The evolving threat of antimicrobial resistance

Options for action

World Health Organization

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The WHO Patient Safety Programme is indebted to the international experts who contributed to this process. A full list of contributors is provided at the end of the book. The working group leads and main authors were Frank M. Aaerestrup, Technical University of Denmark; Awa Aidara-Kane, World Health Organization; Otto Cars and Andreas Heddini, both at Action on Antibiotic Resistance (ReAct), Sweden; Shaoyu Chang and Anthony So, at Duke University, USA; Barry Cookson, at the Health Protection Agency, UK; Petra Gastmeier at Charité University Hospital, Germany; Lindsay Grayson at the University of Melbourne, Australia; Hajo Grundmann, at the National Institute for Public Health and the Environment, The Netherlands; Stuart Levy, from Tufts University School of Medicine, USA; Thomas F O'Brien and John M Stelling, at Brigham and Women's Hospital, USA; and Wing-Hong Seto, from Queen Mary Hospital, Hong Kong SAR, China. The working groups comprised specialists in AMR who together brought their knowledge and understanding of the risks and challenges in the fight against AMR and of the most effective interventions to tackle the problem.

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Foreword

Antimicrobial resistance (AMR) is not a recent phenomenon, but it is a critical health issue today. Over several decades, to varying degrees, bacteria causing common infections have developed resistance to each new antibiotic, and AMR has evolved to become a worldwide health threat. With a dearth of new antibiotics coming to market, the need for action to avert a developing global crisis in health care is increasingly urgent.

In addition to a substantial financial burden that national health-care budgets can ill afford, AMR has economic consequences far beyond the health sector, such as damaging repercussions on international travel and trade resulting from the cross-border spread of resistant infections. The cost of *not* acting against AMR needs to be considered when deciding resource allocation and assessing interventions.

We know how and why AMR develops, what factors favour its emergence and spread, and what measures can be taken to limit it. Why then are we now facing an impending crisis in the treatment of many infections? This book describes the context of the problem, some of the progress made in recent years to tackle it, and what more should be done. Without question, more information and new tools are needed, but available strategies and interventions can go a long way towards minimizing the scale and impact of AMR, and maximizing the effective lifespan of existing antibiotics. Much more could be achieved by better and more widespread application of these measures, and there are many promising opportunities for innovation in this area.

Infections which are increasingly resistant to antibiotics together account for a heavy disease burden, often affecting developing countries disproportionately. The use of vast quantities of antibiotics in food-producing animals adds another dimension to a complex situation. Several sectors and services are involved and each, from public health to animal husbandry, has an important role to play in counteracting AMR. Responsibility needs to be shared, and coordination of the separate necessary inputs requires determined leadership, additional resources, and solid commitment at many levels.

The World Health Organization (WHO) has long recognized AMR as a growing global health threat, and the World Health Assembly, through several resolutions over two decades, has called upon Member States and the international community to take measures to curtail the emergence and spread of AMR. The WHO Global Strategy for Containment of Antimicrobial Resistance, published in 2001, set out a comprehensive set of recommendations for AMR control which remain valid today. This book examines the experiences with implementing some of those recommendations ten years on, the lessons learnt along the way and the remaining gaps. On World Heath Day 2011, WHO again highlighted AMR and urged countries to commit to a comprehensive financed national plan to combat AMR, engaging all principal stakeholders including civil society.

I am pleased to present this book during the campaign year chosen by WHO for special emphasis on the importance of AMR. It testifies to the Organization's commitment to promoting and facilitating global action to contain AMR and ensuring that effective antibiotics will be available worldwide in the future.

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Abbreviations

AGISAR	WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMC	Advanced Market Commitment
AMR	Antimicrobial Resistance
ANDI	African Network for Drugs and Diagnostics Innovation
ANSORP	Asian Network of Surveillance of Resistant Pathogens
APUA	Alliance for the Prudent Use of Antibiotics
ARMed	Antimicrobial Resistance in the Mediterranean
CDC	Centers for Disease Control
CIPARS	Canadian Integrated Programme for Antimicrobial Resistance Surveillance
CLSI	Clinical and Laboratory Standards Institute
CNISP	Canadian Nosocomial Infection Surveillance Programme
CSIR	Council of Scientific and Industrial Research
DDD	Defined Daily Doses
DID	Daily Doses per 1000 inhabitants per day
DRA	Drug Regulatory Agencies
DRG	Diagnosis Related Group
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EML	Essential Medicines List
EMRO	WHO Regional Office for the Eastern Mediterranean
EQA	External Quality Assurance
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EUR	European Region
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GAVI	Global Alliance for Vaccines and Immunization
GFN	Global Foodborne Infections Network
GLI	Global Laboratory Initiative
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Point
HAI	Health care-Associated Infection
HELICS	Hospitals in Europe Linked for Infection Control through Surveillance
HHCCP	Hand Hygiene Culture-change Pilot Programme
HIV	Human Immunodeficiency Virus
HIVResNet	Global HIV Drug Resistance Network
HPV	Human Papilloma Virus
ICSRs	Individual Case Safety Reports
IDSR	Integrated Disease Surveillance and Response
IMI	Innovative Medicines Initiative
IMS	Intercontinental Marketing Services
INICC	International Nosocomial Infection Control Consortium

IPC	Infection Prevention and Control
ISRAR	International Surveillance of Reservoirs of Antibiotic Resistance
LED	Light Emitting Diode
MDR	Multi-drug Resistance
MDR-TB	Multidrug-resistant Tuberculosis
MoH	Ministry of Health
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
MYSTIC	Meropenem Yearly Susceptibility Test Information Collection
NAUSP	National Antimicrobial Utilization Surveillance Program
NCATS	National Center for Advancing Translational Sciences
NDM	New Delhi Metallo-beta-lactamase
NEQAS	National External Quality Assurance Scheme
NGOs	Nongovernmental Organizations
NIH	National Institutes of Health
OIE	World Organisation for Animal Health
OSDD	Open Source Drug Discovery
OTC	Over the Counter
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCR	Polymerase Chain Reaction
PDPs	Product Development Partnerships
PPS	Point Prevalence Survey
R&D	Research and Development
ReAct	Action on Antibiotic Resistance
ReLAVRA	Red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas
SAR	Self-medication with Antibiotics and Resistance Levels in Europe
SEAR	South-East Asia Region
SIDA	Swedish International Development Cooperation Agency
SRL	Staphylococcus Reference Laboratory
STRAMA	Swedish Strategic Programme against Antibiotic Resistance
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
TDR	Research and Training in Tropical Diseases
TPP	Target Product Profile
UMC	Uppsala Monitoring Centre
UNITAID	International facility for the purchase of drugs against HIV/AIDS, Malaria and Tuberculosis
VRE	Vancomycin-resistant enterococci
WHD	World Health Day
WHO	World Health Organization
WPR	Western Pacific Region
WPRO	WHO Regional Office for the Western Pacific
XDR-TB	Extensively Drug-resistance Tuberculosis

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Chapter 1.

The evolving threat of antimicrobial resistance

Introduction

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Introduction

Bacteria which cause disease react to the antibiotics used as treatment by becoming resistant to them, sooner or later. This natural process of adaptation, antimicrobial resistance, means that the effective lifespan of antibiotics is limited. Unnecessary use and inappropriate use of antibiotics favours the emergence and spread of resistant bacteria. A crisis has been building up over decades, so that today many common and life-threatening infections are becoming difficult or even impossible to treat, sometimes turning a common infection into a life-threatening one. It is time to take much stronger action worldwide to avert a situation that entails an ever increasing health and economic burden.

The evolving public health threat of antimicrobial resistance (AMR) is driven by both appropriate and inappropriate use of anti-infective medicines for human and animal health and food production, together with inadequate measures to control the spread of infections. Recognizing the public health crisis due to AMR, several nations, international agencies, and many other organizations worldwide have taken action to counteract it through strategies applied in the relevant sectors. Several World Health Assembly resolutions have called for action on specific health aspects related to AMR, and the World Health Organization published its global strategy to contain AMR in 2001.[1] On World Health Day (WHD) 2011, in a six-point policy package, countries were called upon to (1) commit to a comprehensive, financed national plan with accountability and civil society engagement, (2) strengthen surveillance and laboratory capacity, (3) ensure uninterrupted access to essential medicines of assured quality, (4) regulate and promote rational use of medicines in animal husbandry and to ensure proper patient care, (5) enhance infection prevention and control, and (6) foster innovations and research and development of new tools.[2]

This book describes examples of policy activities and experiences that have addressed AMR in different parts of the world and some of the progress made since the publication of the 2001 strategy. It draws attention to areas where knowledge is lacking and where urgent action is still needed. The aim of this book is to raise awareness about AMR and stimulate further efforts to meet the recommendations outlined in the 2001 strategy and in the 2011 WHD policy package. It does so by examining the current situation and setting out what has been done and what more could be done around the world, in high-, middle- and low-income countries. While much of what is summarized here is well known to the scientific community, awareness at the political level is also essential, but often lacking. A specific objective is therefore to encourage policy decision-makers and the global community to commit to intensified action against AMR.

The book focuses on five of the most important areas for the control of antibiotic resistance as recognized in the WHO 2001 strategy, which are: surveillance, rational use in humans, rational use in animals, infection prevention and control, and innovations. Political commitment is highlighted as one of the policy actions in the 2011 WHD six-point policy package and is recognized as an indispensable prerequisite for action in the five focus areas of this book.

AMR as a public health concern

Many patients around the world suffer harm due to AMR because infections – caused by viruses, bacteria, fungi, protozoa or helminths – are no longer susceptible to the common medicines used to treat them. Reports on AMR are most often generated on the basis of laboratory results on microbes obtained from human patients. These reports are used to inform decisions on the treatment of individual patients, and also as evidence for policies at local, national, and international levels. Data from around the world confirm that AMR, including multidrug resistance, is increasing among many pathogens responsible for infections in health-care facilities and in the community.[3,4]

AMR makes it difficult and more expensive to treat a variety of common infections, causing delays in effective treatment, or in worst cases, inability to provide appropriate therapy. Many of the medical advances in recent years, such as chemotherapy for cancer treatment and organ transplantation, are dependent on the availability of anti-infective drugs. The predictable consequence of resistance is increased morbidity, prolonged illness, a greater risk of complications, and higher mortality rates. The economic burden includes loss of productivity (loss in income, diminished worker productivity, time spent by family) and increased cost of diagnostics and treatment (consultation, infrastructure, screening, cost of equipment, drugs). Both the health and economic consequences of AMR are considerable and costly but difficult to quantify precisely as the available data are incomplete in many countries. The additional human burden associated with it (pain, change in daily activities, psychosocial costs) is also significant, but even more difficult to quantify.

Available quantitative evidence on excess harm caused to patients through drug resistance comes mainly from experiences with malaria, tuberculosis, and to some extent, human immunodeficiency virus (HIV), which are cited below as illustrative examples of the problem. There is a growing body of evidence that AMR is also increasingly important in many of the common bacterial diseases, but there are much less systematic data on its extent and the consequences for patients.

Malaria: Resistance to antimalarial medicines has been documented for all classes of antimalarials, including the artemisinin derivatives, and is a major threat to malaria control.[5] The therapeutic efficacy of medicines is directly monitored by clinical and parasitological outcomes of treatment over at least 28 days. A change of national antimalarial treatment policy is recommended when the overall treatment failure rate exceeds 10%. Changes in policy have been necessary in many countries due to the emergence of chloroquine resistance, which has become so widespread that a combination of medicines including artemisinin (artemisinin-based combination therapy) is now the recommended first-line treatment for uncomplicated falciparum malaria.[5]

Tuberculosis: Resistance is a growing problem in the treatment of tuberculosis. In 2010, there were an estimated 290 000 new multidrug-resistant tuberculosis (MDR-TB) cases detected among the TB cases notified worldwide and about one third of these patients may die annually.[6] However, just over 53 000 MDR-TB cases (18%) were actually notified globally and many cases were not diagnosed. Diagnostic inadequacies also impede appropriate treatment because in most cases diagnosis depends on screening tests followed by lengthy laboratory culture techniques. In 2010, it was estimated that 3.4% of all new TB cases were MDR-TB. Even more problematic has been the emergence of extensively drug-resistant TB (XDR-TB), which occurs when resistance to second-line drugs develops in addition to the resistance associated with MDR-TB. By 2011, XDR-TB cases had been confirmed in 77 countries.

HIV infection: Resistance rates to anti-HIV drug regimens ranging from 10%–20% have been reported in Europe and the USA. However, rates of transmission of HIV drug-resistant infections appear to be low (3.7%) in lower/middle income countries despite improvements in access to treatment, according to a combined analysis of surveys conducted by WHO in 20 countries between 2003 and 2009.[7] Second-line treatments are generally effective in patients when the first-line therapy has failed, but can only be started promptly if virological monitoring is routinely available. To facilitate this, in 2004, WHO developed a Global Strategy for the Prevention and Assessment of HIV Drug Resistance and has established the HIVResNet, a network of over 50 institutions, laboratories and

experts, to support capacity-building, surveillance, and data analysis. In patients infected with HIV, co-infection with AMR bacterial infections (e.g. TB, salmonella) has an adverse effect on HIV disease progression and on the spread of HIV infection.

Common bacterial infections: AMR is an increasingly important problem affecting the range of bacterial infections occurring in hospitals, other health-care facilities, and in the community. Estimates from Europe of the health and economic burdens resulting from resistant infections indicate that the excess mortality due to resistant bacterial hospital infections exceeds 25 000 annually (Table 1.1).[8] Apart from additional patient morbidity/mortality, the attributable health-care costs and productivity losses are estimated to be at least €1.5 billion each year.[8] Estimates from Canada also show very high excess costs associated with resistant infections.[9]

Table 1.1 Estimated annual burden due to selected antibiotic-resistant bacteria in European Union Member States, Iceland and Norway, 2007

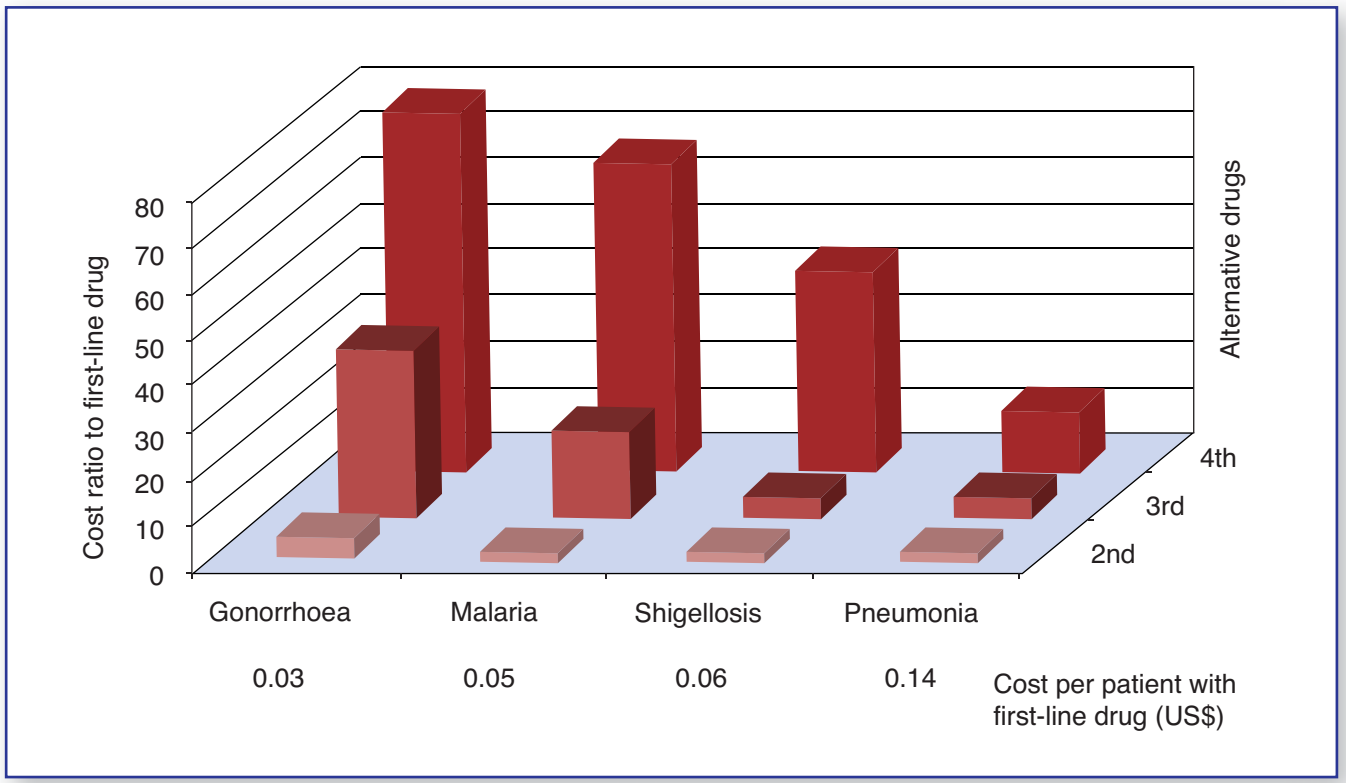
Antibiotic-resistant bacteria	No. cases of infection*	No. extra deaths	No. extra hospital days
Antimicrobial resistant Gram-positive bacteria			
Methicillin-resistant *Staphylococcus aureus* (MRSA)	171 200 (12%)	5400 (37%)	1 050 000 (16%)
Vancomycin-resistant *Enterococcus faecium*	18 100 (9%)	1500 (28%)	111 000 (22%)
Antimicrobial resistant Gram-negative bacteria			
3rd generation cephalosporin-resistant *Escherichia coli*	32 500 (27%)	5100 (52%)	358 000 (27%)
3rd generation cephalosporin-resistant *Klebsiella pneumoniae*	18 900 (27%)	2900 (52%)	208 000 (27%)
Carbapenem-resistant *Pseudomonas aeruginosa*	141 900 (3%)	10 200 (7%)	809 000 (3%)

* Bloodstream infections, lower respiratory tract infections, skin and soft tissue infections, and urinary tract infections. Numbers in parentheses indicate percentage bloodstream infections.
Source: Adapted from [8] with permission.

How AMR affects the overall disease burden is less clear for pathogenic bacteria that cause community-acquired infections. Laboratory reports show increasing resistance among bacteria causing pneumonia, which kills about 1.8 million children annually.[10] Another consequence of AMR in health-care facilities and community-associated infections is the need to change prescribing practices to newer, more costly medicines – some of which are also associated with higher rates of adverse reactions. In industrialized countries,

approximately 90% of all antibiotics used in humans are prescribed in general practice,[11] with antibiotic use generally based on national treatment guidelines. With AMR rates increasing and the risk of treatment failure unknown, the development of treatment guidelines has become difficult for some common infections, and the use of second- and third-line medicines adds higher costs to treatment (Figure 1.1).[12]

Figure 1.1 Escalating costs as recommendations for treatment change



Source: Reproduced from [12] with permission.

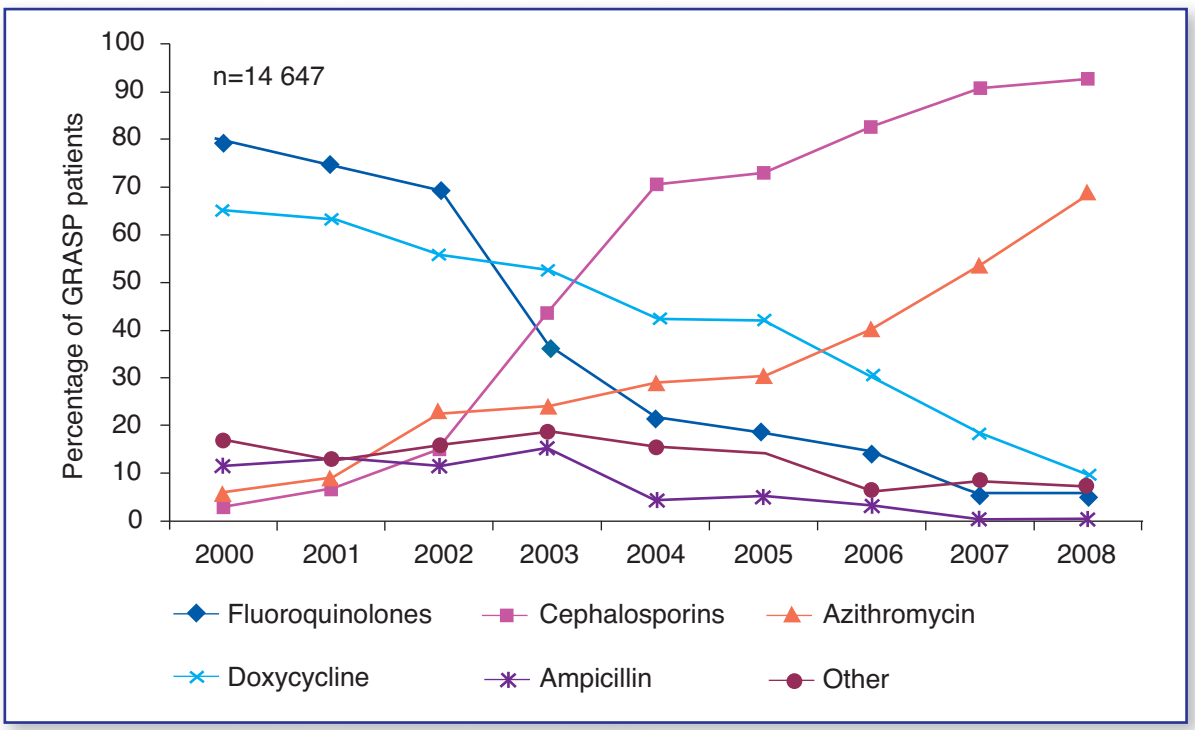
For some bacterial infections including gonorrhoea, recommending first-line therapy has proved problematic from a policy perspective once AMR appears, even if only a small proportion of the infecting bacteria are resistant. The dilemma revolves around whether to spend resources on cheaper first-line therapy that will be ineffective in some of those treated, or switch to more expensive second-line drugs that are associated with low rates of resistance and will be effective in most cases, as described in Box 1.1.

