Memoranda
Mémorandums

Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.

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Control of antibiotic-resistant bacteria: Memorandum from a WHO Meeting*

Control of the prevalence of antibiotic-resistant bacteria is essential for the appropriate use of antibiotics for prophylaxis and treatment of infections. Hospitals are regarded as the place where antibiotic-resistant bacteria might often develop. Control of antibiotic use in hospitals is therefore one of the most important measures for effective control of antibiotic resistance. Another effective means to control antibiotic resistance is to develop a surveillance programme on a national, and international scale. This would be of great assistance, especially for forecasting future changes in the resistance of bacteria. The prevention of disease by measures other than the use of antibiotics could also reduce antibiotic resistance.

This Memorandum of the WHO Scientific Working Group on Antibiotic Resistance describes the measures for controlling the prevalence of antibiotic-resistant bacteria by (a) the surveillance of antibiotic resistance, including surveillance of resistance in human pathogens and resistance determinants in the general population, and (b) control of antibiotic use in hospitals, the essential elements of which are the establishment of appropriate hospital antibiotic policy, elaboration of general strategy, and the monitoring of antibiotic use. Further research needs are also described and a number of areas are indicated where research might lead to improvements in antibiotic use and in methods for the containment of resistance. Guidelines for the appropriate use of antibiotics are presented in an Annex.

MEASURES TO CONTROL THE PREVALENCE OF ANTIBIOTIC-RESISTANT BACTERIA

SURVEILLANCE OF ANTIBIOTIC RESISTANCE

The need for surveillance

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

(1) improve the quality of antibiotic prescribing for the individual patient;

(2) influence the pattern of antibiotic usage in every hospital;

(3) assist governments in the formulation of policy for the supply and use of antibiotics in man and animals;

(4) encourage responsible action by antibiotic manufacturers in the marketing and promotion of their products.

In countries with well developed laboratory facilities, a great deal of valuable information about the susceptibility of micro-organisms to antibiotics 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 (*1*). To these sources of information must be added several special schemes for the surveillance of resistance in individual pathogens,

* This Memorandum is based on the report of the WHO Scientific Working Group on Antimicrobial Resistance, which met in Geneva from 23 to 27 November 1981. The first part of this report appears as an Update article on pages 383–394. The participants at this meeting are listed on pages 430–431. A French translation of this Memorandum will appear in a later issue of the *Bulletin*.

notably enteric pathogens and gonococci, by WHO Reference Centres.

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

Requirements for surveillance

Surveillance of resistance in human pathogens. The primary objective is to assemble information about resistance in pathogenic bacteria, which is most readily available from clinical microbiology laboratories. There is thus a very strong case for basing a surveillance system on the results of routine sensitivity tests from these laboratories and considerable advantages would be gained by making use of local laboratories. The role of the national centre would then 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 the 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, as well as urine from patients with significant urinary-tract infection) in each participating laboratory in an agreed period of time. National centres would apply this scheme according to local circumstances, choose the participating laboratories, and collect and analyse the results. Participating laboratories should be those where standard methods are employed and monitored, and should be as representative as possible of the major geographical regions in the country.

The national centre would indicate the acceptable methods for sensitivity testing according to the guidelines on the requirements for antimicrobial susceptibility tests,[a] and would regularly monitor their performance in the participating laboratories by a system of external quality control. The centre should also evaluate all commercially available reagents (antibiotic discs, sensitivity-test media) and, where suitable, indicate the available locally produced alternatives, as well as provide standard cultures for use in internal quality-control tests.

[a] *Requirements for antibiotic susceptibility tests. I. Agar diffusion tests using antimicrobic susceptibility discs. (Requirements for Biological Substances W26).* Unpublished WHO document, WHO/BS/81.1337, Rev. 1, 1981.

The 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 centre should also be prepared to examine "problem" cultures from local laboratories, including strains that are thought to exhibit "new" resistances. It is not envisaged that such centres should 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.

