WHO/CDS/CSR/DRS/2001.2
DISTR: GENERAL
ORIGINAL: ENGLISH

WHO Global Strategy for Containment of Antimicrobial Resistance

World Health Organization

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Acknowledgements

The World Health Organization (WHO) wishes to acknowledge with gratitude the significant support from the United States Agency for International Development (USAID) and additional assistance for this work from the United Kingdom Department for International Development and the Ministry of Health, Labour and Welfare, Japan.

This strategy is the product of collaborative efforts across WHO, particularly in the clusters of Communicable Diseases, Health Technology and Pharmaceuticals, and Family and Community Health, with significant input from the staff at WHO Regional Offices and from many partners working with WHO worldwide. In particular, WHO would like to acknowledge the important contributions made to the drafting of the strategy by Professor W Stamm, Professor ML Grayson, Professor L Nicolle and Dr M Powell, and the generosity of their respective institutions—Infectious Diseases Department, Harborview Medical Center, University of Washington, Seattle, USA; Infectious Diseases and Clinical Epidemiology Department, Monash Medical Centre, Monash University, Melbourne, Australia; Department of Internal Medicine, University of Manitoba, Winnipeg, Canada; Medicines Control Agency, London UK—that enabled them to spend time at WHO.

WHO also wishes to thank all those who participated and contributed their expertise in the consultations (see Annex B) and those individuals and organizations that provided valuable comments on drafts of this document.

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Designed by minimum graphics
Printed in Switzerland

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Executive Summary

■ Deaths from acute respiratory infections, diarrhoeal diseases, measles, AIDS, malaria and tuberculosis account for more than 85% of the mortality from infection worldwide. Resistance to first-line drugs in most of the pathogens causing these diseases ranges from zero to almost 100%. In some instances resistance to second- and third-line agents is seriously compromising treatment outcome. Added to this is the significant global burden of resistant hospital-acquired infections, the emerging problems of antiviral resistance and the increasing problems of drug resistance in the neglected parasitic diseases of poor and marginalized populations.

■ Resistance is not a new phenomenon; it was recognized early as a scientific curiosity and then as a threat to effective treatment outcome. However, the development of new families of antimicrobials throughout the 1950s and 1960s and of modifications of these molecules through the 1970s and 1980s allowed us to believe that we could always remain ahead of the pathogens. By the turn of the century this complacency had come to haunt us. The pipeline of new drugs is running dry and the incentives to develop new antimicrobials to address the global problems of drug resistance are weak.

■ Resistance costs money, livelihoods and lives and threatens to undermine the effectiveness of health delivery programmes. It has recently been described as a threat to global stability and national security. A few studies have suggested that resistant clones can be replaced by susceptible ones; in general, however, resistance is slow to reverse or is irreversible.

■ Antimicrobial use is the key driver of resistance. Paradoxically this selective pressure comes from a combination of overuse in many parts of the world, particularly for minor infections, misuse due to lack of access to appropriate treatment and underuse due to lack of financial support to complete treatment courses.

■ Resistance is only just beginning to be considered as a societal issue and, in economic terms, as a negative externality in the health care context. Individual decisions to use antimicrobials (taken by the consumer alone or by the decision-making combination of health care worker and patient) often ignore the societal perspective and the perspective of the health service.

■ The World Health Assembly (WHA) Resolution of 1998 (*1*) urged Member States to develop measures to encourage appropriate and cost-effective use of antimicrobials, to prohibit the dispensing of antimicrobials without the prescription of a qualified health care professional, to improve practices to prevent the spread of infection and thereby the spread of resistant pathogens, to strengthen legislation to prevent the manufacture, sale and distribution of counterfeit antimicrobials and the sale of antimicrobials on the informal market, and to reduce the use of antimicrobials in food-animal production. Countries were also encouraged to develop sustainable systems to detect resistant pathogens, to monitor volumes and patterns of use of antimicrobials and the impact of control measures.

■ Since the WHA Resolution, many countries have expressed growing concern about the problem of antimicrobial resistance and some have developed national action plans to address the problem. Despite the mass of literature on antimicrobial resistance, there is depressingly little on the true costs of resistance and the effectiveness of interventions. Given this lack of data in the face of a growing realization that actions need to be taken now to avert future disaster, the challenge is *what to do* and *how to do it*.

■ The WHO Global Strategy for Containment of Antimicrobial Resistance addresses this challenge. It provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms through:

— reducing the disease burden and the spread of infection
— improving access to appropriate antimicrobials
— improving use of antimicrobials
— strengthening health systems and their surveillance capabilities
— enforcing regulations and legislation
— encouraging the development of appropriate new drugs and vaccines.

■ The strategy highlights aspects of the containment of resistance and the need for further research directed towards filling the existing gaps in knowledge.

■ The strategy is people-centred, with interventions directed towards the groups of people who are involved in the problem and need to be part of the solution, i.e. prescribers and dispensers, veterinarians, consumers, policy-makers in hospitals, public health and agriculture, professional societies and the pharmaceutical industry.

■ The strategy addresses antimicrobial resistance in general rather than through a disease-specific approach, but is particularly focused on resistance to antibacterial drugs.

■ Much of the responsibility for implementation of the strategy will fall on individual countries. Governments have a critical role to play in the provision of public goods such as information, in surveillance, analysis of cost-effectiveness and cross-sectoral coordination.

■ Given the complex nature of antimicrobial resistance, the strategy necessarily contains a large number of recommendations for interventions. Prioritization of the implementation of these interventions needs to be customized to national realities. To assist in this process an implementation approach has been defined together with indicators for monitoring implementation and outcomes.

■ Recognition that the problem of resistance exists and the creation of effective national intersectoral task forces are considered critical to the success of implementation and monitoring of interventions. International interdisciplinary cooperation will also be essential.

■ Improving antimicrobial use must be a key action in efforts to contain resistance. This requires improving access and changing behaviour; such changes take time.

■ Containment will require significant strengthening of the health systems in many countries and the costs of implementation will not be negligible. However, such costs must be weighed against future costs averted by the containment of widespread antimicrobial resistance.

Summary of recommendations for intervention

Patients and the general community & prescribers and dispensers

The emergence of antimicrobial resistance is a complex problem driven by many interconnected factors, in particular the use and misuse of antimicrobials. Antimicrobial use, in turn, is influenced by an interplay of the knowledge, expectations and interactions of prescribers and patients, economic incentives, characteristics of the health system(s) and the regulatory environment. In the light of this complexity, coordinated interventions are needed that simultaneously target the behaviour of providers and patients and change important features of the environments in which they interact. These interventions are most likely to be successful if the following factors are understood within each health setting:

- which infectious diseases and resistance problems are important
- which antimicrobials are used and by whom
- what factors determine patterns of antimicrobial use
- what the relative costs and benefits are from changing use
- what barriers exist to changing use.

Although the interventions directed towards providers and patients are presented separately (1 and 2) for clarity, they will require implementation in an integrated fashion.

1 PATIENTS AND THE GENERAL COMMUNITY

Education

1.1 Educate patients and the general community on the appropriate use of antimicrobials.

1.2 Educate patients on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc.

1.3 Educate patients on simple measures that may reduce transmission of infection in the household and community, such as handwashing, food hygiene, etc.

1.4 Encourage appropriate and informed health care seeking behaviour.

1.5 Educate patients on suitable alternatives to antimicrobials for relief of symptoms and discourage patient self-initiation of treatment, except in specific circumstances.

2 PRESCRIBERS AND DISPENSERS

Education

2.1 Educate all groups of prescribers and dispensers (including drug sellers) on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

2.2 Educate all groups of prescribers on disease prevention (including immunization) and infection control issues.

2.3 Promote targeted undergraduate and postgraduate educational programmes on the accurate diagnosis and management of common infections for all health care workers, veterinarians, prescribers and dispensers.

2.4 Encourage prescribers and dispensers to educate patients on antimicrobial use and the importance of adherence to prescribed treatments.

2.5 Educate all groups of prescribers and dispensers on factors that may strongly influence their prescribing habits, such as economic incentives, promotional activities and inducements by the pharmaceutical industry.

Management, guidelines and formularies

2.6 Improve antimicrobial use by supervision and support of clinical practices, especially diagnostic and treatment strategies.

2.7 Audit prescribing and dispensing practices and utilize peer group or external standard comparisons to provide feedback and endorsement of appropriate antimicrobial prescribing.

2.8 Encourage development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials.

2.9 Empower formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials.

Regulation

2.10 Link professional registration requirements for prescribers and dispensers to requirements for training and continuing education.

Hospitals

Although most antimicrobial use occurs in the community, the intensity of use in hospitals is far higher; hospitals are therefore particularly important in the containment of antimicrobial resistance. In hospitals it is crucial to develop integrated approaches to improving the use of antimicrobials, reducing the incidence and spread of hospital-acquired (nosocomial) infections, and linking therapeutic and drug supply decision-making. This will require training of key individuals and the allocation of resources to effective surveillance, infection control and therapeutic support.

3 HOSPITALS

Management

3.1 Establish infection control programmes, based on current best practice, with the responsibility for effective management of antimicrobial resistance in hospitals and ensure that all hospitals have access to such a programme.

3.2 Establish effective hospital therapeutics committees with the responsibility for overseeing antimicrobial use in hospitals.

3.3 Develop and regularly update guidelines for antimicrobial treatment and prophylaxis, and hospital antimicrobial formularies.

3.4 Monitor antimicrobial usage, including the quantity and patterns of use, and feedback results to prescribers.

Diagnostic laboratories

3.5 Ensure access to microbiology laboratory services that match the level of the hospital, e.g. secondary, tertiary.

3.6 Ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and timely and relevant reporting of results.

3.7 Ensure that laboratory data are recorded, preferably on a database, and are used to produce clinically- and epidemiologically-useful surveillance reports of resistance patterns among common pathogens and infections in a timely manner with feedback to prescribers and to the infection control programme.

Interactions with the pharmaceutical industry

3.8 Control and monitor pharmaceutical company promotional activities within the hospital environment and ensure that such activities have educational benefit.

Use of antimicrobials in food-producing animals

A growing body of evidence establishes a link between the use of antimicrobials in food-producing animals and the emergence of resistance among common pathogens. Such resistance has an impact on animal health and on human health if these pathogens enter the food chain. The factors affecting such antimicrobial use, whether for therapeutic, prophylactic or growth promotion purposes, are complex and the required interventions need coordinated implementation. The underlying principles of appropriate antimicrobial use and containment of resistance are similar to those applicable to humans. The WHO global principles for the containment of antimicrobial resistance in animals intended for food (*2*) were adopted at a WHO consultation in June 2000 in Geneva. They provide a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health. Antimicrobials are widely used in a variety of other settings outside human medicine, e.g. horticulture and aquaculture, but the risks to human health from such uses are less well understood and they have not been included in this document.

4 USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

This topic has been the subject of specific consultations which resulted in "WHO global principles for the containment of antimicrobial resistance in animals intended for food"*. A complete description of all recommendations is contained in that document and only a summary is reproduced here.

Summary

4.1 Require obligatory prescriptions for all antimicrobials used for disease control in food animals.

4.2 In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans.

4.3 Create national systems to monitor antimicrobial usage in food animals.

4.4 Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.

4.5 Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.

4.6 Develop guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals.

* http:// www.who.int/emc/diseases/zoo/who_global_principles.html

National governments and health systems

Government health policies and the health care systems in which they are implemented play a crucial role in determining the efficacy of interventions to contain antimicrobial resistance. National commitment to understand and address the problem and the designation of authority and responsibility are prerequisites. Effective action requires the introduction and enforcement of appropriate regulations and allocation of appropriate resources for education and surveillance. Constructive interactions with the pharmaceutical industry are critical, both for ensuring appropriate licensure, promotion and marketing of existing antimicrobials and for encouraging the development of new drugs and vaccines. For clarity, interventions relating to these interactions with the industry are shown in separate recommendation groups (6 and 7).

5 NATIONAL GOVERNMENTS AND HEALTH SYSTEMS

Advocacy and intersectoral action

5.1 Make the containment of antimicrobial resistance a national priority.

— Create a national intersectoral task force (membership to include health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties) to raise awareness about antimicrobial resistance, organize data collection and oversee local task forces. For practical purposes such a task force may need to be a government task force which receives input from multiple sectors.

— Allocate resources to promote the implementation of interventions to contain resistance. These interventions should include the appropriate utilization of antimicrobial drugs, the control and prevention of infection, and research activities.

— Develop indicators to monitor and evaluate the impact of the antimicrobial resistance containment strategy.

Regulations

5.2 Establish an effective registration scheme for dispensing outlets.

5.3 Limit the availability of antimicrobials to prescription-only status, except in special circumstances when they may be dispensed on the advice of a trained health care professional.

5.4 Link prescription-only status to regulations regarding the sale, supply, dispensing and allowable promotional activities of antimicrobial agents; institute mechanisms to facilitate compliance by practitioners and systems to monitor compliance.

5.5 Ensure that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization.

5.6 Introduce legal requirements for manufacturers to collect and report data on antimicrobial distribution (including import/export).

5.7 Create economic incentives for the appropriate use of antimicrobials.

Policies and guidelines

5.8 Establish and maintain updated national Standard Treatment Guidelines (STGs) and encourage their implementation.

5.9 Establish an Essential Drugs List (EDL) consistent with the national STGs and ensure the accessibility and quality of these drugs.

5.10 Enhance immunization coverage and other disease preventive measures, thereby reducing the need for antimicrobials.

Education

5.11 Maximize and maintain the effectiveness of the EDL and STGs by conducting appropriate undergraduate and postgraduate education programmes of health care professionals on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

5.12 Ensure that prescribers have access to approved prescribing literature on individual drugs.

Surveillance of resistance, antimicrobial usage and disease burden

5.13 Designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health care facilities. The standard of these laboratory facilities should be at least at the level of recommendation 3.6.

5.14 Adapt and apply WHO model systems for antimicrobial resistance surveillance and ensure data flow to the national intersectoral task force, to authorities responsible for the national STGs and drug policy, and to prescribers.

5.15 Establish systems for monitoring antimicrobial use in hospitals and the community, and link these findings to resistance and disease surveillance data.

5.16 Establish surveillance for key infectious diseases and syndromes according to country priorities, and link this information to other surveillance data.

6 DRUG AND VACCINE DEVELOPMENT

6.1 Encourage cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines.

6.2 Encourage drug development programmes which seek to optimize treatment regimens with regard to safety, efficacy and the risk of selecting resistant organisms.

6.3 Provide incentives for industry to invest in the research and development of new antimicrobials.

6.4 Consider establishing or utilizing fast-track marketing authorization for safe new agents.

6.5 Consider using an orphan drug scheme where available and applicable.

6.6 Make available time-limited exclusivity for new formulations and/or indications for use of antimicrobials.

6.7 Align intellectual property rights to provide suitable patent protection for new antimicrobial agents and vaccines.

6.8 Seek innovative partnerships with the pharmaceutical industry to improve access to newer essential drugs.

7 PHARMACEUTICAL PROMOTION

7.1 Introduce requirements for pharmaceutical companies to comply with national or international codes of practice on promotional activities.

7.2 Ensure that national or international codes of practice cover direct-to-consumer advertising, including advertising on the Internet.

7.3 Institute systems for monitoring compliance with legislation on promotional activities.

7.4 Identify and eliminate economic incentives that encourage inappropriate antimicrobial use.

7.5 Make prescribers aware that promotion in accordance with the datasheet may not necessarily constitute appropriate antimicrobial use.

8 INTERNATIONAL ASPECTS OF CONTAINING ANTIMICROBIAL RESISTANCE

8.1 Encourage collaboration between governments, non-governmental organizations, professional societies and international agencies to recognize the importance of antimicrobial resistance, to present consistent, simple and accurate messages regarding the importance of antimicrobial use, antimicrobial resistance and its containment, and to implement strategies to contain resistance.

8.2 Consider the information derived from the surveillance of antimicrobial use and antimicrobial resistance, including the containment thereof, as global public goods for health to which all governments should contribute.

8.3 Encourage governments, non-governmental organizations, professional societies and international agencies to support the establishment of networks, with trained staff and adequate infrastructures, which can undertake epidemiologically valid surveillance of antimicrobial resistance and antimicrobial use to provide information for the optimal containment of resistance.

8.4 Support drug donations in line with the UN interagency guidelines*.

8.5 Encourage the establishment of international inspection teams qualified to conduct valid assessments of pharmaceutical manufacturing plants.

8.6 Support an international approach to the control of counterfeit antimicrobials in line with the WHO guidelines**.

8.7 Encourage innovative approaches to incentives for the development of new pharmaceutical products and vaccines for neglected diseases.

8.8 Establish an international database of potential research funding agencies with an interest in antimicrobial resistance.

8.9 Establish new, and reinforce existing, programmes for researchers to improve the design, preparation and conduct of research to contain antimicrobial resistance.

* *Interagency Guidelines. Guidelines for Drug Donations*, revised 1999. Geneva, World Health Organization, 1999. WHO/EDM/PAR/99.4.

** *Counterfeit drugs. Guidelines for the development of measures to combat counterfeit drugs*. Geneva, World Health Organization, 1999. WHO/EDM/QSM/99.1.

PART A

Introduction and background

Introduction

Antimicrobial resistance is a global problem that needs urgent action

Deaths from acute respiratory infections, diarrhoeal diseases, measles, AIDS, malaria and tuberculosis account for more than 85% of the mortality from infection worldwide (*3*). Resistance to first-line drugs in the pathogens causing these diseases ranges from zero to almost 100%. In some instances resistance to second- and third-line agents is seriously compromising treatment outcome. Added to these major killers is the significant global burden of hospital-acquired (nosocomial) infections usually caused by resistant pathogens, the emerging problems of antiviral resistance and the increasing threats of drug resistance in parasitic diseases such as African trypanosomiasis and leishmaniasis.

The massive increases in trade and human mobility brought about by globalization have enabled the rapid spread of infectious agents, including those that are drug resistant. While richer countries, to a large extent, are still able to rely on the latest antimicrobials to treat resistant infections, access to these life-saving drugs is often limited or totally absent in many parts of the world. Urgent global action is needed, as outlined below.

Costs of resistance

The relentless emergence of antimicrobial resistance has an impact on the cost of health care worldwide. Ineffective therapy due to antimicrobial resistance is associated with increased human suffering, lost productivity and often death. Despite a dearth of data on the costs of resistance (*4*), there is growing consensus about the following points.

- In many regions the prevalence of resistance among common pathogens to readily available cheap antimicrobials is so high that these agents are now of limited clinical effectiveness. Increasingly, this results in difficult choices: to spend money on cheap useless drugs, to use more effective but more expensive drugs to treat a fraction of the population needing treatment, or to increase health care expenditure.

- Ineffective therapy leads to increased costs associated with prolonged illness, more frequent hospital admissions and longer periods of hospitalization. In addition, resistant pathogens in the hospital environment result in hospital-acquired infections which are expensive to control and extremely difficult to eradicate.

- The use of antimicrobials outside the field of human medicine also has an impact on human health. Resistant microorganisms in food-producing animals may have major financial implications for both farmers and consumers. Resistant animal pathogens in some food products, especially meat, may cause infections in humans that are difficult to treat. In addition, loss of public confidence in the safety of food affects the demand for products, with potentially serious economic effects on the farming sector.

Risk management and national security

Antimicrobial resistance threatens other health care gains. For example, co-infection with HIV and antimicrobial-resistant pathogens, e.g. tuberculosis, salmonellosis, other sexually transmitted infections, may result in rapid disease progression in the infected individual and has a potential multiplier effect on the dissemination of resistant pathogens to the rest of the population—thereby placing more demands on health care resources. The emergence of antimicrobial resistance is regarded as a major future threat to the security and political stability of some regions (*5*).

Antimicrobial resistance is frequently irreversible

Although a few studies (*6,7*) have suggested that resistant clones can be replaced by susceptible ones,

resistance is generally slow to reverse or is irreversible. This suggests that interventions to stop the development of resistance should be implemented early, before resistance becomes a problem. The earlier interventions are implemented, the slower will be the development of resistance (*4*). However, this implies taking action before the prevalence of resistant infections climbs, based on decisions made whilst the number of people suffering resistant infections is low. Antimicrobial resistance is only just beginning to be considered as a societal issue and, in economic terms, as a negative externality (*8*,*9*). Individual decisions to use antimicrobials (taken by the consumer alone or by the decision-making combination of prescriber and patient) often ignore the societal perspective and the perspective of the health service.

A dwindling supply of new antimicrobials

The development of new antimicrobial agents effective against resistant pathogens and of alternative approaches such as vaccines is crucial to reduce the future impact of resistance. However, new agents are expensive and time-consuming to develop. Interest in antimicrobial research and development among the research-based pharmaceutical industry has declined as infectious diseases in richer country populations appear to have been conquered and as priorities have shifted to the development of lifestyle drugs. Unless the current rate of emerging resistance is controlled and slowed to preserve the life of existing drugs, this decline in new antimicrobial development, even if reversed now, is likely to result in the absence of effective therapies for some pathogens within the next ten years.

A global problem calls for a global response

There can be no doubt that antimicrobial resistance poses a global challenge. No single nation, however effective it is at containing resistance within its boundaries, can protect itself from the importation of resistant pathogens through travel and trade. The global nature of resistance calls for a global response, not only in the geographic sense, i.e. across national boundaries, but also across the whole range of sectors involved. Nobody is exempt from the problem, nor from playing a role in the solution.

The response of the World Health Organization is to:

- raise awareness of the problems posed by antimicrobial resistance
- promote the sharing of information about and understanding of resistance
- provide strategic and technical guidance on interventions to contain resistance
- assist Member States to implement these interventions
- stimulate research to address the knowledge gaps and improve understanding of antimicrobial resistance and to encourage research and development of new antimicrobial agents.

Development of the WHO Global Strategy

Following the Resolution on Antimicrobial Resistance in 1998 (*1*), WHO has worked with many partners to develop the WHO Global Strategy for Containment of Antimicrobial Resistance (referred to as the WHO Global Strategy hereafter). The aim of this strategy is to provide, for all Member States, a framework of interventions to stimulate the prevention of infection, to slow the emergence of resistance and to reduce the spread of resistant microorganisms, in order to reduce the impact of resistance on health and health care costs, while improving access to existing agents and encouraging the development of new agents. The strategy has been formulated on the basis of expert opinion, published evidence, commissioned reviews and the deliberations of international and national bodies (see Annex B) on the key factors contributing to antimicrobial resistance and the interventions needed for its containment. Based on these inputs, a series of recommendations is proposed, directed towards the aims stated above. Part B of this document provides a summary of the evidence on which the recommendations are based.