Box 1.1 **Changing treatment policies for gonorrhoea**

Gonorrhoea needs to be treated with an effective first-line antibiotic because subsequent follow-up of patients is often limited. The choice of medicine is rarely based on the results from AMR testing on a case-by-case basis, but usually on treatment algorithms. Resistance appearing in *Neisseria gonorrhoea* has led to successive changes in recommendations for first-line antibiotic therapy from sulfonamides, penicillins, tetracyclines, and quinolones to cephalosporins.[13] Penicillin, which was initially reserved for sulfonamide-resistant gonococcal infections, became the drug of choice for gonococcal urethritis in 1943 (less than 10 years after the introduction of sulfonamides) and remained so until the mid-1970s. From the mid-1980s, fluoroquinolones became the first-line choice, but by the early 1990s treatment failures due to resistant strains were being reported and this class is no longer recommended as the first choice. Only the third-generation cephalosporins remain an effective first-line treatment for gonorrhoea.[14] The Centers for Disease Control and Prevention (CDC) currently recommends a dual therapy using cephalosporin and either azithromycin or doxycycline.[15]

The evidence for treatment guidelines is often obtained from AMR surveillance data. WHO recommends that an antimicrobial be discontinued for the treatment of gonorrhoea when the proportion of *N. gonorrhoea* infections resistant to it reaches 5% of isolates in the community.[14] Therefore, increasing resistance rates bring about the exclusion of antibiotics from treatment guidelines. Figure 1.2 shows the change in antibiotic choice over time in the United Kingdom (UK) for the treatment of gonorrhoea.[16]

Figure 1.2 Treatment of gonorrhoea in the UK



GRASP: Gonococcal Resistance to Antimicrobials Surveillance Programme
Source: Reproduced from [16] with permission from the Health Protection Agency, UK.

N. gonorrhoea retains resistance to several classes of antibiotics such as tetracycline, penicillin, and quinolones, long after their use has been discontinued.

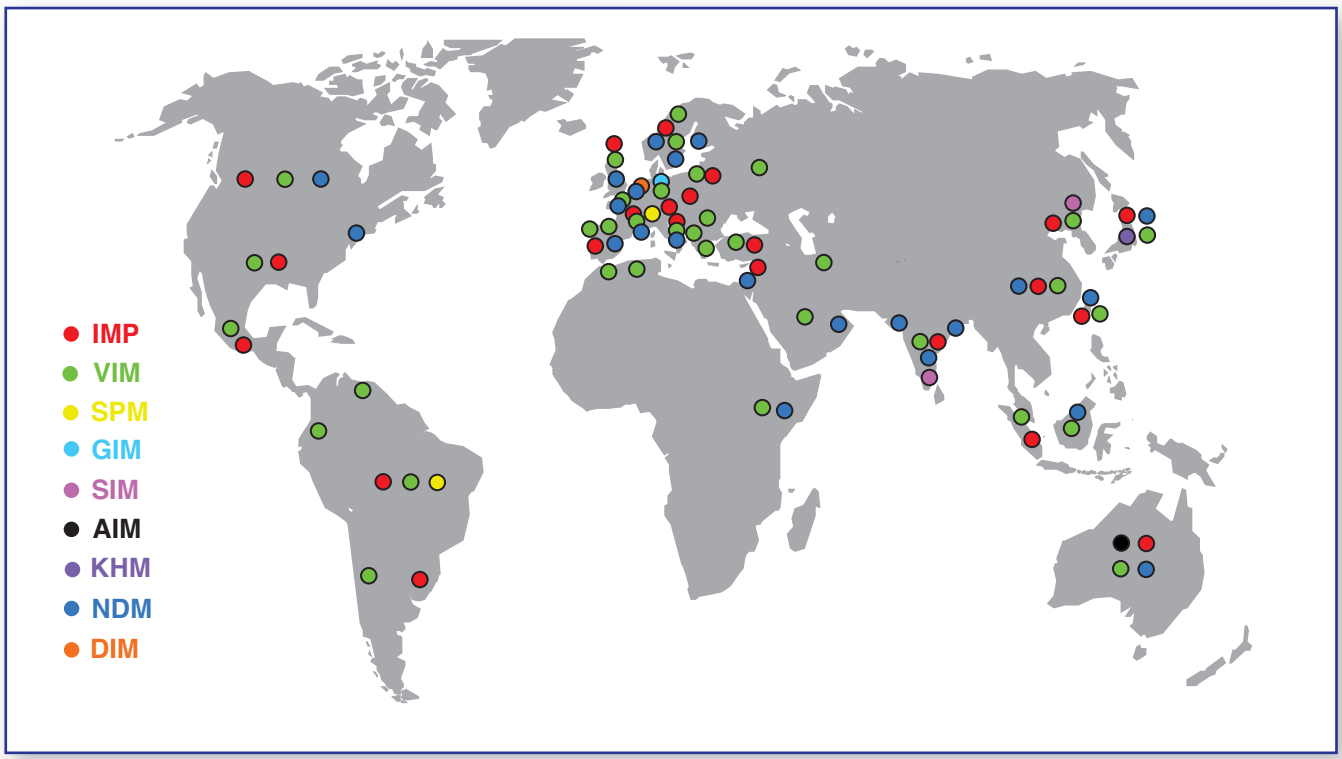
A change in treatment guidelines is always to newer and more costly antibiotics. High-income countries change their recommendations when the risk of treatment failure is still very low. For example, Japan excluded cefixime and all other oral extended-spectrum cephalosporins from their treatment guidelines in 2006 because of a few isolates with decreased susceptibility to cefixime in vitro. Intravenous ceftriaxone is now the first-line therapy in Japan.[14] Recent treatment failures with cefixime have been reported from Australia, Norway, the UK, and the USA. However, treatment failures are likely to be underestimated because of paucity of data from low-income countries with a high burden of sexually-transmitted infections.[14]

Increasing numbers of strains with decreased susceptibility to ceftriaxone are already being detected[17] and treatment failures reported,[18] raising serious concerns about the treatment of gonorrhoea in the future. The public health significance is underscored by the fact that treatment of cases is the main strategy for controlling the spread of this infection.

AMR threatens most clinical and public health practices in both high income countries and in countries with limited resources – from complex therapeutic procedures to routine control of common infectious diseases.

Once resistance has emerged, the resistant bacteria spread in hospitals and in communities. Several bacteria which can inactivate carbapenems, and are resistant to third-generation cephalosporins, already cause significant numbers of health care-associated and community-onset infections in different parts of the world (Figure 1.3).[19]

Figure 1.3 Worldwide distribution of different metallo-beta-lactamases



IMP, VIM, SPM, GIM, SIM, AIM, KHM, NDM, DIM: various metallo-beta-lactamases
Source: Reprinted from [19] with permission from Elsevier.

A recent development, and cause for concern, is an apparent shift in the burden of antibiotic resistance which may be occurring between the main classes of pathogenic bacteria (from Gram-positive to Gram-negative pathogens); this could further stretch the already limited resources of health services as the infections due to resistant Gram-negative organisms will likely outweigh recent achievements in the control of Gram-positive pathogens.[20]

The evolution of AMR, and a dearth of new antibiotics in the pipeline, raises the possibility that untreatable multi-drug resistant (MDR) infections will become more and more common. It is particularly worrisome that once it develops, AMR is either irreversible or very slow to reverse, despite the introduction of AMR containment and stewardship programmes.[21] Consequently, early implementation of interventions to avoid the initial development and/or spread of AMR can be considered a key public health policy.

WHO guidance and actions on AMR

The 2001 WHO global strategy[1] for the containment of AMR addresses *what to do* and *how to do it* and provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial-resistant microorganisms wherever anti-infective medicines are used, through:

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

As stated in the strategy, it was developed with the recognition that "despite the mass of literature on AMR, there is depressingly little on the true costs of resistance and the effectiveness of interventions". It focuses on resistance to antibacterial drugs, addresses AMR in general rather than through a disease-specific approach, and contains a comprehensive set of recommendations for interventions. Much of the responsibility for implementation lies with individual countries, as governments have a critical role in prioritization and provision of public services, such as information, surveillance, cost-effectiveness analysis, and cross-sector coordination. The strategy acknowledges that containment of AMR will require significant strengthening of health systems in many countries and that the associated costs may be considerable. Consequently on World Health Day 2011, WHO urged national commitment for a comprehensive and financed plan with accountability and civil society engagement.[2]

Alliances across countries and continents, such as the transatlantic task force on antimicrobial resistance (TATFAR),[22] and the Jaipur declaration by WHO South-East Asia Region health ministers to combat AMR[23], are welcome developments.

Examining five domains targeted for AMR containment

Five domains, based on the 2001 global strategy recommendations,[1] which correlate to the six-point policy package, presented on WHD 2011,[2] are discussed in more detail in the following chapters:

- Surveillance of antimicrobial resistance and use;
- Rational antimicrobial use and regulation;
- Antimicrobial use in animal husbandry;
- Infection prevention and control;
- Fostering innovations;
- Political commitment.

To tackle AMR in a comprehensive manner, environmental aspects also need to be considered.[24]

The presence of resistant bacteria in water, air and soil and the potential impact on the spread of AMR are being increasingly examined.[25-28] Water and soil have also been shown to contain measurable amounts of antibiotics (derived from contaminated effluent and manure).[25, 29] Interventions such as improving water supplies and sanitation could therefore have a major impact on the spread of bacteria and AMR.[a] Reducing the burden of infections by addressing the social determinants of health could also help to reduce AMR.[b] These are important issues which go beyond the scope of this book.

Surveillance of antimicrobial resistance and use. Data on AMR among local pathogens help define the best possible treatment for individual patients. However, the proportion of resistant bacteria can vary from one area to another, and in many health facilities there are no local data on resistance patterns. Experiences from national and international surveillance networks on antimicrobial use and AMR show that data, where available, can be put to multiple uses, including orienting treatment choices, understanding AMR trends, informing public health policy, identifying priority areas for interventions, and monitoring the impact of interventions to contain resistance. The lack of adequate surveillance in many parts of the world leaves large gaps in existing knowledge of the distribution and extent of AMR.

Rational antimicrobial use and regulation. Any use of antibiotics has the potential to stimulate the development of resistance to it, as this is the natural response of bacteria to threat. Individual decisions (by the consumer, the prescriber, or both) to use antimicrobials often ignore the societal perspective of depleting a "common good" whereby antimicrobial use can be compared to the use of a natural resource, such as water. In both cases, individual use and misuse potentially impact on availability and thus overall utility for other consumers. Overuse plays an important role in the emergence of AMR. Paradoxically, underuse through inappropriate choice, inadequate dosing, poor adherence to treatment, and substandard antimicrobials, also plays an important role in the emergence and spread of AMR. One of the main AMR containment strategies is therefore to increase appropriate use, and to reduce misuse, of antibiotics.

Antimicrobial use in animal husbandry. A substantial proportion of total antibiotic use occurs outside the field of human medicine and is probably a major contributor to the overall problem of emerging AMR. Antimicrobial use in food-producing animals and in aquaculture very often involves large-scale use for growth promotion and mass prophylaxis. Resistant pathogens found in food products can cause infections in humans that can be difficult to treat. Such events may cause a loss of public confidence in food safety with important secondary economic repercussions on the farming sector and the international trade in these products. Unfortunately, regulations and other approaches to controlling antibiotic use in food-producing animals are not consistent worldwide. In countries making sustained efforts in this area, AMR prevalence among zoonotic bacteria and indicator bacteria in locally produced meat is lower than in imported products,[21] demonstrating that the recommended measures can have a measurable impact.

Infection prevention and control. AMR bacteria, like antibiotic-susceptible bacteria can spread, from person to person to the environment, and then back to humans. In addition, the genes that encode AMR are often readily transferable from resistant to susceptible microorganisms, which can then multiply, spread and act as a source of further transfer of resistance genes. Infection prevention and control activities to limit the spread of resistant bacteria are therefore crucial. There are good examples of effective nationally coordinated programmes to limit the spread of specific infections such as HIV, TB and malaria.

Fostering innovations. The discovery of penicillin ushered in the "antibiotic era" and the ability to cure infections which were previously often fatal. However, the antibiotic development pipeline has markedly declined over the past few decades and there are now very few effective drugs available to treat recently emerged MDR infections. In a field which offers little or no financial incentive to the major pharmaceutical companies, innovations are urgently needed to stimulate the research and the discovery of antimicrobials and vaccines, and to devise funding arrangements and partnerships to support research and development (R&D). In addition, there is a need for new technologies and innovations in other areas

[a] http://www.who.int/water_sanitation_health/en/

[b] http://www.who.int/social_determinants/en/

such as rapid and point-of-care diagnostic tests and infection prevention and control, which are also critically important for effective control of AMR.

Political commitment. The final chapter in this book looks ahead to the prospects for containment of AMR and reflects on the key role of governments and policy actors to implement effective actions. Whether the way forward will be towards a future with a continuing supply of effective antimicrobials, or a return to the pre-antibiotic era, will depend on whether sufficient leadership, solid commitment and coordinated efforts can be brought to bear on this growing global health threat.

Methodology

The process for the preparation of this book, led by WHO Patient Safety, started in 2008. The steps in the process were as follows:

- International expert consultations together with facts gathered from published literature informed the preparation of the initial drafts.
- An iterative collaboration involved authors and contributors and WHO staff, and included reviews by experts within and outside WHO to assess overall progress in relation to WHO recommendations (2001 global strategy for containment of AMR) particularly of large-scale or scalable interventions being carried out in different parts of the world, focusing on the common bacterial infections.
- Conflicts of interest were ruled out for all participants in the consultation, as well as for all authors, contributors and reviewers.
- A framework was developed whereby details of actions related to five major domains could be compiled and reviewed, including methodologies to assess and reduce the AMR burden, implementation of interventions on a large scale, regulation, advocacy and education, cost of acting and not acting, and impact of interventions. These were identified using multiple literature searches of scientific and grey literature and input from experts involved in such activities in different parts of the world.
- Within the scope of the book information and examples of ongoing activities were provided to depict overall progress worldwide. The examples were selected through non-systematic reviews of the literature, by expert groups and WHO staff to illustrate interventions that have had a positive measurable impact. Other examples explain concepts and the lessons to be learnt. Attention was paid to including experiences from different parts of the world and from different relevant subject areas.
- The book is based on existing WHO recommendations and does not introduce new recommendations. It aims to raise awareness and encourages relevant authorities and decision-makers in options for action that can be taken to control AMR, based on the WHO global strategy for containment of AMR.
- The final draft text was submitted for review to a panel of international and WHO experts before finalization.

Chapter 2.

Surveillance to track antimicrobial use and resistance

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Surveillance to track antimicrobial use and resistance

Tracking resistant bacteria and how antibiotics are used provides the data needed to measure the degree and distribution of antimicrobial resistance (AMR), to plan the strategies and measures needed, and to mobilize commitment and resources for action. This surveillance is fundamental to local, national and international efforts to combat AMR. Excellent surveillance is carried out in some countries and regions, but more extensive geographic coverage and coordination of AMR surveillance networks are needed.

Summary

Effective surveillance is the cornerstone of national and international efforts to control antimicrobial resistance. Tracking antibiotic use, and the emergence and spread of resistant strains of bacteria provides information, insights, and tools needed to guide policy and to evaluate measures taken to promote appropriate antimicrobial use at all levels, from local to global. The crucial role of surveillance was recognized in the 2001 WHO Global Strategy for Containment of AMR, in which surveillance of resistance, antimicrobial usage and disease burden are included as major components. Their importance was again highlighted by WHO on the occasion of World Health Day 2011. Surveillance data can be used to improve rational antibiotic use locally and to inform policies and identify priorities for action at national level, while providing valuable support for advocacy at regional and global levels.

There are wide variations between regions and countries, and within countries, in their capacity to carry out AMR surveillance. Although many countries have made considerable progress in setting up AMR surveillance, limitations remain related to financial and technical resources and methodologies. This chapter provides examples of such initiatives and the successful use of the data to bring about changes in policies and practice, leading to reductions in antimicrobial use, with reduction in AMR in some cases. Consequences if actions are delayed can also be understood from such data.

There is a long way to go before effective antimicrobial use and resistance surveillance will be established worldwide. In resource-poor countries with comparatively weak health systems, there are constraints related to infrastructure, trained personnel, networking, and coordination. In countries with effective surveillance, political support and strong health systems appear to be critical for success.

The methods for obtaining data are often problematic, especially with regard to data on antimicrobial use. Small-scale well-designed studies and surveys, such as indicator surveys, in different settings can be effective in providing insight into the general situation and in identifying priority areas for intervention; trends may be determined through repetition of these surveys at specific intervals. Data on the burden due to AMR, such as treatment failures or extra costs, are scarce, especially in community settings. Hospital-based data from high-income countries show that these costs can be considerable.

1. How surveillance helps to contain AMR

Surveillance involves the systematic collection and analysis of health-related data, and dissemination to those who will use them in decision-making on public health issues. Ongoing and routine AMR surveillance enables analyses to be made of resistance rates to antimicrobials among bacteria infecting or colonizing individuals in given locations during defined time periods. The surveillance of antimicrobial use tracks both *how much* antimicrobials are being used and *how* they are used by patients and health-care providers (i.e. the pattern of use, including the why?, when?, where? and for what?). The scope of activities ranges from health facility or local community level to broader domains at the subnational and national level or beyond. Local surveillance units could be linked at national and international levels to provide national, regional and global surveillance information.

The ultimate goal of surveillance of antimicrobial use and AMR is to provide the information, insights, and tools needed to guide policy on the appropriate use of antimicrobials and to inform and evaluate resistance containment interventions at local, national and global levels. Decisions on interventions have to balance the need to provide effective antimicrobial therapy to patients today with the need to preserve the usefulness of medicines for future generations.

The information generated through surveillance of use and of resistance can be seen as complementary. At the local level, the data are used to formulate recommendations for rational antibiotic use and standard treatment guidelines and for ensuring that health-care providers comply with recommendations. At subnational or national levels, data on resistance and use together inform policy decisions such as development or revision of essential medicines lists, and identify priorities for public health action, such as education campaigns or regulatory measures. At regional and global levels, surveillance data have proved to be invaluable advocacy tools in stimulating politicians and health-care providers into urgent action, as exemplified in this and other chapters. Conversely, lack of surveillance can lead to misdirected and inefficient policies, wasting of limited resources, inappropriate therapy and ultimately human suffering and death through the inability to provide an effective drug to patients in need.

2. WHO guidance on surveillance to contain AMR

The WHO global strategy for containment of AMR (2001) includes as a key element a call for the surveillance of resistance, antimicrobial usage and disease burden (Appendix 1).[1] This call for action was repeated in a resolution adopted by the World Health Assembly in 2005 (WHA 58.27) and on World Health Day 2011 (Appendix 2).[2] As has been repeatedly stressed, effective surveillance requires the strengthening of laboratory capacity for AMR detection, maintaining a prompt flow of information from laboratories to prescribers and to national/subnational policy-making authorities, and ensuring that the information is used appropriately. The importance of local monitoring of antimicrobial use in health-care facilities and in the community, and linking this to AMR surveillance, is also recognized. The core actions highlighted on the occasion of World Health Day 2011 include engaging in regional and global surveillance networks.

3. The present position regarding these recommendations

Efforts to establish surveillance of antimicrobial use and AMR have been made in different parts of the world, with varying degrees of success, and there are wide variations between regions and countries, and within countries, in their present surveillance capacity and practice. Systematic surveillance is still lacking in many hospitals, particularly in countries with poor laboratory capacity and weak health systems.[30,31-33] The following sections provide some insights and examples on the currently prevailing global status of surveillance for antimicrobial use and AMR, with regard to the methodologies for data generation, existing surveillance networks, efforts to strengthen laboratory capacity for surveillance, and using the data obtained.

3.1 Methods for surveillance of antimicrobial use and resistance

The primary data for surveillance are generated in a large number of different health-care facilities around the world. For AMR surveillance, routine diagnostic laboratories, often within hospitals, are the primary source of data. For the surveillance of drug use the situation is less clear-cut as it is not carried out within a single clinical discipline. Data on the use of antimicrobials could be obtained from many sources such as health-care facilities, pharmacies, and drug procurement/sales services. If data collected in disparate settings are to be reliable and comparable, it is necessary to apply quality standards for obtaining the data. Although the methods used for AMR determination and quality assurance are now better standardized worldwide than in 2001, differences still exist. Different principles are used for surveillance, and no single method is applicable in all settings and throughout the world. Some of these issues are discussed in more detail below.

AMR surveillance

At present, surveillance data are usually by-products of routine diagnostic activities. Laboratory reports originating from routine patient care activities are filed in a database for local analysis and surveillance. If the data are based on uniform standard methods of testing, they could be merged with those of other health-care facilities for combined analyses, to support multi-purpose, multi-centre, multi-level AMR surveillance. However, data drawn from routine diagnostic testing have some disadvantages. For example, laboratory data are often difficult to interpret if not linked to clinical data. Nosocomial pathogens (transmitted within hospitals) may be over-represented if much of the testing is carried out on inpatients who are more likely to develop health care-associated infections than patients outside the hospital. These factors may lead to higher apparent rates of AMR, especially for some bacterial species, when data are drawn from routine diagnostic laboratory tests. Several approaches can be used to minimize such biases, but how they are applied may vary.

Bacteria belonging to the normal flora of healthy individuals in the general population (e.g. nasopharyngeal swabs for pneumococci, or stool for *E. coli*) have also been used for surveillance. This approach enables the analysis and comparison of trends in communities, and measurement of the impact of community-based interventions, but it also has limitations. Often, they focus on only one target bacterium, not fully representing the range of bacteria that therapy must target, hence their direct usefulness for treatment guidelines is limited. Also costs are higher since they include the cost of tests on healthy individuals.

There is general understanding that most laboratories around the world currently use recommendations for testing from the Clinical and Laboratory Standards Institute (CLSI)[a] or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[b] However, the extent of adherence to these recommendations varies, in particular in resource-limited settings.[34] There are inherent differences between the two sets of recommendations, such as the criteria for interpreting the test results.

Monitoring antimicrobial use

Data need to be collected from multiple sources and using different methods because consumption of antimicrobials occurs in different types of health settings. Surveillance of total use and use patterns is currently carried out through review of prescription logs, pharmacy databases, drug purchases or sales, or medicines inventories. However, in many countries these data may either not be available at all (not recorded or not collected) or not obtainable (owned by third parties such as manufacturers or private pharmacies which have no legal obligation to divulge the information to public health authorities). Sales without prescriptions or records, and issues such as inability to ascertain whether the patient actually took the medicines that were dispensed, add to the complexity.

