexidine and iodophors provides a possible alternative to antibiotic prophylaxis in surgery and the prevention of neonatal skin sepsis. Its most clear success to date is in the prevention of catheter-borne urinary-tract infection.<sup>90</sup> Mention must be made of the specific effect of silver salts in preventing the invasion of burns by P. aeruginosa, but plasmid-borne resistance to silver has developed in some gram-negative bacteria.

## 6. RESEARCH AND DEVELOPMENT

The Working Group identified a number of areas in which this might lead to improvements in antibiotic use and in methods for the containment of resistance.

### 6.1 Bacteriological

#### 6.1.1 Rapid methods of diagnosis of infection and antibiotic-sensitivity testing

Many new methods are under investigation; the most urgent needs are for the development of inexpensive methods applicable to a number of different pathogens and their integration into routine laboratory practice.

#### 6.1.2 New means of attacking the resistance mechanisms of bacteria

Chemical substances that inhibit the action of antibiotic-destroying enzymes may restore the usefulness of antibiotics at present rendered ineffective by the prevalence of enzyme-mediated resistance.  $\beta$ -lactamase inhibitors (e.g. clavulanic acid) are now available; their therapeutic value in combination with various penicillins and cephalosporins, their range of activity against various  $\beta$ -lactamases, and their potential impact on the pattern of antibiotic usage, are all matters of great interest. Chemical substances that inhibit other antibiotic-destroying enzymes would be of great potential value. Non-toxic substances that eliminate plasmids from bacteria within the animal and human body might be useful in preventing the spread of resistance in the natural flora.

### 6.1.3 Alternatives to the use of antibiotics

Of available methods of immunological prophylaxis, the use of pseudomonas vaccine is of the greatest interest; study of the "early" immunity elicited by it may have implications for preventing infections by other gram-negative bacteria. The topical application of mild disinfectants is a promising method of preventing bacterial infection from specified sites. The extent of which it could replace antibiotic prophylaxis, and optimal methods of deploying it, require further study by controlled trials.

### 6.1.4 Alternatives to antibiotics for growth-promotion in farm animals

Pressure to use antibiotics for growth promotion, especially where this is not effectively controlled by government action, might be lessened if effective and cheap chemical agents with a similar action could be found.

## 6.2 Clinical

### 6.2.1 Minimal effective dosage

In some infections, for example of the urinary tract, smaller dosage or a shorter course of treatment may perhaps be as effective as those currently employed in effecting clinical cure. Recent experience with uncomplicated urinary-tract infection supports this view; some other infections merit reconsideration.

### 6.2.2 Antibiotic prophylaxis

The guidelines given in the Annex represent a general consensus of current views, but uncertainty exists on some points, e.g. about the relative efficacy of individual antibiotics and the liability of certain proposed regimens to cause undesirable changes in patients' flora when given by different routes. The justification for longer courses of prophylaxis in certain non-surgical conditions, such as underweight neonates and immunodeficient patients, is a subject for controversy. Critical evaluation of their consequences for the patient and others in the unit, and the extent to which these are influenced by various systems of patient-isolation, are needed.

## 6.3 Epidemiological

### 6.3.1 Surveillance of antibiotic resistance and of resistance determinants

The need for establishing an integrated system of surveillance, under the general direction of WHO, to obtain information on a global scale about the frequency and nature of antibiotic resistance in pathogenic bacteria as well as proposals on limited study of the R plasmids in the faecal flora of the general population of the respective countries have been made and arguments in favour of these schemes have been given by the group (see section 5.1).

### 6.3.2 Effects of ceasing to administer antibiotics

There is insufficient information about the effect of the reduced use of individual antibiotics, either as a result of a planned policy or restriction or as a consequence of the introduction of new antibiotics, on the prevalence of resistant bacteria and of clinical infections caused by them. Some can be found in published papers, but the findings of workers in different hospitals are often difficult to compare. Guidelines for recording relevant information are urgently needed. The introduction of detailed schemes for the monitoring of antibiotic use in many hospitals should provide a good starting point for improved studies.

The effect of the duration of antibiotic administration, in communities and individuals, on the persistence of resistant flora after the antibiotic has been withdrawn requires further study.

### 6.3.3 Non-human sources of resistance plasmids

There is still considerable doubt about the relative exposure of human subjects by the oral route to faecal coliform bacteria derived, directly or indirectly, from meat and other animal products, from vegetables, and from other sources. This is very difficult to investigate because the organisms from the various sources are at present indistinguishable in the laboratory. A combination of indirect methods, e.g. quantitative studies of raw products and of the foods actually ingested, and the use of bacterial and non-bacterial markers, might eventually yield a general picture.