Surveillance of resistance determinants in the general population. 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.

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 — where this sort of information is 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.

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. Manual or simple mechanical sorting may be appropriate to give early information locally but computer assistance will be essential for the analysis of national and global data. Regional cooperation in the use of computer facilities might help to meet deficiencies in individual countries.

CONTROL OF ANTIBIOTIC USE IN HOSPITALS

Hospital antibiotic policy

The decision to administer an antibiotic to patients is taken by the doctor responsible for their 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 relevant hospital committee. It may be conveniently codified in a booklet issued to all medical members of the staff. This booklet could provide basic information about the action of common antibiotics, dosage schedules, etc., but its main purpose is to outline the agreed principles for the rational use of antibiotics (see Annex 1, pages 432–433). 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 or the introduction of a new antibiotic, may from time to time dictate modifications. Thus, the antibiotic policy should seek only to define the 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 will be expected to adhere.

General strategy. The following is an outline of a general statement on antibiotic policy, which can be elaborated, with suitable examples, according to local circumstances. Antibiotic treatment should be based on a 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 the results of susceptibility tests (with advice from the laboratory); when immediate treatment is deemed necessary, this should be reviewed when the first reliable 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 on the prophylactic use of antibiotics, see Annex 1).

Tactical modifications of antibiotic policy. Decisions to restrict the use of individual antibiotics, for longer or shorter periods of time, have often been employed as elements in a hospital antibiotic policy. The ultimate measure, which is 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 (*2*). 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. This policy illustrates the idea of "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 (*3*), 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" (*4*) 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.

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.

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 1, pages 432–433, section on efficient laboratory support).

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 subsection above, *Tactical modifications...*).

Restriction of contact between pharmaceutical representatives and physicians. The hospital authorities should enforce the following rules: (1) all pharmaceutical representatives should report to the pharmacy for registration; (2) they should visit physicians only by appointment, and should not in general enter the areas where the patients are; (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.

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.

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 useful information if these records are based on unit doses, if the antibiotics issued to individual wards are identified, and if the drugs given to in-patients and out-patients are recorded separately. It will indicate any trends in the use of particular agents and may identify unusual practices in some departments as well as stimulate fruitful discussion on these matters. Comparison of the pattern of antibiotic use in similar departments in several hospitals is possible if the recording methods are standardized.

More elaborate surveys of particular forms of antibiotic use, e.g., by retrospective examination of patients' records, are more expensive but very valuable. These include studies on the prophylactic use of antibiotics by different surgeons on patients undergoing various surgical operations, and on the therapeutic use of antibiotics in groups of patients identified by the diagnosis at the time of discharge.

Collaborative schemes for monitoring the effects of treatment in relation to the *in vitro* susceptibility of the causative organism (e.g., in gonococcal infection) have contributed materially in preventing the spread of resistant strains (*5*, *6*).

The value of retrospective monitoring depends on the use made of the results. The principle of "peer assessment" of current practices by groups of physicians and surgeons must first be accepted; the potential for profitable "feed-back" on these practices and on programmes of education is very great.

Hospital hygiene and antibiotic resistance

The very high prevalence 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 antibiotics used in hospitals will continue to be considerable, particularly in some departments. For example, from one careful study carried out in a urological ward (*7*), it was concluded that only 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 (*8*), with sufficient trained staff to work in them, is particularly relevant to help control the spread of resistant organisms in parts of the hospital where antibiotic usage is heavy. Such facilities for isolation are needed to accommodate infected patients who are heavy dispersers of resistant organisms, as well as to protect uninfected patients for 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 is an important part of the work of the hospital's infection-control team (*9*), 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 unhygienic lapses, the transfer of patients to the isolation areas, and tactical changes in antibiotic policy.