It is important to recognize that much remains to be learnt about the interplay between the factors responsible for the emergence and spread of resistance and the optimization and cost-effectiveness of appropriate interventions. However, the urgency of the situation requires that implementation of the WHO Global Strategy moves forward on the evidence currently available.

Implementation of the WHO Global Strategy

The approach to implementation is crucial to its efficacy and success. Much of the responsibility for implementing interventions will fall on individual Member States. There are certain actions that only governments can assure, including the provision of public goods such as information, surveillance and analysis of cost-effectiveness of interventions, and the cross-sectoral coordination critical for an effective response (*10*). Given the large number of recommendations for the containment of antimicrobial resistance presented here, there is a practical need for prioritization and customization to the individual national setting. To assist in the implementation of the WHO Global Strategy, an approach to defining a smaller core set of recommendations is presented (Part C). Furthermore, since antimicrobial resistance is a clearly a global issue, international interdisciplinary cooperation is critical and the areas in which this can be most effective are outlined (Part B, Chapter 8).

Background

What is antimicrobial resistance?

Resistance to antimicrobials is a natural biological phenomenon. The introduction of every antimicrobial agent into clinical practice has been followed by the detection in the laboratory of strains of microorganisms that are resistant, i.e. able to multiply in the presence of drug concentrations higher than the concentrations in humans receiving therapeutic doses. Such resistance may either be a characteristic associated with the entire species or emerge in strains of a normally susceptible species through mutation or gene transfer. Resistance genes encode various mechanisms which allow microorganisms to resist the inhibitory effects of specific antimicrobials. These mechanisms offer resistance to other antimicrobials of the same class and sometimes to several different antimicrobial classes.

All antimicrobial agents have the potential to select drug-resistant subpopulations of microorganisms. With the widespread use of antimicrobials, the prevalence of resistance to each new drug has increased. The prevalence of resistance varies between geographical regions and over time, but sooner or later resistance emerges to every antimicrobial.

While much evidence supports the view that the total consumption of antimicrobials is the critical factor in selecting resistance, the relationship between use and resistance is not a simple correlation. In particular, the relative contribution of mode of use (dose, duration of therapy, route of administration, dosage interval) as opposed to total consumption is poorly understood. Paradoxically, underuse through lack of access, inadequate dosing, poor adherence and sub-standard antimicrobials may play as important a role as overuse. There is consensus, however, that the inappropriate use of antimicrobial agents does not achieve the desired therapeutic outcomes and is associated with the emergence of resistance. For this reason, improving use is a priority if the emergence and spread of resistance is to be controlled.

Appropriate use of antimicrobials

The WHO Global Strategy defines the appropriate use of antimicrobials as *the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance*.

The general principles of appropriate antimicrobial use (*11*) are the same as those for all other medicinal products. An additional dimension for antimicrobials is that therapy for the individual may affect the health of society as a result of the selective pressure exerted by all use of antimicrobial agents. In addition, therapeutic failures due to drug-resistant pathogens or superinfections lead to an increased potential for the spread of these organisms throughout hospitals and the community. Although these risks occur even when antimicrobials are used appropriately, inappropriate use increases the overall selective pressure in favour of drug-resistant microorganisms.

The choice of an appropriate antimicrobial agent may be straightforward when the causative pathogen(s) is/are known or can be presumed with some certainty from the patient's clinical presentation. However, in the absence of reliable microbiological diagnosis or when several pathogens may be responsible for the same clinical presentation, empiric treatment, often with broad-spectrum antimicrobials, is common. Ideally, the choice of antimicrobial should be guided by local or national resistance surveillance data and treatment guidelines. The reality is often far removed from this ideal.

Surveillance of antimicrobial resistance

Surveillance of antimicrobial resistance is essential for providing information on the magnitude and trends in resistance and for monitoring the effect of interventions. The actions taken on the basis of surveillance data will depend on the level at which the data are being collected and analysed. For example, local surveillance data should be used to guide clinical management and to update treat-

ment guidelines, educate prescribers and guide infection control policies. The frequency at which surveillance information is updated is also important given that the rise in prevalence of a resistance phenotype may be rapid and the implementation of policy changes is often slow.

Nationally collected surveillance data may be used to inform policy decisions, update national formularies or lists of essential drugs and standard treatment guidelines and evaluate the cost-effectiveness of interventions. Since resistance is a global problem, international collation of resistance data may also have a useful role (see Chapter 8).

National surveillance systems

WHO and its partners have been successful in supporting the surveillance of drug-resistant tuberculosis in many countries (*12*,*13*). Despite the many ongoing activities worldwide in monitoring resistance among other bacteria, few countries have well-established national networks that regularly collect and report relevant data. In many developing countries and countries whose economies are in transition, microbiology laboratory facilities and information networks will require considerable strengthening before reliable surveillance of resistance is a reality.

Standardization of methods to detect resistance

Current methods for monitoring antimicrobial resistance can be classified as *in vivo*, *in vitro* and molecular methods. The extent to which each of these is used depends on the pathogen/disease and the facilities available. *In vivo* methods or therapeutic efficacy tests are the gold standard for monitoring resistance to antimalarial drugs (*14*) but are not used routinely to monitor resistance in other pathogens. However, linking clinical outcome of treatment with *in vitro* detection of resistance is of critical importance to understand the predictive value of *in vitro* tests.

In vitro methods are the techniques of choice for monitoring resistance in the vast majority of bacterial pathogens, including *Mycobacterium tuberculosis*. However, there is no single international standard method. Different methods have gained popularity in different parts of the world—at least ten different methods for antimicrobial susceptibility tests are used in Europe and more than twelve worldwide. International quality assurance standards can help to overcome the potential difficulties arising from the use of different methods.

Modern techniques have enabled the development and application of molecular methods to determine the presence of specific resistance genes in microbes. They are most widely used to detect genotypic resistance in viruses such as HIV and HBV and, in the future, may form the basis of systems to monitor antiviral resistance. However these molecular methods rely on sophisticated technology that is not available in many settings.

Epidemiologically valid patient selection

Currently, epidemiological methods are not applied in most resistance surveillance studies. The terms *incidence* and *prevalence* tend to be used interchangeably and usually refer to the number of resistant isolates among the total number of isolates surveyed. In contrast, from a public health standpoint, one of the goals of surveillance is to detect the incidence of resistant infections among the total number of infections in a population (*15*). Further bias arises since tests to detect resistance are performed on a subset of patients presenting for treatment who may be more likely to have failed empiric therapy previously or to have other complications. Much greater epidemiologic rigour and more active surveillance approaches are needed to better understand the impact of resistance. In this respect, surveillance of drug resistance in tuberculosis is more advanced than that of other bacteria (*12*).

Surveillance of antimicrobial resistance is fundamental to understanding trends in resistance, to developing treatment guidelines accurately and to assessing the effectiveness of interventions appropriately. Without adequate surveillance, the majority of efforts to contain emerging antimicrobial resistance will be difficult.

The prevalence of resistance

The prevalence of resistance varies widely between and within countries, and over time.

Data on the prevalence of resistance in acute respiratory infections, diarrhoeal diseases, malaria, tuberculosis and gonorrhoea can be found in recent reviews (*16*,*17*,*18*,*19*,*20*,*21*).

Conclusion

While it is difficult to quantify the total impact of resistance on health, published data clearly indicate that morbidity and mortality are increased by delays in administering effective treatment for infections caused by resistant pathogens. The pro-

longed illness and hospitalization of patients with resistant infections and the additional procedures and drugs that they may require carry financial implications. There may also be economic implications for the patient in terms of lost productivity. Antimicrobial-resistant infections in food-producing animals may have major financial implications for both farmers and consumers.

In addition, antimicrobial resistance diverts financial resources that could otherwise be used for improving health and threatens the success of global efforts to combat the major infectious diseases of poverty. In this light, implementation of the WHO Global Strategy can be considered appropriate risk management to protect current health care initiatives and the availability of treatment for future generations.

PART B

Appropriate antimicrobial use and emerging resistance: issues and interventions

CHAPTER 1

Patients and the general community

Recommendations for intervention

Education

1.1 Educate patients and the general community on the appropriate use of antimicrobials.

1.2 Educate patients on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc.

1.3 Educate patients on simple measures that may reduce transmission of infection in the household and community, such as handwashing, food hygiene, etc.

1.4 Encourage appropriate and informed health care seeking behaviour.

1.5 Educate patients on suitable alternatives to antimicrobials for relief of symptoms and discourage patient self-initiation of treatment, except in specific circumstances.

Introduction

Patient-related factors are major drivers of inappropriate antimicrobial use and therefore contribute to the increasing prevalence of antimicrobial resistance. In particular, the perception of patients that most episodes of suspected infection require antimicrobial therapy notably influences the prescribing practices of providers. The direct-to-consumer marketing by the pharmaceutical industry increasingly influences patient expectations and behaviour.

Patient-related factors that are thought to contribute to the problem of antimicrobial resistance include the following:

- patients' misperceptions
- self-medication
- advertising and promotion
- poor adherence to dosage regimens.

Patients' misperceptions

Many patients believe that most infections, regardless of etiology, respond to antimicrobials and thus expect to receive a prescription from their physician for any perceived infection. In a study by Macfarlane et al., 85% of patients thought their respiratory symptoms were caused by infection and 87% believed that antimicrobials would help. One-fifth of these patients specifically asked their physician to prescribe an antimicrobial (*22*). Another study showed that patients' expectations for a prescription were met 75% of the time by prescribers (*23*). In a survey of 3610 patients conducted by Branthwaite and Pechère (*24*), over 50% of interviewees believed that antimicrobials should be prescribed for all respiratory tract infections with the exception of the common cold. It was noted that 81% of patients expected to see a definite improvement in their respiratory symptoms after three days and that 87% believed that feeling better was a good reason for cessation of antimicrobial therapy. Most of these patients also believed that any remaining antimicrobials could be saved for use at a later time. Physicians' perceptions of patient expectations are clearly also crucial (see Chapter 2).

Many patients believe that new and expensive medications are more efficacious than older agents; this belief is shared by some prescribers and dispensers and often results in the unnecessary use of the newer agents. In addition to causing unnecessary health care expenditure, this practice encourages the selection of resistance to these newer agents as well as to older agents in their class.

Patients commonly misunderstand the pharmacological actions of antimicrobial agents. Experience suggests that many people do not know the difference between antimicrobials and other classes of drugs and thus will not understand the issues of resistance uniquely related to antimicrobials. In the Philippines, isoniazid is viewed as a "vitamin for the lungs" and mothers purchase isoniazid syrup for children with "weak lungs" in

the absence of documented tuberculosis (*25*). Patients also fail to recognize that many brand names may actually be the same antimicrobial—resulting in the unnecessary overstocking of some agents. For example, specific patient demand caused one pharmacy in South India to stock more than 25 of the 100 or so brands of co-trimoxazole available (*26*).

A greater interaction between health providers and consumers for health and drug (antimicrobial)-related education has been proposed (*27*). The WHO Action Programme on Essential Drugs convened a consultation to address the need for public education in rational drug use (*28*) and has since produced a document "Rational Drug Use: Consumer Education and Information" (*29*). This document discusses the practical issues and dilemmas related to the need for rational drug use education, its priority and content, underlying principles and target population. In a study carried out in Peru, a multifaceted educational intervention directed at the community using media, face-to-face meetings and training on the use of medicines was successful in decreasing the inappropriate use of antidiarrhoeals and antimicrobials for simple diarrhoea (*30*).

Self-medication

Self-medication with antimicrobials is often cited as a major factor contributing to drug resistance (*31*). In a Brazilian study, it was determined that the three most common types of medication used by villagers were antimicrobials, analgesics and vitamins. The majority of antimicrobials were prescribed by a pharmacy attendant or were purchased by the patient without prescription (*32*) despite having prescription-only legal status. In addition to obvious uncertainty as to whether the patient has an illness that will benefit from antimicrobial treatment, self-medicated antimicrobials are often inadequately dosed (*33*) or may not contain adequate amounts of active drug, especially if they are counterfeit drugs (*34*). This is especially important in the treatment of diseases such as tuberculosis.

Advertising and promotion

Direct-to-consumer advertising allows pharmaceutical manufacturers to market medicines directly to the public via television, radio, print media and the Internet. Where permitted, this practice has "the potential to stimulate demand by playing on the consumer's relative lack of sophistication about the evidence supporting the use of one treatment over another" (*35*). These advertising methods are apparently quite effective, since pharmacists are frequently able to guess the feature advertisements of the previous day's television programmes based upon daily customer requests for specific medications (*31*). A survey of physicians in the USA demonstrated that, on average, each had encountered seven patients within the previous six months who had specifically requested prescription-only drugs as a result of direct-to-consumer advertising (*36*). Over 70% of the physicians reported that requests from patients as a result of direct-to-consumer advertisements had led them to prescribe a pharmaceutical agent that they might not have otherwise chosen.

In a telephone survey of consumers regarding direct advertising, 66% believed that advertisements for medications would provide useful information but 88% said that they would seek out more information about a drug that they saw advertised on television or in print before purchasing it. On the other hand, only one-third of interviewees agreed with the statement that most people would know if they were being misled by the advertisements (*37*).

Recently, the United States Food and Drug Administration proposed new guidelines that lift previous restrictions on direct-to-consumer advertising and allow pharmaceutical manufacturers greater freedom on advertised health claims. A two-year evaluation period was proposed to assess the impacts and implications of these guidelines (*27*).

Advertising and promotion can also be used to improve the appropriate use of antibiotics. Public education campaigns in India, which include the use of mass media such as television, appear to have effectively educated even illiterate populations about antimicrobial resistance in some regions (Bhatia, personal communication).

Interventions to address the effects of advertising and promotion are discussed in Chapter 7.

Poor adherence to dosage regimens

In a 1988 literature search, over 4000 English language articles were available on the topic of patient adherence to dosing instructions, more than 75% of which had been published within the previous ten years (*38*). In the majority of studies, it was reported that a lack of patient understanding and provider communication led to most

instances of non-adherence (*39*,*40*). Patients who fail to complete therapy have a higher likelihood of relapse, development of resistance and need for re-treatment; this applies especially to those patients requiring prolonged treatment, e.g. those with tuberculosis or HIV infection. Previous antimicrobial treatment and excessive duration of treatment are considered two of the most important factors in the selection of resistant microorganisms (*41*,*42*).

Many methods have been used to ensure adherence to antimicrobial therapy. These include the use of fixed dose combinations to minimize the number of tablets or capsules, special calendars, blister packing, DOT (directly observed therapy) for tuberculosis (*12*,*13*,*43*,*44*), other course-of-therapy packaging using symbols in labelling, and more simplified therapy (*45*,*46*). Directly observed therapy, short-course (DOTS) is the WHO strategy for TB control that has been shown to significantly decrease acquired resistance in tuberculosis (*47*,*48*). Education of patients on the name, dosage, description and common adverse effects of their medication(s) has been used to increase adherence (*49*) (see also Chapter 5, Recommendations).

Price is a powerful factor in determining how consumers use antimicrobials—economic hardship can lead to early cessation of therapy. For example, antimicrobials are purchased in single doses in many developing countries and are taken for only a fraction of the recommended effective duration, until the patient feels better. This practice has the potential for fostering the selection of resistant microorganisms and therefore has a higher likelihood of treatment failure (*50*,*51*). This is especially important for diseases such as tuberculosis and endocarditis (*43*,*52*). Government schemes which subsidize the cost of certain preferred antimicrobials are one economic means of improving the appropriateness of antimicrobial use. Where insurance systems exist, charging differential co-payments to patients, with lower payments for the more desirable drugs, may encourage appropriate use.

CHAPTER 2

Prescribers and dispensers

Recommendations for intervention

Education

2.1 Educate all groups of prescribers and dispensers (including drug sellers) on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

2.2 Educate all groups of prescribers on disease prevention (including immunization) and infection control issues.

2.3 Promote targeted undergraduate and postgraduate educational programmes on the accurate diagnosis and management of common infections for all health care workers, veterinarians, prescribers and dispensers.

2.4 Encourage prescribers and dispensers to educate patients on antimicrobial use and the importance of adherence to prescribed treatments.

2.5 Educate all groups of prescribers and dispensers on factors that may strongly influence their prescribing habits, such as economic incentives, promotional activities and inducements by the pharmaceutical industry.

Management, guidelines and formularies

2.6 Improve antimicrobial use by supervision and support of clinical practices, especially diagnostic and treatment strategies.

2.7 Audit prescribing and dispensing practices and utilize peer group or external standard comparisons to provide feedback and endorsement of appropriate antimicrobial prescribing.

2.8 Encourage development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials.

2.9 Empower formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials.

Regulation

2.10 Link professional registration requirements for prescribers and dispensers to requirements for training and continuing education.

Introduction

Prevention of infection should be the primary goal to improve health and reduce the need for antimicrobial therapy. Where appropriate, vaccine uptake should be improved to achieve this. Both the emergence and maintenance of resistant microorganisms are promoted by antimicrobial use. Furthermore, once they are widespread, resistant strains are difficult to replace by their susceptible counterparts. Early action to optimize prescribing patterns and to reduce inappropriate use is thus crucial. The difficulty is that multiple factors influence prescribers and dispensers in deciding when to use antimicrobials. These factors appear to vary in importance depending on geographical region, social circumstances and the prevailing health care system. Often, the most important factors are interlinked. Many traditional approaches to improving antimicrobial use rely on providing correct information about drugs or diseases, with the implicit assumption that prescribers and dispensers will incorporate the new knowledge and make appropriate adjustments in their practice. However, experience and reviews of well-designed research studies (*53*,*54*,*55*) have shown that this is rarely the case. Effective interventions to improve antimicrobial use must address the underlying causes of current practice and barriers to change (*56*).

Lack of knowledge and training

Lack of knowledge about differential diagnoses, infectious diseases and microbiology and about the appropriate choice of antimicrobials for various infections all play a role in inappropriate prescribing practices (*34*). Even in developed countries,

the pharmacology of antimicrobial agents, their modes of action and spectrum of activity and issues relating to resistance receive limited coverage in medical school curricula, resulting in poorly informed prescribers (*57*). It is not uncommon for drug company sales representatives and the commercially oriented publications they provide to be the main sources of information for prescribers (*58*).

Lack of knowledge is a major factor responsible for inappropriate antimicrobial use globally. In one study in China, 63% of antimicrobials selected to treat proven bacterial infections were found to be inappropriate (*59*). In a retrospective study in Viet Nam, more than 70% of patients were prescribed inadequate dosages (*60*). Gumodoka et al. (*61*) reported that one in four patients in their medical districts received antimicrobials by injection and that approximately 70% of these injections were unnecessary. Studies in many European countries and in the USA demonstrate widespread unnecessary use of antimicrobials in patients with viral upper respiratory tract infections (*62*).

Printed materials are the most common and least expensive educational interventions but inappropriate prescribing is rarely due to a lack of knowledge alone. Many studies have found that the use of printed material only, without other forms of supporting interventions, is ineffective in altering prescribing behaviours (*63*,*64*,*65*). Continuing education and in-service training programmes have traditionally involved lecture- and seminar-style presentations oriented to the presentation of factual information. A large body of research has shown that these approaches are not necessarily the most effective for improving practice (*66*). Academic detailing, or unadvertisements, and educational programmes directed to physicians have been shown to decrease antimicrobial use/misuse (*67*,*68*,*69*,*70*). One consistently successful method has been educational outreach, which consists of brief, targeted, face-to-face educational visits to clinicians by specially trained staff (*67*,*71*,*72*). In developing countries where individual educational outreach visits may not be practical or cost-effective, interactive problem-oriented educational sessions with small groups of physicians, paramedics, or pharmacy counter attendants have demonstrated similar success, especially when sessions are repeated over time or reinforced with improved clinical supervision (*53*). Another promising approach involves engaging local opinion leaders in the process of disseminating targeted educational messages to their peer group (*73*,*74*). Unfortunately, none of these studies looked at resistance as an outcome or impact indicator. Increasing problem-based pharmacotherapy training for medical and paramedical students can have a positive impact on long-term good prescribing habits. The use of a WHO manual (*75*) designed to support problem-based learning for medical students has been demonstrated to have a positive impact on prescribing skills of students in seven medical schools (*76*).

In countries with limited resources, the dispensing of antimicrobials by unauthorized persons lacking appropriate knowledge is common. In a study of 40 randomly selected health facilities in Ghana, only 8.3% of dispensers had received formal training (*77*). Bruneton et al. (*78*) found that drug sellers in seven sub-Saharan African countries frequently recommended antimicrobials not present on the regions' Essential Drugs List and rarely suggested that the patient should consult a physician.

Improving the drug education of non-physician prescribers and dispensers is another recommended step in improving drug use. A study in Ghana showed that educational interventions aimed at dispensers significantly improved drug use by increasing the percentage of appropriately labelled containers and by increasing patient knowledge of their medications (*77*). Interventions targeted at local drug sellers in the Philippines significantly improved their quality of practice (*79*).

Lack of access to information

Even relatively well-trained prescribers often lack the up-to-date information required to make appropriate prescribing decisions. This tends to result in the excessive use of newer antimicrobial agents, often with a broader spectrum of action. Conversely, lack of surveillance data and updated treatment guidelines may lead to the inappropriate prescription of older antimicrobials which are either no longer effective due to the emergence of resistance or should have been replaced by newer agents with improved cost-effectiveness or reduced toxicity.

Use of clinical practice guidelines is a core managerial strategy in every health system for improving diagnosis and therapy. Despite the abundance of guidelines, research has shown that they have little effect on clinical practice unless they are actively disseminated (*80*). Factors that increase the likelihood of guidelines being adopted

include local involvement of end-users in the process of development, the presentation of key elements in a simple algorithm or protocol, and dissemination in a multi-component programme that includes interactive education, monitoring of adherence and reinforcement of positive changes. A combination of national prescribing guidelines and educational campaigns on the appropriate use of antimicrobials targeted at prescribers has had some success in reducing the prevalence of specific antimicrobial resistance (*7*). There has also been some success in the use of educational campaigns targeted at prescribers and patients to recognize that not all infections require the use of antimicrobials. Included in one such campaign was a message to parents discouraging them from sending their sick children to day care in order to reduce the opportunities for transmission of infection (*81*).