### 6.4 Health service research

Opinions differ about optimal methods of education on matters concerned with the administration of antibiotics. Studies of the effects of various types of education in imparting information and in affecting prescribing practice are indicated, and perhaps also of the effects of internship experience in different types of hospital department. The attitudes of physicians to the objective assessment of their prescribing habits, and ways of encouraging acceptance of "peer assessment", need investigation.

## 7. CONCLUSIONS AND RECOMMENDATIONS

### 7.1 General

The increasing frequency of acquired resistance to antibiotics among bacteria of medical importance is a worldwide health problem that demands international attention. The World Health Organization has kept the situation under review for twenty years, during which time it has promoted research into various aspects of the problem. However, the rapidity with which new resistances are appearing and existing resistances are becoming more prevalent indicate the need for more precise information about the situation and for action to control it.

The importance of antibiotics to health care in all countries is reflected in the composition of the WHO Model List of Essential Drugs,<sup>91</sup> and, potentially, the Organization has an important coordinating role to play in ensuring that these drugs are used everywhere to optimum advantage.

### 7.2 Surveillance of bacterial resistance

The group is in full agreement with the emphasis placed by previous WHO meetings<sup>1,2,3</sup> on surveillance of bacterial resistance at both the national and the international level with a view to providing health authorities, doctors and pharmaceutical companies with data on which the use and future development of antibiotics may be rationalized. Efficient integration of surveillance activities internationally will depend upon the establishment of regional and national reference centres, and their subsequent collaboration both in standardizing methods of antibiotic susceptibility testing, and training personnel working in peripheral laboratories and institutes of quality control; WHO could play an important role in promoting these activities.

### 7.3 National surveillance of antibiotic use

Information is urgently needed about the pattern of antibiotic use in each country with the objective of assessing the extent of overuse, misuse (and underuse) of various agents in the common clinical situations encountered in the country. The extent to which the advertising of products in the lay and medical press contributes to this requires investigation. The expected effect of various regulatory measures, the provision of reliable information, cost, etc., on the quality of antibiotic use should be studied. Areas should be defined in which further investigations are needed to determine the relative efficacy, in relation to cost, and the safety, of regimens of antibiotic administration currently employed in the various countries.

(a) Importation and manufacture of antibiotics

Countries should develop their own schemes for antibiotic manufacture and import control of what antibiotics are manufactured in the country or imported into it. Countries should introduce a strong and well designed national formulary for antibiotics and update this regularly on the advice of pharmacologists and microbiologists; WHO provides guidance for this.<sup>91</sup> Special mention must be made of the widespread use, particularly in developing countries, of preparations containing two or more antibiotics in fixed ratios. Their spectrum of activity is often so wide that they have undesirable effects on the body flora, few of them have notable therapeutic advantages, and they are generally costly. Only the few such combinations that are of clinically proven value, should be available.

(b) Availability of antibiotics

The unrestricted sale of antibiotics to the general public encourages excessive and inappropriate use. Legislation making them available only on prescription by designated classes of professional persons (e.g. medical and veterinary practitioners) is therefore highly desirable and strongly recommended; however, such laws have proved very difficult to enforce in some countries. A possible solution to this difficulty may be through limiting the routes by which antibiotics are distributed to the hospitals, the government primary health care service, and registered pharmacists, coupled with increased supervision of pharmacists who provide antibiotics directly to the public and attempts to educate them in the indications for antibiotic use. In countries with an acute shortage of doctors in primary health care it may be necessary to empower health workers who have received little formal training to administer antibiotics. High priority should be given to the in-service training of these workers in the use of antibiotics and to monitoring their prescribing practices. Consideration should be given, in countries in which the control of antibiotic use is particularly difficult, to restricting the supply of certain antibiotics required for the treatment of very serious infections to hospitals, or even to selected hospitals.

(c) Education

Countries should provide, through their programme of health education for the general public, simple advice about the types of illness in which the use of antibiotics is not indicated. They have a responsibility to ensure that the correct use of antibiotics receives adequate attention in the training not only of medical students but of all categories of health workers who may be concerned in the administration of antibiotics. Adequate facilities should be provided for the continuing postgraduate education of medical practitioners, whether or not they are in the government service. Countries should also disseminate reliable and up-to-date information to all medical practitioners about the efficacy of, indication for, and contra-indications to, and unwanted side effects from the use of individual antibiotics by means of a periodical publication (see the British "Prescriber's Journal" and "Drugs and Therapeutics Bulletin", and the American "AMA Drug Evaluations").