Antimicrobial consumption is reported in many ways – for example, programmes may report total quantity of use in grams or financial costs, or using standardized measures such as "defined daily doses" (DDDs),[35] or percentage of patients receiving antibiotics. Other alternative measures are also described.[36,37] Using

[a] http://www.clsi.org/

[b] http://www.eucast.org/

appropriate measurements is important to reach appropriate conclusions. For instance, using the number of consumed packages/inhabitants as a measure of antibiotic consumption, does not take into consideration possible changes in the number of DDD per package, which may occur over time, and may lead to wrong conclusions.

Total use data also have limitations, mostly as they provide little insight into why antimicrobials are used, and therefore whether or not their use is appropriate. A number of different strategies may need to be used to elucidate why a patient seeks an antimicrobial and why a provider prescribes a certain antimicrobial, such as: detailed, structured questionnaires for patients, health-care workers, and/or dispensers; exit interviews with patients in health-care facilities or at dispensing places; focus group discussions; and using "simulated patients". Facilities with electronic medical records could capture all antimicrobial dispensing records for analysis and even link them to microbiology reports. Each approach provides complementary information, and the decision to implement one or more depends on policy, needs, and the available resources and expertise.

Another option is to use point prevalence survey formats described by the European Surveillance of Antimicrobial Consumption (ESAC) initiative (Box 2.1). This methodology can be applied to any type of health-care institution including long-term care facilities. Repeated surveys at specific time intervals could be used to follow prescribing trends.

Box 2.1 **ESAC point prevalence survey of antimicrobial use in hospitals**

The core action of ESAC* since its establishment has been the collection of quantitative statistics on total antimicrobial use in health care at the national level. This has enabled broad comparisons of total usage of antimicrobials across Europe, but does not directly provide insights into why antimicrobials were prescribed and whether or not their usage was appropriate.

To better understand antimicrobial use practices in hospitals, ESAC coordinated three point prevalence surveys (PPSs) in which a total of 31 European countries involving over 200 hospitals participated. In addition, two PPSs were carried out in nursing homes (>300 institutions). Each participating institution conducted a "snapshot survey" of use. For each patient on antimicrobials, data were collected on the indication for use and the patient's diagnosis. Findings from such surveys confirm the usability of this method in a large number of facilities at national and regional levels and have permitted hospital doctors and national authorities to develop interventions targeting inappropriate use and to assess their effectiveness. Quantifiable outcome measures and targets for quality improvement are: duration of surgical prophylaxis; proportion of oral versus parenteral use; treatment of some specific diseases (e.g. community-acquired pneumonia) excluding certain antibiotics (e.g. quinolones); reason for prescription in notes; and compliance with guidelines.[38]

* ESAC moved to ECDC in 2011 and is now named ESAC-Net

There are important differences between the factors which influence antibiotic use in hospitals and in ambulatory care settings and so surveillance of drug use in both of these patient populations is useful for the selection of suitable interventions. For example, Canada uses information on prescriptions dispensed by retail pharmacies to understand use in ambulatory care,[39] while ESAC has attempted to develop quality indicators for outpatient antibiotic use.[40] However, starting with surveillance of hospital-based use may be easier logistically, as hospital data are often more complete and accessible. Data collected locally could potentially feed into national databases that can be used to track consumption nationwide and to participate in regional and global surveillance.

WHO recommends the use of simple indicators to follow trends in antimicrobial use, particularly in settings where there is no systematic surveillance, and provides guidance for local agencies in the identification of deficiencies and priority areas for intervention.[41,42] Indicators which allow identification

of use patterns include the percentages of encounters with an antibiotic prescribed, pneumonia cases treated with recommended antibiotics, cases of upper respiratory tract infections treated with antibiotics, cases of diarrhoea treated with antibiotics, and patients receiving antibiotics without prescription. Local and national surveys using these indicators could prove valuable for monitoring changes over time in response to the measures taken.[43,44]

3.2 Examples of surveillance of use and resistance worldwide

AMR surveillance in the public sector is carried out in many countries, often linked to multi-centre, national or even international networks. Surveillance of antimicrobial use and related networks are present mainly in high-income countries. However, data on use in other parts of the world could be obtained from local surveys, and also from other sources such as market sources tracking sales. Some examples are provided below to illustrate the range and variety of current data collection efforts.

AMR surveillance

Existing surveillance networks vary widely in scope. They range from networks covering sentinel laboratories to those that include all patient-care laboratories. They may be selective for only some bacteria or specimen types, or comprehensive covering all species and specimen types (Table 2.1).[45] Outputs can also vary from summaries to full reports on all isolates. The networking may be local, multi-centre, national or international. Features of two international surveillance systems are compared in Box 2.2.

Table 2.1 Pathogen-specific surveillance networks

Global Foodborne Infections Network (GFN) for foodborne pathogens, e.g. *Salmonella* and *Campylobacter* spp
Gonococcal Antimicrobial Surveillance Programme (functional in three WHO regions: Western Pacific, South-East Asia and the Americas)
Sistema Regional de Vacunas (SIREVA) for vaccine-preventable pathogens including *S. pneumoniae, H. influenzae*, and *N. meningitidis*
Laboratory Centre for Disease Control, Canada (LCDC) and PAHO collaborative project on *Salmonella* and *Shigella spp*, and *Vibrio cholerae*

Source: Adapted from [45] with permission from Elsevier.

Box 2.2 Description of two International AMR surveillance networks: PAHO and EARS-Net

Over a decade the Pan American Health Organization (PAHO) and the European Antimicrobial Resistance Surveillance Network (EARS-Net), formerly EARSS, have each built an international quality-assured public sector hospital-based AMR surveillance network. The PAHO surveillance system analyses susceptibility data from all isolates at country level and then collates the data from participating countries.[c] EARS-Net analyses at a central level the susceptibility data from a growing list of species isolated from blood and cerebrospinal fluid. PAHO data inform and support locally relevant interventions to contain AMR, while EARS-Net benchmarks national AMR and correlates it with antimicrobial consumption at the European level.[d]

[c] http://www.paho.org/english/hcp/hct/eer/antimicrob.htm

[d] http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx

A number of regional surveillance initiatives have been launched in all WHO Regions (Table 2.2).[45] While some are coordinated by WHO regional offices, others are led by other regional agencies.

Table 2.2 AMR Surveillance networks for common bacterial pathogens in the WHO Regions

Region	Programme name	Years of activity	Participants	Organisms under surveillance
AFR	Integrated Disease Surveillance and Response (IDSR)	2002–present	43 countries	8 epidemic-prone pathogens
AMR	Red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas (Re-LAVRA)	1996–present	21 countries 519 laboratories	16 pathogens All sample types
EMR	Antimicrobial Resistance in the Mediterranean (ARMed)	2001–2005	9 countries 27 laboratories	7 pathogens Blood and CSF
	Regional Programme for Surveillance of AMR	Proposed		28 species All sample types
EUR	European Antimicrobial Resistance Surveillance (EARSS)	1999–2009	33 countries 917 laboratories	7 pathogens Blood and CSF
	European Antimicrobial Resistance Surveillance Network (EARS-Net)	2010–present	28 countries 886 laboratories	
SEAR	National and regional surveillance system	Proposed in 2010		
WPR	Regional Programme for Surveillance of AMR	1990–2000	13 countries	22 species All sample types

AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asia Region; WPR: Western Pacific Region; CSF: Cerebrospinal fluid.
Source: Adapted from [45] with permission from Elsevier.

In addition to the AMR data from routine clinical laboratories, reference laboratories produce more detailed information on selected isolates. Some of these are public health laboratories (e.g. for serotyping salmonella isolates). Privately funded initiatives such as the Asian Network of Surveillance of Resistant Pathogens (ANSORP), the SENTRY Antimicrobial Surveillance and the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) have also contributed data on important resistant bacteria. Integrating such data generates additional information and could also help in cross-validating clinical laboratory results.

Other initiatives such as the International Surveillance of Reservoirs of Antibiotic Resistance (ISRAR), coordinated by the Alliance for the Prudent Use of Antibiotics (APUA), collect and analyse environmental

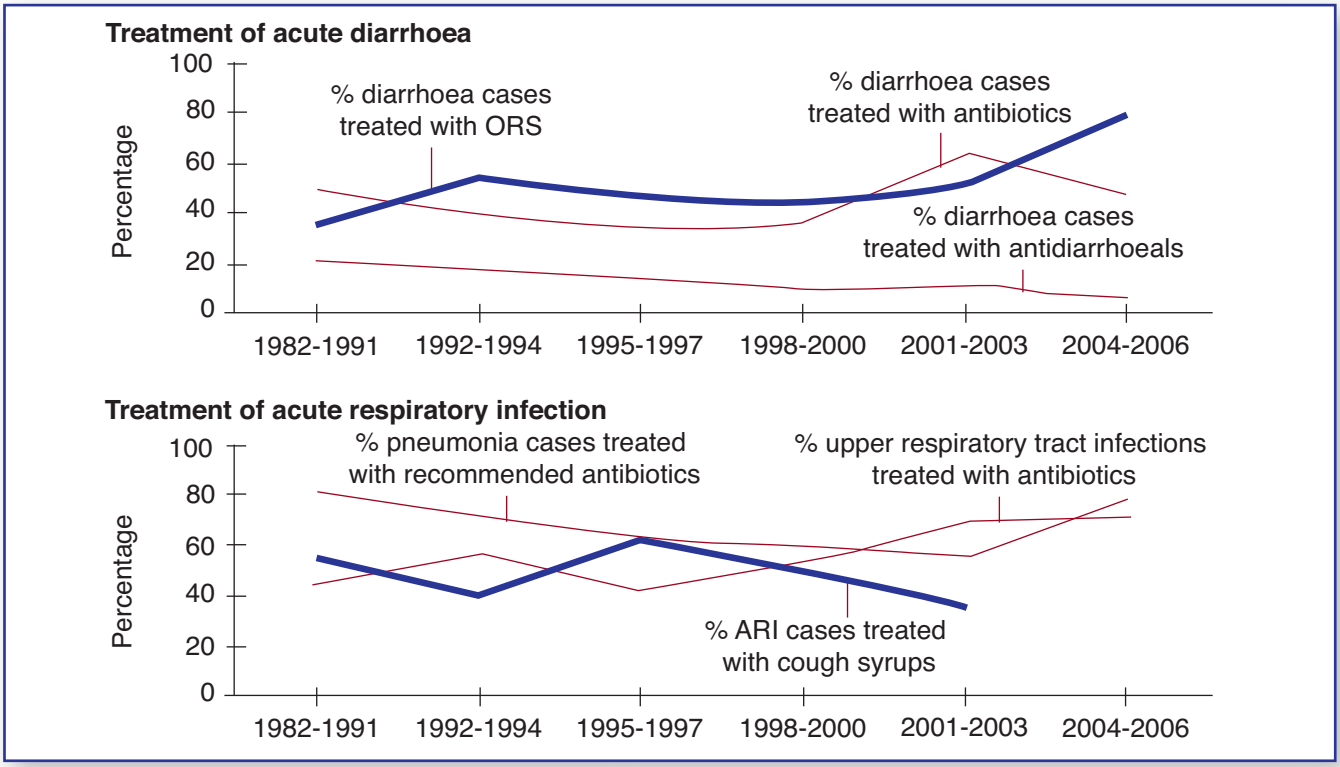
and veterinary commensal organisms which may serve as reservoirs for AMR. APUA Global Chapters, together with local laboratories in India, the Republic of Korea, Turkey, Thailand, Viet Nam, Bangladesh, Georgia, and Uganda, collect bacteria from soil, water, and animals, and carry out preliminary characterization and resistance analyses.[e] The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) attempts to integrate surveillance of antimicrobial resistance in food-producing animals worldwide[f] (see also Chapter 4).

Monitoring antimicrobial use

In many countries data on antimicrobial use in patients seeking care in the public sector may be readily available. National statistics on use in hospital and community settings from 34 European countries are collected by ESAC, currently coordinated by ECDC (Box 2.5). ESAC also runs a web-based point prevalence survey consisting of annual snapshots of antimicrobial use for both treatment and prophylaxis in hospitals.[46-48]

To understand usage patterns in developing and transitional countries, WHO has created a database from 679 studies in 97 countries published between 1990 and 2006 on the use of medicines in primary care.[30,49] Inappropriate antibiotic use for upper respiratory infections and diarrhoea over a period of time, as understood from these data, is shown in Figure 2.1. Such data provide information on antimicrobial use and indicate options for intervention.

Figure 2.1 Antibiotic use for upper respiratory infections and diarrhoea in low- and middle-income countries (1980s - 2006)



ARI: Acute Respiratory Infection; ORS: Oral Rehydration Solution.
Source: Reproduced from [49] with permission from World Health Organization.

[e] http://www.tufts.edu/med/apua/research/israr.shtml
[f] http://www.who.int/foodborne_disease/resistance/agisar/en/index.html

Sales data collated from different sources are also used to assess total antibiotic use (Box 2.3). This type of data has proved valuable in comparing use in different countries in the same region over a period of time, and for informing policies.

Box 2.3 **Antimicrobial use data based on sales**

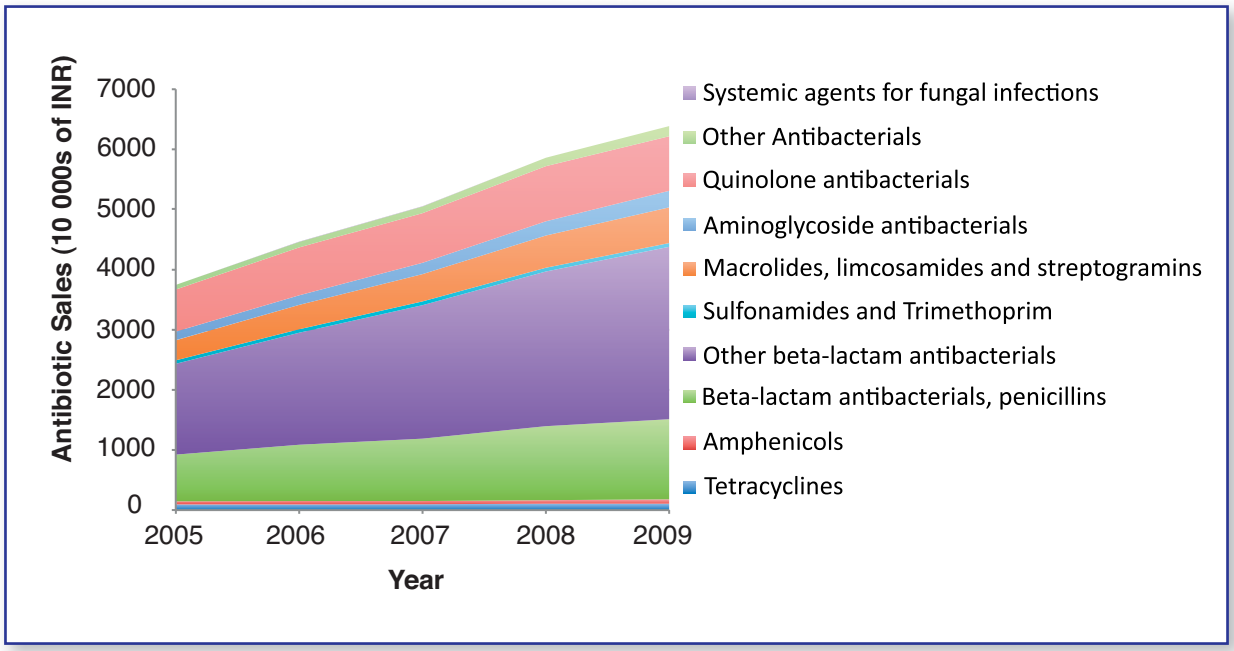
(1) Data from retail sales in Latin American countries

Retail sales data from the private sector on oral and injectable antibiotics between 1997 and 2007 were analysed for Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay, and Venezuela. The kilogram sales of each antibiotic were converted into DDD per 1000 inhabitants per day, with the results expressed using 1997 as the reference point. Total antimicrobial use increased in Peru, Venezuela, Uruguay, and Brazil, with the largest relative increases observed in Peru and Venezuela. In Mexico and Colombia the use of some classes of antibiotics decreased, and Argentina and Chile showed major reductions in the use of some antibiotics during the middle of the study period. However, in all countries the use of quinolones increased and there were increases in the use of other categories of antibiotics as well, suggesting a shift in use patterns. The data collected provide a relevant evidence base for policy decisions to improve the use of antimicrobials.[50]

(2) Use in India based on Intercontinental Marketing Services (IMS) data

IMS data show that in general, expenditure increased in India between 2005 and 2009 for all classes of antimicrobials studied (Figure 2.2).[32]

Figure 2.2 Antimicrobial use in India (2005 - 2009)



INR: Indian Rupee

Source: Reproduced from [32] with permission from The Center for Disease Dynamics, Economics & Policy.

Many health-care facilities, especially in high-income countries, routinely collect and archive individual patients' illness-related data electronically, for purposes such as recording and accounting. There are new initiatives which address how best these routinely collected data can be used for understanding and improving antimicrobial use (Box 2.4).

Box 2.4 **Detecting and eliminating bacteria using information technology – DebugIT**

The DebugIT project, which receives funding from the European Union's Seventh Framework Programme, aims to address the challenges of improving antibiotic therapy by making use of data that are already routinely collected and stored electronically in clinical information systems in hospitals and primary care clinics. Such data sets usually include information on patients and their illnesses, pathogens and drug treatments. The aim is to acquire new knowledge through advanced data mining, and to use this knowledge for better decision-making on the management of infectious diseases[g].

There are also reports which identify obvious overuse of antimicrobials causing a significant financial burden for strained public health budgets, and document the positive impact of regulatory and educational campaigns.[51,52]

Combined surveillance of use and resistance

In countries with functioning health systems, combined surveillance of antibiotic use and resistance has been shown to be feasible and beneficial. Combined surveillance is contributing to a better understanding of the relationship between consumption and resistance and supports important policy changes which modify AMR trends. An initiative of this type involving several countries is described in Box 2.5.

Box 2.5 **Surveillance of antimicrobial use and resistance in Europe**

Significant improvements in some aspects of antimicrobial use and resistance have been made in several European countries over the past decade. An important element contributing to these achievements has been the collaborative efforts of two EU-funded projects currently managed by ECDC.[h]

- European Surveillance of Antimicrobial Consumption Network (ESAC-Net, formerly European Surveillance of Antimicrobial Use, ESAC): ESAC-Net collects data from national statistics on antimicrobial consumption in hospital and community settings from 34 European countries. ESAC-Net has developed and validated protocols for quantitative measurement and qualitative description of antimicrobial use patterns, and has been a forceful advocate with national authorities and the European Commission to improve the use of antimicrobials in Europe[i].
- European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly European Antimicrobial Resistance Surveillance System, EARSS): EARS-Net collects data on seven pathogens of public health importance from blood and cerebrospinal fluid samples from over 1400 health-care facilities in over 30 European countries[j].

ESAC-Net and EARS-Net findings are highlighted each year by the ECDC on European Antibiotic Awareness Day (November 18), an annual campaign targeting national authorities, health-care providers, the media, and the general public to raise awareness of the threat posed by the misuse of antimicrobials and the challenges posed by resistant organisms[k].

[g] http://www.debugit.eu/
[h] http://www.ecdc.europa.eu/en/activities/surveillance/european_surveillance_networks/Pages/european_surveillance_networks.aspx
[i] http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx
[j] http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net
[k] http://www.ecdc.europa.eu/en/eaad/Pages/Home.aspx

The southern and eastern Mediterranean antibiotic resistance and use project (ARMed) was able to gather data on antimicrobial use, but only from a few hospitals and not at all from community settings.[53] However, an overall high level of consumption was found in the region when compared to southern Europe, findings which could provide evidence in favour of measures to reduce the use of antibiotics.

Community-based integrated surveillance of resistance and use is limited, especially from low- and middle-income countries, and mostly available from pilot research (Box 2.6).

Box 2.6 **Community-based surveillance of resistance and use: pilot projects**

Community-based pilot surveillance projects for antimicrobial resistance and use undertaken in South Africa and India showed that it is feasible to set up such systems and to collect useful data for deciding local policies and targeted interventions. AMR surveillance using *E. coli* isolated from outpatients was carried out in laboratories attached to large hospitals. Data on antibiotic use were collected from several types of facilities including clinics and pharmacies in the public and private sectors, in defined geographical areas. A high level of fluoroquinolone use for many different infections in the community was seen in India, and high fluoroquinolone resistance rates were found among *E. coli* isolates.

Lessons learnt from these projects could inform surveillance initiatives in resource-constrained settings. Issues related to design, methodology, data management, logistics and financing need to be addressed in order to create sustainable surveillance systems and ensure that the data are comparable across sites.[34]

3.3 Laboratory capacity building for AMR surveillance

Laboratory capacity and information technology at facility levels are imperative for the generation, collation, analysis and sharing of surveillance data.[54] Competent laboratories are still lacking, particularly in low-income countries.[2] A WHO worldwide survey in 2007 found that overall only 61% of countries that responded have national level reference laboratories for AMR surveillance (55% in low-income, 55% in middle-income, and 84% in high-income countries).[43]

The quality of laboratory test results is without doubt critical to the value of surveillance. This requires that laboratories have in place ongoing quality assurance programmes, such as internal quality control practices and participation in external quality assurance (EQA) programmes. Many countries already have such systems in operation. Several quality assurance systems have been set up together with surveillance initiatives in the WHO Regions (Table 2.3), some of which serve more than one Region.[45]

Table 2.3 Regional external quality assurance programmes for common bacterial pathogens

AFR: External Quality Assurance Programme – WHO Lyon and National Institute for Communicable Diseases, South Africa
AMR: Red Latinoamericana de Vigilancia a las Resistencias Antimicrobianas (ReLAVRA) – PAHO and Malbrán Institute, Argentina
EMR: External Quality Assurance Programme – WHO Lyon and Bacteriology Central Laboratory, Oman Antimicrobial Resistance in the Mediterranean (ARMed) – National External Quality Assurance Scheme (NEQAS), United Kingdom
EUR: National External Quality Assurance Scheme (NEQAS) in collaboration with EARSS/EARS-Net
WPR: Royal College of Pathologists of Australia Quality Assurance Programs Regional External Quality Assessment Programme – Pacific Paramedical Training Center, New Zealand

AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; WPR: Western Pacific Region.
Source: Adapted from [45] with permission from Elsevier.