Lack of diagnostic support

Lack of access to or use of appropriate diagnostic facilities and slow or inaccurate diagnostic results encourage prescribers to cover the possibility that infection may be responsible for a patient's illness, even when this is not the case (*58*). In particular, the lack of accurate tests at point-of-care to achieve a rapid diagnosis is a significant problem for many diseases and is an area in which future research could be very beneficial. Empiric treatment of infections with a reasonably well-defined clinical presentation is more likely to be appropriate than that of infections with an undifferentiated presentation e.g. malaria presenting as fever alone. In this latter situation the differential diagnosis may be wide and therefore empiric treatment protocols will necessarily need to be broad—leading to a higher likelihood of unnecessary antimicrobial therapy. A careful history and access to adequate diagnostic facilities allow the differential diagnosis to be narrowed and therapy more targeted. A study of barefoot doctors in a district of Bangladesh found that antimicrobials were prescribed for 60% of all patients seen in areas without diagnostic services—a higher rate than noted in other districts (*82*). Other studies have had similar findings (*83*,*84*). In developed countries, empiric antimicrobial therapy is sometimes considered to be more cost-effective than awaiting laboratory proof of infection before commencing treatment.

For conditions such as acute respiratory infections, diarrhoea and malaria in children, and sexually transmitted disease in adults, treatment algorithms have been developed (*55*,*85*,*86*). These diagnostic and treatment algorithms are based on detailed research studies, generally in resource-poor regions, in which the patients' clinical presentations have been correlated with subsequent microbiological confirmation of disease. This syndromic approach is particularly useful in health care settings where diagnostic capabilities are limited, since it allows a rational approach to determining the need for antimicrobial therapy and the most appropriate agents.

Fear of bad clinical outcomes

Prescribers may overuse antimicrobials because they fear that their patients may suffer poor outcomes in the absence of such therapy. Prescribing just to be safe increases when there is diagnostic uncertainty, lack of prescriber knowledge regarding optimal diagnostic approaches, lack of opportunity for patient follow-up, or fear of possible litigation (*87*,*88*).

Perception of patient demands and preferences

Prescribers' perceptions regarding patient expectations and demands substantially influence prescribing practices (*22*,*23*,*58*,*87*,*89*). Although these perceptions may be incorrect, they can lead to a perpetual cycle whereby patients who repeatedly receive unnecessary antimicrobials develop the misconception that antimicrobials are frequently necessary for most ailments and therefore request them excessively (*22*,*90*). Prescribers and dispensers may also respond to patient demand for particular formulations of antimicrobials, e.g. capsules rather than tablets. In some cultural settings, antimicrobials given by injection are considered more efficacious than oral formulations. This tends to be associated with the overprescribing of broad-spectrum injectable agents when a narrow-spectrum oral agent would be more appropriate (*61*).

In an effort to reduce re-consultation of patients, Macfarlane et al. (*23*) utilized a patient information leaflet regarding coughs. Among patients not prescribed antimicrobials, those given the educational leaflet appeared less likely to re-consult; this result, however, was not statistically significant. The use of delayed prescribing techniques has been proposed when physicians feel pressured by their patients into prescribing antimicrobials (*45*,*87*). Some physicians say that

they promise a free return visit if the patient feels that a re-consultation is necessary because they did not receive antimicrobials (*87*).

Economic incentives

Many health providers practise in environments with financial incentives to prescribe or dispense greater numbers of drugs overall or of specific types. Prescribers may fear the potential loss of future patient custom and revenue if they do not respond to perceived demands for antimicrobials (*91*). Furthermore, in some countries, prescribers profit from both prescribing and dispensing antimicrobials, such that it is in their financial interest to prescribe antimicrobials even when they are not clinically indicated. Additional profit is sometimes gained by recommending newer more expensive antimicrobials in preference to older cheaper agents. In countries where physicians are poorly paid, pharmaceutical companies have been known to pay commissions to prescribers who use their products (*92*). Other less direct incentives such as financial support for attendance at meetings, entertainment, or payment for enrolling patients in marketing research studies may also influence prescribing practices. Even in health systems where there is no overt incentive to prescribe, there is usually no incentive not to prescribe (*8*).

It is desirable to minimize financial conflicts of interest in therapeutic decision-making by health providers, such as allowing physicians to profit from dispensing drugs that they prescribe or allowing pharmacists who sell drugs to prescribe them as well. Coast et al. (*9*) and Smith and Coast (*93*) explored economic perspectives of policies used to decrease antimicrobial resistance. They discuss techniques such as regulation (controlling prescription practices by means of policies and guidelines or by enforcing a global limit to the prescription of antimicrobials), permits (allowing physicians to prescribe up to a certain quantity of antimicrobials per permit) and charges (levying taxes on antimicrobials). In their model, they suggest that the use of permits may offer a method for reducing antimicrobial resistance.

Several countries have introduced health provider reimbursement strategies that are designed to encourage physicians to limit overall use of medicines and often to share in the resulting financial savings. Examples of these strategies are capitation payments that include pharmaceutical costs, general practice fundholding (*94*) and bonuses tied to practice pharmaceutical budgets. While these strategies may reduce inappropriate use of antimicrobials, they may also reduce appropriate use. Nevertheless, a number of Scandinavian studies have suggested that national antibiotic policies together with changes in reimbursement policy can be safe and effective (*95*,*96*,*97*).

Peer pressure and social norms

In focus group studies, prescribers expressed concern that, if they did not prescribe antimicrobials, patients would seek other sources of care where they could obtain antimicrobials (*91*). In addition, the physician offering the latest and often the most expensive and broad-spectrum antibiotic may be perceived to be the most informed and desirable source of care.

Understanding prescribing patterns is crucial to identifying areas for potential intervention to improve use (*58*). Drug use patterns and prescribing behaviour, including the influence of various social and patient pressures, can be described using the indicators and methods in the WHO manual "How to investigate drug use in health facilities" (*98*). After undertaking interventions to improve drug use, these same indicators can be used to measure impact.

Factors associated with the prescriber's working environment

In busy clinical practices, health care providers may not have time to explain to patients why they have chosen to prescribe or not prescribe antimicrobial therapy (*99*). Some clinicians in this situation may believe it is simply most time-effective to prescribe an antimicrobial. Lack of privacy in consultation facilities may also impact on prescribing behaviour since some conditions, such as urinary tract sepsis and sexually transmitted diseases, require diagnostic specimens and/or physical examination that are difficult to undertake in public. The lack of opportunity for health care workers to follow up their patients to assess progress after treatment and poor continuity of care in general negatively influence communication and the development of trust between the patient and health care provider. It is thus often easier for both prescriber and patient if an antimicrobial agent is prescribed on first contact.

Lack of appropriate legislation or enforcement of legislation

Absence of appropriate legislation or its enforcement may result in the proliferation of locations where untrained or poorly trained persons dispense antimicrobials, leading to overuse and inappropriate use (see Chapter 5).

Inadequate drug supply infrastructure

In many parts of the world, the ability of prescribers and dispensers to provide appropriate antimicrobial therapy is limited by the lack of availability of the necessary drugs (*100*).

CHAPTER 3

Hospitals

Recommendations for intervention

Management

3.1 Establish infection control programmes, based on current best practice, with the responsibility for effective management of antimicrobial resistance in hospitals and ensure that all hospitals have access to such a programme.

3.2 Establish effective hospital therapeutics committees with the responsibility for overseeing antimicrobial use in hospitals.

3.3 Develop and regularly update guidelines for antimicrobial treatment and prophylaxis, and hospital antimicrobial formularies.

3.4 Monitor antimicrobial usage, including the quantity and patterns of use, and feedback results to prescribers.

Diagnostic laboratories

3.5 Ensure access to microbiology laboratory services that match the level of the hospital, e.g. secondary, tertiary.

3.6 Ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and timely and relevant reporting of results.

3.7 Ensure that laboratory data are recorded, preferably on a database, and are used to produce clinically- and epidemiologically-useful surveillance reports of resistance patterns among common pathogens and infections in a timely manner with feedback to prescribers and to the infection control programme.

Interactions with the pharmaceutical industry

3.8 Control and monitor pharmaceutical company promotional activities within the hospital environment and ensure that such activities have educational benefit.

Introduction

Hospitals are a critical component of the antimicrobial resistance problem worldwide. The combination of highly susceptible patients, intensive and prolonged antimicrobial use, and cross-infection has resulted in nosocomial infections with highly resistant bacterial pathogens such as multi-resistant Gram-negative rods, vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) as well as resistant fungal infections. Some of these resistant strains have now spread outside the hospital causing infections in the community. Hospitals are also the eventual site of treatment for many patients with severe infections due to resistant pathogens acquired in the community, including penicillin-resistant *Streptococcus pneumoniae*, multi-resistant salmonellae and multi-resistant *Mycobacterium tuberculosis*. In the wake of the AIDS epidemic, the prevalence of such infections can be expected to increase, both in the community and in hospitals. Hospitals can thus serve both as a point of origin of and as a reservoir for highly resistant pathogens which may later enter the community or chronic care facilities.

Infection control

Transmission of highly resistant bacteria from patient to patient within the hospital environment (nosocomial transmission) amplifies the problem of antimicrobial resistance and may result in the infection of patients who are not receiving antimicrobials. Transmission of antimicrobial-resistant strains from hospital personnel to patients or vice versa may also occur. The key element in minimizing such horizontal transmission of infection within hospitals is careful attention to infection control practices (*101*).

Failure to implement simple infection control practices such as handwashing and changing gloves before and after contact with patients is common (*102*,*103*,*104*,*105*). In some cases, especially in resource-poor regions, this may be due to the ab-

sence of suitable handwashing facilities. However, inadequate handwashing is generally due to lack of recognition of its importance in maintaining good infection control, understaffing or health care worker forgetfulness. Regardless of the reasons, poor infection control practices result in the increased dissemination of resistant bacterial strains in hospital and health care facilities. The spread of resistance appears to be widening as patients move more rapidly from intensive care wards to general wards and then to the community or between hospitals and nursing homes (*51*,*106*,*107*).

Infections can also be transmitted via non-sterile injection and surgical equipment. In a study of health facilities in Tanzania, 40% of supposedly sterilized needles and syringes were bacterially contaminated (*61*). Poor decontamination or failures in sterilization of equipment can have an enormous impact on the spread of viral infections such as HIV (*108*), hepatitis B and C. Re-use of single-use needles and syringes has played a major role in the spread of viral hepatitis following immunization programmes in some countries and among intravenous drug users (*109*,*110*,*111*,*112*). Any practice that permits the spread of infection permits the spread of resistant infections.

Infection control activities are best coordinated by an active and effective infection control programme. The SENIC study, conducted by the Centers for Disease Control (CDC) and which included a large sample of hospitals in the USA, demonstrated that hospitals having infection control programmes with both active surveillance and control elements were effective in reducing rates of nosocomial infection (*113*,*114*,*115*). In particular, interventions such as education and motivation programmes, improvement of equipment, and performance feedback can increase adherence to improved handwashing (*104*). Barrier precautions have been shown to be effective in reducing infection transmission rates and thereby the spread of resistance. Mayer et al. (*116*) showed that improved handwashing and the use of gloves and gowns decreased infection rates.

With respect to the control of antimicrobial resistance within the hospital setting, the major evidence of effectiveness stems from the management of outbreaks or clusters of resistant infections. In these situations, a variety of techniques including targeted cohorting of infected patients, enhanced surveillance, isolation or rigorous barrier precautions, early discharge and alteration in antimicrobial usage have been effective.

The key elements of an effective infection control programme include:

— development and implementation of appropriate barrier precautions (handwashing, wearing of gloves and gowns) and isolation procedures

— adequate sterilization and disinfection of supplies and equipment

— the use of aseptic techniques for medical and nursing procedures

— training of health care personnel in appropriate sterile techniques and infection control procedures

— maintenance of appropriate disinfection and sanitary control of the hospital environment, including air

— active surveillance of infections and antimicrobial resistance, with data analysis and feedback to prescribers and other staff

— recognition and investigation of outbreaks or clusters of infections.

The programme should have a qualified chairperson and staff and adequate resources to accomplish these goals. The most effective infection control team consists of a physician (preferably trained in infectious diseases), a microbiologist, infection control nurses, pharmacist(s) and hospital management representatives, with the responsibility for the day-to-day management of resistance issues. Increased efficiency may be achieved by an overlap in the membership of the infection control team and the hospital therapeutics committee.

Appropriate facilities for optimal infection control practices, including sufficient basins and clean towels to regularly wash hands between patient contacts, may be difficult to achieve in some countries. Nevertheless, such facilities are vital if nosocomial transmission of infections is to be controlled. Handwashing, isolation practices, sufficient beds (and space between them), as well as clean ventilation are needed in hospitals to prevent the spread of bacteria, including resistant strains.

Control of antimicrobial use in hospitals

Hospitals provide an important training ground for students to learn about prescribing practices. Unfortunately, antimicrobial prescribing in hospitals is often irrational. In an analysis of prescrib-

ing practices in ten studies from teaching hospitals worldwide, 41% to 91% of all antimicrobials prescribed were considered inappropriate (*117*). Patterns of prescribing become entrenched and, if they are not consistent with appropriate antimicrobial treatment guidelines, they may have an enormous effect on the emergence of resistant pathogens and on the pharmacy budget of a hospital if the drugs are expensive. For many clinicians, a common source of information regarding hospital antimicrobial use is the literature provided by pharmaceutical representatives. Such information is less likely to be objective than national or regional treatment guidelines (see Chapter 7).

Antimicrobial prophylaxis for surgical procedures is a common reason for excessive prescribing in many hospitals. Numerous studies have outlined those procedures in which patients benefit from such prophylaxis and those in which they do not (*118*,*119*,*120*,*121*,*122*,*123*,*124*), but inappropriate prophylaxis is still widely used. A further problem is the continuation of antimicrobials, initially administered as prophylaxis, well beyond the required 12 to 24 hour post-surgical period without clear medical indication other than the opinion of the surgeon. Such prescribing patterns result in high rates of antimicrobial exposure among hospitalized patients, potentially leading to high colonization rates of resistant nosocomial pathogens and antibiotic-associated diarrhoea. For these reasons a variety of approaches have been utilized to modify antimicrobial prescribing practices within the hospital setting. These have the overall goal of reducing the total consumption of antimicrobials and of altering the type of usage in favour of regimens less likely to foster the emergence of resistant strains.

Hospital therapeutics committees

An active and effective hospital therapeutics committee is considered a key element for the control of antimicrobial usage in hospitals, although there are only limited published data to support this view and there are few data regarding the impact of hospital therapeutics committees in developing countries. However, their beneficial role in the promotion of rational prescribing habits, monitoring of drug usage and cost containment is well established in developed countries (*125*,*126*). For this reason, the establishment of such a committee is considered important. The premise that any clinician should be allowed to use any antimicrobial considered necessary without any peer-review process is generally inconsistent with optimizing antimicrobial use. All clinicians should be prepared to justify their antimicrobial usage patterns.

The following activities represent some of the key roles of an effective therapeutics committee.

- Development of written policies and guidelines for appropriate antimicrobial usage in the hospital, based on local resistance surveillance data. Policies should be developed locally, with broad input and consensus from health care providers and microbiologists.
- Selection and provision of appropriate antimicrobials in the pharmacy after consideration of local clinical needs.
- Establishment of formal links with an infection control committee, preferably with some overlap in membership.
- Definition of an antimicrobial utilization review programme, with audit and feedback on a regular basis to providers, and promotion of active surveillance of the nature and amount of antimicrobial use in the hospital.
- Overseeing antimicrobial use through a system of monitoring the quantity used and the indications for use.

With regard to the last point, it is important to recognize that such seemingly basic data collection can be difficult to undertake accurately, even in the best medical centres. Nevertheless, accurate antimicrobial usage information is crucial to rational decision-making and the interpretation of antimicrobial resistance data. In systems where prescribing data are collected routinely, utilization review (or audit) combined with feedback of performance data to prescribers has become a common strategy to influence patterns of prescribing practice. The success of audit and feedback programmes is mixed (*127*). Audit and feedback programmes using manually collected samples of prescribing data and simple performance indicators have been successful at improving antibiotic prescribing in some developing country settings (*53*). Although a decrease in resistance prevalence can be achieved with the use of control programmes, once monitoring is relaxed, the prevalence of drug-resistant organisms may quickly increase again (*128*).

Formularies

Hospital formularies, or lists of drugs routinely stocked by the hospital pharmacy for inpatient and outpatient use, guide the parallel processes of antimicrobial selection, procurement and supply, and represent a means for decreasing inappropriate antimicrobial prescribing and reducing expenditures. In conjunction with clinical guidelines, formularies encourage the proper use of preferred drugs within each category of antimicrobial. Antimicrobial formularies should relate to local or regional treatment guidelines and should ideally be based on relative efficacy, cost-effectiveness data and local patterns of resistance (*129*). This, however, is difficult in many hospitals. In a USA survey in which a great majority of hospitals had implemented formularies as a method of decreasing antimicrobial costs, many noted that expenditures actually increased—this was usually considered to be due to drug resistance (*130*). Although some authors have suggested that a restrictive hospital formulary may actually contribute to the selection of resistant bacteria by narrowing and focusing selective pressures, there are few data to support this view (*131*). Thus, formularies are useful in avoiding the unnecessary keeping in stock of a range of antimicrobials that duplicate their spectrum and in reinforcing the importance for clinicians to understand an appropriate range of antimicrobials well. However, the specific effectiveness of a formulary in reducing the emergence of antimicrobial resistance is unclear.

Cycling of antibiotics

The cycling of antimicrobials within a health care institution has been suggested as a possible intervention to decrease drug resistance. This technique alternates formulary antimicrobials between drug classes every couple of months and theoretically reduces the selective pressure of one antimicrobial class (*132*). However, in a recent review of the topic, there was no evidence that cycling reduced antimicrobial resistance (*133*). Cycling may have only a temporary effect on resistance patterns and ultimately may simply replace one resistance problem with another (*134*).

Use of clinical practice or treatment guidelines

Clinical practice guidelines (*80*) can improve decision-making and therefore improve patient care. They should be developed locally or regionally with wide input and consensus and should utilize information from local surveillance data whenever possible. Programmes that utilize clinical practice guidelines supported by other interventions such as education and peer review are more effective than those without such support (*135*). In an observational study of one hospital with a computerized prescribing guideline system that encouraged appropriate use of antimicrobials, trend analysis showed that resistance patterns in selected hospital-acquired infections stabilized over a seven-year period (*136*). Another study noted a reduction in one type of resistance when controls on selected agents were applied, but an increase in resistance to other antimicrobials which were not controlled—the so-called "squeezing the balloon" effect (*137*). Nevertheless, treatment guidelines are particularly useful in resource-poor countries where they can be used to streamline treatment protocols and limit the range of antimicrobials stocked in pharmacies. However, such treatment guidelines need to be developed carefully and their implementation reviewed regularly. Their appropriateness is dependent on accurate and updated resistance surveillance and clinical outcome data.

Other techniques to control or modify antimicrobial use in hospitals

Several types of innovative tools to guide antimicrobial prescribing and dispensing have been tested; some have been shown to be effective in changing antimicrobial use in hospital settings. Antimicrobial order forms have been used with mixed success, showing improvement in antimicrobial prescribing in some hospitals but not in others (*138*,*139*,*140*). Automatic review of the use of selected antimicrobials by a consultant or automatic cessation of antimicrobial administration after a defined period may also reduce unnecessary use (*46*). However, these control measures are either labour-intensive or require reasonably sophisticated computerized pharmacy records—both of which are not generally available.

Integrated interventions

Multi-disciplinary and integrated approaches to reduce antimicrobial use in hospitals have been proposed as a solution (*105*,*141*,*142*,*143*). Hospital administrators, clinicians, infectious diseases specialists, infection control practitioners, microbiologists, clinical epidemiologists and

hospital pharmacists all have a role—but coordination of their activities is vital. Such activities include the selection of formulary drugs, the development of formulary-based guidelines, monitoring and evaluating drug use, surveillance and reporting of bacterial resistance patterns, detection and appropriate care of patients with resistant organisms, and promotion and monitoring of basic infection control practices (*143*). Interactions with the pharmaceutical industry must also be considered, including appropriate control of the access of sales representatives to clinical staff and monitoring industry-sponsored educational programmes for providers. Targeted antimicrobial control policies in combination with improved hygiene and education have reduced antimicrobial resistance in some settings (*144*,*145*). However, in one study, prescriber education combined with hospital antimicrobial control policies led to decreased antimicrobial costs and improved prescribing, but only limited change in resistance (*146*).

The microbiology laboratory and antimicrobial resistance

Delayed or incorrect laboratory diagnostic data frequently result in prolonged empiric antimicrobial therapy (see also Chapters 2 and 5). The hospital microbiology laboratory plays an important role in the recognition and surveillance of antimicrobial resistance, both within the hospital and in the community. The laboratory must provide high quality diagnostic testing to correctly identify infection and accurate antimicrobial susceptibility testing to guide appropriate treatment. Appropriately trained personnel, adequate supplies, materials and equipment, and internal quality control and external quality assurance procedures, are essential. The laboratory should produce and disseminate meaningful local surveillance data both with respect to the predominant pathogens/syndromes and their antimicrobial resistance patterns. The laboratory should work closely with hospital infection control personnel, with the hospital therapeutics committee and with providers to ensure that appropriate antimicrobials are tested and reported in order to recognize outbreaks or unusual infections and identify trends in antimicrobial resistance. Software tools such as WHONET are available to facilitate analysis and data sharing (*147*). Depending on resources, the laboratory should also provide specialized testing, e.g. molecular typing of bacterial strains, to assist epidemiological investigations.

Interactions between the hospital and the community

Following discharge from hospital, patients may still be colonized or infected with resistant bacteria acquired in hospital. In general, little action is necessary in such circumstances if the patient is healthy and discharged home. However, this is the likely mechanism through which highly resistant hospital-acquired pathogens eventually become widespread in the community. Of greater concern is the transfer of such patients to chronic care facilities where they have been shown to be the source of strains that subsequently spread throughout the facility. Patients known to be colonized or infected with resistant pathogens upon discharge to a care facility should generally be identified so that appropriate precautions can be taken.