(d) Manufacturers and importers of antibiotics should be required to provide the same information to users in all countries in which their products are sold; this should always include the generic name of the product, the indications and contraindications for use, and the side effects. The Working Group welcomed the efforts of WHO's Expert Committee on Essential Drugs to prepare data sheets for international use.<sup>91</sup> It is the duty of countries to ensure that evidence is obtained through the existing WHO certification scheme for drugs moving in international commerce. The same standards should be enforced in respect of drugs manufactured in the country. Countries should monitor the claims made by antibiotic manufacturers and distributors in advertisements in the medical and lay press.

7.4 Emergency actions

The Working Group considered lines of action that might be taken if an epidemic of severe infections caused by an organism resistant to all available antibiotics occurred in a developing country. To meet such an emergency, manufacturers of "new" antibiotics should be invited to contribute a limited supply of these to the WHO Emergency Relief Office, where they would be held in reserve for prompt issue, under WHO coordination, to the government of the affected country.

### 7.5 Veterinary use of antibiotics

Since the use of antibiotics is an important means of treating bacterial diseases in animals, as in human medicine, (a) antibiotics for this purpose should be available only on prescription by a licensed person; national authorities should organize the education of these persons in the proper use of antibiotics; (b) countries should be encouraged to prohibit the therapeutic use in animals of certain newer antibiotics of value for the treatment of serious infections in man (e.g. gentamicin and related aminoglycosides, spectinomycin, rifampicin); (c) the recommendation of an earlier WHO Working Group<sup>1</sup> that chloramphenicol should be reserved for use in man is endorsed. However, it is recognized that this antibiotic is still widely used for the oral treatment of salmonellosis in animals. In order to restrict its use to the treatment of infected animals under the care of a veterinary surgeon, this drug should be available for veterinary use only as a parenteral preparation; (d) large numbers of antibiotic preparations for intramammary administration in cases of mastitis are being marketed. Often these are mixtures of several antibiotics. For reasons given earlier (section 4.2), the use of fixed-ratio combinations of antibiotics, other than a few of proven efficacy, should be discouraged, if necessary by administrative action; (e) the routine use of antibiotic prophylaxis in the absence of proven infection is no substitute for good hygiene in animal rearing establishments.

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ANNEX

GUIDELINES FOR THE APPROPRIATE USE OF ANTIBIOTICS

1. Objectives

The first of these is the successful treatment of infection in the patient, but treating one patient may increase the risk to others of acquiring an infection with resistant organisms. To minimize this risk:

- (1) the antibiotic used should be the one to which the infecting organism has been shown to be sensitive; or, if this is not practicable, to which the putative infecting organism can be expected to be sensitive;
- (2) it should have as narrow a spectrum of activity as possible;
- (3) it should be given in dosage and by a route appropriate to effect cure; and
- (4) it should be used for the least possible time.

2. The therapeutic use of antibiotics

The correct use of antibiotics for treatment depends on accurate clinical diagnosis supported whenever possible by laboratory evidence of the nature of the infecting organism and its susceptibility to antibiotics.

2.1 Good clinical practice

Under optimal conditions the physician will obtain assistance in interpreting the patient's signs and symptoms from ancillary services (laboratory tests, radiographs, and so on). He must know how to deploy these and to interpret their results correctly. In many cases, however, it is necessary to begin treatment before the causative organism has been isolated, and in others it may not be possible to obtain laboratory evidence of its identity. "Best-choice" treatment of severe infections must in these circumstances be based on experience and on a knowledge of the current antibiotic susceptibility of the more likely causes of the infection. Physicians without laboratory support, notably those working in developing countries, need special training in the performance of simple laboratory procedures, such as the microscopic examination of cerebrospinal fluid, pus and other exudates, counting of leucocytes, and selected serological tests.

2.2 Efficient laboratory support

A good laboratory service can do much to improve the quality of antibiotic prescribing. Reporting of results should be as rapid as possible; provisional reports, based on microscopic examination or preliminary cultural and sensitivity tests, if given by telephone with suitable explanation, are particularly valuable in guiding initial treatment in meningitis, septicaemia and other serious infections. Rapid methods, e.g. of blood culture, detecting bacterial antigens in exudates, and antibiotic-sensitivity testing, should be employed whenever possible in these infections.

The laboratory should report only relevant information; it has a responsibility to assess the clinical significance of its findings and report in the light of this. When the physician does not provide enough clinical information for this to be done, the laboratory should not hesitate to seek this from him or his staff. Selective reporting of the results of antibiotic-sensitivity tests is a useful method of influencing the choice of antibiotic. Results should be given only in respect of organisms thought to be of clinical significance. For significant organisms, results for antibiotics of first choice only are given, those for other antibiotics being withheld and released only on request from the physician. Generic names of antibiotics should be used.