ALTERNATIVES TO THE USE OF ANTIBIOTICS

The prevention of disease by measures 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 reduce the need to use antibiotics for treatment as well as for prophylaxis. Other examples of specific measures might be expected to have a similar effect.

Immunoprophylaxis

Immunization in the general population would in some instances reduce antibiotic consumption, e.g., by 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 rapid onset, and there is insufficient time for active immunity to develop before the infection appears. The proven efficacy of pseudomonas vaccine, when given to patients with burn injuries, 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 period of susceptibility to infection can be predicted, e.g., in pregnancy and after delivery, there may be time to initiate the development of active immunity. There is evidence that giving staphylococcal vaccines to pregnant women reduces somewhat the incidence of puerperal mastitis and neonatal skin sepsis, but the present infrequency of these conditions in most countries hardly justifies the use of this vaccine. A similar procedure for preventing neonatal group-B streptococcal infection by means of a polysaccharide vaccine is under investigation.

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, 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 such immunization.

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 surgical and neonatal cases for the prevention of skin sepsis. The best example of success to date is in the prevention of catheter-borne urinary-tract infections (*10*). Mention must be made of the specific effect of silver salts in preventing the invasion of burns by *Ps. aeruginosa*, but plasmid-borne resistance to silver has developed in some Gram-negative bacteria.

RESEARCH AND DEVELOPMENT

The Working Group identified a number of areas where research might lead to improvements in antibiotic use and in methods for the containment of resistance. These are described below.

BACTERIOLOGICAL RESEARCH

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.

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. β-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 β-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.

Alternatives to the use of antibiotics

Among the available methods of immunological prophylaxis, the use of pseudomonas vaccine is of the greatest interest; study of the rapid immunity provided by this vaccine may have implications for preventing infections by other Gram-negative bacteria. The topical application of mild disinfectants is a promising method for preventing bacterial infection in certain sites; the extent to which it could replace antibiotic prophylaxis and the optimal methods for deploying it require further study in controlled trials.

Alternatives to antibiotics for growth promotion in farm animals

Pressure to use antibiotics for animal 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.

CLINICAL RESEARCH

Minimal effective dosage

In some infections, e.g., in the urinary tract, a 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 also merit reconsideration in this regard.

Antibiotic prophylaxis

The guidelines given in Annex 1 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 the patients' bacterial flora when given by different routes. The justification for long courses of prophylaxis in certain non-surgical conditions, e.g., in underweight neonates and immunodeficient patients, is a subject of controversy. Critical evaluation of their consequences for the patient and others in the same unit, and the extent to which these are influenced by various systems for isolating patients are needed.

EPIDEMIOLOGICAL RESEARCH

Surveillance of antibiotic resistance and of resistance determinants

There is a 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; proposals on a limited study of the R plasmids in the faecal flora of the general population of the respective countries have been made. Arguments in favour of these schemes are given above (see pages 423–424).

Effects of stopping the administration of 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 information 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 in many hospitals of detailed schemes for the monitoring of antibiotic use 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 also requires further study.

Non-human sources of resistance plasmids

There is still considerable doubt about the relative exposures 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. Investigation of this problem is very difficult 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.

HEALTH SERVICES RESEARCH

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

CONCLUSIONS AND RECOMMENDATIONS

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 (*11*), and, potentially, the Organization has an important coordinating role to play in ensuring that these drugs are used everywhere to optimum advantage.

SURVEILLANCE OF BACTERIAL RESISTANCE

The group is in full agreement with the emphasis placed by previous WHO meetings (*12–14*) 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, based 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 the methods of antibiotic susceptibility testing and in training personnel working in peripheral laboratories and institutes of quality control. WHO could play an important role in the promotion of these activities.

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 where further investigations are needed to determine the relative efficacy, in relation to cost, and the safety of different regimens of antibiotic administration currently employed in various countries.