Experiences from the regions show that quality assurance and oversight systems, set up for surveillance, bring the added benefit of improving laboratory functioning as a whole (Box 2.7).

Box 2.7 Regional AMR surveillance network improves quality of testing: PAHO

For over a decade AMRO/PAHO* has developed networks of AMR surveillance laboratories in member countries. The activities include cycles of data entry and inspection, problem detection and notification, proficiency testing, collegial review and problem solving at annual working meetings, laboratory inspections and recurring reviews to improve test quality as a by-product of the regional AMR surveillance network. The process follows the classic management methods of continuous quality improvement, building on collegiate engagement, interaction and support for widely dispersed laboratory workers.[3]

*AMRO/PAHO: WHO Regional Office of the Americas/Pan American Health Organization

To facilitate analysis of antimicrobial susceptibility test results, WHONET[l], a Windows-based database software, has been developed and improved since 1989 by the WHO Collaborating Centre for Surveillance of AMR at the Brigham and Women's Hospital in Boston, USA. WHONET is available for use free of charge and is currently used in over 100 countries to support local, national, and regional surveillance activities in over 1 500 clinical, public health, veterinary, and food laboratories (Table 2.4). Box 2.8 explains the application of WHONET to understand MRSA trends.

[l] www.whonet.org

Table 2.4 WHONET software use by WHO Region

WHO Regions	Number of countries
African Region	13
Eastern Mediterranean Region	15
European Region	39
Region of the Americas	25
South-East Asia Region	6
Western Pacific Region	13
Total	111

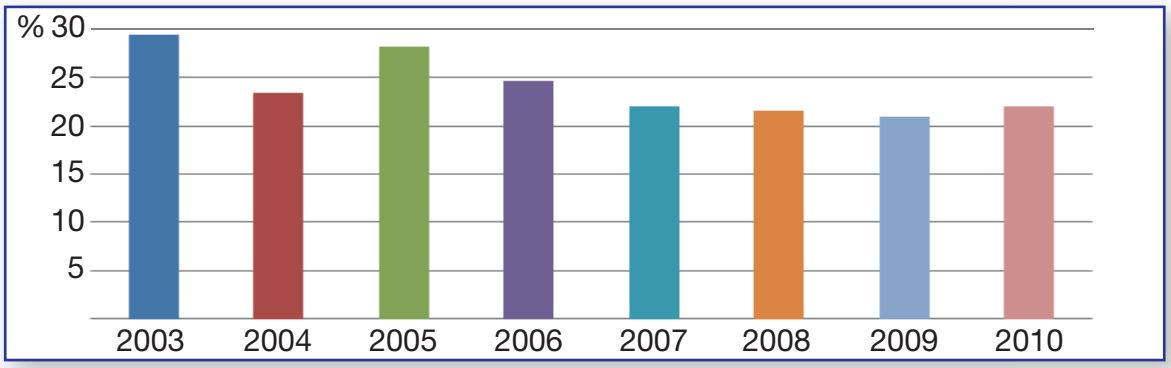
Source: WHONET. Reproduced with permission.

Users can be linked using web-based programmes. Advances in technologies make it possible to improve user-friendliness and functions such as automatic interpretation of data and alerts. Analysed electronic reports can be issued rapidly, based on entered patient results. The integration of the free outbreak detection software SaTScan[m] into WHONET has enabled enhanced detection of both community and hospital-based outbreaks.[55,56] Other more sophisticated software suitable for these purposes is also available.

Box 2.8 Monitoring MRSA in Malaysia

The Malaysian National Surveillance of Antibiotic Resistance programme was initiated in 1990. Results from routine antibiotic susceptibility tests are collected from 16 major hospitals and analysed using WHONET software. The MRSA rates decreased from 29.5% in 2003 to 22% in 2010.

Figure 2.3 MRSA rates in 16 Malaysian hospitals (2003 - 2010)



Source: Institute for Medical Research, Ministry of Health, Malaysia. Unpublished data, personal communication, 2011. Reproduced with permission.

[m] www.satscan.org

Laboratory capacity strengthening and networking is also being addressed in relation to specific infections. The WHO global laboratory networks for MDR/XDR-TB surveillance and HIV drug resistance surveillance are successful examples. The Global Laboratory Initiative (GLI) is a network of international partners dedicated to accelerating and expanding access to quality-assured laboratory services in response to the diagnostic challenges of TB, notably HIV-associated and drug-resistant TB. The GLI provides a focus on TB within the framework of a multi-faceted yet integrated approach to laboratory capacity strengthening.[n]

Laboratory capacity building is also being addressed in surveillance for foodborne and other enteric infections. The Global Foodborne Infections Network (GFN) is strengthening the capacities of national and regional laboratories in the surveillance of major foodborne pathogens and antimicrobial resistance. Several countries contribute funding and experts for the training courses.[o]

Some countries with routine surveillance capacities have also started exploring the use of molecular technologies to increase the value of the information obtained (Box 2.9).

Box 2.9 **Including molecular testing in surveillance: country examples**

Greece has an AMR surveillance network[p] which analyses test results on isolates from 40 hospitals, files the analysis results on a website and provides results for inclusion in the EARS-Net. It also uses the data to select isolates for molecular studies to identify new problems and targets for intervention (e.g. detection of a hospital cluster of the first *Proteus mirabilis* isolates to carry the VIM-1 metallo-beta-lactamase).[57]

Argentina has an AMR surveillance network which analyses test results on isolates from 70 hospitals, sends annual analysis summaries for inclusion in the AMRO/PAHO AMR surveillance reports and has begun to explore detailed collaborative analyses of merged files with several other PAHO member countries. An associated laboratory collects selected isolates from the network for additional molecular testing, e.g. of extended-spectrum beta-lactamases.

The Latin American Antimicrobial Resistance Surveillance Network developed horizontal collaborative procedures to ensure support on the identification of emerging resistant mechanisms in Latin America and the Caribbean. It confirmed the first New Delhi metallo-beta-lactamase (NDM) in Latin America, isolated in a *Klebsiella pneumoniae* strain.

The Staphylococcus Reference Laboratory (SRL) working group is the largest initiative to date.[58] It traces clones of *S. aureus* (MSSA and MRSA) of particular public health importance on a continental scale in Europe. Initiated by EARSS participants, it includes reference and expert laboratories which collect and type isolates from over 400 hospitals in 28 European countries. Results are made available through an interactive geo-tool[q].

3.4 Surveillance data used at national and international levels

Surveillance in itself does not reduce AMR, but the data collected can be used to track the emergence and spread of resistant strains, promote awareness, and most importantly provide "information for action" at hospital, national and international levels to reduce or to promote appropriate antimicrobial use.

Information is made easily accessible by several agencies which provide frequently updated visuals of AMR rates in defined geographic areas and/or updated reports (e.g. EARS-Net). Some of the most advanced interactive websites provide data in real time to raise awareness, for advocacy and to stimulate actions (Figure 2.4).

[n] http://www.stoptb.org/wg/gli/default.asp
[o] http://www.who.int/gfn/en/index.html
[p] http://www.mednet.gr/whonet/
[q] www.spatialepidemiology.net/srl-maps

Figure 2.4 Examples of distribution of some AMR pathogens in geographically defined areas

The maps at this site depict frequently updated rates of different AMR pathogens over time.
Source: The Center for Disease Dynamics, Economics & Policy[r]. Accessed 9 January 2012. Reproduced with permission.

AMR data has been used in many countries to assess the current situation and to detect trends.

Data on the use of antimicrobials have stimulated national level discussions, advocacy and successful actions to improve use (Figure 2.5).[59] The impact of interventions can also be assessed from such data. Several countries in Europe received political and other necessary support to initiate large-scale campaigns to reduce the use of antibiotics and the spread of bacterial pathogens based on the evidence provided by surveillance data. The example of how France turned the tide is detailed in Chapter 3.

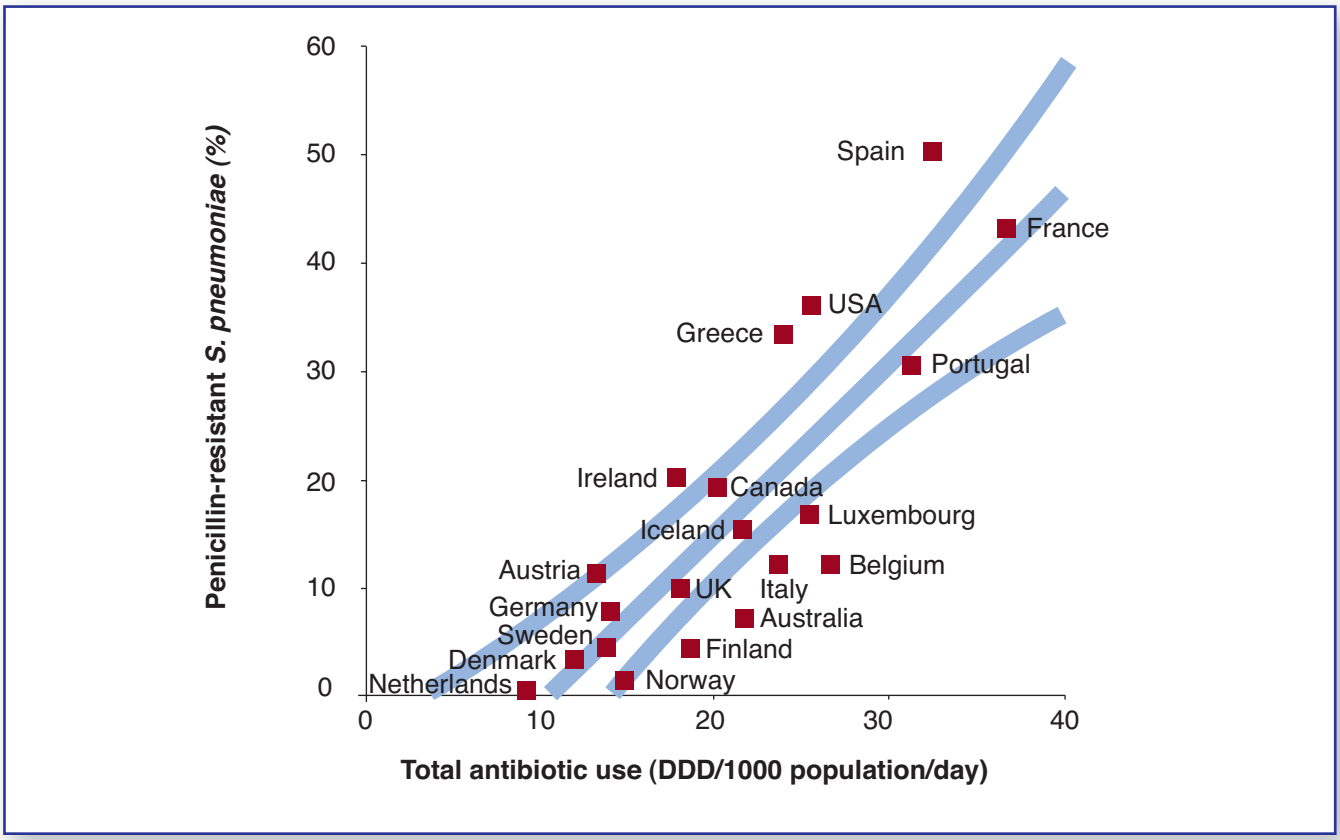
Figure 2.5 Total antibiotic use in ambulatory care in 32 countries in 2009

The use of antibiotics in ambulatory care, i.e. outside the hospital, is expressed in defined daily doses per 1000 inhabitants per day (DID).
Source: Reproduced and adapted from [59 s] with permission from ESAC.

[r] http://www.cddep.org/resistancemap
[s] http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036

Data from integrated surveillance have been used effectively to demonstrate associations between antibiotic use and AMR and to influence policy. Data showing increasing use and increasing resistance exist from several high-income countries, and these findings have stimulated actions to reduce the use of antibiotics. In Austria, for example, increasing use of fluoroquinolones in ambulatory care was accompanied by an increase in resistance to this class of antibiotic, from 7% in 2001 to 25.5% in 2007, among invasive *E. coli* isolates.[60] Total antibiotic use and AMR in a target bacterium in different countries are shown in Figure 2.6.[61]

Figure 2.6 Antibiotic use and AMR from 1990–2000 in selected countries



DDD: Defined Daily Doses

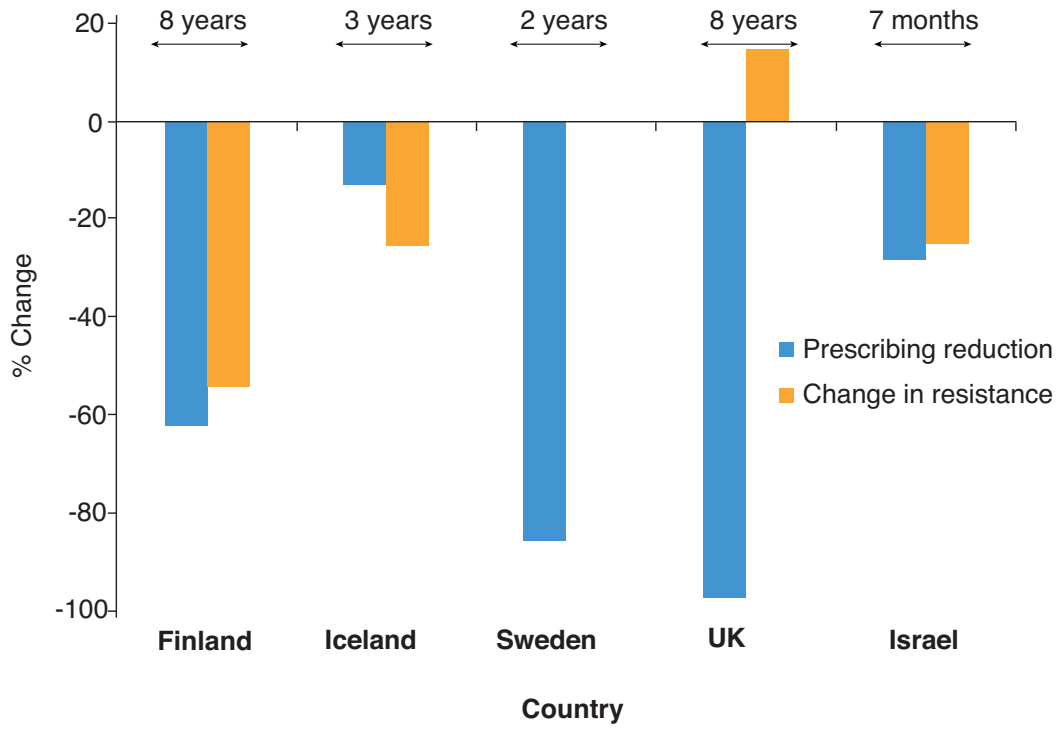
Total antibiotic use in outpatients versus prevalence of penicillin-nonsusceptible *Streptococcus pneumoniae* in 20 industrialized countries.

Source: Reproduced from [61] with permission.

Surveillance data have also shown that the impact of reducing antibiotic use on reduction of resistance rates is complex, highlighting the difficulties involved in reversing resistance once it has become established.

Figure 2.7 illustrates that decreasing the use of antibiotics has not always led to a decrease in resistance.[62] As a more encouraging example, data from Israel showed that a nationwide restriction on quinolone use led to an immediate increase in the susceptibility rates of urine isolates of *E. coli* to quinolones.

Figure 2.7 Effect of reductions in antibiotic use on the prevalence of AMR in the community



Each pair of columns indicates the percentage changes in the prescribing of antimicrobials and the corresponding effect on resistance prevalence. Finland – macrolide use and macrolide resistance, *S. pyogenes*; Iceland – overall antimicrobial prescribing in children and penicillin resistance, *S. pneumoniae*; Sweden – trimethoprim use and trimethoprim resistance, *E. coli*; UK – sulphonamide use and sulphonamide resistance, *E. coli*; Israel – quinolone use and quinolone resistance, *E. coli*. Source: Reproduced from [62] with permission from Oxford University Press.

From the mixed experiences documented, a "successful" intervention may be reflected only in stable rates of resistance or a difficult-to-quantify "decrease in the rate of increase in resistance". Such findings have stimulated research into many different aspects to gain better understanding of the relationship between antibiotic use and AMR.

At local health-care facility levels, where surveillance data are used to guide treatment decisions for individual patients, such data have also triggered actions to improve the use of antibiotics, infection prevention and control, and research.

4. Harm to patients and society due to AMR

The burden due to AMR infections in hospitals and in communities may well vary between countries and regions but data collected systematically to demonstrate this are scarce. Using hospital-based data collected by the European Surveillance network, attributable mortality and extra costs were calculated using earlier published relative risks. These calculations indicate that the excess death toll from selected resistant bacterial hospital infections exceeded 25 000 per year in that region and that the extra health-care costs and productivity losses were at least €1.5 billion per year.[8] In outpatients in the USA, resistant infections are implicated in more than 63 000 deaths per year.[63] Canada estimates excess direct cost of hospitalization for resistant infections as compared to susceptible infections to be $9–$14 million. Screening patients on admission to detect carriers of resistant organisms adds another $10 million. To place carriers under precautions to prevent spread to other patients adds approximately another $16 million.[9] There is limited information on the impact of AMR on community-acquired infections. The impact on hospital and community infections is likely to be greater in lower and middle-income countries.

Pharmacovigilance could provide an opportunity to capture data on the impact of AMR on individual patients (Box 2.10).

Box 2.10 **Pharmacovigilance to detect treatment failure due to AMR**

WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem." The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) conducted a pilot study on behalf of the Seventh Framework Programme of the European Commission, to investigate the feasibility of identifying treatment failure due to AMR by using individual case safety reports (ICSRs).

In the WHO global ICSR database, VigiBase, terms related to lack of expected therapeutic effect were the ninth most frequently reported adverse reaction. A total of 138 400 such reports were screened for local patterns of disproportionately greater reporting of antimicrobial treatment failure and/or resistance. Observed-to-expected ratios for the number of reports on treatment failure for different antimicrobial active ingredients were computed across a range of database subsets, specifically looking for clusters related to country and/or time periods. Such outlying reporting patterns were ranked and the top five investigated in greater detail.

The top outlying reporting patterns reflected localized hospital outbreaks of AMR infections including one with an index case of multi-resistant *Pseudomonas* in an outpatient. For two of the case clusters it was stated that the antimicrobial in question was not of poor quality, whereas no such assurance was provided for the other three temporal clusters. More detailed investigation is required to exclude the possibility of substandard/counterfeit products.

This pilot study demonstrates a potential global approach for the detection of impact of AMR, and for detecting possible substandard/counterfeit products (WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) unpublished data, personal communication, 2011).

Since there are many different antibiotics to which many different pathogens may develop resistance, it is not easy to express the magnitude of AMR in a readily comprehensible manner. The concept of a "Drug Resistance Index" has recently been suggested as a means of communicating this complex relationship. The Drug Resistance Index provides aggregate information, using a "basket" of resistance and consumption data for different antibiotics. The data on resistance are weighted according to the intensity of use for each antibiotic to produce indices that indicate the magnitude of the resistance problem as a whole and capture trends across time and space.[64]

5. Gaps and challenges

Surveillance of AMR has advanced considerably in the past decades, but is still far from fulfilling the goal of good quality global coverage. For existing AMR surveillance networks, two factors seem to have contributed greatly to their success: developments in computerized information technology which have reduced the effort involved in participation, and support from public health and other leaders which facilitates participation. Some of the continuing gaps and challenges are as follows:

Lack of common definitions for surveillance: Globally accepted definitions for multi-drug resistance (MDR) in common bacterial infections, like those that exist for TB, may enhance the ability to share, compare and evaluate resistance information.

Lack of geographically representative data: Only a tiny fraction of the world's AMR test results are utilized for surveillance and those often in ways that yield only a fraction of their potential benefit. Several parts of the world still do not have capacity to test for AMR in infecting or potentially infecting bacteria. The resulting lack of data from vast areas in the world minimizes the benefits from surveillance and precludes accurate analysis of trends over time.

Gaps in laboratory capacity: The WHO 2001 Strategy and 2011 World Health Day policy package both identify strengthening laboratory capacity as an essential intervention for AMR surveillance. This involves improving existing laboratories and adding new ones and also enhancing the ability of staff to extract, interpret and distribute information from each test. Many countries still lack competent laboratories for diagnostic testing. Establishing sustainable and quality-assured laboratories with reliable supply chains involves consideration by policy-makers and managers of many elements such as human resources, laboratory infrastructure, external quality assessment, supply systems, standard protocols, and training.

Gaps in diagnostic testing: Where resources are limited, testing for susceptibility to antimicrobials competes for scarce funding with provision of treatment, and often the costs are met by the patient as an out-of-pocket payment. Even in high-income countries, diagnostic tools are currently not always optimally used. Support for more routine use of diagnostics and development of rapid diagnostic tests adapted for resource-limited settings would improve surveillance as well as the care of individual patients.

Gaps in data management and networking capabilities: Sustainable networks at subnational or national level are absent in many parts of the world. Where networks exist, the capacity to collect, manage and utilize data appropriately may be inadequate. Rapid advances in informatics make it necessary to evaluate and continually enhance existing systems.

Methodological obstacles: Establishing reliable surveillance systems for antimicrobial use is even more challenging than setting up AMR surveillance networks. Differences that exist in health-seeking behaviour, health-care delivery, availability of records, drug policies and many other differences, make this a daunting task in most parts of the world. There is no single applicable method for collecting total consumption data or patterns of use from all facilities, countries or regions worldwide. Several aspects related to methodology still need to be resolved before comparable data from different parts of the world can be collected. As for AMR surveillance, in many countries facility level capacity for data collection, management, analyses, feedback and follow-up actions based on results need to be addressed. In addition, unlike AMR, surveillance of antimicrobial use does not belong within a single clinical specialty, and so is often left to the self-taught interest of pharmacists, pharmacologists and other professionals. Formal inclusion in a specific discipline could help in capacity-building.