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3. The prophylactic use of antibiotics

Antibiotics should be used prophylactically only when there is good evidence that this will significantly reduce the frequency of infection. With a few exceptions that will be noted below, this will be in situations in which the risk of infection is short-lived and it is practicable to give the antibiotic before the infecting organism has multiplied significantly at the expected point of its entry into the body.

3.1 Prophylaxis in surgery

Acceptable indications include "contaminated" surgery when the risk of infection is high, and "clean" surgery when though the risk of infection is low its consequences would be disastrous. There is no justification for its use in other classes of "clean" surgery (e.g. herniography, thyroidectomy, craniotomy), nor does it appear to be very effective. Many surgeons seek to compensate for poor hygienic conditions in their operating theatre or wards by employing prophylaxis as a routine for "clean" surgery; this results in excessive antibiotic use and is certainly counterproductive.

Clinical trials support the use of antibiotics in relation to the following procedures: in "clean" surgery, for the amputation of ischaemic limbs, the insertion of prosthetic devices, and in cardiac surgery; in "contaminated" surgery: abdominal (large bowel, small bowel with blind loop, gall-bladder in high-risk patients, penetrating accidental wounds); pelvic (vaginal hysterectomy, Caesarian section with ruptured membranes); urological, when the urine is infected; recent compound fracture; human bites.

Prophylaxis should be strictly perioperative. It should not begin more than a few hours before the operation. The aim is to maintain high tissue levels of antibiotic for the duration of the operation and for a few hours afterwards. It should not be given for a total period exceeding 24 hours. The presence of a drainage device in the wound does not justify prolonging this period.

The prophylactic agent chosen should be effective against organisms likely to invade from the site of the operation, e.g. gram-positive cocci in cardiac surgery and joint replacement, gram-negative aerobes and anaerobes in abdominal surgery, clostridia in leg amputation. Dosage should be high enough for maximal tissue concentrations to be attained. The systemic route is generally preferred. For intestinal procedures some surgeons prefer to give prophylactic agents orally or by suppository in combination with mechanical cleansing of the bowel. It is particularly important not to begin these forms of prophylaxis too soon.

3.2 Non-surgical prophylaxis

There are few clear indications for this in hospital patients, though it is widely practised in hospitals, with many consequent ill-effects: adverse drug reactions and superinfection in the patient, infections with resistant organisms in other patients, and high hospital costs. Fortunately, most of the conditions in which non-surgical prophylaxis is clearly beneficial occur in single patients or small groups of patients scattered throughout the general population. The adverse consequences of prophylaxis in these circumstances are less.

Non-surgical prophylaxis may be justified for the following purposes:

- (1) Prevention of rheumatic fever: (a) "primary" prevention in patients with no previous history of the disease; and (b) "secondary" prevention of subsequent attacks.
- (2) Prevention of secondary cases of meningococcal or H. influenzae meningitis in family contacts of cases.
- (3) Prevention of tuberculosis in high-risk groups.

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- (4) Prevention of endocarditis in patients with damaged heart valves when dental or genitourinary procedures are performed.
- (5) Long-term low-dose administration of cotrimoxazole or certain other agents for the prevention of recurrent urinary-tract infection in selected patients.

Conditions for which prophylaxis has not been clearly shown to be effective include the following:

- (1) Cardiac catheterization and the insertion of pacemakers.
- (2) Prevention of recurrences in acute glomerulonephritis.
- (3) Prevention of pneumonia in patients with viral infection of the upper respiratory tract or measles.
- (4) Prevention of pneumonia and septic complications in patients with a variety of serious medical conditions, including coma, respiratory failure, congestive heart failure.
- (5) Prevention of acute exacerbations in chronic bronchitis.
- (6) Protection against infection of patients with immuno-deficiency, either natural or therapeutically induced, unless the condition is limited in duration and facilities are available for strict protective isolation of the patient.

3.3 Other prophylactic uses of antibiotics

The topical application of broad-spectrum antibiotics to chronic skin lesions, including varicose and decubitus ulcers and burns, is a relatively ineffective means of prophylaxis and a potent cause to the dissemination of resistant bacteria; it is believed to have contributed considerably to the increasing frequency of aminoglycoside resistance in staphylococci and gram-negative bacteria. It may also induce hypersensitivity with an associated risk of cross-allergy to related antibiotics.

Oral tetracycline is reported to be an effective means of inhibiting the development of acne lesions and is widely used for this purpose. There is evidence that it selects for antibiotic resistance in the natural flora of patients, and that the resistant organisms may be transmitted to family contacts. The prophylactic use of tetracycline should therefore be considered only in severe cases of acne.<sup>88, 90</sup>