Importation and manufacture of antibiotics

Countries should develop their own schemes for antibiotic manufacture and for import controls on those that are not manufactured in the country. Countries should introduce a well-designed national formulary for antibiotics and update this regularly on the advice of pharmacologists and microbiologists; WHO has provided guidance on this matter (*11*). 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 combinations that are of clinically proven value should be permitted.

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 certain designated classes (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 hospitals, government primary health care services, 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 where the control of antibiotic use is particularly difficult, to restricting the supply of certain antibiotics that are required for the treatment of very serious infections to hospitals only, or to selected hospitals.

Education

Countries should provide, through programmes on health education for the general public, simple advice about the types of illness for which antibiotics should

not be used. They have a responsibility to ensure that the correct use of antibiotics is given adequate attention in the training not only of medical students but of all categories of health workers who may be involved 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, indications for, contraindications to, and unwanted side-effects from the use of individual antibiotics by means of a periodical publication (examples are *Prescriber's Journal*, *Drugs and Therapeutics Bulletin*, and *AMA Drug Evaluations*).

Quality control

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 the WHO Expert Committee on Essential Drugs in preparing data sheets for international use (*11*). 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.

EMERGENCY ACTIONS

Among the 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, it was proposed that manufacturers of "new" antibiotics should be invited to contribute a limited supply of these to the WHO Emergency Relief Operations, where they would be held in reserve for prompt issue, under WHO coordination, to the government of the affected country.

VETERINARY USE OF ANTIBIOTICS

Recognizing that the use of antibiotics is an important means of treating bacterial diseases in animals, as in human medicine, the Working Group recommended the following: (*a*) antibiotics for veterinary use should be available only on prescription by a licensed person; training courses for these persons in the proper use of antibiotics should be organized by the national authorities; (*b*) countries should be encouraged to prohibit the therapeutic use in animals of certain newer antibiotics that are required for the treatment of serious infections in man (e.g., gentamicin and related aminoglycosides, spectinomycin, rifampicin); (*c*) chloramphenicol should be reserved for use in man, which was also recommended by an earlier WHO Working Group (*12*); as this antibiotic is still widely used for the oral treatment of salmonellosis in animals, its use should be restricted to the treatment of infected animals under the care of a veterinary surgeon and the drug should be available for such use only as a parenteral preparation; (*d*) since large numbers of antibiotic preparations for intramammary administration in cases of mastitis are being marketed (often as mixtures of several antibiotics) and for the reasons given earlier (pages 425–426), the use of fixed-ratio combinations of antibiotics (other than the few of proven efficacy) should be discouraged, if necessary by administrative action; (*e*) the routine use of antibiotics prophylactically, in the absence of proven infection, should be avoided because it is no substitute for good hygiene in animal rearing establishments.

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LIST OF PARTICIPANTS

J. F. Acar, Service de Microbiologie médicale, Hôpital Saint-Joseph, Paris, France

J. Fleurette, Laboratoire de Bactériologie-Virologie, Faculté de Médecine Alexis Carrel, Lyon, France

Hu Zhen, Institute of Epidemiology and Microbiology, Chinese Academy of Medical Sciences, Beijing, China

E. H. Kampelmacher, Rijksinstituut voor de Volksgezondheid, Bilthoven, Netherlands

C. M. Kunin, Department of Medicine, University Hospital, Columbus, OH, USA

J. Kupersztoch, Departmento de Genética, Centro da Investigacion y de Estudios, Mexico City, Mexico

S. B. Levy, Departments of Medicine and of Molecular Biology and Microbiology, Tufts University School of Medicine, Boston, MA, USA