CHAPTER 4

Use of antimicrobials in food-producing animals

This topic has been the subject of specific consultations which resulted in "WHO global principles for the containment of antimicrobial resistance in animals intended for food"*. A complete description of all recommendations is contained in that document and only a summary is reproduced here.

Recommendations for intervention

Summary

4.1 Require obligatory prescriptions for all antimicrobials used for disease control in food animals.

4.2 In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans.

4.3 Create national systems to monitor antimicrobial usage in food animals.

4.4 Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.

4.5 Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.

4.6 Develop guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals.

Introduction

Antimicrobial use in food-producing animals may affect human health by the presence of drug residues in foods and particularly by the selection of resistant bacteria in animals. The consequences of such selection include:

— an increased risk for resistant pathogens to be transferred to humans by direct contact with animals or through the consumption of contaminated food or water

— the transfer of resistance genes from animal to human bacterial flora.

Increasingly, data suggest that inappropriate antimicrobial use poses an emerging public health risk (*148*,*149*,*150*,*151*).

Factors associated with the emergence of antimicrobial resistance in food-producing animals and the farming industry appear to be similar to those responsible for such resistance in humans. Inadequate understanding about and training on appropriate usage guidelines and the effects of inappropriate antimicrobial use on resistance are common among farmers, veterinary prescribers and dispensers.

There are three modes of antimicrobial use in animals—prophylaxis, treatment and growth promotion. Overall, the largest quantities of antimicrobials are used as regular supplements for prophylaxis or growth promotion in the feed of animal herds and poultry flocks. This results in the exposure of a large number of animals, irrespective of their health, to frequently subtherapeutic concentrations of antimicrobials (*152*). Furthermore, a lack of diagnostic services and their perceived high cost means that most therapeutic antimicrobial use in animals is empiric, rather than being based on laboratory-proven disease. For animals and birds that are farmed in large herds or flocks, the identification of a few ill individuals generally results in the entire herd or flock being treated to avoid rapid dissemination and stock losses. Clearly this is a different situation to most human diseases where decisions are generally made about the need for individual therapy, rather than the empiric treatment of an entire population. In addition to these issues, veterinarians in some countries earn as much as 40% or more of their income by the sale of drugs, so there is a disincentive to limit antimicrobial use (*153*,*154*).

* http:// www.who.int/emc/diseases/zoo/who_global_principles.html

As in human medicine, inefficient and inadequately enforced regulatory mechanisms regarding antimicrobial supply contribute to excessive and inappropriate drug use. Discrepancies between regulatory requirements and prescribing/dispensing realities for animal antimicrobial use are often worse than in human medicine (*155*). In addition, antimicrobials that are used as growth promoters are generally not even considered as drugs and are either not licensed or licensed solely as feed additives. Poor manufacturing quality assurance in some settings results in the supply of sub-standard drugs. Marketing practices of antimicrobials for therapeutic, prophylactic or growth promoter purposes in animals by private industry influence the prescribing patterns and behaviour of veterinarians, feed producers and farmers.

In North America and Europe it is estimated that about 50% in tonnage of all antimicrobial production is used in food-producing animals and poultry (*156*). The increased intensity of meat production under crowded industrialized conditions contributes to the increased use of antimicrobials since they are used in subtherapeutic doses as growth promoters, given as prophylaxis for disease prevention and used therapeutically for the treatment of infected animals. In addition, the impact of antimicrobial metabolites and non-metabolized drug in animal sewage that is released into the environment is not clear.

Use of antimicrobials as growth promoters

Some antimicrobials, particularly those that target Gram-positive bacteria, are associated with an increase in the rate of animal growth when they are provided in subtherapeutic quantities in stock feed to food-producing animals. The mechanism of this effect is uncertain. However, these drugs also alter the gut flora of exposed animals such that they frequently contain bacteria that are resistant to the antimicrobial used. When such antimicrobial growth promoters belong to a class similar to that of antimicrobials used in human medicine, these resistant animal bacteria are often also resistant, i.e. cross-resistant, to important human use antimicrobials (*157*). Five growth promoters (bacitracin, tylosin, spiramycin, virginiamycin and avoparcin [a similar agent to vancomycin]) have recently been banned by the European Union due to fears of such cross-resistance (*158*,*159*).

Scientific data strongly suggest that avoparcin use in animals contributes to an increased pool of vancomycin-resistant enterococci (VRE) (*160*, *161*). However, the extent to which the microbial gene pool in animals contributes to the prevalence of VRE colonization and infection in humans is less well defined. VRE cause serious infections, mainly in hospitalized immunocompromised patients. Such infections are difficult to cure due to the limited number of effective treatment options and are thus associated with increased morbidity and mortality. There are also concerns that the genes that cause resistance to vancomycin may spread from enterococci to other bacteria, such as *Staphylococcus aureus*, for which vancomycin is one of the drugs of last resort.

Studies in Denmark have shown that the ban of avoparcin in animals has led to a reduction in the prevalence of VRE in poultry and pigs (*162*,*163*). Similarly, studies in Germany and the Netherlands suggest that banning avoparcin has led to a reduction in the prevalence of VRE in healthy individuals in the community (*164*,*165*). Sweden banned the use of growth promoters in livestock and poultry in 1987 and focused on the implementation of disease prevention methods that did not involve antimicrobials and on the prudent use of antimicrobials for therapeutic purposes. The subsequent national antimicrobial consumption has reduced by approximately 50% (*166*,*167*). Furthermore, the prevalence of antimicrobial resistance in pathogenic bacteria isolated from animals in Sweden has been maintained at a low prevalence since 1985 (*168*).

Use of antimicrobials that affect food-borne pathogens such as *Salmonella* and *Campylobacter* spp.

Non-typhoidal *Salmonella* spp. and *Campylobacter jejuni* are among the most commonly identified causes of bacterial diarrhoea in humans. Such species are generally transmitted to humans via food or direct contact with animals (*169*). Data demonstrate that antimicrobial use in animals selects for resistance among non-typhoidal *Salmonella* spp., thus limiting the effective available treatment options (*170*,*171*,*172*). A recent example is a clone of *Salmonella typhimurium* DT104 that has become prevalent in many countries including the UK, Germany and the USA—it is resistant to commonly used agents including ampicillin, tetracycline, streptomycin, chloramphenicol and sulphonamides (*171*,*173*,*174*). Multi-drug resistance has likewise been noted in other *Salmonella* spp. (*175*).

Following the introduction of fluoroquinolones for use in food-producing animals, the emergence of *Salmonella* serotypes with reduced susceptibility to fluoroquinolones has been observed in countries such as France, Germany, Ireland, the Netherlands, the Russian Federation, Spain and the UK (*176*,*177*,*178*). Little has been documented about the impact of this resistance on human health to date, but there is concern about the potential human health consequences. This has been substantiated by a recent outbreak of quinolone-resistant *S. typhimurium* DT104 resulting in treatment failures in hospitalized patients in Denmark (*179*).

The introduction of fluoroquinolone use in poultry has been associated with a dramatic rise in the prevalence of fluoroquinolone-resistant *Campylobacter jejuni* isolated in live poultry, poultry meat and from infected humans (*180*,*181*, *182*). Prior to fluoroquinolone use in poultry, no resistant strains were reported in individuals without previous exposure to these agents (*178*,*183*). Because of their broad antibacterial spectrum, fluoroquinolones are often used for empiric treatment of gastrointestinal infections in severely ill or immunocompromised patients. Fluoroquinolone resistance among *Campylobacter* spp. is associated with a higher rate of clinical treatment failure than for susceptible strains when fluoroquinolones are used for treatment of disease (*184*,*185*,*186*). A recent review by APUA (*187*) provides further material on this topic.

CHAPTER 5

National governments and health systems

Recommendations for intervention

Advocacy and intersectoral action

5.1 Make the containment of antimicrobial resistance a national priority.

— Create a national intersectoral task force (membership to include health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties) to raise awareness about antimicrobial resistance, organize data collection and oversee local task forces. For practical purposes such a task force may need to be a government task force which receives input from multiple sectors.

— Allocate resources to promote the implementation of interventions to contain resistance. These interventions should include the appropriate utilization of antimicrobial drugs, the control and prevention of infection, and research activities.

— Develop indicators to monitor and evaluate the impact of the antimicrobial resistance containment strategy.

Regulations

5.2 Establish an effective registration scheme for dispensing outlets.

5.3 Limit the availability of antimicrobials to prescription-only status, except in special circumstances when they may be dispensed on the advice of a trained health care professional.

5.4 Link prescription-only status to regulations regarding the sale, supply, dispensing and allowable promotional activities of antimicrobial agents; institute mechanisms to facilitate compliance by practitioners and systems to monitor compliance.

5.5 Ensure that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization.

5.6 Introduce legal requirements for manufacturers to collect and report data on antimicrobial distribution (including import/export).

5.7 Create economic incentives for the appropriate use of antimicrobials.

Policies and guidelines

5.8 Establish and maintain updated national Standard Treatment Guidelines (STGs) and encourage their implementation.

5.9 Establish an Essential Drugs List (EDL) consistent with the national STGs and ensure the accessibility and quality of these drugs.

5.10 Enhance immunization coverage and other disease preventive measures, thereby reducing the need for antimicrobials.

Education

5.11 Maximize and maintain the effectiveness of the EDL and STGs by conducting appropriate undergraduate and postgraduate education programmes of health care professionals on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

5.12 Ensure that prescribers have access to approved prescribing literature on individual drugs.

Surveillance of resistance, antimicrobial usage and disease burden

5.13 Designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health care facilities. The standard of these laboratory facilities should be at least at the level of recommendation 3.6.

5.14 Adapt and apply WHO model systems for antimicrobial resistance surveillance and ensure data flow to the national intersectoral task force, to authorities responsible for the national STGs and drug policy, and to prescribers.

5.15 Establish systems for monitoring antimicrobial use in hospitals and the community, and link these findings to resistance and disease surveillance data.

5.16 Establish surveillance for key infectious diseases and syndromes according to country priorities, and link this information to other surveillance data.

Introduction

Placing antimicrobial resistance high on the national agenda should be a priority in tackling the problem of resistance. National governments and health care systems can have considerable impact on limiting the emergence and development of antimicrobial resistance through the introduction of legislation and policies concerning the development, licensing, distribution and sale of antimicrobial agents. Health and pharmaceutical regulations shape the way antimicrobials are used. Key regulatory frameworks include professional licensing, the ability to prescribe and dispense medicines, drug registration, product quality, pricing and movement of drugs in the supply system. Although pharmaceutical regulations represent a powerful tool, implementing them to influence patterns of antimicrobial use can be a two-edged sword, achieving both intended and unintended effects. For example, active enforcement of regulations regarding the sale of antimicrobials without prescription in pharmacies and drug shops may reduce unnecessary use while at the same time limiting access to appropriate therapy, especially among the poor. The unintended effects of proposed regulations should be carefully considered before and monitored during their implementation.

National governments also have the responsibility for coordinating surveillance networks and for directing educational efforts to improve understanding about appropriate antimicrobial use.

Government legislation—drug licensing

Marketing authorization

Many countries have legislation that requires all medicinal products to undergo licensure before being placed on the market. Marketing authorization usually follows a detailed assessment of data provided by the applicant, generally by a designated government department and sometimes with input from an expert advisory group(s). Some countries are willing to license new medicines based on their prior approval in other countries, such as the USA or EU. Whatever the process, the fundamental requirement is that the data should support the quality, safety and efficacy of the product (*188*,*189*). The use of antimicrobials that do not meet appropriate standards in each of these three areas has implications for human health and for antimicrobial resistance.

Quality

As with all medicinal products, control of the quality of antimicrobial agents is vital for the delivery of accurate dosage units to patients—doses that have been shown to be safe and effective in clinical trials (*188*,*189*,*190*). Antimicrobial agents containing less than the stated dose may produce suboptimal levels of circulating drug, which may result in both therapeutic failure and selection of drug-resistant strains. Similar problems may arise as a result of counterfeit products, which commonly contain little or none of the active substance stated on the label and may even contain entirely different active ingredients. The Counterfeit Intelligence Bureau estimated that, in 1991, 5% of all the world's trade was in counterfeit goods, with this percentage likely to be higher for pharmaceuticals since they are easily transportable (*191*). Excessive drug content may lead to concentrations in the body associated with certain adverse events. Unnecessarily high concentrations may also lead to a marked disruption of the normal flora and an increased risk of superinfections such as fungal disease and *C. difficile* enterocolitis.

Government-initiated inspection of drug manufacturing plants for adherence to Good Manufacturing Practice (GMP) with certification for defined time periods, adherence to the product specifications agreed upon at the time of licensure, and the elimination of unauthorized medicines from the market are essential. Strict controls limiting drug importation and exportation to those products and manufacturers that have been inspected and approved can serve to reduce

the risks posed by substandard and counterfeit medicines. Countries that carry out spot checks and drug analyses are able to make a major contribution to reducing the production of poor quality and counterfeit products.

Safety and efficacy

The scope and quality of data presented to support the safety and efficacy of new drugs are determined mainly by the requirements of the US Food and Drug Administration (FDA), the European Commission, and the Japanese Ministry of Health, Labour and Welfare (MHLW) (*188*,*189*, *192*). The individual regulations issued by these bodies, together with the activities of the International Conference on Harmonisation (*193*), have greatly influenced the content and conduct of preclinical and clinical development programmes for pharmaceuticals. Dossiers meeting these international standards are generally acceptable worldwide, although there may be additional local stipulations. In this way, all countries may benefit from high quality development programmes that better identify the safety and efficacy of new drugs. In one sense, the emergence of resistance associated with the use of a particular antimicrobial could be viewed as an adverse event. However, current regulatory and licensure bodies do not regard the emergence of resistance in this manner.

Countries that do not have systems for the adequate assessment of safety and efficacy before and after drug licensure face an increased risk of exposure to drugs of inferior efficacy and unacceptable toxicity, as well as a potentially higher market penetration of counterfeit drugs. The establishment of Assessment Report Sharing Schemes has facilitated assessment of the safety and efficacy of antimicrobial agents by resource-poor countries. Participating countries are able to request detailed reports of pharmaceutical, preclinical and clinical data that have been prepared by drug regulatory authorities in other countries. The Product Evaluation Report (PER) network and the arrangements made by the European Agency for the Evaluation of Medicinal Products (EMEA) are examples of schemes which allow countries access to information to assist in making licensing decisions. In addition, regional associations of regulatory bodies, e.g. AFDRAN in Africa, have contributed to the application of similar standards and requirements for drug approvals in many countries.

Prescribing information

Wherever there are formal procedures for drug licensure, the content of the prescribing information is subject to approval by the licensing authorities. Requirements for international alignment on the essential content of the prescribing information and on the reporting of safety data have led to the development of core datasheets by many pharmaceutical companies (*194*,*195*). These describe the minimal prescribing information, including contraindications, warnings and potential adverse reactions, which should be available to users in all countries where the product is marketed. However, it may not be feasible for all companies, especially those that are large and multinational, to regularly audit compliance with the use of core datasheets in all regions or to require that national or regional offices fully adopt stated corporate standards. Also, in countries where there are inadequate regulations to ensure the availability of prescribing information to prescribers and users, health care professionals may have little or no access to independently-assessed material regarding antimicrobial agents (see also Chapters 2 and 7).

Failure to specify precisely in the prescribing information the types of infections for which safety and efficacy have been demonstrated in clinical trials may serve to encourage antimicrobial use for conditions that have not been studied. An example is the use of the term "lower respiratory infections" instead of specifying the types of pneumonia or bronchitis that were studied. Thus, without careful attention to detail and to translation, even the approved prescribing information may inadvertently encourage inappropriate antimicrobial use.

The product literature usually reflects the dosage regimens shown to be efficacious in clinical trials for each indication. Identification of optimal antimicrobial treatment regimens for various diseases is important to ensure that the drug is given in an appropriate dose and for an appropriate duration to maximize the likelihood of cure, while minimizing the risk of toxicity. Low dose regimens may be associated with less toxicity, but may result in insufficient drug concentrations at the site of infection to effect bacterial eradication and may therefore encourage the development of resistance among target pathogens. In contrast, higher dose regimens may result in greater effects on the host's normal flora increasing the likelihood of superinfections, including those caused by highly resistant nosocomial pathogens. How-

ever, clinical trials to support antimicrobial drug approval are almost always designed to show equivalence to a licensed comparative agent. Therefore there is a tendency to use perhaps unnecessarily high dose or long duration regimens so as to avoid any risk of treatment failure (*196*, *197*,*198*). Companies are often reluctant to explore a variety of dosage and treatment regimens in clinical trials with a new drug because of the study costs involved and the risk of failing to meet the specified regulatory requirement (*199*). Dose regimens in clinical trials are often chosen by comparing the pharmacokinetics of the drug in man with the *in vitro* susceptibilities of the main target pathogens. Increasingly, the pharmacokinetic and pharmacodynamic characteristics of new antimicrobial agents are being used in pre-clinical studies to better predict the optimal clinical dosing regimens in man (*200*,*201*,*202*). While this approach does not replace clinical trials, the pharmaceutical industry and regulatory authorities have both recognized that this may also have benefits in terms of reducing the risk of selecting for drug-resistant organisms.

Government legislation—control of drug supply, distribution and sales

Some countries are unable to control the supply, distribution and sale of medicines. In many regions there is minimal control over public access to antimicrobials and these can be purchased over the counter without prescription (*34*,*203*). There are also marked international differences in the types of retail outlets that provide access to prescription-only and non-prescription drugs, as well as whether these outlets require government registration. Where there is adequate legislation regarding the licensure of medicinal products, a legal classification system generally determines the mode of sale, supply and dispensing. In such countries, antimicrobial agents are almost uniformly prescription-only medicines (POM), with dispensing restricted to registered outlets and by suitably qualified personnel (*204*). In reality, however, the degree of drug law enforcement and the penalties imposed for infringements vary enormously between countries. For example, all systemic antibacterial agents are legally subject to prescription control in the EU, yet they can be purchased over the counter in pharmacies in several EU member states (*205*). Antimicrobials can be purchased without prescription in many resource-poor countries (*59*,*129*,*206*). In a study of chemist shops in Nairobi, it was noted that 64% of chemists sold antimicrobials without physicians' prescriptions and most sold incomplete treatment courses at the request of the patient (*207*). In a study of a rural village in Bangladesh, 95% of all medications consumed were obtained from pharmacies with only 8% having been prescribed by graduate physicians; one-third of these medications were antimicrobials (*208*). Poor enforcement of prescription-only regulations is almost universally associated with inappropriate antimicrobial usage.

Although the cost of antimicrobial agents without prescription is generally carried by the patient, in some regions this may actually be less expensive than the combined costs of a time-consuming visit to a distant and/or very busy health care facility and the physician's consulting fee. Therefore, depending on the structure and funding of the national health care system, restricting antimicrobial agents to prescription-only may actually limit the access of many patients to these drugs, even when they are really needed. On the other hand, requiring a prescription for access to antimicrobial agents provides an opportunity to dissuade patients from unnecessary antimicrobial therapy and hopefully results in a trained health care worker selecting the drug and the treatment regimen. This potential point of intervention should help reduce inappropriate antimicrobial usage, especially if accompanied by an education programme on the appropriate use of antimicrobial agents (see Chapter 2).

With or without implementation of prescription-only access to antimicrobial agents, legislation that restricts the sale of antimicrobials to registered outlets would allow local policing and prevention of over-the-counter non-prescription sales. Ideally, such registered outlets should be staffed by personnel with at least a basic knowledge of antimicrobials. Legislation that compels registered outlets to keep records of the sources of drugs purchased and quantities sold would allow the auditing of antimicrobial sales and possibly of usage data. Such surveillance may result in greater restriction of the sales of counterfeit and substandard medicines. However, in regions where prescribers earn a considerable portion of their income either by directly dispensing antimicrobials or via subsequent pharmacy sales, such legislation is likely to be less effective. These circumstances provide a disincentive to appropriate antimicrobial prescribing and prescribers are more likely to recommend antimicrobial use, particularly the more expensive agents, regardless of whether

cheaper drugs may be just as appropriate (see also Chapter 2).

Government legislation—inspection and enforcement

The existence of appropriate legislation regarding the manufacture, licensure, sale, supply and dispensing of antimicrobial agents cannot improve the quality and appropriate use of these drugs unless it is enforced. Individual countries may not have the financial or human resources needed to support policing activities by suitably qualified personnel. There may be reluctance on the part of governments to take action because the introduction of restrictions could prove unpopular with patients, physicians and the pharmaceutical industry. Increasing international recognition of inspections of manufacturing plants by teams from other countries has relieved the burden on some governments and facilitated the quality control of medicines and adherence to Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). The possibility of expanding these international cooperative efforts by using suitably qualified staff from non-governmental organizations (NGOs) to aid policing efforts in other areas of drug law compliance may be worthy of serious consideration by some countries (see also Chapter 8).

Health care systems and drug policies

Health care systems

The organization and funding of health care systems varies between countries, with a mixture of public- and privately-funded health care facilities and diagnostic laboratories being common. The structure and organization of these systems can be an important factor in determining the reliability and practicality of data collection regarding antimicrobial use, surveillance of antimicrobial resistance and the impact of resistance on clinical outcomes. In addition, the system may have a direct influence on undergraduate medical curricula, on the existence and maintenance of registration systems for all health care professionals, and on the attention paid to their continuing professional education and accreditation. Whether or not antimicrobials are prescription-only, undergraduate and postgraduate medical and pharmacist education concerning appropriate antimicrobial use is vital (see Chapter 2), as is the need for evidence-based prescribing information.

Surveillance of resistance and antimicrobial use

Surveillance of both antimicrobial resistance and antimicrobial use are fundamental to the effective implementation of any strategy for the containment of antimicrobial resistance, as a means to monitor the efficacy of various interventions. However, designing and implementing comprehensive surveillance systems that are practical, cost-effective and interlink with the national healthcare system is a challenge. It is likely that in many resource-poor countries, laboratory facilities and information networks will require considerable strengthening before reliable surveillance of resistance can be undertaken.