Coordination of surveillance networks: There is also a growing need for network integration and oversight. Public health agencies will need to take a more active role in organizing and coordinating multi-centre AMR surveillance networks and their functions, including data analyses and feedback.[65] Integrating surveillance programmes with antibiotic stewardship programmes at facility and national levels is a logical step towards best use of the data collected. One of the earliest and most lasting benefits of launching a surveillance initiative could be the impetus that it brings to capacity-building by participating institutions, quality improvement, and constructive collaboration among network partners, as experienced in some of the examples described above.

Integration of data from animals: Surveillance should ideally incorporate antibiotic use and AMR in veterinary practice and animal husbandry (see Chapter 4).[66] Countries which have national antimicrobial consumption and AMR databases in both humans and animals may be able to determine the correlation between total use and AMR at the national level. The Danish integrated antimicrobial resistance monitoring and research programme[t] is an example where summaries and trends from these two sectors are produced as one easily accessible document. The Canadian Integrated Programme for Antimicrobial Resistance Surveillance (CIPARS) is another example.[u] Other countries are also gathering similar data, as part of different initiatives.

Lack of data on clinical impact: Although there are examples of surveillance of AMR and antimicrobial use, there is very little systematic data collection on clinical impact, such as treatment failures due to AMR, and this is a major gap. More efforts are needed to develop methodologies and data collection systems to understand the harm suffered by patients and society as a consequence of AMR.

[t] www.danmap.org
[u] http://www.phac-aspc.gc.ca/cipars-picra/index-eng.php

Chapter 3.

Measures to ensure better use of antibiotics

Chapter 3.

Measures to ensure better use of antibiotics

Much of the antimicrobial resistance problem stems from the misuse of antibiotics, particularly excessive use. If antibiotics were always prescribed appropriately and only when needed, the treatment correctly followed, never used in agriculture or aquaculture, and if substandard and counterfeit products could be abolished, there would be only limited selective pressure on bacteria to become resistant. Regulations and practical measures are needed to tackle all of these issues. Political will and leadership are indispensable to put the necessary regulations and measures into practice.

Summary

The emergence of resistance to antimicrobials is a consequence of their use. This relationship is evident both for individual patients and for populations. While antibiotics are essential to cure some infections, significant misuse occurs in most parts of the world, usually in the form of unnecessary overuse, which increases the selective pressure on bacteria to develop resistance.

Many options for action are available to reduce unnecessary use, but putting the measures into practice is often problematic. Political leadership in countries is needed, but commitment to addressing the issue through policies and regulations may be difficult to obtain. How to implement the interventions is often unclear – and while reducing unnecessary overuse, access to these essential medicines for those who need them has to be ensured. The 2001 WHO Global Strategy for Containment of AMR provides a number of specific recommendations based on a strategy that includes education, supporting treatment decisions through improved diagnostic services and treatment guidelines, encouraging restrictions in prescriptions, instituting prescription audits and feedback, and implementing regulations on quality, dispensing and drug promotion.

There are encouraging examples from different parts of the world of action to reduce the excessive use of antimicrobials, with successful outcomes including improved antibiotic use, reduced use and cost savings, and in some cases an impact on AMR has also been demonstrable. However, the extent to which interventions are implemented and integrated into health systems varies greatly across countries.

At a global level, AMR does not have the level of political commitment that is warranted by the actual threat, and priorities and capacities of health systems differ between countries. Tackling inappropriate antibiotic use at national level requires a system-wide approach for which the government has the ultimate responsibility. Regulation is needed to ensure the quality of medicines and secure the supply chain, and to control the prescription and dispensing of medicines, but the necessary legal and regulatory framework appears inadequate in many countries. Policy leadership and support for actions at facility level are needed to improve prescribing and to obtain data to inform local policies. Interventions targeting dispensers and other sellers are being tested and implemented, but need to be scaled up. A bottom-up process involving communities, patients, and health professionals could prove useful, with education and awareness-raising to engage all stakeholders. This chapter considers the available measures to improve the use of antimicrobials and the gaps and challenges to be met in applying them worldwide.

1. How rational drug use helps to reduce AMR

Antimicrobial resistance is a consequence of antimicrobial use, and there is a clear relation between use and emergence of resistance at both the individual and population levels. Consumption of antibiotics correlates with the frequency of resistance at country level, as evidenced by data from the European Surveillance of Antimicrobial Consumption (ESAC-Net) and European Antimicrobial Resistance Surveillance Network (EARS-Net).[67] The more antibiotics are used, particularly when misused, the greater the selective pressure placed on bacteria to acquire resistance genes, hence the need to limit the use of these medicines to what is necessary and appropriate.

Rational use of medicines requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.[68] There are at least two additional factors that need to be considered in relation to the rational use of antibiotics:

- For an antibiotic to be effective it must be of good quality, and the bacteria causing the infection need to be susceptible to it. The rational use of antibiotics therefore requires information derived from microbiological susceptibility testing and assured quality of the antibiotic being used.
- The use of antibiotics has consequences for both the individual patient and for society. Individual use can lead to selection of antibiotic-resistant bacteria which may then infect other members of the population, causing infections that may be difficult to treat. Antimicrobials are the only class of today's medicines for which obsolescence results from use.

Unfortunately, for the first of these factors there is often a lack of timely and locally relevant diagnostic information, and the second is often ignored because the perceived benefit to an individual patient is considered to outweigh the long-term impact on society.

Irrational use includes over-prescription, under-prescription, and prescription and dispensing of unnecessary antibiotic combinations. Physicians may prescribe too many drugs, expensive drugs or inappropriate drugs because of fear of treatment failure, lack of knowledge of the local AMR situation, real or perceived patients' expectations, drug company promotional efforts, or for personal financial gain. Commercial outlets may seek to maximize their income by dispensing medicines without prescriptions. Consumers may practice self-medication using unnecessary or ineffective antibiotics, or insufficient quantities of an appropriate antibiotic.

There are many examples and reasons why misuse, usually overuse, occurs. Upper respiratory tract infections, frequent causes of medical consultations, are usually caused by viruses and, therefore, do not require antibiotics. However, antibiotics are frequently prescribed, for instance accounting for 60% of all antibiotic use in general practice in England.[69] Diarrhoeal diseases, again usually viral in etiology or self-resolving, are often incorrectly treated with antibiotics. The self-limitation of a viral infection could then be misinterpreted as the effect of medication. Misuse also occurs for prophylaxis, for example the inappropriate and excessive use to prevent infections following surgery.[70] Apart from lack of knowledge, other reasons for antibiotic misuse include financial motivation on the part of prescribers, demand by patients for a variety of cultural, social and economic reasons, fear of litigation, lack of unbiased information on medicines, heavy workload with short consultation times that preclude making a proper diagnosis, and junior prescribers following the poor example of their senior colleagues.

Overuse of antibiotics is an enormous public health problem, and interventions to deal with it have been developed over the last 30 years. This chapter discusses options for action and gaps in relation to WHO recommendations to reduce the misuse of antibiotics. Often there is no lack of information on what to do but guidance is missing on how to put the appropriate measures into practice and how to generate the necessary political commitment for their implementation. As with climate change and other environmental issues, it has to be understood that the results of interventions today may take years to become evident in society, but that both individual and collective efforts are crucial now. Bringing about change involves many actors and many considerations, and change will have economic implications that need to be incorporated into the relevant budgets.

2. WHO guidance on rational use to contain AMR

The 2001 WHO Global Strategy for Containment of AMR includes many recommendations to promote rational use of antimicrobials, providing guidance that is still valid today for prescribers, dispensers, hospitals and governments (Appendix 1).[1] The strategy includes: educating prescribers and dispensers on appropriate use of antimicrobials; supporting treatment decisions through improved diagnostic services and treatment guidelines; encouraging restrictions in prescriptions to a selected range of antimicrobials; instituting prescription audits and feedback; and establishing and implementing regulations on quality, dispensing and promotion of antimicrobials. Including rational use as part of the curriculum for professional courses and educating patients on antimicrobial use are also recommended. The policy briefs published on World Health Day 2011[2] reiterated these important measures for reducing irrational use (Appendix 2) and highlighted the need for stewardship programmes in hospitals, for engaging professional and civil societies and patient organizations, and for taking into consideration the local factors that drive irrational use in different settings.

3. The present position regarding these recommendations

Because many diverse factors contribute to irrational use – including knowledge, perceptions, attitudes and behaviour of policy-makers, prescribers, manufacturers, dispensers and consumers – there is no single or simple solution to the problem. Although the AMR burden due to misuse is likely to be immense, global data on its magnitude are very limited. Scanty data on the antimicrobial use per capita show extreme variations in use between countries and within countries (Chapter 2). Most available information on irrational use is from the public sector, but irrational use could be even more prevalent in the private sector due to stronger economic incentives. And the roles of informal sectors such as traditional healers also need to be considered.

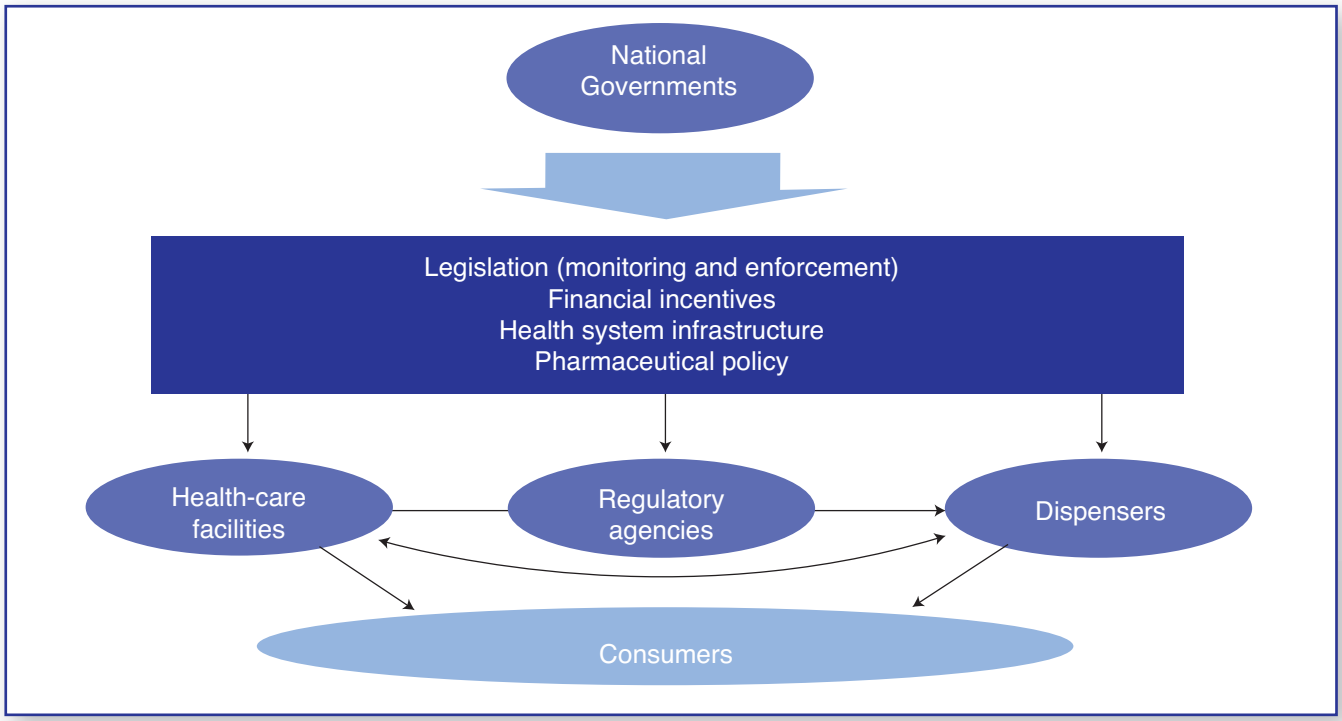
A WHO Fact Book summarizing results from studies on drug use in primary care reported between 1990 and 2006 included 679 studies conducted in 97 countries.[49] Less than 70% of bacterial pneumonia cases were treated with an appropriate antibiotic, but unnecessary overuse was frequent, particularly for viral infections, as exemplified by the high proportions of upper respiratory tract infections and diarrhoea cases treated with antibiotics (Chapter 2). Overall the percentage of patients receiving antibiotics remained stable at about 40%–50% over the time period studied. The use of medicines in the public sector was substantially better than in the private sector for the prescribing indicators used and also for the treatment of acute respiratory infections. Low-income settings reported a higher percentage of patients treated with an antibiotic, suggesting that overuse may be occurring.[43]

Published reports confirm several large and small-scale efforts to improve antimicrobial use with good outcomes, but systematic measures integrated into health systems appear to be limited mainly to high income countries. The following sections provide some insights into the promotion of rational use.

3.1 A system-wide perspective to promote rational use

An important reason for the relatively low political priority accorded to AMR at a global level could be the lack of data on the size of the health and economic burden caused by AMR and on the extent of irrational use worldwide. Although the priorities and capacities of health systems differ in different parts of the world, tackling the issue of irrational use is complex and probably requires a system-wide perspective as depicted in Figure 3.1.[71]

Figure 3.1 Health systems perspective and structures influencing the use of medicines



Source: Compiled from [71].

Actions required at different levels of the health system have been detailed by professionals working in this area.[72] Strategies involving different parts of the health system and drug supply chains can reduce antibiotic consumption, as results from several countries have shown (Box 3.1).

Box 3.1 **France – turning the tide against AMR**

In the late 1990s, the spread of antibiotic resistance in France became a major public health concern.[73] The situation was serious in both general practice and in hospitals. Rapid spread and hyper-endemic occurrence of MRSA was observed in hospitals. In general practice, the rate of *S. pneumoniae* strains with reduced susceptibility to penicillin G rose sharply from 5% in 1988 to 48% in 1997. During the year 2000, France had the highest outpatient antibiotic consumption per capita in the European Union.

In 1999, an extensive national consultation to define a coordinated scheme for the control of antibiotic resistance was launched by the Réseau National de Santé Publique. This consultative process involved health professionals in human and animal health from the public and private sectors, with experts in the use and the manufacturing of antibiotics and in resistance control. It resulted in proposals for a range of interventions to be incorporated in a national plan of action to control antibiotic resistance. The plan included surveillance of antibiotic consumption and bacterial resistance in humans and animals, control and prevention of AMR spread, and promotion of research on resistance (Table 3.1). In addition, annual public awareness campaigns on the prudent use of antibiotics, continuing education for health professionals, and promotion of rapid testing for *S. pyogenes* tonsillitis were introduced.

As a result of these measures, the consumption of antibiotics was reduced by 23% between 2002 and 2007. At the same time, a 7-valent protein-conjugate pneumococcal vaccine for young children was introduced in 2002. The general decrease in antibiotic consumption combined with the introduction of the new pneumococcal vaccine resulted in reversing trends in penicillin resistance in *S. pneumoniae*.

Additionally, several data sources confirm a substantial decrease in incidence and prevalence of MRSA. Data from EARS-Net show a decrease in the proportion of MRSA among *S. aureus* from blood cultures in France, from 33% in 2001 to 26% in 2007.[74]

Table 3.1 National plan of action to control antibiotic resistance (Ministry of Health, France)

	Actions	Type of actions	Level
Surveillance	a. Monitoring	Regulations, developing tools *	International, national, hospital, community
	b. Sentinel network	Regulations, developing tools *	Experimental, community
	c. Alert	Regulations	National, hospital, community
	d. ONPCM**	Regulations	National, hospital, community
	e. COM.MED***	Regulations	Local, hospital
Control	a. Distribution / hospital	Educating population, health-care staff training, developing tools *	National, hospital
	b. Distribution / community	Educating population, health-care staff training, regulations	National, community
	c. Good practice / hospitals	Health-care staff training, regulations, developing tools*	National, hospital
	d. Good practice / community	Educating population, health-care staff training, regulations, developing tools *	National, community

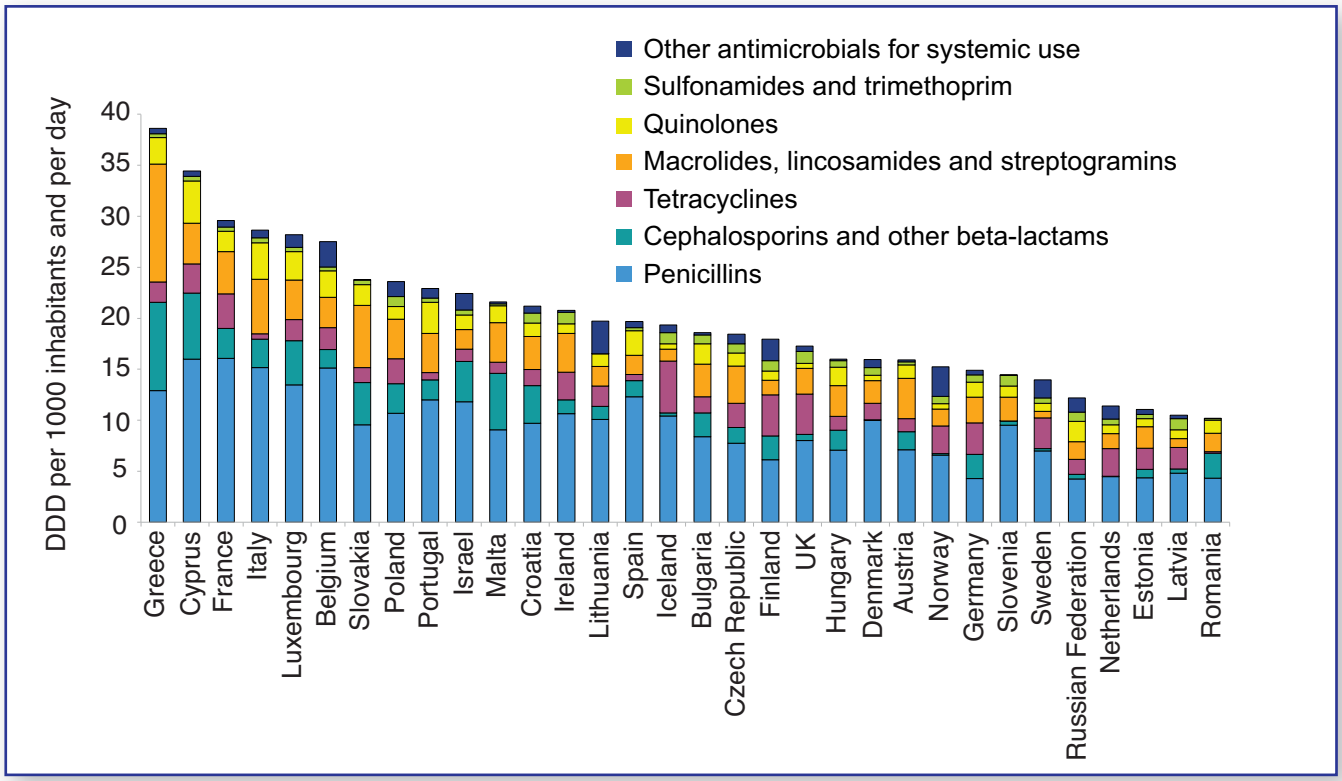
* Developing tools (methods and standardization of monitoring, information systems, prescription guides, diagnosis and therapeutic tests)
** Observatoire National des Préscriptions et Consommations des Médicaments (National Observatory for Prescriptions and Medicines Consumption)
*** Medicines Committee
Source: Reproduced and adapted from [73] [a] with permission.

[a] http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19

The French national action plan summarized in Box 3.1 provides an example of the range of actions that national governments can undertake to improve the use of antibiotics and reduce AMR.

Functioning regulatory systems are considered important prerequisites, necessary to support the application of effective strategies for the appropriate use of antimicrobials and containment of AMR. This represents a significant challenge in many countries with weak regulatory systems. However, even data from European countries with strong regulatory frameworks illustrate the great diversity between and within countries with more or less similar disease patterns, in antibiotic prescribing and sales (Figure 3.2), suggesting that irrational use is still ongoing.[59]

Figure 3.2 Outpatient use of selected antibiotics in 2009 in 32 countries



DDD: Defined Daily Doses
Source: Reproduced and adapted from [59] [b] with permission.

[b] http://www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50036

The following sections discuss regulations and other measures to facilitate rational prescribing from a system-wide perspective.

Securing the supply of good quality medicines through regulation

Ensuring access to good quality medicines and securing the supply chain from manufacturer to end-user form part of a government's responsibility for protecting the health of its people. In many parts of the world, however, the drug supply chain is inadequately and variably secured because regulations related to quality, procurement, storage and sales are either lacking or insufficiently enforced.

Ensuring quality: Drug regulation is a process by which the pertinent authorities, generally at the national level, assess medicinal products to ensure that they are marketed only if they are efficacious, safe and of sufficient quality, and that the information provided with respect to them is reliable and complete.[75] Effective drug regulation should ensure that illegal and substandard manufacturing are detected and appropriately sanctioned. In many settings, this will require quality surveillance of marketed products. Poor quality products at the point of sale can be due to problems with manufacturing or with the quality or integrity of the supply chain. For example, many heat- and moisture-labile antibiotics may become degraded if shipped or warehoused under ambient conditions in tropical countries. Many countries already have regulatory frameworks in place to ensure manufacturing of high quality products. However, weak supervision, incentives to bypass regulations, corruption, and constrained resources may lead to system failures of varying magnitudes.

In almost all countries, governments are responsible for establishing national Drug Regulatory Agencies (DRA) which are accountable to both the government and the public.[76] A ministry of health (MoH) is likely to be aware of the need for a broad public policy related to antibiotics, but responsibility for the pharmaceutical industry may be with a ministry handling trade, commerce, industry or national development with objectives which may be primarily economic and hence not fully aligned with the health-related objectives of the MoH. There is an increasing trend towards drug regulation through autonomous self-financing bodies, mainly because the technical nature of the work is highly specialized and different from that of the MoH. However, in most countries there is representation from the MoH in the governing bodies of the DRA, or the DRA remains under the leadership of the MoH. It is essential to avoid conflicts of interest in the operations of the DRA , as well as built-in monitoring mechanisms.

The sale and use of substandard and counterfeit drugs are common problems, particularly in low- and middle-income countries, although most countries have legislation that prohibits counterfeit drug manufacturing and selling.[77] While substandard drugs can be identified through testing, identification of counterfeits is often more difficult.