I. Lind, Neisseria Department, Statens Seruminstitut, Copenhagen, Denmark

A. H. Linton, Department of Microbiology, University of Bristol Medical School, Bristol, England (*Rapporteur*)
A. Manten, Chemotherapy Laboratory, Rijksinstituut voor de Volksgezondheid, Bilthoven, Netherlands
D. G. Montefiore, Department of Medical Microbiology, University College Hospital, Ibadan, Nigeria
R. L. Nichols, Department of Microbiology, Harvard School of Public Health, Boston, MA, USA
T. F. O'Brien, Harvard Medical School, Boston, MA, USA
M. T. Parker, formerly at the Cross-Infection Reference Laboratory, Central Public Health Laboratory, London, England (*Chairman*)
V. I. Pokrovski, Central Institute of Epidemiology, Moscow, USSR
K. B. Sharma, Department of Microbiology, Lady Hardinge Medical College, New Delhi, India (*Rapporteur*)
E. A. Vedmina, Central Institute of Advanced Medical Training, Moscow, USSR
F. Vymola, Research Unit on Bacterial Resistance to Antibiotics, Reference Laboratory for the Control of Chemotherapy, Institute of Hygiene and Epidemiology, Prague, Czechoslovakia

Observer

B. Gedek, Institut für Medizinische Mikrobiologie, Ludwig-Maximilians-Universität, Munich, Federal Republic of Germany

WHO Secretariat

G. M. Antal, Bacterial and Venereal Infections, Division of Communicable Diseases
G. Y. Causse, Bacterial and Venereal Infections, Division of Communicable Diseases (*Secretary*)
J. F. Dunne, Pharmaceuticals, Division of Diagnostic, Therapeutic and Rehabilitative Technology
L. Houang, Health Laboratory Technology, Division of Diagnostic, Therapeutic and Rehabilitative Technology
T. Kereselidze, Bacterial and Venereal Infections, Division of Communicable Diseases
Z. Matyas, Veterinary Public Health, Division of Communicable Diseases
A. H. W. Wahba, Development of Comprehensive Health Services, WHO Regional Office for Europe, Copenhagen

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Annex 1

GUIDELINES FOR THE APPROPRIATE USE OF ANTIBIOTICS

Objective

The main objective is the successful treatment of infections in patients, but treating one patient may increase the risk that others will acquire the infection with resistant organisms. To minimize this risk:

(1) the antibiotic used should be 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) the antibiotic should have as narrow a spectrum of activity as possible;
(3) it should be given in a dosage and by a route appropriate to effect cure; and
(4) it should be used for the shortest possible time.

The therapeutic use of antibiotics

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

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 leukocytes, and selected serological tests.

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, may be given by telephone with suitable explanations and are particularly valuable in guiding the initial treatment of 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 to 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 such significant organisms, the results indicating antibiotics of first choice only are given, the names of other antibiotics being withheld and released only on request from the physician. International nonproprietary or generic names of antibiotics should be used.

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 (see below), its use 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 where it entered the body.

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 certain classes of "clean" surgery (e.g., herniorrhaphy, thyroidectomy, craniotomy), for which it does not 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 in their "clean" surgical cases; 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, for 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), and urological cases (when the urine is infected), recent compound fractures, and human bites.

Prophylaxis should be strictly perioperative, beginning not 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 that are likely to invade from the site of the operation, e.g., Gram-positive cocci in cardiac surgery and joint replacements, Gram-negative aerobes and anaerobes in abdominal surgery, and clostridia in leg amputations. 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.

Non-surgical prophylaxis

There are few clear indications for this in hospital patients, though it is widely practised in hospitals, with the following 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 *Haemophilus influenzae* meningitis in family contacts of cases.

(3) Prevention of tuberculosis in high-risk groups.

(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, and congestive heart failure.

(5) Prevention of acute exacerbations in chronic bronchitis.

(6) Protection against infection of patients with immunodeficiency, either natural or therapeutically induced, unless the condition is limited in duration and facilities are available for strict protective isolation of the patient.

Other prophylactic uses of antibiotics

The topical application of broad-spectrum antibiotics for chronic skin lesions, including varicose and decubitus ulcers and burns, is a relatively ineffective means of prophylaxis and a potent cause of 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 favours the development of 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 (*8*, *10*).