Epidemiologically sound surveillance of resistance in key pathogens, using standardized microbiological methods, may be developed on the basis of an existing laboratory surveillance system for antimicrobial resistance and routine diagnostic microbiology (see Part A, Background). To assist in this aim, WHO is developing "Surveillance standards for antimicrobial resistance" which propose practical epidemiological methods for several infections and key pathogens (*209*). Where possible, such surveillance should be integrated with other national and hospital laboratory services to maximize efficiency and ensure surveillance of clinically relevant isolates (see Chapter 3).

Measurement of antimicrobial usage could be approached through the registration of outlets that dispense antimicrobials, requiring them to maintain accurate records of antimicrobial supply and sales. Incomplete patient adherence to treatment protocols means that antimicrobial dispensing data will not necessarily be the same as antimicrobial consumption, but it is likely to be the most accurate achievable surrogate available. Targeted research to measure the correlation between the quantity of antimicrobials dispensed and the quantity consumed could be used to adjust national dispensing data, providing a more accurate assessment of antimicrobial consumption. Establishing surveillance systems of antimicrobial usage and control of drug supply and dispensing outlets will require a major commitment from national governments in countries which do not currently have effective prescription-only regulations for antimicrobials. Implementation of an integrated surveillance system for antimicrobial resistance and antimicrobial usage will require national governments to re-assess many regulatory aspects of their health care system, including legislation related to drug licensure (including quality, safety and efficacy) and drug supply, distribution and sales.

Essential Drugs Lists and policies

In 1977 the first WHO Model List of Essential Drugs was developed to promote the availability of a selected number of drugs, including antimicrobials, and their rational use. The Model List has been revised regularly and serves as a guide for countries in determining their national drug policies. At present over 120 countries have implemented an Essential Drugs List. A retrospective study of prescribing practices in Ethiopia found a significant decrease in the prescribing of non-essential drugs after the introduction of an Essential Drugs List (*210*). Studies have demonstrated that in those areas in which an Essential Drugs Programme is in operation, significantly more essential drugs are available, significantly fewer injections and antimicrobials are utilized, and drug stocks last about three times longer than in regions without such a programme. Thus, such programmes appear to improve access to essential drugs, especially when they are supported by educational programmes and follow-up (*83*,*117*).

Establishing national treatment guidelines

Evidence-based national treatment guidelines encourage appropriate antimicrobial prescribing. Using local laboratory and clinical surveillance data on antimicrobial resistance, these guidelines can be appropriately modified for community and hospital use in various regions, but should be updated regularly. The use of such guidelines is most effective when combined with supportive interventions such as educational training and supervision programmes (*83*,*211*).

CHAPTER 6

Drug and vaccine development

Recommendations for intervention

6.1 Encourage cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines.

6.2 Encourage drug development programmes which seek to optimize treatment regimens with regard to safety, efficacy and the risk of selecting resistant organisms.

6.3 Provide incentives for industry to invest in the research and development of new antimicrobials.

6.4 Consider establishing or utilizing fast-track marketing authorization for safe new agents.

6.5 Consider using an orphan drug scheme where available and applicable.

6.6 Make available time-limited exclusivity for new formulations and/or indications for use of antimicrobials.

6.7 Align intellectual property rights to provide suitable patent protection for new antimicrobial agents and vaccines.

6.8 Seek innovative partnerships with the pharmaceutical industry to improve access to newer essential drugs.

Introduction

The pharmaceutical industry is the predominant source of new antimicrobial agents and new disease prevention modalities, including novel vaccines and immunomodulating therapies. It is vital that there are incentives for companies to invest resources into research and development in these areas even though the development of other types of medicinal products may ultimately be more profitable. Encouraging research into vaccines and antimicrobial agents that will predominantly be used in low-resource countries poses particular challenges given the need for pharmaceutical companies to make a profit. However, the continuation and expansion of anti-infective drug and vaccine research is now a crucial issue for all nations given the emergence of antimicrobial resistance among human pathogens.

New drug and vaccine development

The fact that there are currently several novel antimicrobial agents and vaccines in clinical trials reflects the awareness of the industry of the problems of antimicrobial resistance and the enormous investment by some companies in anti-infective drug development. At the same time, however, there are concerns within the industry that efforts to encourage the more appropriate use of antimicrobials may have a negative impact on sales. This concern may potentially discourage companies from either initiating or maintaining investment in antimicrobial research and development. An overall drop in the antimicrobial-generated revenues of pharmaceutical companies may also influence the quantity of antimicrobial agents and vaccines that they donate, or provide at reduced cost, to some regions of the world.

Schemes that encourage investment in antimicrobial and vaccine research must therefore recognize the need for companies to recoup their development costs as well as make a profit from post-licensing sales. A range of incentives to the industry, including both push and pull mechanisms, are currently under discussion (*212*). Some countries, such as Australia, have devised provisions by which companies which conduct research aimed at identifying new therapies and which perform some sections of the development programme in the home country can benefit from tax reductions and incentive payments. This approach also attracts some companies to establish research facilities in supportive countries, which may have employment and other benefits.

Drug discovery may also be stimulated by co-operative research agreements between companies and academic institutions. These agreements can stimulate basic science research and the sharing of knowledge which may speed up the identification

of promising compounds or vaccines. This approach may potentially reduce overall costs by reducing the duplication of research activities (see Chapter 8). Public-private partnerships are increasingly being exploited for speeding up drug discovery and development and addressing unmet medical needs where the market opportunities are less attractive (*213*).

Vaccines

Vaccines potentially provide a major means of limiting the clinical impact of emerging antimicrobial resistance. Pneumococcal and *Haemophilus influenzae* type b (Hib) vaccines have had a dramatic effect in reducing the incidence of clinical disease in some age groups and regions (*214*, *215*,*216*,*217*). Recent studies of a nonavalent pneumococcal conjugate vaccine demonstrated a significant reduction in the carriage of penicillin-resistant and cotrimoxazole-resistant strains of *S. pneumoniae* in children nine months after vaccination, compared to controls (*214*). Thus, by reducing the incidence of disease and carriage of resistant strains, pneumococcal vaccination may limit the impact of antimicrobial resistance. When the information is available, knowledge of a patient's vaccination status for pneumococcal, Hib and other diseases may aid the differential diagnosis if the patient presents with an acute illness and thereby allow narrower-spectrum agents to be employed for empiric therapy.

Vaccines have also proven effective for some diarrhoeal diseases and enteric fever. A number of typhoid vaccine preparations are now available, but their use has previously been limited mainly to travellers to endemic areas. With the new oral preparations, wider use may now be more feasible once they can be produced at reasonable cost. Given recent outbreaks of ciprofloxacin-resistant typhoid fever, vaccination has been suggested as an adjunct to sanitation measures in some regions (*218*,*219*,*220*,*221*). Vaccines for other diarrhoeal diseases such as shigellosis, cholera, *E. coli* ETEC and rotavirus are also under trial (*218*).

As the medical treatment of HIV, hepatitis B and C becomes more widespread, antiviral resistance will become a major limiting factor. Childhood vaccination against hepatitis B, either universal or targeted to high risk groups depending on the prevalence of hepatitis B in the population, is a very cost-effective means of controlling the disease and avoiding the problems of resistance (*109*,*222*,*223*). Effective vaccines against hepatitis C and HIV could likewise have enormous clinical impact.

Licensure and patent protection

To hasten the licensure of some new products, fast-track evaluation of innovative medicines is offered by some licensing authorities (*188*,*224*), allowing truly innovative products to reach the public domain as early as possible. Such schemes benefit both the companies and the community—although careful post-licensure surveillance of adverse effects is vital. Some products may be considered clinically useful but of limited commercial value due to infrequent disease occurrence—for these, some countries provide special licensure under an orphan drug scheme which has variable eligibility requirements.

The safeguarding of intellectual property rights is a major concern to the pharmaceutical industry. There may be opportunities to encourage research by furthering international agreements and cooperation on innovative new approaches to patents and time-limited exclusivity arrangements. Time-limited exclusivities on new clinically useful formulations and/or additional indications for use on some current agents might serve to stimulate the additional pharmaceutical and clinical studies which are needed to support licensure for these additional indications.

Clinical development programmes

Clinical development programmes are designed to undertake trials which will support drug registration. These programmes offer possibilities to investigate not only the most effective treatment regimens but also those which are least likely to result in the emergence of antimicrobial resistance. However, these pre-registration clinical trials rarely assess the degree to which *in vitro* susceptibility data correlate with the *in vivo* clinical outcomes of infected patients receiving treatment. Although these correlations are of vital clinical importance, such trials can be difficult to perform. In most pre-registration clinical antimicrobial trials, the number of treatment failures is generally too few to allow such assessments and, in any case, the primary goal of these studies is to assess equivalence of efficacy or drug toxicity, not the correlation between *in vitro* and *in vivo* outcomes. In addition, a number of design features of licensure studies make such correlations even more difficult. Firstly, some protocols require that enrolled patients found to be infected with pathogens that

are resistant *in vitro* to one of the trial drugs should be withdrawn from the study. However, others allow such patients to continue receiving trial therapy if they are doing well, despite *in vitro* resistance. Such design issues have an important impact on the ability to accurately analyse correlation data. Furthermore, the site of infection may influence the level of antimicrobial penetration and therefore the likely concentrations of active drug available under routine dosing conditions, e.g. drug concentrations in cerebrospinal fluid are generally lower than those achievable in serum. Therefore, *in vitro* definitions of resistance will depend on potentially achievable drug concentrations *in vivo*, meaning that the MIC breakpoints for individual pathogens may need to vary depending on the site of infection.

Since clinical trials with antimicrobials are almost exclusively designed to demonstrate equivalence to an approved comparative agent, this means that results cannot be used as a basis for recommending one treatment over another. Thus, these studies generally do not provide clear evidence on which to base guidelines for the best choice of antimicrobial or the optimal mode of management of a particular infection. In addition, clinical drug trials have not been designed to determine the most appropriate duration of antimicrobial therapy. Many scientists and clinicians believe that shorter treatment courses for many infections may be as effective as longer courses (*225*). Potential benefits of shorter course therapies are to decrease disruption of the normal flora and the selective pressure of antimicrobials favouring drug-resistant microorganisms. Shorter durations of therapy are also likely to encourage patient adherence (see Chapter 1). It should be noted that, at the present time, relatively few clinical antimicrobial studies are conducted on paediatric populations and that this may be an area for greater attention in the future.

Microbiological and pharmacological issues

A number of important microbiological and pharmacological features of antimicrobials appear to influence their likelihood of selecting and promoting resistant strains (*51*,*226*). Pharmacodynamic and pharmacokinetic parameters can be used to help identify the optimal dose and dosing intervals for each antimicrobial (*202*). The parameters most appropriate in terms of encouraging the emergence of resistance have been investigated and debated extensively (*132*,*227*,*228*). In addition, the use of antimicrobials in combinations has been suggested for some infections, since a reduced incidence of resistance has been noted with combination therapy (*229*,*230*).

Cost-effectiveness

Cost-effectiveness studies are increasingly becoming a major component of clinical development programmes. While these are not required for licensure, they may be needed in some countries for negotiations on drug supply contracts. While companies may have some cost-effectiveness data available, few release such data to the public. Many published cost-effectiveness studies are at risk of bias in favour of the new agent, since few studies of older agents, that are often no longer patent-protected, are undertaken due to insufficient research funding support. Furthermore, studies focus neither on the cost of resistance nor on the clinical impact of resistance and there is a need for new approaches to incorporate such evaluations into cost-effectiveness studies (*8*). Thus, current clinical development programmes rarely support decision-making regarding the cost-effectiveness or optimal dose of various antimicrobials. However, such programmes may provide some unique opportunities to gain more useful information in future if innovative modifications are made to current trial designs.

CHAPTER 7

Pharmaceutical promotion

Recommendations for intervention

7.1 Introduce requirements for pharmaceutical companies to comply with national or international codes of practice on promotional activities.

7.2 Ensure that national or international codes of practice cover direct-to-consumer advertising, including advertising on the Internet.

7.3 Institute systems for monitoring compliance with legislation on promotional activities.

7.4 Identify and eliminate economic incentives that encourage inappropriate antimicrobial use.

7.5 Make prescribers aware that promotion in accordance with the datasheet may not necessarily constitute appropriate antimicrobial use.

Introduction

National governments have an important legislative role in ensuring the appropriate manufacture, licensure and sale of antimicrobials (see Chapter 5) and also an important responsibility in ensuring that these drugs are promoted in a fair and accurate manner. Government controls on drug promotional activities and compliance of the pharmaceutical industry with both legislation and agreed codes of practice are important factors if appropriate antimicrobial use is to be encouraged.

The power of promotional activities

Promotional activites include drug advertisements in the media and over the Internet, personal contacts during visits from company representatives, sponsored symposia and guest lectures or lecture tours funded by companies, and other inducements to prescribe a particular product or brand. The target audience for promotional activities depends on the product and the local regulatory environment, but generally includes doctors, pharmacists, dentists, nurses and the general community. The close relationships between drug promotion, prescribing habits and drug sales have been demonstrated in several studies (*34*,*231*). Since drug promotion increases usage, it may be assumed that it can contribute to the prevalence of antimicrobial resistance, particularly if it results in increased inappropriate use of antimicrobial agents.

Promotional literature and prescribing information

A number of studies have shown that advertisements and other promotional literature distributed by companies at conferences and symposia are major influential sources of information for health professionals (*231*,*232*). Indeed, the content of advertisements and literature provided by companies may be the only readily accessible sources of information on antimicrobial agents in some countries. In the absence of legislation or its enforcement for promotional materials to reflect approved prescribing information, companies may present to potential prescribers, suppliers and users a very selective and biased view of the efficacy and safety of a drug. It has been suggested that physicians may not even be aware of these influences. Avorn et al. (*232*) found that most prescribers believed that drug advertisements and pharmaceutical representatives played a role of minimal importance in influencing prescribing patterns whereas academic sources of information were very important yet the opposite appeared to be true. This finding was supported by a study of prescribing habits of physicians in Peru (*231*). The study concluded that advertising materials distributed by pharmaceutical companies appeared to be a key source of information for prescribers, despite claims by more than two-thirds of the physicians surveyed that their primary source of drug information came from medical literature. A review of the literature on the interactions between physicians and the pharmaceutical industry concluded that there was strong evidence that these

interactions influence prescribing behaviour (*233*). Thus, pharmaceutical promotional material that contains misinformation may ultimately encourage inappropriate antimicrobial use and the emergence of resistance.

Promotional materials must not only reflect approved prescribing information correctly but must also be accurate, comprehensive and up to date. Particular difficulties may be encountered with older antimicrobials for which the initially licensed indications may now be considered excessively broad or vague, e.g. upper respiratory infections, and may no longer reflect current thinking on the optimal evidence-based management of certain infections. Although pharmaceutical companies may apply to update sections of the prescribing information, they are unlikely to do so voluntarily if there is a risk of a negative impact on sales. Licensing authorities may require that the prescribing information be updated or modified but are unlikely to do so without strong evidence to support the changes, due to the possibility of a legal challenge from companies. Furthermore, the fact that many older agents are no longer patent-protected means that license holders may not consider that the drug's market value warrants such applications and effort.

Prescribers

Promotion of products to health professionals informs prescribers about the range of drugs available and alerts them to the availability of new agents. Inherently, pharmaceutical marketing results in the highlighting of potential benefits and advantages of new agents over existing agents to the extent allowable. Under these circumstances it is often difficult for prescribers to identify the most appropriate role of the new agents within the context of existing protocols. Promotional materials often emphasize simple messages in preference to more complex ones, not infrequently resulting in over-prescribing.

It is also difficult to regulate the provision of inducements such as meals, event tickets, and travel to conferences. These perks may serve as rewards for using a company's products and as enticements to prescribe newly-introduced drugs (*234*,*235*). This may also encourage prescribers to prescribe using brand names rather than generic names, which may markedly increase specific company sales in those countries which do not allow pharmacists to substitute between brands of the same active substance when dispensing prescriptions (see Chapter 2).

Patients

Health care professionals in all countries, including those subject to prescription control, often feel pressured by patients to prescribe antimicrobials for minor infections which do not need specific therapy (see Chapter 2). Direct-to-public advertisements in countries with prescription-only restrictions on antimicrobial agents may enhance the pressures on health care professionals to prescribe when their clinical judgement suggests that specific therapy is unnecessary. In addition, advertising on the Internet is gaining market penetration yet is difficult to control with legislation due to poor enforceability. To counter this problem, education campaigns directed at health care professionals and the general public are underway in some countries where antimicrobial agents are available by prescription only. The aim of such a campaign in the UK, ongoing in 2000, was to inform all parties about those infections least likely to require antimicrobial treatment—thereby reducing patient expectation of the need for an antimicrobial agent. Data on the effects of such efforts are awaited.

The effects of direct-to-public promotion on total and specific antimicrobial usage are likely to be much greater in countries where these agents are available without prescription. In these circumstances, even promotion in accordance with the prescribing information is likely to result in unnecessary antimicrobial use as purchasers are less able to fully appreciate the information provided and to weigh the possible risks and benefits. Inappropriate antimicrobial use as a result of over-the-counter availability may therefore be greatly exacerbated by direct-to-public advertising.

Sales

Pharmaceutical promotion directed towards health care professionals who sell antimicrobials may result in a conflict of interest. The desire to profit from making the sale and/or to favour a particular company's product in expectation of rewards may override clinical judgement. In this manner, the decision regarding the necessity for treatment and the choice of the most suitable agent are less likely to reflect appropriate clinical management. Sales of antimicrobial drugs through outlets not staffed by health care professionals are likely to be driven predominantly by profit margins with only limited potential for control of antimicrobial usage.

Control of drug promotion

Legislation and enforcement

Where licensing, supply and sales legislation are in place, the regulation of promotional activities is frequently linked to the legal classification of medicines (*236*,*237*,*238*). In such countries, e.g. the European Union, it is common to restrict the promotion of prescription-only products to health professionals, whereas over-the-counter medicines may be promoted to the general public. Certain countries, e.g. the USA, adopt a middle course by allowing direct promotion to the public while enforcing restricted access to prescription-only products. Promotional activities that are considered acceptable, and the regulations regarding them, vary by country. Any legislation applicable to promotional activities may be supplemented by voluntary codes that have been agreed nationally between companies, or internationally between federations of pharmaceutical companies.

Advertisements in peer-reviewed journals, magazines and newspapers and broadcast via radio or television can be reviewed and made subject to controls. However, the advent of advertising on the Internet has provided a means by which companies can circumvent regulations, reaching wide audiences and global markets with unrestrained messages about their products.

Codes of practice

In addition to legislative control mechanisms, there are various codes of practice regarding appropriate promotional activities that have been drawn up by national and international associations of pharmaceutical companies (*239*,*240*,*241*). Unfortunately, these codes vary between countries and in the manner in which they are executed (*235*), such that there are many pharmaceutical companies that have not agreed to any such code of practice. When these companies market products in countries in which there is little or no governmental control on promotional activities, there is no way of monitoring the situation and preventing misinformation to health care professionals and to the public.

Some pharmaceutical associations carry out inspections of the promotional activities of their members in order to monitor compliance. Companies may also complain to these associations about the activities of rivals when these seem to go beyond the agreed codes of practice. Several non-governmental organizations undertake audits and investigate complaints regarding some forms of promotion (*234*). Whereas none of these bodies has legal empowerment, they may exert considerable pressure to improve compliance with voluntary codes of practice and internationally accepted standards. Nevertheless, despite these codes and monitoring activities, there is clearly a need for greater effort to ensure that health professionals receive accurate information regarding the efficacy and safety of antimicrobial agents (*117*) and of the problems of antimicrobial resistance.

CHAPTER 8

International aspects of containing antimicrobial resistance

Recommendations for intervention

8.1 Encourage collaboration between governments, non-governmental organizations, professional societies and international agencies to recognize the importance of antimicrobial resistance, to present consistent, simple and accurate messages regarding the importance of antimicrobial use, antimicrobial resistance and its containment, and to implement strategies to contain resistance.

8.2 Consider the information derived from the surveillance of antimicrobial use and antimicrobial resistance, including the containment thereof, as global public goods for health to which all governments should contribute.

8.3 Encourage governments, non-governmental organizations, professional societies and international agencies to support the establishment of networks, with trained staff and adequate infrastructures, which can undertake epidemiologically valid surveillance of antimicrobial resistance and antimicrobial use to provide information for the optimal containment of resistance.

8.4 Support drug donations in line with the UN interagency guidelines*.

8.5 Encourage the establishment of international inspection teams qualified to conduct valid assessments of pharmaceutical manufacturing plants.

8.6 Support an international approach to the control of counterfeit antimicrobials in line with the WHO guidelines**.

8.7 Encourage innovative approaches to incentives for the development of new pharmaceutical products and vaccines for neglected diseases.

8.8 Establish an international database of potential research funding agencies with an interest in antimicrobial resistance.

8.9 Establish new, and reinforce existing, programmes for researchers to improve the design, preparation and conduct of research to contain antimicrobial resistance.

Background—the changing global context of public health

Multiple global factors are influencing the epidemiology of infectious diseases, the contexts in which they need to be managed, and thus the demands on health care systems. Increasing urbanization, with its associated overcrowding and inadequate housing, poor sanitation and lack of clean water supplies, has a major influence on the burden of infectious disease. Pollution and environmental change, including deforestation, changing weather patterns and desertification, may also affect the incidence and distribution of infectious diseases. Demographic changes resulting in a growing proportion of elderly people and the expanding use of modern medical interventions are increasing the risks of acquiring infections, especially those caused by multi-resistant hospital pathogens. The AIDS epidemic has greatly enlarged the population of immunocompromised patients at risk of infections. Changing patterns of lifestyle also have an effect, e.g. the increase in cigarette smoking in many societies and the consequent increase in associated respiratory diseases, including pneumonia.

An increased incidence of infections leads to more antimicrobial use and consequently a greater selection pressure in favour of resistant microorganisms. Furthermore, the increased food requirements of expanding populations may promote an

* *Interagency guidelines. Guidelines for Drug Donations*, revised 1999. Geneva, World Health Organization, 1999. WHO/EDM/PAR/99.4.