Regulating drug promotion: Drug promotion by the pharmaceutical industry may influence prescribing behaviour leading to potential misuse. However, promotional activities and resulting behaviour by prescribers are difficult to quantify. Interventions that counter this influence include government regulation, free and abundant provision of non-commercial therapeutic information to health-care professionals and the public, and media exposure of abusive promotion.[78] The critical monitoring and regulation of drug promotional activities is unfortunately not carried out effectively in many countries. Internet and social networking sites have become widely used forums for the marketing of pharmaceutical products to individual patients worldwide. This new, virtual market has the potential to provide novel opportunities for counterfeit and substandard drug sellers and is likely to create new challenges for regulators.[79] Enforcement of ethical codes of conduct for prescribers is a complementary measure which also appears to be lacking in many countries.

Improving dispensing: Medicines are generally categorized as *controlled substances*, *prescription-only* or *over-the-counter* (OTC), with antibiotics grouped in the prescription-only category.

In industrialized countries, the dispensing of antimicrobials is mainly based on prescriptions from qualified medical professionals. This is difficult to enforce in many middle- and low-income countries for many reasons, including the need to ensure access to medicines when qualified health workers and dispensers are scarce. Therefore OTC sales of antibiotics are common even when there are regulations mandating the requirement for valid prescriptions. A recent systematic

review of published literature from 1970 to 2009 on non-prescription antimicrobials showed that OTC sales occurred worldwide and accounted for 19%–100% of antimicrobial use outside northern Europe and North America.[80] Many dispensers may not be trained or equipped to diagnose infections, or in some cases even to procure, store and dispense medicines. OTC sales may also contribute to promoting unreliable drug quality and pricing. Experience from Chile shows that a short-term reduction in antimicrobial use based on the regulation of sales was not sustainable over the long-term (Box 3.2), for reasons yet to be fully elucidated.

Box 3.2 **Chile – Impact of regulation on "prescription only" sales of antibiotics**

In the late 1990s in Chile, indiscriminate use of antibiotics increased the incidence of bacterial resistance which led to the use of more expensive antibiotics in the health-care system.[81,82] As a part of "The Action Plan to Assure Rational Antibiotic Use", the Ministry of Health intoduced regulatory measures in September 1999. The principal measures were to restrict sales of antibiotics to prescription only, and establish and enforce supervision by regulatory authorities. In addition, posters and leaflets about the correct use of these drugs were distributed.

Information on antibiotic sales in private community pharmacies from 1996 to 2002 was obtained from the International Marketing System, an auditing system for pharmacy sales. After the introduction of regulation, there was a reduction in defined doses/1000 inhabitants/day for the seven antibiotics monitored. Furthermore, the total sales of oral-use antibiotics decreased by 43% from US$ 45.8 million in 1998 to US$ 26.1 million in 2002. However, these reductions were not sustainable in the long-term. Antimicrobial use has increased since 2002, returning to levels close to the baseline in 1997.

Regulatory enforcement prohibiting the sale of certain antibiotics without a prescription has not always been successful in reducing their overall consumption.[50] The reasons are often unclear, but these experiences may illustrate the need for other interventions, such as those for improving the knowledge and attitudes of consumers and prescribers, to be implemented together with regulations.

Improving access to antibiotics: Although over-consumption is a key driver of resistance development, paradoxically the limited access to effective treatment in many low-income countries is also an important factor for the emergence of resistant bacteria. Using the wrong antibiotic when the correct one is not available not only means that the infection will not be cured, but that selection pressure for resistance is unnecessarily applied. Exposing bacteria to drug levels lower than that required to kill them also promotes resistance. The use of ineffective drugs, inadequate dosing, or no treatment at all also facilitate the spread of pathogens including those with AMR.

The availability of, and access to, antiretroviral, antimalarial and anti-TB drugs have in part been addressed by initiatives such as the Global Fund for AIDS, Tuberculosis and Malaria, but there is no similar funding or distribution mechanism to cater for the corresponding needs for effective antibiotics against the broad range of common bacterial infections in developing countries, or to contain AMR.

The use of left-over drugs for a variety of indications is another type of self-medication which is widely practised, including in industrialized countries. The "Self-Medication with Antibiotics and Resistance Levels in Europe" (SAR) project showed consistent associations between prescribed antibiotic use and self-medication from left-overs.[83] Regional differences were identified, with self-medication higher in eastern and southern Europe compared to northern and western Europe.[84]

Facilitating appropriate choice of treatment

Antimicrobial use and AMR surveillance (Chapter 2) provide local data to guide decisions on treatment choices. Maintaining an updated essential medicines list and implementing standard treatment guidelines informed by local data should encourage better antimicrobial use and hence improved patient outcomes. WHO published the first essential drugs list in 1977, on the principle that some medicines are more

useful than others and that essential medicines were often inaccessible to many populations. Since then, the Essential Medicines List (EML) has been updated regularly and expanded to include new developments. The WHO model EML is to be adapted by countries to take account of local situations including patterns of antimicrobial susceptibility and the costs of medicines.

Antimicrobial stewardship programmes aim to promote appropriate use of antimicrobials – right choice, duration, dose, and route of administration. Several strategies, including prescriber education, formulary restriction, prior approval, streamlining, antibiotic cycling, and computer-assisted programmes have been proposed. Although rigorous clinical data in support of these strategies are lacking, effective antimicrobial stewardship will involve a comprehensive programme incorporating multiple strategies and collaboration among various specialties within a given health-care institution.[85,86] Recent data confirm that such programmes increase appropriate antibiotic prescribing, reduce pathogen resistance and improve clinical outcomes of community-acquired pneumonia managed within hospitals.[87]

A series of measures taken by Australia to promote rational drug use, including a national EML and therapeutic guidelines, are outlined as an example in Box 3.3.

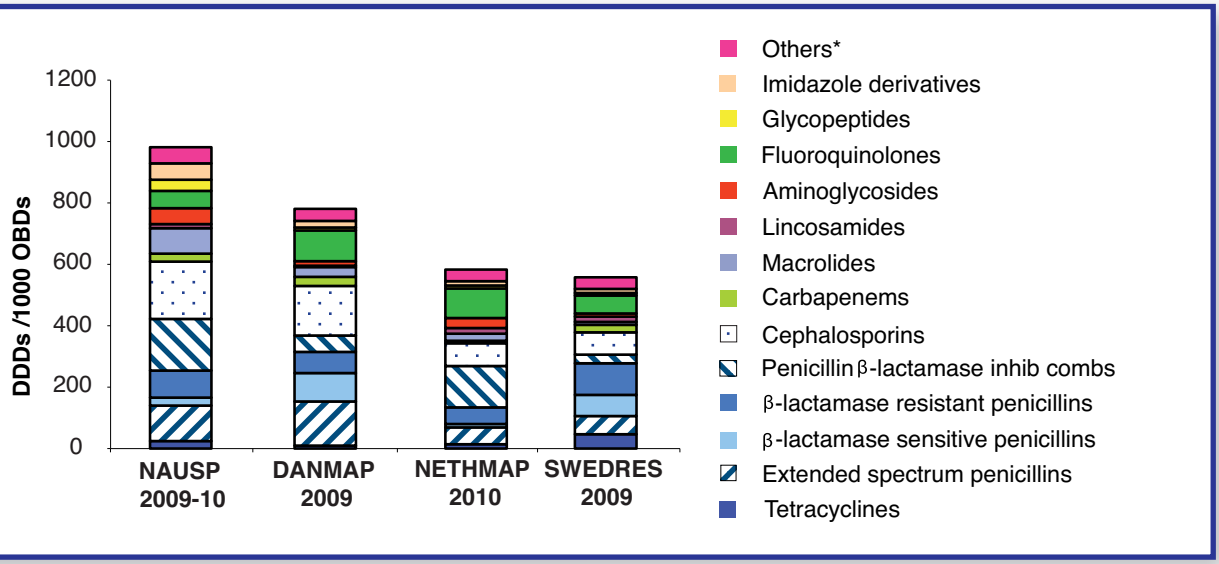
Box 3.3 **Low levels of fluoroquinolone resistance in Australia**

An integrated package of measures to improve antimicrobial use is enforced in Australia. The impact of interventions to guide prudent use is measured using surveillance data in this example. The frequently updated essential drug list and national guidelines on the treatment of most infections and on prophylaxis, aim to guide antimicrobial use within both hospital and community settings. Indications for the use of fluoroquinolones are limited, and community use is controlled by the Pharmaceutical Benefit Scheme. Antimicrobial stewardship is implemented as an initiative under the Australian Commission on Safety and Quality in Health Care. In addition, the National Prescribing Service regularly conducts campaigns to reduce unnecessary antibiotic use.

Compared to other countries with existing rational use programmes and low usage of antibiotics, Australia has a higher use of antimicrobials in general but lesser use of fluoroquinolones, as evidenced by data from the National Antimicrobial Utilization Surveillance Program (NAUSP) annual report 2009–2010 (Figure 3.3). Fluoroquinolone resistance among Gram-negative bacilli remains below 5%, according to the Australian Group on Antimicrobial Resistance 2006 surveillance report, which is lower than resistance rates found in most other countries including those with generally low AMR rates.[88]

Australia also implements interventions to reduce antibiotic use in animal husbandry and has regulations in place to restrict the use of fluoroquinolones in this sector.

Figure 3.3 Antibiotic use in Australia (2009–2010) compared to European countries with low use



NAUSP 2009/2010 includes Australian data from July 2009 to June 2010, **DANMAP** 2009 rates represent 2009 usage, **NETHMAP** 2010 rates represent 2008 usage, **SWEDRES** 2009 rates use numerator data from 2009 and denominator data from 2008.
*** Others** includes lipopeptides, monobactams, methenamine, nitrofurans, oxazolidinones, polymyxins, rifamycins, short-acting sulphonamides, streptogramins, steroids, sulphonamide/trimethoprim combinations, trimethoprim. DDD: Defined Daily Doses; OBD: Occupied Bed Day.
Source: Reproduced from [88] with permission.

A number of developing countries have also launched coordinated programmes to improve antimicrobial use. The "Antimicrobial Smart Use" project in Thailand, for example, is a bottom-up approach, engaging communities and local health services, working hand-in-hand with a top-down approach providing policy support (Box 3.4).[89]

Box 3.4 **The Antibiotic Smart Use programme in Thailand**

The Antibiotic Smart Use programme aims to improve prescribing of antibiotics in Thailand by targeting both prescribers and patients. Scale up is taking place in phases and there are plans to expand the AMR containment strategy to other sectors.

Phase I used multifaceted treatment guidelines and patient education to change prescribing behaviour. In phase II decentralized networks between local and central partners were developed to scale up the programme. Phase III aims at promoting sustainability.

Phase I showed an 18%–46% reduction in antibiotic use and 97% of targeted patients recovered or improved regardless of whether they had taken antibiotics or not.

This combined bottom-up and top-down model tried to achieve sustainable promotion of rational use of antibiotics by initiating behaviour change at an individual level and scaling up and sustaining achievements via three strategies: development of collaborative networks, policy advocacy, and forming a social norm.

Economic considerations

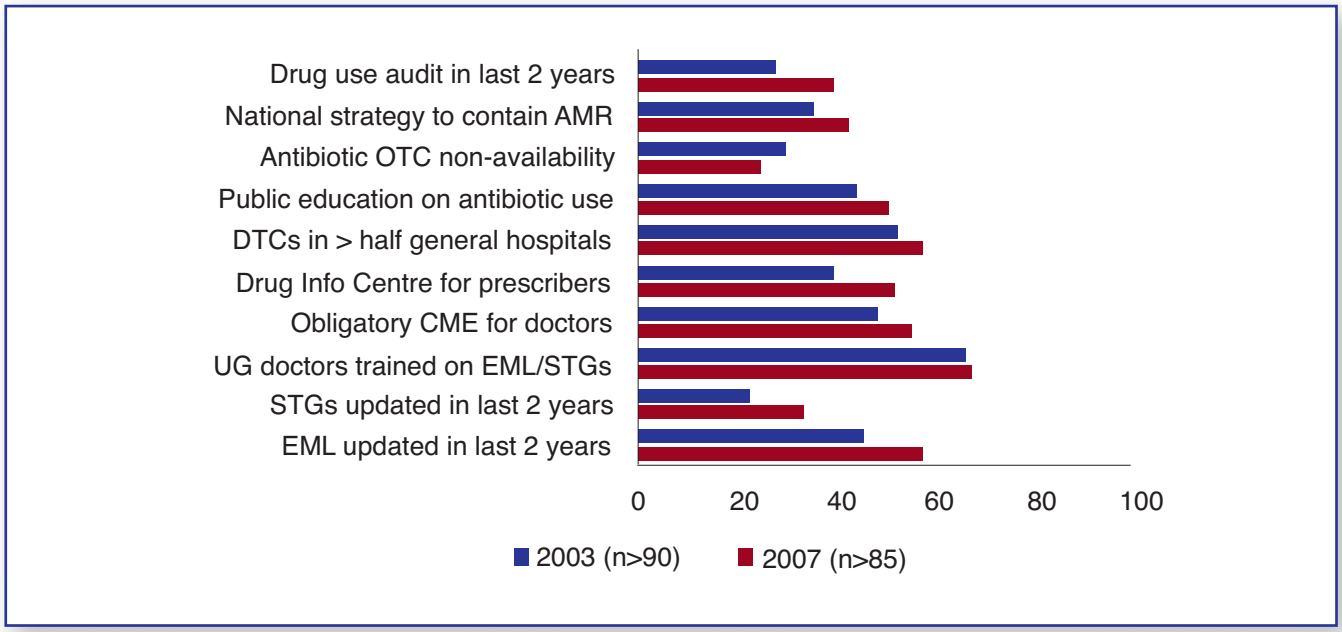
Antimicrobial use and the development of resistance may be influenced by the economic behaviour of individuals and institutions.[90] Measures that improve rational use of drugs have cost implications, which need to be weighed against the costs saved by reducing unnecessary use and the future costs that would result from not taking action. By extrapolation from a study in a single Chicago hospital,[91] the total additional costs in all U.S. hospitals for treating resistant versus susceptible infections could be as high as US$ 25–35 billion.

Substantial savings can be made through rational use of antibiotics. For example in the UK, a multi-disciplinary team (including a consultant microbiologist and a clinical pharmacist) promoted rational use of antibiotics in two directorates within one national health service trust. This intervention has succeeded in reducing costs by 42% and 24% respectively without any detrimental effects on patients.[92] Cost savings from effective antibiotic stewardship schemes for hospitals is discussed further in section 3.2. Additional savings of £7300 per 100 000 population could be made if national guidelines for antibiotic prescribing for respiratory tract infections in primary care were implemented, according to a sample calculation.[93]

Implementation of policies

WHO surveys in 2003 and 2007 were carried out to analyse a range of national policy interventions to improve the use of antibiotics, using questionnaires sent to the ministries of health of all Member States. The results from those which responded showed widespread inadequacies in the level of implementation (Figure 3.4), indicating a need for more comprehensive national strategies.[43,44]

Figure 3.4 Implementation level of national policies to improve rational drug use



Bars represent various national policy interventions. CME: Continued Medical Education, DTC: Drugs and Therapeutics Committee, EML: Essential Medicines List, OTC: Over-the-counter, STG: Standard Treatment Guidelines, UG: Undergraduate

Source: Based on [43,44]. Reproduced with permission.

3.2 Health care facility-level interventions to improve antimicrobial use

A significant proportion of prescriptions for antibiotics are unnecessary and/or inaccurate with respect to dosage, duration of treatment or the antibiotic chosen. Ensuring rational use at health care facility-level requires a coordinated programme of continuous education together with other measures for promoting appropriate use. In antibiotic stewardship schemes, a multi-disciplinary team supported by the hospital administration carries out a range of essential functions, such as formulary restrictions, audit and feedback, education, development and implementation of standard treatment guidelines, and advice and planning of treatments.[94] Local surveillance data inform many of these activities. Effective antibiotic stewardship programmes have consistently shown significant cost savings and reduction in antimicrobial use, demonstrating that this can be a financially viable strategy for improving antibiotic use in hospitals. The stewardship approach is currently being followed in many health-care facilities in both wealthy and low-income countries.

It is important to recognize that a physician's ability to prescribe correctly can be compromised by a lack of laboratory diagnostic services or by poor laboratory performance, and failure to use the available diagnostic tests also promotes inappropriate use.

Education of health-care workers is an integral part of all AMR containment activities. Inclusion of appropriate use of antibiotics in curricula at both graduate and postgraduate levels, as well as continuing education on new developments in the field of antimicrobial therapy, have been achieved to varying extents in different countries (Box 3.5). Prescription audit or drug use evaluation, with feedback to prescribers, have been effective in changing behaviour with respect to the prescription and use of antimicrobials.[49]

Box 3.5 AMR in the undergraduate medical curriculum of the University of Zambia School of Medicine

In 2010, the University of Zambia School of Medicine revised their undergraduate medical curriculum. The topics of AMR and rational use of medicines were inserted prominently. The aim is that graduates enter clinical practice with the right skills and attitudes to be both effective practitioners and committed stewards of AMR containment.[95]

Political decisions to encourage appropriate prescribing and use of antimicrobials at facility level, and encouraging guideline-recommended treatment for specific indications, can have a powerful influence in changing national practices, as demonstrated in Sweden (Box 3.6).

Box 3.6 A new Swedish government initiative for improving the use of antibiotics

Incentives to encourage rational use at several levels in the health-care system are important. In 2010, the Swedish government announced a strong financial commitment to improve the use of antibiotics. That year, the average use of antibiotics in outpatient care in Sweden was 390 prescriptions per 1000 inhabitants. A new national target was set: a maximum of 250 prescriptions per 1000 inhabitants per year to be reached by 2014. Annual rewards would be shared between those of the 21 county councils that had formed a multidisciplinary working group with a clear mandate to coordinate local activities according to the model proposed by the Swedish Strategic Programme against Antibiotic Resistance (Strama[c])[96] Participants were to increase the level of compliance with treatment recommendations and reduce the numbers of prescriptions for antibiotics in accordance with annual targets.

It is also useful to introduce interventions targeting dispensers and other sellers, especially in areas where the implementation of regulations may be relatively weak (Box 3.7).

Box 3.7 Viet Nam – Improving private pharmacy practice in Hanoi

Following health sector reforms in Viet Nam in the late 1990s, private pharmacies became increasingly important sources of health-care delivery. Major public health problems such as sexually transmitted diseases and acute respiratory infections are treated with antibiotics regularly dispensed without prescriptions, often inappropriately.

A study of antimicrobial use was conducted in Hanoi from 1997 to 2000.[97] Among a total of 789 private pharmacies in the urban area, 68 were randomly selected and assigned to control or intervention groups. The intervention package consisted of three parts: regulation enforcement with inspection for prescription-only drugs; face-to-face education on pharmacy treatment guidelines; and group meetings of pharmacy staff. After the intervention, practices were monitored using a simulated client method and improvements were identified: there were significant reductions in antibiotic dispensing for acute respiratory infections, and dispensing of cefalexin without prescription decreased from 95% to 56%. Interventions of this type could have a significant impact, considering the high level of utilization of private pharmacy services by those seeking health care in Viet Nam.

[c] http://en.strama.se/dyn/,84,,.html

3.3 Civil society engagement to reduce the misuse of antibiotics

Patient-doctor contacts where patients are expecting an antibiotic to be prescribed, or where the physician assumes this expectation, are more likely to result in the prescription of an antibiotic, as several studies have shown.[98]

Self-medication, including the use of left-over antibiotics from previous treatment courses or sharing of unused antibiotics with others, occurs regularly and has been recognized as one of the contributing factors for inappropriate use.[84] Societal behaviour also influences self-medication by individuals: migrants from countries with relatively low antimicrobial use moving to a place where self-medication is practiced more readily, are more likely to carry out self-medication.[99] Direct-to-consumer advertising of medicines, as described earlier, is another factor influencing the behaviour of patients.[100]

There have been various attempts to educate the general public about the correct use of antibiotics.[101] Several clinical trials at the community level, mostly in the USA, have shown at least moderate benefits of educating patients on the use of antibiotics.[102,103] In several countries, public campaigns have been carried out on a larger scale (Box 3.8). As demonstrated in Thailand, engaging civil society organizations may be an important step to support the process of developing and/or implementing rational use policies, and in turn stimulate broader acceptance of recommendations on rational use.[104] A recently published guide to building coalitions at local and regional levels to address AMR aims to help stakeholders organize a collaborative effort to address drug resistance locally.[105] The priority interventions outlined in the WHO Strategy are coupled with advocacy efforts to achieve the critical mass of activity needed for a coordinated, multidisciplinary, coalition-based approach to containing drug resistance.

Box 3.8 **Public education campaigns in high-income countries**

In a recent review, a total of 22 public education campaigns to promote a more prudent use of antibiotics at national or regional levels in high-income countries between 1990 and 2007 were identified and the characteristics and outcomes evaluated. The campaigns were distributed in Europe (16), North America (3), Oceania (2), and Israel (1). In the USA, the *Get Smart* programme included more than 30 different regional campaigns. In most cases, the campaigns were part of a national strategy to reduce antimicrobial use. All campaigns focused mainly on respiratory tract infections and education was mostly symptom-oriented. The intensity of the campaigns varied widely, from simple use of internet distribution channels to expensive mass-media campaigns. Most campaigns that were formally evaluated appeared to reduce antibiotic use. However, the impact on AMR could not be assessed from the data available.[101]

3.4 International initiatives to influence rational use

WHO has played a lead role in attempts to improve the use of medicines. In addition to developing the model EML and carrying out surveys to assess the current AMR situation in general, and the specific role of irrational use as a contributor to resistance development, WHO provides published information and guidance in several areas related to improving antimicrobial use.

