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Executive Summary



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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 1998¹ 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

¹ World Health Organization. World Health Assembly (fifty-first). *Emerging and other communicable diseases: antimicrobial resistance*. WHA51.17, 1998, agenda item 21.3.

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 and 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 food² 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"². A complete description of all recommendations is contained in that document and only a summary is reproduced here.

² World Health Organization. *WHO global principles for the containment of antimicrobial resistance in animals intended for food.* 2000. www.who.int/emc/diseases/zoo/who_global_principles.html



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.

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.