** *Counterfeit drugs. Guidelines for the development of measures to combat counterfeit drugs*. Geneva, World Health Organization, 1999. WHO/EDM/QSM/99.1.

increased use of antimicrobial agents in agriculture, in turn contributing to the emergence of antimicrobial resistance in zoonotic pathogens. Increases in global trade and travel have increased the speed with which both infectious diseases and resistant microorganisms can spread between continents.

A call for international cooperative action

Containing antimicrobial resistance must involve concerted international action. While the majority of the interventions recommended in earlier chapters of this document are directed at the national level, interventions also need to be undertaken at an international level. It is no longer justifiable for countries to exempt themselves from taking action to contain resistance, since inaction will have both national and international consequences.

At the same time it is important to recognize the barriers to action and work to remove them. Antimicrobial resistance is a multi-faceted problem which calls for a multi-sectoral response, but it is a challenge to get all the sectors on board when the magnitude of the problem is unknown. There is a lack of coordination between different groups and disciplines working in this field and even a lack of knowledge that the different groups exist. Thus messages concerning antimicrobial use and resistance are often confusing and conflicting. Many countries lack the money, the skilled professionals and sufficient laboratory capacity to tackle even the definition of the size of the problem of resistance.

Closer cooperation between national governments and agencies, professional societies, non-governmental organizations (NGOs) and international agencies would raise the importance of antimicrobial resistance and its threat to health and development up the political agenda and provide additional resources for the implementation of the containment strategy. The development of consistent messages is critical. International organizations and NGOs can be particularly effective in raising the awareness of their members and the public about the importance of antimicrobial resistance and in lobbying governments about the issue so that antimicrobial resistance is seen by governments as being important. By including the containment of antimicrobial resistance in their aims and objectives, relevant NGOs and professional societies can educate their members. Furthermore, such international organizations can encourage both the health and education sectors of national governments to ensure that sufficient education on infectious disease, antimicrobial use and infection control is provided to all students in health care professions.

Experience of the successful implementation of interventions to contain resistance is a resource that should not be wasted; sharing information between nations should be given high priority to maximize the success of national strategies. These are areas in which organizations such as WHO can and should play a leading role. A summary of currently available national programmes and strategies to contain antimicrobial resistance is shown in Annex A; some of these have been analysed in more detail (*187*).

Legal issues associated with antimicrobial resistance

Existing laws at international level require reporting of a limited number of infectious diseases (*242*) but do not extend to any systematic reporting of antimicrobial resistance. In the revision of the International Health Regulations (IHR) currently under evaluation, potential international threats posed by resistant infections could be recognized. Some countries have now made certain multiresistant pathogens, e.g. MRSA, notifiable at the national level. However, the global nature of the antimicrobial resistance problem means that national legal measures alone are insufficient. At the same time, the creation of new international duties would be undermined if not incorporated into national law (*88*).

Antimicrobial resistance as a Global Public Good for Health

The concept of Global Public Goods for Health (GPGH) and their development to assist in the prevention and containment of communicable diseases is growing in importance (*243*,*244*). In the context of the current review by the Commission for Macroeconomics and Health, epidemiologically sound surveillance of antimicrobial use, resistance and the overall burden of infectious diseases is an important component of GPGH. These are public goods which have quasi-universal health benefits in terms of countries, populations and generations, both current and future, or at least meet the needs of current generations without foreclosing development options for future generations (*243*). Given the increasing ease of trans-

mission of infectious diseases between populations and across national boundaries, and the importance to future generations of the current development of resistance, antimicrobial resistance is clearly a global public "bad" for health, with the inverse, i.e. the containment of resistance, thus being a global public "good" for health.

Given that there is no global government as final arbiter, the challenge is to determine how the containment of antimicrobial resistance as a GPGH can be implemented so as to benefit the world's people. The large number of participants, e.g. governments, private sector, NGOs and citizens, complicates coordination of effort, especially in an area such as this where there is significant technical uncertainty. The potential for free riding (nations benefiting from the action of others without reciprocation) and prisoners' dilemma (lack of communication resulting in a suboptimal decision for all parties compared to the decision which could have occurred with improved communication) are significant considerations. Thus, identifying who will define the global political agenda, the priorities for resource allocation and the enforcement of penalties if needed, are important international issues if the containment of antimicrobial resistance is to successfully become a GPGH.

There are also practical problems in seeking to implement global initiatives under the banner of the GPGH concept. For example, there may be financial and technological barriers to accessing information about containing antimicrobial resistance. Some countries may not be able to collaborate on certain global initiatives, such as surveillance or adhering to certain treatment protocols, due to deficiencies in their health care infrastructure—in this context, strengthened health systems may themselves become a GPGH.

Nevertheless, GPGH aspects of containment could be of great benefit. For instance, surveillance systems could include mechanisms for alerting governments about the emergence of new resistant strains. The maintenance of a global database regarding antimicrobial resistance could be valuable to individual nations, although the differences worldwide in interpretation of laboratory susceptibility tests currently pose a challenge to this idea. The availability of a database on the distribution of antimicrobials could assist countries, especially those with limited resources, to undertake such data collection independently. Data gathering is likely to be most effective if coordinated, or at least facilitated, internationally.

International surveillance

Surveillance of antimicrobial resistance and antimicrobial use should be performed at local and national levels to guide clinical management and infection control, to monitor treatment guidelines and to update lists of essential drugs. Surveillance is also a critical tool to monitor the effectiveness of interventions to contain resistance. International collaboration on surveillance may also be of value, to share information as an early warning of new or unusual resistance events. At present there are no formal mechanisms or international legal instruments that require reporting (see above); such resistance events are detected through research studies published in scientific journals. Furthermore, surveillance for rare events such as a new resistance phenotype has different requirements in terms of populations to test and sample size, etc. from those required for routine surveillance. Given the lack of standardization of methods and the worldwide lack of national surveillance systems generating epidemiologically valid data on antimicrobial resistance, the first priority should be at the national level. International organizations and donors should contribute to the strengthening of laboratory capacity in developing countries such that diagnostic services and resistance surveillance can be provided effectively. The development of international surveillance standards is needed—for example, WHO antimicrobial resistance surveillance standards (*209*), WHO guidelines for the management of drug-resistant tuberculosis (*245*) and WHO protocols for detection of antimalarial drug resistance (*14*).

International agencies, professional societies and the pharmaceutical industry could play a role in defining the mechanisms for the establishment and maintenance of an international resistance alert. In addition, assurance should be sought from the editorial boards of international scientific journals that public notification of an international alert does not jeopardise subsequent publication.

International cooperation should also be sought to extend the availability of External Quality Assurance Schemes to resource-poor nations to assist in improving the quality of surveillance data from microbiology laboratories.

Antimicrobial quality and availability

Drug donations

Generous drug donations by pharmaceutical companies, either in the form of actual drug or by release of patent, have had a dramatic effect on the

availability of treatment in complex emergencies and in elimination and eradication programmes for certain disabling diseases in resource-poor settings e.g. leprosy, onchocerciasis (river blindness) and lymphatic filariasis. Such donations should be strongly encouraged, but in certain situations may need to be better coordinated to optimize the selection of drugs provided and their distribution and accessibility to avoid duplication and wastage.

Donors may inadvertently promote inappropriate use of antimicrobials, thereby contributing to the resistance problem, through supporting donations that are inappropriate in terms of the type and quantity of drug, or because a lack of local infrastructure and capacity prevents the appropriate use of the donated drugs. Thus, donor agencies should ensure that the advice they give to governments in drawing up their national health plans takes into account antimicrobial resistance issues. International action should be taken to ensure that all donations follow the interagency guidelines (*246*). Alternatively, financial donations to countries to ensure the purchase of the most effective antimicrobials for their needs together with strategies for distribution and use may be more appropriate. International programmes concerned with drug donations should have capacity-building, training and supervision components, and should be evaluated using indicators that are relevant at the community level, i.e. at household and primary health care facility, where most antimicrobial use takes place.

International inspections of pharmaceutical manufacturing

National quality control of medicines and the monitoring of compliance with Good Manufacturing Practice (GMP) are important to ensure that products meet the required standards. Some countries, e.g. in the EU, already accept findings of inspections that have been performed by appropriately qualified persons from another country. However, not all countries have the resources to perform regular detailed inspections of manufacturing plants; consequently, these do not get inspected unless they are the target of an inspection by a team from another country into which the product(s) is/are exported. In these instances, there may be scope for more extensive sharing of inspection reports between the authorities of the originator country and the inspecting country. It may also be possible to set up international GMP inspection teams, made up of employees of larger agencies who might contribute a limited number of hours per year to the team. Such teams might conduct inspections of a selection of manufacturing sites at the invitation of, and on behalf of, licensing authorities in resource-poor countries.

Assessment report sharing schemes

Drug licensing authorities in many resource-poor countries are often willing to license new medicines on the basis of their prior approval by other regulatory agencies, e.g. the US FDA or the EU. In other countries, where a formal national review of application dossiers is performed, the assessment of safety and efficacy of new medicinal products has sometimes been assisted by the existence of certain assessment report sharing schemes. Expansion of such schemes might benefit regulatory authorities thereby expediting the licensing of new drugs.

The WHO Certification Scheme is an international voluntary agreement, devised to enable countries with limited regulatory capacity to obtain partial assurance from exporting countries concerning the safety, quality and efficacy of the products they plan to import. The scheme requires that the regulatory authorities of exporting countries issue certificates when requested by importing countries.

Counterfeits

Antimicrobials are among the most frequently counterfeited drugs (*191*). Such drugs have potentially major clinical consequences in terms of treatment failure and prolonged, or even increased, suffering. Concerted action to reduce the distribution of counterfeit drugs is beyond the scope of this document and will require the implementation of a separate coordinated package of interventions. National and international authorities should collaborate to ensure the enforcement of relevant laws.

International codes of good marketing practice

Adherence to national and international codes of marketing practices (*240*) is critical to maintaining and improving the quality and accuracy of drug promotion practices. The effective policing of adherence to these codes of practice requires international commitment, cooperation and supervision (see also Chapter 7).

Research and development of new drugs and vaccines

Research and development of new drugs and vaccines is expensive and time-consuming. The establishment of international research networks and further international cooperation on the standardization of new drug registration requirements could assist pharmaceutical companies with drug development programmes and so facilitate the availability of new drugs and vaccines.

International collaboration to improve and standardize clinical trial designs in order to optimize the clinical relevance of the data produced would be helpful. More trials are needed that aim not only to demonstrate equivalence of the new drug to the comparative agent but also to assist in identifying regimens which optimize treatment while minimizing resistance emergence. Such studies are required for products already on the market as well as for new antimicrobials.

There is currently a general lack of interest among companies in developing therapies for infections that primarily affect resource-poor regions of the world. Innovative incentives, both push and pull mechanisms, need to be carefully considered in collaboration with the pharmaceutical industry, so as to facilitate research into drugs and vaccines that would have dramatic health benefits but would likely not be profitable to develop. International agreements and cooperation on intellectual property rights, and new approaches to patents and to time-limited exclusivity arrangements should also be considered, particularly as a means to stimulate additional pharmaceutical and clinical studies to support the licensure of older products for additional, previously unregistered, indications.

Research to address knowledge gaps

Understanding all the issues associated with antimicrobial resistance is probably impossible, but it is clear that there are a number of key knowledge gaps. A clear research agenda highlighting the most important knowledge gaps needs to be defined to guide future research efforts. In this manner, new data that are important to understanding and combating resistance can be channelled back to improve future containment initiatives. To avoid potentially wasteful duplication of effort and finances, international cooperation to develop a common, shared research agenda should be encouraged. Defining a summary of major gaps in the current knowledge regarding antimicrobial resistance and its successful containment, and keeping this summary up to date, could aid this process.

The various research-funding bodies have different priorities in terms of geographical and scientific emphasis, and process individual application protocols rather than using one generic format. The creation of a single entry point through which researchers could access information about potential funding agencies, including specific contact details, their areas of interest and application requirements, could be extremely beneficial. This may also assist greater coordination of effort between the various grant-giving bodies and avoid unnecessary duplication. WHO may be well placed to provide such a service if grant-giving bodies were prepared to collaborate.

The quality of research proposals is the key to their likelihood of getting funding and producing useful data. Thus, programmes that educate potential researchers on the preparation of high-quality research proposals would serve to improve the overall quality of research and reduce wasted research time and money. Greater coordination of international effort to provide such training, either via the Internet or by means of targeted workshops, could be most beneficial.

International support for national antimicrobial resistance containment

Much of the responsibility for implementing interventions will fall on national governments and there are certain actions that only governments can assure, including the provision of public goods. However, many countries will need significant financial and technical support to address the problem of antimicrobial resistance within the wider priorities of strengthened health systems and disease control and prevention programmes. By directing bilateral support to antimicrobial containment, international donors can play a major role in the containment of antimicrobial resistance, not only for the benefit of individual countries, but for the global good.

PART C

Implementation of the WHO Global Strategy

Implementation of the WHO Global Strategy

Introduction

To control the most prevalent infectious diseases, especially those that are related to poverty and for which vaccines are not available, antimicrobials need to be used more wisely, and in some cases, more widely. Appropriate access to effective antimicrobial agents is a major public health issue. Although many patients, especially in sub-Saharan Africa, continue to die as a result of inadequate access to antimicrobials, an emerging problem globally is the widespread indiscriminate use of antimicrobials, especially antibacterial agents. As a result, many antimicrobials have now become less effective due to the emergence of resistance. Simply expanding access to antimicrobials is thus not sufficient; priority must also be given to their appropriate use.

Antimicrobial resistance affects a very broad range of human diseases, including tuberculosis, malaria, AIDS and infections caused by other bacterial, viral, fungal and parasitic pathogens (*12*,*13*,*14*,*43*,*247*,*248*). Despite this wide range of pathogens, the factors responsible for the emergence of resistance are very similar, with excessive and inappropriate drug usage being the key drivers. Thus the broad management approach to containing antimicrobial resistance is similar for each of these pathogens and diseases, although there are some differences such as clinical presentation, diagnostic difficulty, treatment strategies and resistance detection, which are summarized in Table 1. Effective implementation of the WHO Global Strategy needs to recognize and be coherent with these differences.

The various factors identified to be responsible for the emergence of antimicrobial resistance have been discussed in the Part B—Issues and interventions, and recommendations for interventions have been developed on the basis of these factors. However, the identification and prioritization of those factors especially relevant in each national and regional context is more difficult. In addition, given the large number of recommendations for intervention (hereafter referred to simply as interventions) set out in the WHO Global Strategy, there is a practical need to identify priorities. The identification of a core set of interventions to contain resistance could provide great assistance to governments and health care workers charged with the responsibility of implementing national policy.

Prioritization and implementation

STEP 1

The diseases requiring antimicrobial therapy can be used as the basis for the first step in prioritization. National priorities for the containment of antimicrobial resistance can be guided by identifying those diseases that are major problems in the country. On the basis of the evidence used to formulate the WHO Global Strategy, the factors most relevant for antimicrobial resistance in selected diseases can be identified (see Tables 2–5). For each of these factors, those groups of interventions that are likely to be most effective are indicated. In this manner, the process for selecting the necessary interventions to limit emerging antimicrobial resistance can be based on the diseases most prevalent in the country. In some instances, the interventions may be the most challenging to implement. Countries in which all major disease infections are common will need to address all groups of interventions.

Bacterial infections (other than tuberculosis)

The bacterial infections which contribute most to human disease are also those in which emerging antimicrobial resistance is most evident. In this document they are grouped as four key diseases:

- diarrhoea (Table 2)
- respiratory tract infections and meningitis (Table 3)
- sexually transmitted infections (Table 4)
- hospital-acquired infections (Table 5)

The problems related to resistance to the treatments-of-choice for these diseases are presented in detail in accompanying documents (*19*,*20*,*21*,*101*). Tables 2–5 summarize the important factors influencing the emergence and spread of resistance and set out the groups of interventions which need to be implemented to make an impact.

Tuberculosis

Tuberculosis is a leading cause of morbidity and mortality worldwide and resistance to antituberculous therapy has increased dramatically in recent years with evidence of substantive clinical treatment failures and increased person-to-person transmission (*12*,*13*,*43*). The spread of HIV infection, with its associated immunosuppression, has resulted in an enormous increase in TB cases, most frequently among resource-poor communities and in regions with weak health care systems. Inadequate treatment, including insufficient drugs (inadequate supply or mono-therapy), poor quality drugs, and/or poor adherence to treatment regimens have been major factors in the emergence of multi-drug resistant TB (MDR-TB).

Although tuberculosis is a bacterial infection, it is considered different enough to warrant a distinct focus. In addition, WHO has initiated approaches to the containment of anti-tuberculosis drug resistance. Faced with the global emergency of tuberculosis, WHO adopted the DOTS (directly observed treatment, short-course) intervention strategy for effective TB control (*245*,*249*). The principles of DOTS are the following:

— government commitment to a National Tuberculosis Programme

— case detection through case-finding by sputum smear microscopy examination of TB suspects in general health facilities

— standardized short-course chemotherapy to, at least, all smear-positive TB cases under directly observed therapy (DOT) under proper case management conditions

— regular uninterrupted supply of all essential anti-TB drugs

— monitoring system for programme supervision and evaluation.

The implementation of DOTS, presently in 119 countries (*12*,*43*), prevents the generation of MDR-TB through the cure of drug-susceptible TB patients, who will evolve to MDR-TB if they are not properly treated under a DOTS-based programme. However, the control of existing MDR-TB also has an extremely high priority. The Global Project on Anti-Tuberculosis Drug Resistance Surveillance (managed jointly by WHO and the International Union against Tuberculosis and Lung Disease) has identified high prevalence of MDR-TB in some countries of Eastern Europe, Latin America, Africa, and Asia (*12*,*245*,*250*). MDR-TB does not respond as effectively as drug-susceptible TB to short-course chemotherapy with first-line drugs (*48*). Therefore, WHO and its partners have launched DOTS-Plus (*43*,*247*,*251*) to manage MDR-TB with second-line drugs. DOTS-Plus includes the five components of DOTS together with other aspects regarding long-term (18–24 months) therapeutic regimens with second-line drugs, and the use of drug susceptibility testing for diagnosis and therapeutic follow-up. Recommendations for therapeutic regimens for the treatment of MDR-TB were compiled by a panel of experts convened by WHO (*245*,*249*). Pilot projects with some of the recommended treatment regimens are underway to assess the feasibility and cost-effectiveness of using second-line drugs under programme conditions. Surveillance for drug resistance at the pilot sites is a prerequisite. Data generated through this initiative will be used to design evidence-based policy guidelines for the management of MDR-TB, which in turn will play a critical role in the containment of drug resistance in tuberculosis.

Thus, many of the interventions that will need to be implemented to contain resistance in other bacterial infections, such as political commitment, improvement in national regulatory frameworks, drug distribution and educational initiatives regarding antimicrobial resistance, are in line with, and will further support, current initiatives to contain drug-resistant tuberculosis. Intervention priorities have been identified for tuberculosis (Table 6).

Malaria

The majority of deaths in malarious areas continue to be due to the lack of drug availability (*252*). However, emerging resistance is also greatly undermining the efficacy of antimalarial treatment regimens in many regions and is likely to pose a major problem worldwide in the future.

As summarized in Table 7, one of the key drivers behind the emergence of antimalarial resistance is poor patient understanding about the

disease and its appropriate treatment, resulting in indiscriminate short-course therapy with antimalarial agents. In addition, inappropriate prescribing/dispensing and ineffective drug distribution systems encourage such behaviour. The frequent lack of appropriate diagnostic facilities makes the decision to treat difficult, since malaria so frequently presents in an undifferentiated manner, as fever with, or without, headache. Thus, without the ability to confirm the diagnosis, the tendency is to treat every patient with a fever with antimalarials if they reside in a malaria endemic region. Systems for surveillance of antimicrobial resistance are often weak and thus unable to inform about the need to change treatment guidelines. Despite early promising data, it appears that vaccines effective against malaria are still some years away (*253*). The priority for the containment of antimalarial resistance is thus to concentrate on the implementation of intervention groups 1, 2, 5 and 6. This is in line with WHO policy as expressed in a document in preparation by the WHO Regional Office for Africa (*254*).

Viral infections

With the increasing development and use of effective antiretroviral agents, resistance is becoming apparent. *In vitro* resistance to antiretroviral agents among HIV strains appears to correlate with prior antiretroviral therapy and with clinical treatment failure (*255*,*256*,*257*,*258*,*259*). Highly effective combination therapy is considered to be less associated with the emergence of resistance. However, this is a rapidly progressing area of scientific research in which the factors that drive resistance are less clearly defined than for bacterial infections and malaria. As the knowledge base expands, a prioritization of interventions can be developed. At present it seems clear that improved patient and prescriber education (Intervention Groups 1 and 2), government regulations regarding licensure and surveillance of resistance (Intervention Group 5) and issues of drug and vaccine development (Group 6) will all be important.

Conclusion of Step 1

Given the disease-specific aspects of containment of antimicrobial resistance associated with tuberculosis, malaria and HIV infections and the programmes already in place, it is proposed that the first phase of implementation of the WHO Global Strategy should be directed to bacterial infections other than tuberculosis. The valuable lessons that will be learned during this first phase should impact on the implementation approaches used for containment of resistance in tuberculosis, malaria and viral infections. However, due to the commonality of factors leading to antimicrobial resistance in all diseases, many of the interventions, instigated for containing resistance in bacterial infections—such as political commitment, regulatory framework, laboratory strengthening, surveillance and education—will also contribute to resistance containment in other diseases at national level.

STEP 2

Defining a core set of interventions to contain antibacterial resistance

While prioritization by disease group provides some direction for implementation, the identification of a core set for national implementation is required, within each group of interventions. This is particularly relevant to intervention groups 1, 2, 3, 5 and 7. Issues related to group 4 (use of antimicrobials in food-producing animals) have recently been the subject of an extensive consultative process at WHO and primarily involve interventions in the agricultural industry (*2*). Thus they are not considered further here. Interventions relating to drug and vaccine development and international aspects of containing antimicrobial resistance are extremely important, but since they depend on supra-national factors, a number of which involve the (multi-national) research-based pharmaceutical industry, their prioritization at national level is less relevant.

Implementation of the WHO Global Strategy at national level therefore requires prioritization among interventions in groups 1, 2, 3, 5 and 7. The prioritization presented in Step 3 is based on available evidence (summarized in Part B); where evidence is lacking, it is based on the consensus of a suitably qualified group of experts convened by WHO for this purpose.