Containing AMR remains an important priority for public health actions and research for many bodies such as the European Commission and the European Centre for Disease Prevention and Control. There are policies, directives and recommendations to facilitate actions in its Member States and also several activities in this direction. Improvement of antimicrobial use is a core element of the European Community strategy to contain AMR.[106]

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established by presidential declaration in 2009 at the annual summit between the EU presidency and the US president. The purpose of the taskforce is to identify urgent antimicrobial resistance issues that could be better addressed by intensified cooperation

between the USA and the EU within key areas including appropriate therapeutic use of antimicrobials in both medical and veterinary practice.[22]

In addition, several agencies and nongovernmental organizations (NGOs) address different aspects of rational drug use promotion globally, including the Alliance For Prudent Use of Antibiotics[d], the Center for Global Development[e], the Global Antibiotic Resistance Partnership of the Center for Disease Dynamics, Economics and Policy[f], Strengthening Pharmaceutical Systems project of Management Sciences for Health[g], ReAct – Action on Antibiotic Resistance[h], and the South American Infectious Diseases Initiative[i]. Many national and international professional societies also promote rational drug use through their activities and working groups such as the one formalized by the International Society of Chemotherapy[j].[107]

4. Gaps and challenges

The main gaps and challenges that need to be addressed in global and national efforts to improve the use of antimicrobials include the following:

Lack of comprehensive strategies: Despite numerous activities and programmes addressing irrational use, many countries have yet to put in place coherent and comprehensive strategies to improve the use of antibiotics. Understanding the current situation in relation to recommendations made in the 2001 Global Strategy and as part of the 2011 World Health Day policy package, may support the planning of adequate sets of interventions. A multidisciplinary, nationally appointed group could help to engage constituents from the different sectors involved, such as health care, drug regulation, agriculture and animal husbandry, and civil society in taking the process forward. Political support is essential for such a group to carry out this complex task.[108]

Lack of adequate regulatory frameworks: Many countries do not have a solid legal and regulatory framework to mandate and support the rational use of medicines. Countries with weak regulatory systems are hindered with regard to ensuring access to quality medicines and securing the supply chain. Other relevant regulatory options include strengthening dispensing functions, and measures to curb the circulation of substandard and counterfeit drugs as expressed in the 2001 Global strategy and 2011 WHD policy packages.

Poor awareness at all levels: There is still a need to educate and raise awareness among those involved in antimicrobial use worldwide, including policy-makers, regulators, the pharmaceutical industry, prescribers, dispensers, consumers and donors, using locally relevant information. Local data on many factors related to irrational use are still lacking in most parts of the world and there is scope for more use of antibiotic stewardship programmes in hospitals to improve local use. Local factors that may affect prescribing decisions are many and may include (to varying degrees) previous education, behaviour of role models, economic incentives, patients' demands, availability of antibiotics, quality of diagnostic tests, drug promotion, availability of unbiased information on antibiotics, clinical guidelines and essential medicines lists, workload of prescribers, and supervision.

Insufficient education on AMR for professionals: Both graduate and postgraduate as well as continuing medical education on the appropriate use of medicines are deficient in many countries,[44] leaving many prescribers dependent on the pharmaceutical industry for up-to-date information on medicines. Face-to-face educational sessions as well as distance learning, electronic education and knowledge-sharing methods have tremendous potential to improve antimicrobial use.

[d] http://www.tufts.edu/med/apua/
[e] http://www.cgdev.org/
[f] http://www.cddep.org/projects/global_antibiotic_resistance_partnership
[g] www.msh.org/projects/sps/
[h] http://www.reactgroup.org/
[i] http://www.usaidsaidi.org/
[j] http://inventory.infectionnet.org/

Incentives that encourage overuse: In all situations where pharmaceutical sales constitute a direct source of income for hospitals, health centres and individual health-care providers, there may be non-medical incentives for prescribing medicines.[49,44] Financial incentives that encourage the overuse of antibiotics exist in both human and veterinary medical practice and in animal husbandry (Chapter 4).

Inadequate laboratory testing: Laboratory services for diagnostic testing are not readily available in many developing countries, and where they exist there is wide variation in the quality of testing. Novel diagnostic tools, especially point-of-care and rapid tests, could be expected to have a positive impact on antimicrobial use by reducing or eliminating empiric use and helping to minimize delays in initiating appropriate treatment.

Chapter 4.

Reducing the use of antibiotics in animal husbandry

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Antibiotics are used widely and in vast quantities to ensure the health and promote the growth of livestock, poultry and fish reared for food production. The fact that greater quantities are used in healthy animals than in unhealthy humans is a cause for serious concern, particularly as some of the same antibiotics are involved and food animals have been shown to carry resistant human pathogens. Some countries have banned the use of antibiotics as growth promoters but the practice remains widespread. Legislation and regulation with enforcement are needed to control the use of antibiotics for these purposes in many countries.

Summary

Antibiotics are used in greater quantities in healthy food-producing animals than in the treatment of disease in human patients. In animal husbandry, antibiotics are used extensively for disease prevention and as growth promoters, involving mass administration to many animals at the same time. This practice constitutes the main difference between the use of antibiotics in animals and in humans. Some of the same antibiotics or classes are in use in food animals and in human medicine, carrying the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and people. The importance of food animals as reservoirs of resistant human pathogens is well documented. The spread of resistance genes from animal bacteria to human bacteria is another potential danger. The problems associated with the use of antibiotics in animal husbandry, including in livestock, poultry, and fish farming, are growing worldwide without clear evidence of the need for or benefit from it, leading to increasing recognition that urgent action is needed.[109]

There appear to be major differences in the amounts of antimicrobials used per kilogram of meat produced in high-income countries, which together account for 70% of global meat production. Working groups hosted by WHO, the Food and Agriculture Organization (FAO), and the World Animal Health Organisation (OIE) have proposed options for actions to be taken by national and international authorities. Large-scale interventions are already being instituted in a number of countries, mainly aimed at reducing the use of specific classes of antimicrobial agents, especially those used in human clinical practice. The steps to be taken include the introduction and enforcement of regulations, methods to promote the prudent use of antibiotics, and measures to improve animal health so that less antibiotic treatment is needed. Several such interventions have led to a demonstrable reduction in AMR, though this is not always the case.

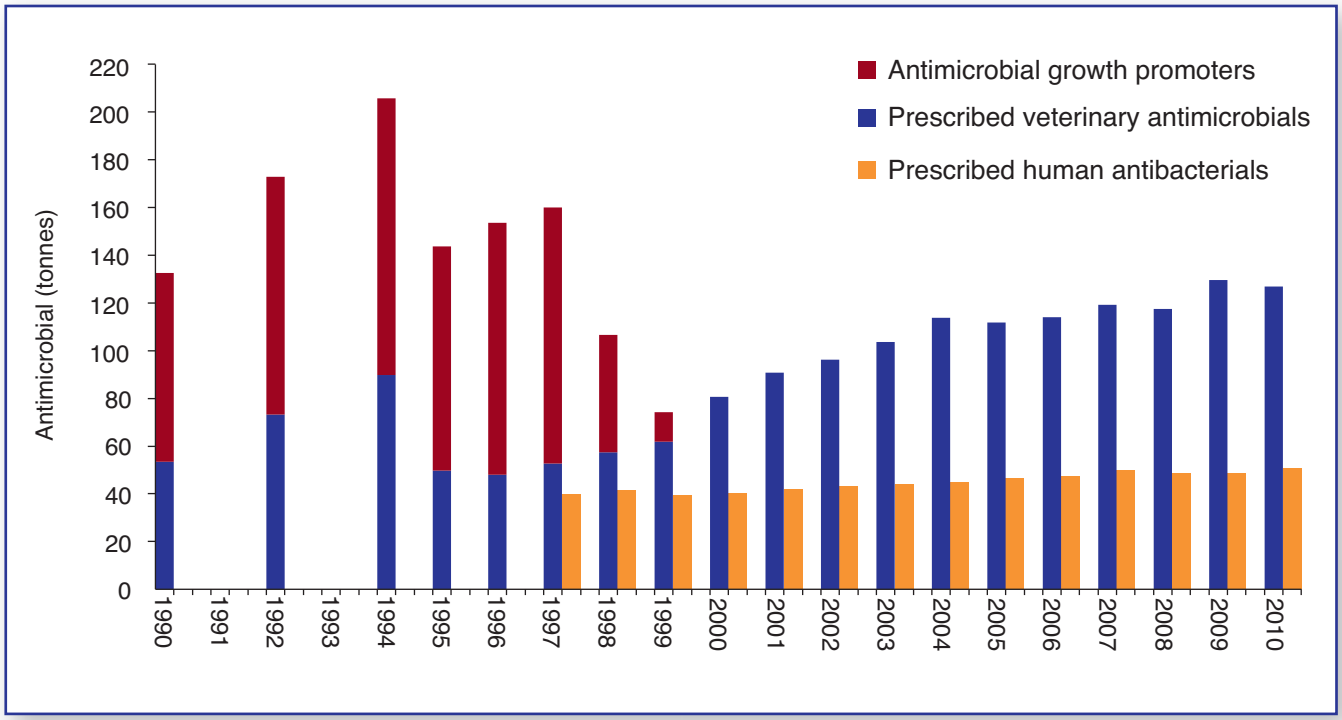
Important gaps and challenges remain. More information is needed on the prevalence of AMR in bacteria of animal origin and its impact on human health, on the quantity of antibiotics used for different indications and on the classes of antibiotics used. Risk assessments and risk management are impeded by a lack of data and/or inability to access available data. Legislations and regulatory frameworks for the approval of veterinary medicines and for controlling their use need strengthening in many countries. Capacity to implement interventions varies and the potential impact of specific interventions in different settings is largely unknown. This chapter considers the present situation and the range of options for action, citing examples of experiences with different interventions.

1. Reducing antimicrobial use in animal husbandry to reduce AMR

As in medical care for people, the introduction of antimicrobials was a significant milestone in veterinary practice. As in humans, these medicines are used for the treatment of infectious diseases in individual domestic pets and in farm and food-producing animals to ensure animal welfare and global food production. The development and spread of AMR is therefore also of concern in veterinary medicine. Furthermore, resistant bacteria carried by food-producing animals can spread to people, mainly via the consumption of inadequately cooked food, handling of raw food or by cross-contamination with other foods, but also through the environment (e.g. contaminated water) and through direct animal contact.

Use is the main driver for resistance in all of these situations. For companion animals such as cats, dogs and horses, the use is similar to that in general human medical practice, with individual animal treatment being the norm. The main difference between antibiotic use in humans and animals is seen in the context of food production, where there is mass administration of antimicrobials to many animals at the same time for the purposes of disease prevention and growth promotion. Such practices provide favourable conditions for the emergence, spread and persistence of AMR bacteria capable of causing infections not only in animals, but also in people. The antimicrobial agents used for food-producing animals are frequently the same, or belong to the same classes, as those used in human medicine. The total amount used in animals accounts for well over 50% of total antibiotic use, according to the available evidence (Figure 4.1).[21]

Figure 4.1 Annual antibiotic use for human and veterinary practice in Denmark



Source: Reproduced from [21] with permission.

The importance of food animals as reservoirs of AMR bacteria which are pathogenic for humans is well documented for zoonotic bacteria such as non-typhoidal *Salmonella enterica* serovars[110] and *Campylobacter* spp.[111] It has been frequently demonstrated that the use of antimicrobial agents in food animals favours the development of resistance among bacteria which can then be transmitted to people, and may cause infections and illness. Bacteria and resistance to critically important antimicrobial agents associated with food animals include: *Escherichia coli* and *Salmonella* spp resistant to 3rd and 4th generation cephalosporins and to fluoroquinolones; *Campylobacter* spp resistant to macrolides and fluoroquinolones; *Staphylococcus aureus* resistant to all beta-lactam-type drugs (i.e. MRSA); enterococci resistant to vancomycin (VRE) and *C. difficile.*

There are significant direct and indirect effects of antimicrobial use in animals on AMR in human pathogens, as several lines of evidence have indicated. Data are as yet insufficient to allow this relationship to be fully evaluated, but it is clear that action is needed to reduce the use of antibiotics in food animals, and to obtain further information on the impact on AMR. This chapter describes experiences with the implementation of some of the most important interventions worldwide, recognizing the differences in situations between countries and regions.

2. WHO guidance on reducing antimicrobial use in animal husbandry

The 2001 WHO Global Strategy for Containment of AMR includes specific recommendations on the use of antimicrobials in animal husbandry which are based on *WHO global principles for the containment of antimicrobial resistance in animals intended for food, 2000* (Box 4.1).[109] The recommendations include phasing out the use in food animals of antimicrobials which are used in human medicine, improving their use through regulation, education and guidelines, and monitoring use and resistance in this sector (Appendix1).[1]

Box 4.1 WHO principles for the containment of AMR in animals intended for food

- Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.
- Monitor resistance to identify emerging health problems and take timely corrective action to protect human health.
- Develop guidelines for veterinarians to reduce the overuse and misuse of antimicrobials in food animals.
- Require obligatory prescriptions for all antimicrobials used for disease control in food animals.
- 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 the treatment of humans.
- Create national systems to monitor antimicrobial use in food animals.

The importance of the problem and the urgent need to take action were again stressed during the 2011 World Health Day. The core actions called for in the WHD policy briefs include the creation and enforcement of an enabling regulatory framework, strengthening surveillance and monitoring, promoting education and training on antimicrobial use in food-producing animals, and reducing the need for antimicrobials through better animal husbandry. The needs for national leadership and intersectoral collaboration are also emphasized (Appendix 2).[2]

3. The present position regarding these recommendations

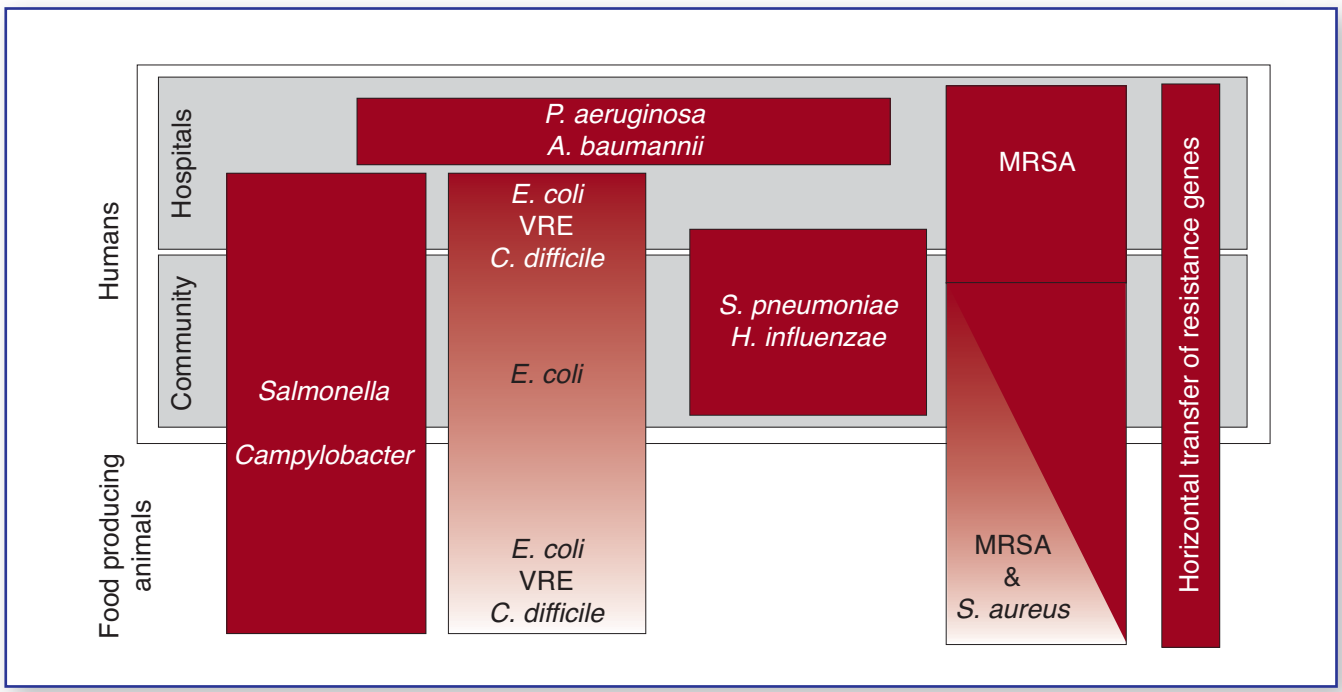
The following sections examine key factors in the role of antimicrobial use in food animals which contribute to the growing threat of AMR, and national and international actions taken to tackle the problem, illustrated by experiences from different parts of the world.

3.1 Increasing recognition of the problem of AMR through food of animal origin

Extensive and effective monitoring of AMR in animals is carried out in only a very limited number of countries, and frequently these monitoring systems are not comparable due to differences in methodology. However, AMR among bacteria of animal origin is certainly prevalent throughout the world, at varying rates in individual countries and regions. With increasing global trade in food products of animal origin, the numbers of reports documenting resistant bacteria spreading from one country to another through food, and thereby causing infections, are also increasing. The international spread of resistant pathogens calls for urgent global initiatives to minimize the risk of AMR bacteria developing and spreading from food animals to people, and further within communities and hospitals. Working groups hosted by WHO, FAO and OIE have reviewed these issues extensively and proposed options for action to be taken by national and international authorities.[109,112-114]

Figure 4.2 is a schematic overview depicting the overlap between different reservoirs for some AMR pathogens. While some are strictly confined to the human reservoir, others have a mainly or partially animal reservoir.[66]

Figure 4.2 Reservoirs of AMR bacteria causing human infections



Schematic overview of some of the most important antimicrobial resistant pathogens and the overlap between the different reservoirs. As indicated some pathogens are strictly confined within the human reservoir, whereas others have a mainly or partly animal reservoir.
Source: Reproduced from[66] with permission

The use of fluoroquinolones (e.g. enrofloxacin) in food animals resulted in the development of ciprofloxacin-resistant *Salmonella*, *Campylobacter* and *E. coli*, which have caused human infections and spread worldwide through travel and food trade. An increasing number of studies indicate that a major proportion of resistant *E. coli* that cause extra-bowel infections in humans may have originated in food animals, especially poultry.[115,116]

Since 2003, a new variant of MRSA has emerged and spread among food animals, primarily in pigs, in many countries. The importance of this new farm-associated MRSA for human health has not yet been fully assessed, but it is already a problem for the control of MRSA in some countries and the prevalence appears to be increasing.[117]

C. difficile colonizes many food animals and also causes disease in food animals such as piglets, with an associated high mortality rate[118] and has been found in 4.6%–45% of retail meat samples.[119] Since 2005, in the Netherlands and other countries, there has been an increase in community-acquired human infections caused by *C. difficile* strain types similar to those found in food animals.[120] Community human carriage of *C. difficile* is likely to increase the risk of *C. difficile* disease, especially among patients who enter health-care facilities and are treated with antibiotics. It may also increase the likelihood of *C. difficile* spores contaminating the hospital environment and spreading from person to person. However, the overall contribution of animal *C. difficile* to human disease is not well documented.

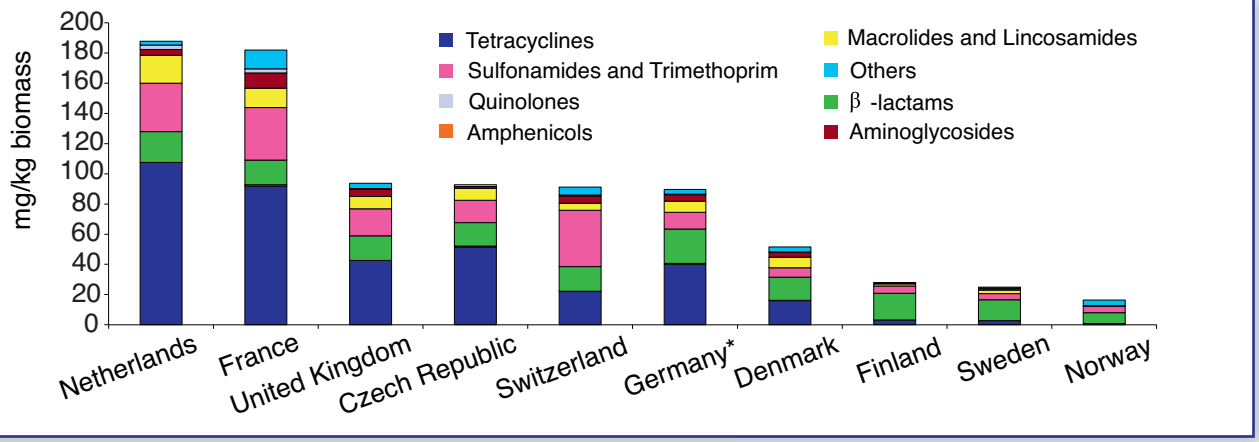
As well as selecting for resistant bacteria, the use of antimicrobial agents in food animals also selects for transferable resistance genes. This phenomenon raises the possibility that resistance genes could be transferred from animals to humans via non-pathogenic bacteria in food products, and that they could then be transferred to bacterial pathogens in the human gastro-intestinal tract. Consistent with this hypothesis is the presence of similar vancomycin and cephalosporin resistance genes in both human and animal bacteria.[121]

3.2 Antimicrobial use in food production

In modern food production systems, there is widespread and intensive use of antimicrobial agents. The impact of this practice may vary considerably between countries and regions, influenced by the interaction between human populations (social structure), land use, contaminated water sources, animal demography (species, distribution, and density), national policies (production, trade, food security, animal health, etc), and national and international trade. The production systems also vary between countries according to technological, social, and economic circumstances. More than 50% of the world's pork production and over 70% of poultry meat currently originate from industrialized countries.

In general, the quantities and classes of antimicrobials used in food animals today are insufficiently documented or controlled worldwide. Monitoring of antimicrobial consumption is carried out in only a limited number of countries and, with very few exceptions, this is restricted to total amounts used, and not categorized by animal species and antimicrobial classes. Initial crude estimates from different countries which do measure antimicrobial use show major differences in the amounts used per kilogram of meat produced (Figure 4.3). This implies that there is considerable scope for reduction in countries where the higher amounts of antimicrobials are in use.[122]

Figure 4.3 Estimated antimicrobial use to produce one kilogram of meat in different countries



Amounts in mg of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data
Source: Reproduced from [122] with permission from Oxford University Press.