STEP 3

Intra-group prioritization of interventions

Interventions within each group have been prioritized according to the relative merits of each intervention and ranked according to sequence and importance of implementation. This complex task required consideration of multiple factors relating to each intervention including:

— overall importance of the intervention to improving the appropriate use of antimicrobials and containing antimicrobial resistance

— likely impact, allowing for the expected cost of implementation

— complexity of implementation considering the capacity of various health care systems and political realities

— time required for implementation and the expected lag period before outcomes could be expected

— the accuracy with which most health care systems could assess the efficacy of each intervention

— the interrelationship between various interventions, including the need to undertake some interventions in a logical sequence.

Inter-group prioritization of interventions

Following the prioritization within each group, interventions were ranked according to their overall importance and timing (sequence) of implementation without consideration of their group. Although it was recognized that some priorities might vary depending on the health care system in which they are to be implemented, it was found that this consideration did not impact to any significant extent on the priority given to the majority of very high priority interventions.

The results of Step 3 are shown in Table 8. Interventions are grouped according to those which should be undertaken first, through to those which, although important, are either dependent on the implementation of the earlier interventions or are of lower priority. Within each priority i.e. first, second, third, interventions are not ranked but listed in numerical order only and should be considered of equal importance. For example, for group 1, both interventions 1.2 and 1.3 are considered to be of similar priority for implementation, but both 1.2 and 1.3 are given higher priority than either 1.1 (second priority) or 1.4 and 1.5 (third priority).

Comparisons across the groups of interventions are more difficult but are important to achieve a logical and effective implementation. Within the national reality, consideration of the sectors involved in implementation of the interventions should allow a plan of action to be elaborated.

It must be emphasized that this prioritization process only provides a guide to implementation and is not a rigid set of rules. Differences in national circumstances, health care systems and burden of the different infections may influence the practicality with which some interventions can be implemented and the local importance of one intervention over another in a manner that is not accurately reflected in Table 8. However, Table 8 provides a working guide to the prioritization and sequence of implementation of interventions in groups 1, 2, 3, 5 and 7.

Implementation guidelines

Effective implementation requires a number of key features, including a clear action plan, delegation of authority and power to act, resources and sound mechanisms to assess the effectiveness of interventions, allowing feedback of results to influence future implementation strategies. Thus, interventions identified in the prioritization process as being of fundamental and first priority (see Table 8) have been considered in greater detail, specifically identifying the following aspects as important for successful implementation:

— the optimal approach to implementation

— who should initiate the intervention, undertake and manage the intervention, and evaluate the intervention

— what process and outcome indicators should be used for evaluation.

The proposed guidelines for implementation are detailed in "Suggested Model Framework for Implementation of Core Interventions".

Monitoring outcomes

Ability to monitor the process to ensure that interventions are appropriately designed and targeted and their impact on the use of antimicrobials and the prevalence of resistance will be crucial to the successful implementation of the WHO Global Strategy. Without accurate information about antimicrobial usage and antimicrobial resistance and their respective trends, the impact of interventions will be difficult to interpret. Thus, an early priority in the implementation of the WHO Global Strategy for all countries should be the establishment of an appropriate framework to monitor accurately antimicrobial use and antimicrobial resistance (Intervention Group 5).

Summary

This model implementation plan for the WHO Global Strategy is a guide only. Differences in national circumstances, health care systems and prevalent diseases may influence the approaches taken by governments to contain antimicrobial resistance. However, this is a complex area in which it is often difficult to see the wood for the trees. The stepwise approach described above attempts to highlight the interventions that are most important and to identify a logical sequence for implemention. The manner in which the WHO Global Strategy for Containment of Antimicrobial Resistance is implemented will depend largely on the decisions and actions of each nation, but the consequences are likely to be felt worldwide.

Recommendations for intervention

1. PATIENTS AND THE GENERAL COMMUNITY

Education

1.1 Educate patients and the general community on the appropriate use of antimicrobials.

1.2 Educate patients on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc.

1.3 Educate patients on simple measures that may reduce transmission of infection in the household and community, such as handwashing, food hygiene, etc.

1.4 Encourage appropriate and informed health care seeking behaviour.

1.5 Educate patients on suitable alternatives to antimicrobials for relief of symptoms and discourage patient self-initiation of treatment, except in specific circumstances.

2. PRESCRIBERS AND DISPENSERS

Education

2.1 Educate all groups of prescribers and dispensers (including drug sellers) on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

2.2 Educate all groups of prescribers on disease prevention (including immunization) and infection control issues.

2.3 Promote targeted undergraduate and postgraduate educational programmes on the accurate diagnosis and management of common infections for all health care workers, veterinarians, prescribers and dispensers.

2.4 Encourage prescribers and dispensers to educate patients on antimicrobial use and the importance of adherence to prescribed treatments.

2.5 Educate all groups of prescribers and dispensers on factors that may strongly influence their prescribing habits, such as economic incentives, promotional activities and inducements by the pharmaceutical industry.

Management, guidelines and formularies

2.6 Improve antimicrobial use by supervision and support of clinical practices, especially diagnostic and treatment strategies.

2.7 Audit prescribing and dispensing practices and utilize peer group or external standard comparisons to provide feedback and endorsement of appropriate antimicrobial prescribing.

2.8 Encourage development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials.

2.9 Empower formulary managers to limit antimicrobial use to the prescription of an appropriate range of selected antimicrobials.

Regulation

2.10 Link professional registration requirements for prescribers and dispensers to requirements for training and continuing education.

3. HOSPITALS

Management

3.1 Establish infection control programmes, based on current best practice, with the responsibility for effective management of antimicrobial resistance in hospitals and ensure that all hospitals have access to such a programme.

3.2 Establish effective hospital therapeutics committees with the responsibility for overseeing antimicrobial use in hospitals.

3.3 Develop and regularly update guidelines for antimicrobial treatment and prophylaxis, and hospital antimicrobial formularies.

3.4 Monitor antimicrobial usage, including the quantity and patterns of use, and feedback results to prescribers.

Diagnostic laboratories

3.5 Ensure access to microbiology laboratory services that match the level of the hospital, e.g. secondary, tertiary.

3.6 Ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and timely and relevant reporting of results.

3.7 Ensure that laboratory data are recorded, preferably on a database, and are used to produce clinically- and epidemiologically-useful surveillance reports of resistance patterns among common pathogens and infections in a timely manner with feedback to prescribers and to the infection control programme.

Interactions with the pharmaceutical industry

3.8 Control and monitor pharmaceutical company promotional activities within the hospital environment and ensure that such activities have educational benefit.

4. USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

This topic has been the subject of specific consultations which resulted in "WHO global principles for the containment of antimicrobial resistance in animals intended for food"*. A complete description of all rec-

* http:// www.who.int/emc/diseases/zoo/who_global_principles.html

ommendations is contained in that document and only a summary is reproduced here.

Summary

4.1 Require obligatory prescriptions for all antimicrobials used for disease control in food animals.

4.2 In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans.

4.3 Create national systems to monitor antimicrobial usage in food animals.

4.4 Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.

4.5 Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.

4.6 Develop guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals.

5. NATIONAL GOVERNMENTS AND HEALTH SYSTEMS

Advocacy and intersectoral action

5.1 Make the containment of antimicrobial resistance a national priority.

- Create a national intersectoral task force (membership to include health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties) to raise awareness about antimicrobial resistance, organize data collection and oversee local task forces. For practical purposes such a task force may need to be a government task force which receives input from multiple sectors.
- Allocate resources to promote the implementation of interventions to contain resistance. These interventions should include the appropriate utilization of antimicrobial drugs, the control and prevention of infection, and research activities.
- Develop indicators to monitor and evaluate the impact of the antimicrobial resistance containment strategy.

Regulations

5.2 Establish an effective registration scheme for dispensing outlets.

5.3 Limit the availability of antimicrobials to prescription-only status, except in special circumstances when they may be dispensed on the advice of a trained health care professional.

5.4 Link prescription-only status to regulations regarding the sale, supply, dispensing and allowable promotional activities of antimicrobial agents; institute mechanisms to facilitate compliance by practitioners and systems to monitor compliance.

5.5 Ensure that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization.

5.6 Introduce legal requirements for manufacturers to collect and report data on antimicrobial distribution (including import/export).

5.7 Create economic incentives for appropriate use of antimicrobials.

Policies and guidelines

5.8 Establish and maintain updated national Standard Treatment Guidelines (STGs) and encourage their implementation.

5.9 Establish an Essential Drugs List (EDL) consistent with national STGs and ensure the accessibility and quality of these drugs.

5.10 Enhance immunization coverage and other disease preventive measures, thereby reducing the need for antimicrobials.

Education

5.11 Maximize and maintain the effectiveness of the EDL and STGs by conducting appropriate undergraduate and postgraduate education programmes of health care professionals on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.

5.12 Ensure that prescribers have access to approved prescribing literature on individual drugs.

Surveillance of resistance, antimicrobial usage and disease burden

5.13 Designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health care facilities. The standard of these laboratory facilities should be at least at the level of recommendation 3.6.

5.14 Adapt and apply WHO model systems for antimicrobial resistance surveillance and ensure data flow to the national intersectoral task force, to authorities responsible for the national STGs and drug policy, and to prescribers.

5.15 Establish systems for monitoring antimicrobial use in hospitals and the community, and link these findings to resistance and disease surveillance data.

5.16 Establish surveillance for key infectious diseases and syndromes according to country priorities, and link this information to other surveillance data.

6. DRUG AND VACCINE DEVELOPMENT

6.1 Encourage cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines.

6.2 Encourage drug development programmes which seek to optimize treatment regimens with regard to safety, efficacy and the risk of selecting for resistant organisms.

6.3 Provide incentives for industry to invest in the research and development of new antimicrobials.

6.4 Consider establishing or utilizing fast-track marketing authorization for safe new agents.

6.5 Consider using an orphan drug scheme where available and applicable.

6.6 Make available time-limited exclusivity for new formulations and/or indications for use of antimicrobials.

6.7 Align intellectual property rights to provide suitable patent protection for new antimicrobial agents and vaccines.

6.8 Seek innovative partnerships with the pharmaceutical industry to improve access to newer essential drugs.

7 PHARMACEUTICAL PROMOTION

7.1 Introduce requirements for pharmaceutical companies to comply with national or international codes of practice on promotional activities.

7.2 Ensure that national or internationally codes of practice cover direct-to-consumer advertising, including advertising the Internet.

7.3 Institute systems for monitoring compliance with legislation on promotional activities.

7.4 Identify and eliminate economic incentives that encourage inappropriate antimicrobial use.

7.5 Make prescribers aware that promotion in accordance with the datasheet may not necessarily constitute appropriate antimicrobial use.

8. INTERNATIONAL ASPECTS OF CONTAINING ANTIMICROBIAL RESISTANCE

8.1 Encourage collaboration between governments, non-governmental organizations, professional societies and international agencies to recognize the importance of antimicrobial resistance, to present consistent, simple and accurate messages regarding the importance of antimicrobial use, antimicrobial resistance and its containment, and to implement strategies to contain resistance.

8.2 Consider the information derived from the surveillance of antimicrobial use and antimicrobial resistance, including the containment thereof, as global public goods for health to which all governments should contribute.

8.3 Encourage governments, non-governmental organizations, professional societies and international agencies to support the establishment of networks, with trained staff and adequate infrastructures, which can undertake epidemiologically valid surveillance of antimicrobial resistance and antimicrobial use to provide information for the optimal containment of resistance.

8.4 Support drug donations in line with the UN interagency guidelines*.

8.5 Encourage the establishment of international inspection teams qualified to conduct valid assessments of pharmaceutical manufacturing plants.

8.6 Support an international approach to the control of counterfeit antimicrobials in line with the WHO guidelines**.

8.7 Encourage innovative approaches to incentives for the development of new pharmaceutical products and vaccines for neglected diseases.

8.8 Establish an international database of potential research funding agencies with an interest in antimicrobial resistance.

8.9 Establish new, and reinforce existing, programmes for researchers to improve the design, preparation and conduct of research to contain antimicrobial resistance.

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* *Interagency guidelines. Guidelines for Drug Donations*, revised 1999. Geneva, World Health Organization, 1999. WHO/EDM/PAR/99.4.

** *Counterfeit drugs. Guidelines for the development of measures to combat counterfeit drugs*. Geneva, World Health Organization, 1999. WHO/EDM/QSM/99.1.

TABLE 1. **COMPARISON OF DISEASE-RELATED RESISTANCE ISSUES**

Issues	**Bacterial infections**	**TB**	**Malaria**	**HIV**
Appropriate use important	Yes	Yes	Yes	Yes
Inappropriate use contributes to ↑ resistance	Yes	Yes	Yes	Yes
Need for new drug development	Yes	Yes	Yes	Yes
Detection of pathogen	Reasonably easy & feasible	Easy	Easy	Easy
Detection of *in vitro* resistance	Reasonably easy & feasible	Feasible but expensive	Difficult, expensive rarely feasible	Difficult, expensive limited availability
Treatment indication	Generally pathogen-based (± resistance)	Pathogen-based	Frequently syndromic	Pathogen-based
Observed treatment	No	Yes–DOT	No	No
Antimicrobial treatment	Single agent Short duration	Multiple agents Long duration	≥1 agent Short duration	Multiple agents Lifelong
HIV interaction	Some: Especially nosocomial risk	Massive: Personal & nosocomial risk	Possibly	—
Potential impact of one programme on another	Yes Some antibiotics could affect malaria resistance.	Little Except: Rifampicin use on *Staph*. spp.	Some e.g. doxycyline, sulphadoxine-pyrimethamine	Yes e.g. cotrimoxazole + isoniazid prophylaxis

TABLE 2. **BACTERIAL INFECTIONS (OTHER THAN TUBERCULOSIS): DIARRHOEAL DISEASES**

Pathogens	Important factors				
	Human misuse in the community	Human misuse in hospitals	Misuse in animal & agricultural industry	Surveillance of antibacterial resistance important	Vaccines potentially useful future option
Campylobacter spp.	+/–	–	+++	++	–
Shigella spp.	++	–	+/–	++	–
Salmonella spp:					
S. typhi & *S. paratyphi*	++	–	–	+++	+
Non-typhoidal salmonellae	–/+	–	+++	+++	–
Vibrio cholerae	+	–	–	+++	+
Diarrhoeal disease overall	+/++		++/++	+++	–/+
	High priority Intervention Groups 1, 2, 5 & 7		**High priority** Intervention Groups 4 & 7	**High priority** Intervention Group 5	Moderate priority Intervention Group 6

High priority interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 4 Use of antimicrobials in food-producing animals
Group 5 National governments and health systems
Group 7 Pharmaceutical promotion

TABLE 3. **BACTERIAL INFECTIONS (OTHER THAN TUBERCULOSIS): RESPIRATORY TRACT INFECTIONS AND MENINGITIS**

Pathogens	Important factors				
	Human misuse in the community	Human misuse in hospitals	Misuse in animal & agricultural industry	Surveillance of antibacterial resistance important	Vaccines potentially useful future option
Streptococcus pneumoniae	+++	+	–	+++	+++
Haemophilus influenzae	++	–	–	++	+++
Neisseria meningitidis	+	–	–	+	+
Respiratory disease overall	+++	+		++/+++	+++
	High priority Intervention Groups 1, 2, 5 & 7	Moderate priority Intervention Groups 3 & 7		**High priority** Intervention Group 5	**High priority** Intervention Group 6

High priority Interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 5 National governments and health systems
Group 6 Drug and vaccine development
Group 7 Pharmaceutical promotion

TABLE 4. BACTERIAL INFECTIONS (OTHER THAN TUBERCULOSIS): SEXUALLY TRANSMITTED INFECTIONS

Pathogens	Important factors				
	Human misuse in the community	Human misuse in hospitals	Misuse in animal & agricultural industry	Surveillance of antibacterial resistance important	Vaccines potentially useful future option
Neisseria gonorrhoeae	+++	–	–	+++	–
Haemophilus ducreyi	+++	–	–	+++	–
Treponema pallidum	–	–	–	–	–
Chlamydia trachomatis	–	–	–	–	–
Sexually transmitted disease overall	+++			+++	
	High priority Intervention Groups 1, 2, 5 & 7			**High priority** Intervention Group 5	

High priority interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 5 National governments and health systems
Group 7 Pharmaceutical promotion

TABLE 5. BACTERIAL INFECTIONS (OTHER THAN TUBERCULOSIS) : HOSPITAL-ACQUIRED INFECTIONS

Pathogens	Important factors				
	Human misuse in the community	Human misuse in hospitals	Misuse in animal & agricultural industry	Surveillance of antibacterial resistance important	Vaccines potentially useful future option
Gram-positive spp:					
Staphyloccus aureus	+	+++	–	+++	–
Streptococci	–	+	–	–	–
Enterococci	–	+++	+/++	++	–
Gram-negative spp:					
Escherichia coli	+	++	+	++	–
Enterobacter spp	+	+++	–	+++	–
Klebsiella spp	+	+++	–	+++	–
Pseudomonas aeruginosa	–	+++	–	++	–
Fungi	–	++	–	–	–
Hospital-acquired infections overall	+	++/+++	+	+++	
	High priority Intervention Groups 1, 2, 5 & 7	**High priority** Intervention Groups 3 & 7	Moderate priority Intervention Group 4	**High priority** Intervention Group 5	

High priority interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 3 Hospitals
Group 5 National governments and health systems
Group 7 Pharmaceutical promotion

TABLE 6. **TUBERCULOSIS**

Pathogens	Important factors				
	Human misuse in the community	**Human misuse in hospitals**	**Misuse in animal & agricultural industry**	**Surveillance of antibacterial resistance important**	**Vaccines potentially useful future option**
Mycobacterium tuberculosis	++	–	–	+++	+/–
Tuberculosis overall	++			+++	+
	High priority Intervention Groups 1, 2 & 5			**High priority** Intervention Group 5	Moderate priority Intervention Group 6

High priority interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 5 National governments and health systems

TABLE 7. **MALARIA**

Pathogens	Important factors				
	Human misuse in the community	**Human misuse in hospitals**	**Misuse in animal & agricultural industry**	**Surveillance of antibacterial resistance important**	**Vaccines potentially useful future option**
Plasmodium vivax / ovale / malariae	+	–	–	+	–
Plasmodium falciparum	+++	–	–	+++	+/–
Malaria overall	++			+++	+/–
	High priority Intervention Groups 1, 2 & 5			**High priority** Intervention Group 5	Moderate priority Intervention Group 6

High priority interventions:
Group 1 Patients and the general community
Group 2 Prescribers and dispensers
Group 5 National governments and health systems

TABLE 8. **PRIORITIZATION OF INTERVENTIONS: CORE SET FOR NATIONAL IMPLEMENTATION (EXCLUDING GROUPS 4 AND 6)**

Intervention Group	Priority of implementation			
	Fundamental	First	Second	Third
1. Patients and the general community		1.2 1.3	1.1	1.4 1.5
2. Prescribers and dispensers		2.1 2.2 2.3 2.8	2.6 2.7 2.9	2.4 2.5 2.10
3. Hospitals		3.1 3.5 3.6	3.2 3.3 3.4 3.7 3.8	
5. National governments and health systems	5.1 5.13	5.3 5.5 5.8 5.9 5.11	5.2 5.4 5.12 5.14 5.15 5.16	5.6 5.7
7. Pharmaceutical promotion			7.1 7.2 7.3	7.4 7.5

Suggested model framework for implementation of core interventions (excluding group 4)

INTERVENTIONS—PRIORITY OF IMPLEMENTATION : FUNDAMENTAL

Intervention 5.1	Make the containment of antimicrobial resistance a national priority. • Create a national intersectoral task force (membership to include health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties) to raise awareness about antimicrobial resistance, organize data collection and oversee local task forces. For practical purposes such a task force may need to be a government task force which receives input from multiple sectors. • Allocate resources to promote the implementation of interventions to contain resistance. These interventions should include the appropriate utilization of antimicrobial drugs, the control and prevention of infection, and research activities. • Develop indicators to monitor and evaluate the impact of the antimicrobial resistance containment strategy.
Implementation:	• Develop a National Strategy and make it a national priority
Who should initiate:	• Ministry of Health • Other interested parties should contribute (e.g. Professional Societies) • WHO to assist and contribute
Who should undertake and manage:	• National Intersectoral Task Force appointed by the Ministry of Health • Sufficient resources should be allocated
Who should evaluate:	• WHO through the Regional Offices
Process Indicators:	• Appointment of the National Intersectoral Task Force • Allocation of sufficient resources
Outcome Indicators:	• Has a National Strategy been developed?

Intervention 5.13	Designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health care facilities. The standard of these laboratory facilities should be at least at the level of recommendation 3.6.
Implementation:	• Establishment by government mandate
Who should initiate:	• Ministry of Health • Sufficient resources should be allocated
Who should undertake and manage:	• Reference laboratories—accountable to Government Health Department
Who should evaluate:	• Internal and external, (e.g. international), quality assurance programmes and performance assessments • National Intersectoral Task Force audit
Process Indicators:	• Evidence of overseeing national resistance surveillance • Documentation of resistance data
Outcome Indicators:	• Regular communication of resistance data to National Intersectoral Task Force and Government Health Department • Commitment to teaching and training of laboratory staff including technology transfer

INTERVENTIONS—INTERVENTION PRIORITY: FIRST	
Intervention 1.2	Educate patients on the importance of measures to prevent infection, such as immunization, vector control, use of bednets, etc.
Implementation:	• Develop a National Strategy and make it a national priority
Who should initiate:	• Ministry of Health • Other interested parties should contribute (e.g. Professional Societies) • WHO to assist and contribute
Who should undertake and manage:	• National Intersectoral Task Force (e.g. appointed by the Ministry of Health) • Sufficient resources should be allocated
Who should evaluate:	• WHO through the Regional Offices • Ministry of Health
Process Indicators:	• Appointment of the National Intersectoral Task Force • Allocation of sufficient resources
Outcome Indicators:	• Has a National Strategy been developed? • Immunization rates

Intervention 1.3	Educate patients on simple measures that may reduce transmission of infection in the household and community, such as handwashing, food hygiene, etc.
Implementation:	• Develop a National Strategy and make it a national priority
Who should initiate:	• Ministry of Health • Other interested parties should contribute (e.g. Professional Societies) • WHO to assist and contribute
Who should undertake and manage:	• National Intersectoral Task Force (e.g. appointed by the Ministry of Health) • Sufficient resources should be allocated
Who should evaluate:	• WHO through the Regional Offices • Ministry of Health
Process Indicators:	• Appointment of the National Intersectoral Task Force • Allocation of sufficient resources
Outcome Indicators	• Has a National Strategy been developed?

Interventions 2.1 and 2.2	2.1 Educate all groups of prescribers and dispensers (including drug sellers) on the importance of appropriate antimicrobial use and containment of antimicrobial resistance. 2.2 Educate all groups of prescribers on disease prevention (including immunization) and infection control issues.
Implementation:	• Develop a National Strategy and make it a national priority • Identify interested organizations and opinion leaders, educators and sources of appropriate information
Who should initiate:	• National Intersectoral Task Force
Who should undertake and manage:	• Organizations delegated by the National Intersectoral Task Force

INTERVENTIONS—INTERVENTION PRIORITY: FIRST (continued)	
Who should evaluate:	• Ministry of Health • National Intersectoral Task Force • Professional organizations, universities, delegated organizations
Process Indicators:	• Opinion leaders identified, quantitative and qualitative assessments of educational exposure
Outcome Indicators:	• Levels of knowledge, attitudes and beliefs about antibiotic use, awareness of antimicrobial resistance and disease prevention issues in target populations

Intervention 2.3	Promote targeted undergraduate and postgraduate educational programmes on the accurate diagnosis and management of common infections for all health care workers, veterinarians, prescribers and dispensers.
Implementation:	• Develop a National Strategy and make it a national priority • Identify interested organizations and opinion leaders, educators and sources of appropriate information • Create and/or strengthen in-service training, professional development and continuing education for all health care workers appropriate to local context and problems.
Who should initiate:	• National Intersectoral Task Force—delegating to suitable interested organizations and opinion leaders
Who should undertake and manage:	• Organizations delegated by the National Intersectoral Task Force
Who should evaluate:	• National Intersectoral Task Force • Professional organizations, universities and organizations delegated by the National Intersectoral Task Force
Process Indicators:	• Opinion leaders identified • Curriculum developed and implemented; quantitative and qualitative assessments of educational exposure
Outcome Indicators:	• Levels of knowledge, attitudes and skills regarding management of common infections and containment of antimicrobial resistance

Intervention 2.8	Encourage development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials.
Implementation:	• National Intersectoral Task Force—delegating to suitable interested organizations, opinion leaders and educators • Use of evidence-based principles of effective guideline development, including maximal participation of health care providers most involved in managing the condition, involvement of end-users, systematic review and appraisal of evidence, involvement of consumers
Who should initiate:	• National Intersectoral Task Force
Who should undertake and manage:	• Organizations delegated by the National Intersectoral Task Force
Who should evaluate:	• National Intersectoral Task Force • Organizations delegated by the National Intersectoral Task Force
Process Indicators:	• Production of guidelines and dissemination plan
Outcome Indicators:	• Level of uptake and indicators of appropriate use of antimicrobials among target health care providers

INTERVENTIONS—INTERVENTION PRIORITY: FIRST (continued)	
Intervention 3.1	Establish Infection Control Programmes, based on current best practice, with the responsibility for effective management of antimicrobial resistance in hospitals and ensure that all hospitals have access to such a programme.
Implementation:	• Establishment by government mandate • Where possible the infection control programme should be part of hospital (public and private) accreditation • Sufficient resources should be allocated for implementation
Who should initiate:	• Hospital management delegating to an infection control committee
Who should undertake and manage:	• Infection Control Committee
Who should evaluate:	• National Intersectoral Task Force • Ideally, external audit by a competent authority delegated by the National Intersectoral Task Force; in the absence of external evaluation, use benchmarking to other comparable institutions
Process Indicators:	• Infection control strategies, policies, guidelines documented • Evidence of relevant data collection
Outcome Indicators:	• Data being used to reduce rates of hospital-acquired infection and antimicrobial resistance below an agreed target
Intervention 3.5	Ensure access to microbiology laboratory services that match the level of the hospital, e.g. secondary, tertiary.
Implementation:	• Hospital management, through government if appropriate • Sufficient resources should be allocated for establishment and maintenance of laboratories
Who should initiate:	• Hospital management—in consultation with appropriately trained staff and learned societies
Who should undertake and manage:	• Microbiologists, or medical/scientific staff adequately trained in microbiology
Who should evaluate:	• Benchmarking by Microbiology and Hospital management to other laboratories servicing similar institutions about range of diagnostic and susceptibility tests
Process Indicators:	• Implementation of Recommendations 3.6 and 3.7
Outcome Indicators:	• Implementation of Recommendations 3.6 and 3.7
Intervention 3.6	Ensure performance and quality assurance of appropriate diagnostic tests, microbial identification, antimicrobial susceptibility tests of key pathogens, and timely and relevant reporting of results.
Implementation:	• Microbiology laboratory
Who should initiate:	• Microbiology laboratory management
Who should undertake and manage:	• Microbiology laboratory management
Who should evaluate:	• An internal and external (national or international) quality assurance programme • National Laboratory accreditation schemes where they exist
Process Indicators:	• Evidence of participation in quality assurance activities

INTERVENTIONS—INTERVENTION PRIORITY: FIRST (continued)	
Outcome Indicators:	• Performance level in quality assurance activities • Continuing laboratory accreditation, where accreditation schemes exist
Interventions 5.3 and 5.5	5.3 Limit the availability of antimicrobials to prescription-only status, except in special circumstances when they may be dispensed on the advice of a trained health care professional. 5.5 Ensure that only antimicrobials meeting international standards of quality, safety and efficacy are granted marketing authorization.
Implementation:	• Ministry of Health establishing and delegating to a Government Drug Regulation Authority
Who should initiate:	• Ministry of Health delegating to a Government Drug Regulation Authority • National Intersectoral Task Force
Who should undertake and manage:	• Government Drug Regulation Authority • National Intersectoral Task Force
Who should evaluate:	• Ministry of Health via Government Drug Regulation Authority • National Intersectoral Task Force
Process Indicators:	• Presence of appropriate legislation • Categorization of drugs, GMP inspection in place, restriction of drugs to registered outlets
Outcome Indicators:	• Results of Regulations enforcement—number of inspections, prosecutions, etc.
Interventions 5.8 and 5.9	5.8 Establish and maintain updated national Standard Treatment Guidelines (STGs) and encourage their implementation. 5.9 Establish an Essential Drugs List (EDL) consistent with the national STGs and ensure the accessibility and quality of these drugs.
Implementation:	• National Intersectoral Task Force—to establish a suitable Committee consisting of interested organizations, opinion leaders and educators • Government Drug Regulation Authority
Who should initiate:	• National Intersectoral Task Force—to establish a suitable Committee consisting of interested organizations, opinion leaders and educators • Government Drug Regulation Authority
Who should undertake and manage:	• Ministry of Health • National Intersectoral Task Force
Who should evaluate:	• Ministry of Health • National Intersectoral Task Force
Process Indicators:	• Production of national Standard Treatment Guidelines and EDL • Plan for implementation and dissemination
Outcome Indicators	• Level of uptake, including indicators of appropriate use of antimicrobials among target health care providers and use of EDLs

INTERVENTIONS—INTERVENTION PRIORITY: FIRST (continued)	
Intervention 5.11	Maximize and maintain the effectiveness of the EDL and STGs by conducting appropriate undergraduate and postgraduate education programmes of health care professionals on the importance of appropriate antimicrobial use and containment of antimicrobial resistance.
Implementation:	• Ministry of Health • National Intersectoral Task Force—delegating to universities and other training institutions, including suitable interested organizations, opinion leaders and educators
Who should initiate:	• Ministry of Health • National Intersectoral Task Force
Who should undertake and manage:	• Training institutions and organizations delegated by the National Intersectoral Task Force • Professional bodies responsible for registration of health care professionals
Who should evaluate:	• National Intersectoral Task Force • Training institutions and organizations delegated by the National Intersectoral Task Force
Process Indicators:	• Curriculum developed and implemented; quantitative and qualitative assessments of educational exposure • Presence of specific registration requirements for health care professionals
Outcome Indicators:	• Levels of knowledge, attitudes and skills regarding appropriate antimicrobial use and containment of antimicrobial resistance • Assessment of Registration suitability based on continuing education on antimicrobial use and containment of antimicrobial resistance

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Annexes

ANNEX A

National Action Plans

Canada:

http://www.hc-sc.gc.ca/hpb/lcdc/bid/nosocom/fact1.html

European Union:

http://www.earss.rivm.nl/

France:

http://www.invs.sante.fr/

Norway:

http://odin.dep.no/shd/norsk/publ/handlingsplaner/030005-990326/index-dok000-b-n-a.html

Sweden:

http://www.sos.se/FULLTEXT/0000-044/0000-044.htm

United Kingdom:

http://www.doh.gov.uk/publications/pointh.htm

USA (Centers for Disease Control and Prevention, Atlanta):

http://www.cdc.gov/drugresistance/actionplan/

ANNEX B

Participation in WHO Consultations

WHO Global Strategy for the Containment of Antimicrobial Resistance

Workshop to develop the framework document (*260*) Geneva, 4–5 February 1999

List of participants

Dr Tasleem Akhtar, Pakistan Medical Research Council, Shahnaki-e-Jamurait Sector G5/2, Islamabad, Pakistan

Dr Susan Bacheller, Office of Health and Nutrition, USAID/G/PHN/HN/HPSR, Washington, USA

Dr Richard Bax, Director and Vice-President, Antiinfective Therapeutic Unit, Clinical Research and Development, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK

Dr Tom Bergan, President, International Society of Chemotherapy, Institute of Medical Microbiology, Rikshospitalet (National Hospital), Oslo, Norway

Dr Nancy Blum, United States Pharmacopeia, Rockville, USA

Dr Otto Cars, Department of Infectious Diseases, Uppsala University Hospital, Uppsala, Sweden

Dr Keryn Christiansen, Clinical Microbiologist, Department of Microbiology & Infectious Diseases, Royal Perth Hospital, Western Australia

Dr Andres de Francisco, International Health Specialist, Global Forum for Health Research, c/o World Health Organization, 1211 Geneva 27, Switzerland

Dr David Fidler, Indiana University School of Law, 211 South Indiana Avenue, Bloomington IN 47405-1001, USA

Professor Widjoseno Gardjito, Department of Surgery, Dr Soetomo Hospital, Jalan Professor Dr Moestopo 6–8, Surabaya 60286, Indonesia

Dr Judy Gilley, (British Medical Association), Cornwall House Surgery, Cornwall Road, London N3 1LD, UK

Dr Neal Halsey, Director of Division of Disease Control, Johns Hopkins University, Baltimore, USA

Professor Pentti Huovinen, Antimicrobial Research Laboratories, National Public Health Institute, Turku, Finland

Dr Keith Klugman, The South African Institute for Medical Research, PO Box 1038, Johannesburg 2000, South Africa

Dr Richard Laing, Associate Professor, Department of International Health, Boston University School of Public Health, 715 Albany St, Boston, MA 02118-2526, USA

Dr David Lee, Deputy Director, Drug Management Program, Management Sciences for Health, Arlington, USA

Dr Joel Lexchin, 121 Walmer Road, Toronto, Canada

Dr Donald E Low, Microbiologist-in-Chief, Mount Sinai Hospital, The Toronto Hospital, Toronto, Canada

Dr Peter Mansfield, Director, MaLAM, Australia

Dr Shaheen Mehtar, Western Cape, South Africa

Dr Le Van Phung, Central Biomedical Laboratory, Hanoi Medical School, Hanoi, Vietnam

Dr Mair Powell, Medicines Control Agency, Market Towers, Room 1534, 1 Nine Elms Lane, London, UK

Dr Gro Ramster Wesenberg, Norwegian Medicine Control Authority, Sven Oftedsalsvei 6, Oslo 0950, Norway

Dr Dennis Ross-Degnan, DACP, Drug Policy Research Group, Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, USA

Dr Budiono Santoso, Department of Clinical Pharmacology, Faculty of Medicine, Gadjah Mada University Sekip, Yogyakarta, Indonesia

Dr Anthony Savelli, Director, Rational Pharmaceutical Management, Management Sciences for Health, Arlington, USA

Dr Ben Schwartz, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Dr Wing Hong Seto, Department of Microbiology, Queen Mary Hospital, Hong Kong

Dr Walter Stamm, Head, Division of Allergy and Infectious Diseases, University of Washington, Seattle, USA

Professor Mark Steinhoff, Department of International Health, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, USA

Dr J Todd Weber, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Dr H Wegener, Danish Zoonosis Centre, National Veterinary Laboratory, Copenhagen, Denmark

Professor M Wierup, Swedish Animal Health Service, Johanneshov, Sweden

Representatives from USAID

Dr Susan Bacheller

Dr Anthony Boni

Dr Caryn Miller

WHO Global Strategy for the Containment of Antimicrobial Resistance

Prioritization and Implementation Workshop Geneva, 12–14 September 2000

List of participants

Dr Samuel Azatyan, Head of the Department of Pharmacovigilance and Rational Use of Drugs, Armenian Drug and Medical Technology Agency (ADMTA), Yerevan, Armenia

Dr Luis Bavestrello, Infectious Diseases Specialist and Clinical Pharmacologist, Jefe, Unidad de infectología, Hospital dr. Gustavo Fricke, Viña del Mar, Chile

Dr Mike Bennish, Director, Africa Centre for Health and Population Studies, Mtubatuba, South Africa

Dr Richard E Besser, Respiratory Diseases Branch (C-23), Centers for Disease Control and Prevention, Atlanta, USA

Dr Christopher C Butler, Senior Lecturer, Department of General Practice, University of Wales College of Medicine, Llanedeyrn Health Centre, Cardiff, UK

Dr John Chalker, Management Services for Health, Arlington, USA

Professor Ranjit Roy Chaudhury, National Institute of Immunology, Shahid Jeet Sing Marg, New Delhi, India

Dr Narong Chayakula, Secretary General, Food and Drug Administration, Ministry of Public Health, Muang, Nonthaburi, Thailand

Professor Thomas Cherian, Christian Medical College, Vellore, India

Mrs Parichard Chirachanakul, Food and Drug Administration, Ministry of Public Health, Muang, Nonthaburi, Thailand

Dr Scott Fridkin, Medical Epidemiologist, Hospital Infections Program (E-55), Centers for Disease Control and Prevention, Atlanta, USA

Dr Marcelo F Galas, Profesional Servicio Antimicrobianos, Instituto Nacional de Enferme-dades Infecciosas—ANLIS—"Dr. Carlos G. Malbran", Buenos Aires, Argentina

Dr Manuel Guzmán-Blanco, President of the Committee on Antibiotics of the Sociedad Panamericana de Infectología, (Pan American Society of Infectious Diseases), Unidad de Microbiología y Enf. Infecciosas, Hospital Vargas, Centro Médico de Caracas, Caracas, Venezuela

Professor King Holmes, University of Washington, Harborview Medical Center, Seattle, USA

Dr Abdulrahman Hassan Ishag, Hospitals Administration, Department of Curative Medicine, Ministry of Health, Riyadh, Kingdom of Saudi Arabia

Professor KK Kafle, Institute of Medicine, TU Teaching Hospital, Kathmandu, Nepal

Dr Adeeba Kamarulzaman, Associate Professor, Head, Infectious Diseases Unit, Department of Medicine, University Malaya, Kuala Lumpur, Malaysia

Dr Göran Kronvall, Clinical Microbiology—MTC, Karolinska Hospital, Stockholm, Sweden

Dr David Lee, Deputy Director, Drug Management Program, Management Services for Health, Arlington, USA

Dra Alina Llop, Directora del Laboratorio Nacional de Referencia de Microbiología, Sub-Directora Instituto Medicina Tropical "Pedro Kouri", La Habana, Cuba

Mrs Precious Matsoso, Department of Health, Pretoria, South Africa

Dr Thomas O'Brien, Microbiology Laboratory, Brigham and Women's Hospital, Boston, USA

Dr David Ofori Adjei, Director, Nogouchi Memorial Institute for Medical Research, University of Ghana, Legon, Accra, Ghana

Dr Philip Onyebujo, Department of Health, Pretoria, South Africa

Associate Professor Neil Paget, Royal Australasian College of Physicians, Sydney, Australia

Dr Ricardo Pérez-Cuevas, Investigador Asociado, Unidad de Investigacion Epidemiologica y en Servicios de Salud CMN Siglo XXI, Instituto Mexicano del Seguro Social, Mexico, Mexico

Dr Mair Powell, Medical Assessor, Licensing Division, Department of Health, Medicines Control Agency, London, UK

Dr Dennis Ross-Degnan, Associate Professor, Drug Policy Research Group, Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, USA

Professor Sidorenko Sergei, Department of Microbiology, Russia Medical Academy of Postgraduate Studies, National Research Centre of Antibiotics, Moscow, Russia

Dr Richard Smith, Senior Lecturer, Health Economics Group, School of Health Policy and Practice, University of East Anglia, Norwich, UK

Soeparmanto, Dr Sri Astuti S, Kepala Badan Litbang Kesehatan, Head, National Institute of Health Research and Development, Jakarta, Indonesia

Dr Christian Trigoso, Head of the Bacteriology Department, Instituto de Laboratorio de Salud, La Paz, Bolivia

Dr Peet Tüll, Medical Director, Division of Communicable Diseases Control, The National Board of Health and Welfare, Stockholm, Sweden

Associate Professor John Turnidge, Women's and Children's Hospital, North Adelaide, Australia

Dr Kris Weerasuriya, Professor of Pharmacology and Secretary of the Drug Evaluation Sub-Committee (DESC), Ministry of Health, Department of Pharmacology, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka

Representatives from WHO Regional Offices

Dr Massimo Ciotti, Communicable Diseases, WHO Regional Office for Europe, Copenhagen

Dr Sudarshan Kumari, Regional Advisor, Blood Safety and Clinical Technology, WHO Regional Office for South East Asia, New Delhi, India

WHO Meeting on International Aspects of the Containment of Antimicrobial Resistance

Geneva, 11–12 January 2001

List of participants

Alliance for the Prudent Use of Antibiotics (APUA)

Kathleen T Young, Executive Director, Boston, USA

American International Health Alliance

Thomas O'Brien, Head, Department of Microbiology, Brigham and Women's Hospital, Boston, USA

James P Smith, Executive Director, Washington, USA

Centers for Disease Control and Prevention (CDC)

David Bell, Assistant to the Director for Antimicrobial Resistance, National Center for Infectious Diseases, Atlanta, USA

Conféderation Mondiale de L'Industrie de la Santé Animale (COMISA)

Anthony J Mudd, Vice President/Secretary General, Representative Body of the Worldwide Animal Health Industry, Brussels, Belgium

European Commission—Luxembourg

Hartmut Buchow, Euroforum Building, Luxembourg

European Society for Clinical Microbiology and Infectious Disease (ESCMID)

Peter Schoch, ESCMID Basel, Switzerland

Global Forum for Health Research

Andres De Francisco, Senior Public Health Specialist, c/o World Health Organization, Geneva, Switzerland

International Association of Medical Laboratory Technologists (IAMLT)

Martha A Hjálmarsdóttir, President, Reykjavík, Iceland

International Committee of the Red Cross

Ann Aerts, Head of Health Services, Geneva, Switzerland

International Council of Nurses

Tesfamicael Ghebrehiwet, ICN Consultant, Nursing & Health Policy, Geneva, Switzerland

International Council of Women

Pnina Herzog Ph. C.M.R. Pharm.S., President, Jerusalem , Israel

International Federation of Infection Control (IFIC)

Anna Hambraeus, Division for Hospital Control, University Hospital, Uppsala, Sweden

International Federation of Pharmaceutical Manufacturers' Association (IFPMA)

Peter Hohl, Pharma Research Preclinical Infectious Diseases, F. Hoffmann—La Roche Ltd, Basel, Switzerland

Patricia Hogan, Senior Manager, Pfizer Inc., New York, USA

Tony White, Anti-Infectives Strategic Product Development, Smithkline Beecham Pharmaceuticals, Harlow, Essex ,UK

International Pharmaceutical Federation (FIP)

Diane Gal, FIP Project Coordinator, Den Haag, The Netherlands

International Society of Chemotherapy

Jean-Claude Pechère, Secrétaire général, Université de Génétique et Microbiologie, Université de Geneva CHU, Geneva 4, Switzerland

International Society for Infectious Diseases (ISID)

Keryn Christiansen, Co-Chair, ISID Antibiotic Task Force, Department Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Australia

Permanent Mission of Norway to the United Nations Office and other International Organizations at Geneva

O Christiansen, Counsellor, Geneva, Switzerland

The Wellcome Trust

Robert E Howells, Director of Science Programmes, London, UK

Richard Lane, Head of International Programmes, London, UK

UNICEF

Abdel W El Abassi, UNICEF, New York, USA

USAID Rational Pharmaceutical Management Project

John Chalker, Arlington, USA

UK Department of Health

Jane Leese, Senior Medical Officer, Skipton House, London, UK

US Department of Health and Human Services /National Institute of Allergy and Infectious Diseases

Marissa A Miller, Antimicrobial Resistance Program Officer, Bethesda, Maryland, USA

World Self-Medication Industry (WSMI)

Jerome A Reinstein, Director-General, London, UK

World Trade Organization

João Magalhães, Counsellor, Agriculture and Commodities Division, Centre William Rappard, Geneva, Switzerland

World Veterinary Association

Herbert P Schneider, Vice-President, AGRIVET Consultants, Windhoek, Namibia

WHO Temporary Advisors

M Lindsay Grayson, Austin and Repatriation Medical Centre, Melbourne, Australia

Stuart B Levy, President APUA, Boston, USA

Jean-Claude Pechère, also representing the International Society of Chemotherapy

Mair Powell, Medicines Control Agency, London, UK

Richard Smith, School of Health Policy and Practice, University of East Anglia, Norwich, UK

Representatives from WHO

David Heymann, Executive Director, Communicable Diseases

Guénaël Rodier, Director CSR

Hans Troedsson, Director CAH