Data on antimicrobial use are necessary for risk analysis, interpreting resistance surveillance data, and to assess the impact of interventions to promote prudent use. Sales data are the usual source of information on antimicrobial use. Data which can have an impact on policies and practice are very often lacking from developing countries, but Kenya is a notable exception where both the total amounts and the classes of antibiotics are monitored: from 1995–1999, Kenya used on average 14 594 kg of antibiotics distributed as 7975 kg of tetracyclines, 3104 kg of sulfonamides, 955 kg of aminoglycosides, 905 kg of betalactams, 94 kg of quinolones, 35 kg of macrolides and 24 kg of others, including tiamulin.[123]

Depending on the species of animals, periods of higher risk for infection can be identified. For example, when animals from different origins are assembled and first placed together, physiological stress is at its highest level and there is increased potential for inter-animal transmission of infections. Antimicrobial prophylaxis of all animals is often carried out to prevent clinical disease in such situations. In some countries, mass treatment is timed to an epidemic (either started or expected), a practice termed "metaphylaxis". The regulatory status of such use often resides on the fringe of labelled use for the 'control' of disease. To facilitate administration to a large number of animals, oral routes (water and/or feed) are used in addition to parenteral injections. Prophylaxis and metaphylaxis practices need to be carefully assessed to find an appropriate balance between the need to prevent diseases during high-risk periods and the potential to contribute to AMR.

3.3 Actions being taken worldwide

Awareness of the risks for human health which can result from the use of antibiotics in animal husbandry appears to be on the increase, as evidenced by the many media reports and scientific publications on this topic in recent years, and the large-scale interventions which are being instituted in different parts of the world.

There are several international networks which coordinate AMR surveillance in human and animal populations (see Chapter 2). The WHO-Global Foodborne Infections Network (GFN) and the international molecular subtyping network for foodborne disease surveillance (PulseNet International[a]) are examples. The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) has developed guidance documents for global standardization of methods for monitoring AMR and antimicrobial use in food animals[b].

[a] http://www.pulsenetinternational.org/Pages/default.aspx
[b] http://www.who.int/foodborne_disease/resistance/agisar/en/index.html

Most interventions are aimed at reducing the use of specific classes of antimicrobial agents in food animals, especially those classes which are used in human clinical practice. The measures which have been implemented include the introduction and enforcement of regulations governing the use of antimicrobials, methods to promote the prudent use of antibiotics by end-users, and measures to improve animal health so that less antibiotic treatment is needed.

Regulations to restrict the use of antibiotics in animals

National and international efforts to control AMR require a firm legal and regulatory foundation on which measures can be introduced and enforced. Regulations can contribute at many levels, from licensing to end use of antimicrobials. While regulatory frameworks exist in most countries, there are differences in the extent to which regulations are implemented. In most countries, veterinary pharmaceutical products undergo a licensing process that assesses the risk/benefit balance of the proposed products, similar to the process followed for human use products. For antimicrobials, an evaluation of the potential impact on human health is also included in many countries. Initially this evaluation focused on avoiding antimicrobial residues in food products, but more recently it has been extended to include effects on AMR in bacterial populations in slaughter-ready animals. The approval process may also include consideration as to whether specific antimicrobials are of critical importance for human health,[124] often with measurable impact on AMR (Box 4.2). WHO has categorized antimicrobials which are critically important for human use.[125] However, current national legislations do not always restrict the use of such critical antibiotics in animals.

In many countries, it can be difficult to withdraw approval for an already licensed pharmaceutical product. However, it is often possible within the existing legislation to implement restrictions on the approved usages of licensed antimicrobials (Box 4.2). For example, it is possible to limit off-label / extra-label use or to restrict use to individual animals.

Box 4.2 **Approval and regulations on use of antimicrobials of critical importance**

The U.S. Food and Drug Administration successfully withdrew the approval of fluoroquinolones for use in poultry on 12 September, 2005.[126] To achieve the withdrawal, the agency had to demonstrate that the use of enrofloxacin in poultry causes the development of fluoroquinolone-resistant Campylobacter in poultry, that these fluoroquinolone-resistant organisms are transferred to humans, that they may cause the development of fluoroquinolone-resistant Campylobacter in humans, and that fluoroquinolone-resistant Campylobacter infections in humans are a health hazard. The process began in 2000, involved the collection and evaluation of thousands of studies, expert testimony, an oral hearing, and a complex risk assessment.

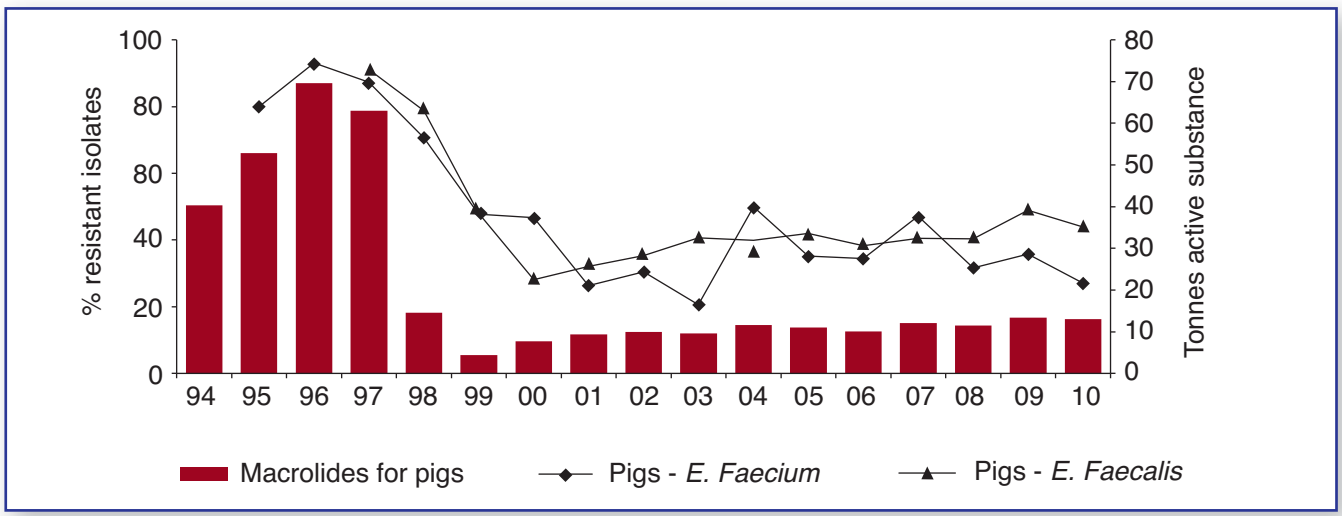
In Australia, fluoroquinolones (e.g. ciprofloxacin), which are antimicrobials of 'critical importance' in human use, have never been approved for use in food production animals. Fluoroquinolone-resistant bacteria are either at very low levels or else non-existent in food animals and resistance is very low in Australian human bacterial isolates in comparison with other countries. Data from the Australian Group on Antimicrobial Resistance 2006 surveillance report show fluoroquinolone resistance in 2006 to be less than 5% in clinical isolates of Gram-negative bacilli.[127]

The approval of fluoroquinolones for use in food animals in 1993 in Denmark saw the rapid emergence of resistance to this class, with 23% of C. coli isolates from pigs found to be resistant during 1995 to 1996. Consequently, in 2002 restrictions were imposed on the veterinary use and prescription of fluoroquinolones for food-producing animals: fluoroquinolones could only be used in food-producing animals for the treatment of infections proven by laboratory tests to be resistant to all other antimicrobials, and administered only by injection by a veterinarian, with the use reported to the regional veterinary officer. This reduced fluoroquinolone use in animals in Denmark from 183 kg in 2001 to 49 kg in 2006 and it has remained low since then. Resistance was detected in just 12% of C. coli isolates from pigs tested in 2009.[21]

Restrictions on the mode of administration could be another useful means of limiting use in animals, particularly for antimicrobials that are critically important for human use, for example, by limiting them to injection-only. However, this type of restriction is applicable in individual animal treatment, but may not always be feasible for large numbers, for example in poultry flocks.

Increasing numbers of countries are banning the use of antibiotics as growth promoters, a very positive development which has been highlighted in recent media reports. Experiences following cessation of use of antimicrobial agents are encouraging. By January 2000, the use of all antimicrobials as growth promoters had been prohibited in Denmark. This has resulted in an overall reduction in resistance among bacteria in animals. The temporal association between the reduction of macrolide use and the prevalence of AMR among enterococci isolated from pigs in Denmark is shown in Figure 4.4. Resistance will probably never return to pre-antibiotic use levels, and so consumption of antimicrobials needs to be kept at low levels as excessive use could again rapidly drive AMR upwards.

Figure 4.4 Macrolide use and resistance among *enterococci* in pigs, Denmark

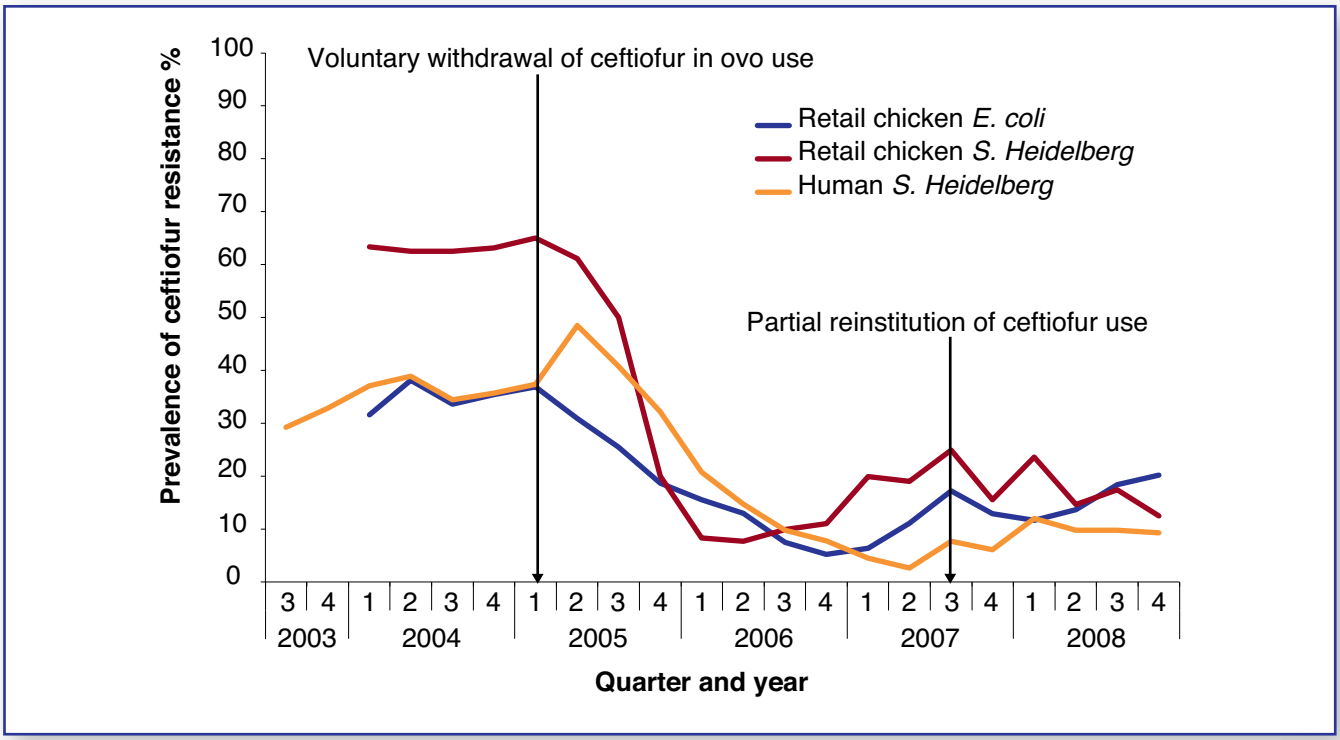


Source: Reproduced from [21] with permission.

In 1995 a ban of the growth promoter avoparcin (a glycopeptide) which selects for vancomycin-resistant enterococci (VRE) in Denmark led to a reduction in the prevalence of VRE among animals and in the general human population. However, VRE has persisted for up to 12 years in poultry farms after the ban and is likely to persist for many more years. The complex relationship between reducing use and the levels of resistance is being explored.[128-130]

Experience has shown that any negative effects due to the prohibition of growth promoters are minimal in the long term, once industry adapts to the changes.[131] Apart from prohibitions on the use of antibiotics in food animals, there have also been a number of voluntary withdrawals. In Canada and the USA, ceftiofur, a 3rd generation cephalosporin, may legally be used in an extra-label manner for routine administration into eggs or one day-old chicks in hatcheries, to prevent infections. Surveillance in the province of Quebec, Canada, demonstrated a marked increase in the prevalence of resistance to 3rd generation cephalosporins and penicillins among *S. enterica* serotype Heidelberg isolates from humans and chickens in early 2005. A survey of antimicrobial use in hatcheries in Quebec confirmed that in 2004 all chicken hatcheries switched to exclusive use of ceftiofur. In early 2005, Quebec hatcheries stopped this use voluntarily, after which there was a dramatic decline in the prevalence of ceftiofur resistance (Figure 4.5). Anecdotal reports indicate that the industry has subsequently re-introduced alternating use of ceftiofur with other antimicrobials, and that this has been followed by a resurgence of resistance.[132]

Figure 4.5 Cephalosporin resistance after stopping its use in poultry in Quebec, Canada



Source: Reproduced from [132] with permission.

Unfortunately, there are few incentives to encourage voluntary withdrawal of growth promoters and no barriers or sanctions for re-introducing them.

Easy access to antimicrobials through sources such as online pharmacies, animal feed outlets and pet shops contributes to their overall excessive use and makes it increasingly difficult to enforce regulations on the use of these products.

Financial incentives

Ideally, sales of an antimicrobial should never involve financial benefit for the prescriber. Limitations on the sales profits obtained by veterinarians in Denmark from 1994 to 1995 led to major reductions in the therapeutic use of antimicrobials, especially tetracyclines, without any obvious overall harm to animal health.

Prudent use guidelines and education

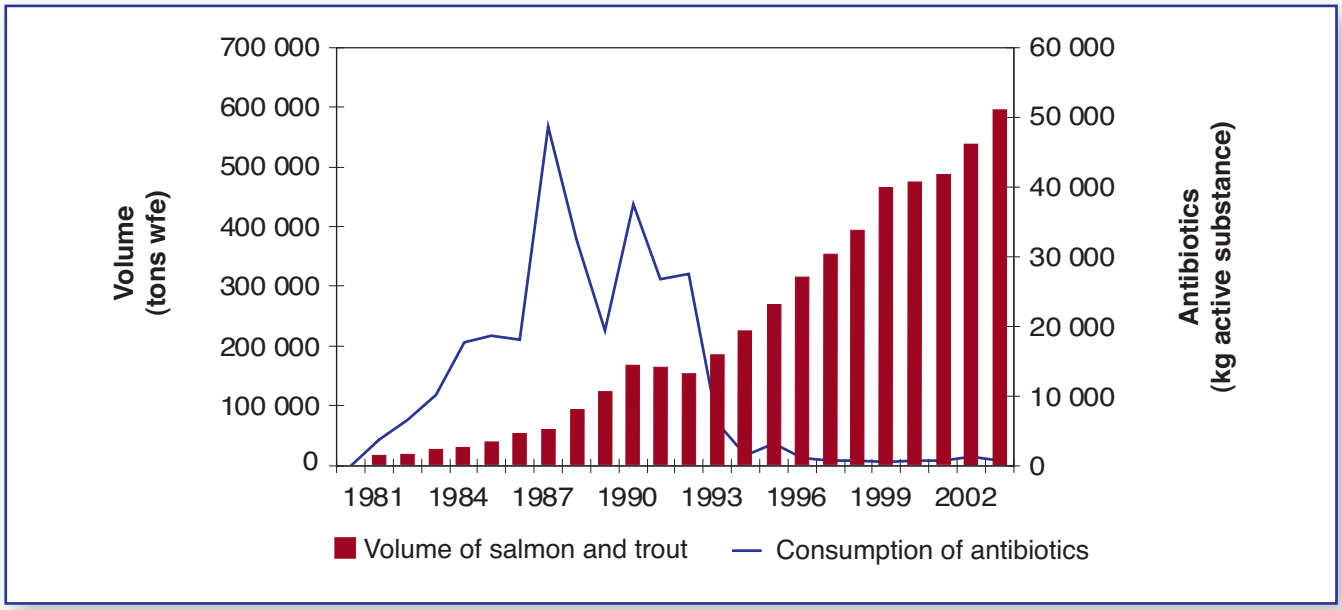
To reduce inappropriate use and promote prudent use, developing treatment guidelines and popularising them among veterinarians and farmers is likely to be helpful. Prudent use guidelines have been issued in the Netherlands (1986), Denmark (1998), USA (1999/2000), Germany (2000), and in many other countries more recently. However, the influence of these guidelines has not been monitored adequately, for example the Netherlands is still among the highest users of antimicrobials in food animals in Europe.

Improving animal health to reduce the need for antibiotics

The most effective means to reduce the use of antimicrobials and thus prevent AMR is to reduce the need for antimicrobial treatment. This could be achieved by improving animal health through measures such as immunization against prevalent infections. In Norway, the introduction of effective vaccines in farmed salmon and trout in 1987 and improved health management reduced the annual use of antimicrobials in farmed fish by 98% between 1987 and 2004 (Figure 4.6).[133] Many countries and

the EU already have regulations in place to enforce and promote vaccination as a method of reducing infections in food animals. However, even if health improves, it is not certain that established practices and consumption will change, since most antimicrobial agents for growth promotion and prophylaxis are used without any evidence of the need for, or benefit from, their use.

Figure 4.6 Reduction in antimicrobial use after the introduction of vaccination in aquaculture



Wfe: whole fish equivalent.
Source: Reproduced from [133] with permission.

Improving hygiene in food production

The FAO/WHO Codex Alimentarius[c] provides recommendations for many aspects of food production including hygiene, from primary production through to final consumption, highlighting the key controls at each stage. It recommends a *Hazard Analysis and Critical Control Point (HACCP)* approach. Good agriculture practices particularly at the farm level have also been defined. The Codex Task Force on Antimicrobial Resistance recently developed a risk analysis and management tool to assess the risks to human health associated with foodborne antimicrobial resistance.

In 2006, the EU put in place a programme with specific targets for reduction in salmonella contamination. Based on data from 27 EU Member States in 2009, 18 have reached the EU reduction targets in breeding flocks of fowl and the decreasing trend in human salmonellosis cases is continuing.[134] Microbiological criteria for a maximum acceptance level for certain types of AMR *Salmonella enterica* in food animals have been implemented in Denmark. The impact of these interventions has not yet been fully evaluated but Denmark has a low rate of domestically-acquired salmonella infections.

Applying advances in data management technology

Herd Health and Production Management (HHPM) programmes have been used to improve productivity

[c] http://www.codexalimentarius.org/

incrementally, mainly in intensive production systems. HHPM monitors the interaction between farm management, herd health and production, and integrates these components in order to obtain optimal results. These programmes use computer-based Management Information Systems (MIS) and the databases thus developed could direct attention to AMR and allow recognition of the contributions of local management, and of environmental and biological factors, to the development of AMR (Box 4.3).

Box 4.3 **Computer-based monitoring of antimicrobial use and resistance to improve production**

The MIS database used in Costa Rica records both prophylactic use (uterine infusion after artificial insemination, dry-off treatment etc), and therapeutic use (disease treatment, mastitis treatment, uterine infusions, etc) of antimicrobial agents in cattle. It includes a module for drugs, which allows the personnel responsible for use to register the drug used. This module enables data gathering for surveillance of antimicrobial use, AMR, and monitors the actions of veterinarians and/or producers. Similar HHPM programmes could be used more widely to monitor AMR at farm level, and correlate the data with environmental and managerial aspects to identify risk factors for AMR.

4. Gaps and challenges

Data on AMR associated with animal husbandry: The extent of AMR in foodborne bacteria, and the global burden of human infections due to such bacteria, are unknown. Continuous and updated information on foodborne pathogens, their spread and the status of AMR is necessary to guide risk profiling, risk assessment and risk management and to measure the impact of interventions. However, very few countries appear to have these monitoring systems in place, and where data are collected, they are often not comparable because of methodological differences (Chapter 2). Regional and national laboratory networks using standard methods would alleviate this situation.[135] There is scope for widening participation in existing networks and for strengthening the capacity of the participating laboratories. Databases could also be usefully improved to include phenotypic and genotypic features of the bacteria being monitored.

Data on quantities used: Data on total volumes of antimicrobials used and the indications for which they are used are also limited. The use of antimicrobials in animal husbandry is generally not based on sound scientific principles. Although use for growth promotion is being reduced in many countries, the practice is still widespread in many parts of the world. Correct use for prophylaxis and metaphylaxis is the subject of ongoing debate, and more could be done to limit antimicrobial use in these areas. The agents used and the modality of use differs widely between countries and within countries. OIE has published a list of critical antimicrobial agents needed for animal health[136] with an overview of the agents used and considered important in different countries.

Regulatory provisions: In many countries, the legal and regulatory framework to control the use of antimicrobials in animals could be strengthened. Regulations governing the approval of veterinary medicines and restrictions on their use are often lacking, or not adequately enforced. Restricting the use in food production animals of antibiotics that are "critically important" for human health is recommended by many experts and authorities. Currently, WHO gives priority to restricting the use of 3rd generation cephalosporins and fluoroquinolones.[125] Regulations could also include provisions for prohibiting for animal use any new drug class developed for human medicine, and of those that are used only in human medicine (e.g. linezolid, daptomycin, carbapenems, glycopeptides). Regulations also have a potentially valuable role in supporting compliance with the international standards for food safety practices in the production of food of animal origin, developed by the FAO/WHO Codex Alimentarius and OIE.

Data for registration of antimicrobials: It is standard practice for regulatory agencies to require data on the efficacy of a new medicine prior to registration, but these data are rarely available in the public domain.

This particularly applies to older products that have not been subjected to recently-introduced rigorous approval processes. Pharmacovigilance systems in place in many countries include the obligation to declare lack of efficacy, which could be a problem with drugs that have been in use for a longer period of time.

Routine, usually qualitative, assessments of risks for developing AMR are now incorporated into the pre-market authorization process for veterinary antimicrobials in some countries. However, these assessments are made difficult by the complexities of the producer-to-consumer continuum and lack of data in several important areas. Positive, albeit modest, developments include quantitative risk assessment for specific antimicrobial/organism combinations (e.g. fluoroquinolone resistance in *C. jejuni*). Improvements in methodologies for risk assessment, risk management and risk communication could be beneficial and additional guidance in this area from Codex Alimentarius would be helpful. The application of such guidance at national/regional and international levels could be improved.

Evaluation of impact: The potential impact of different interventions in different settings is still largely unknown. Measuring impact on food safety, enteric and other zoonotic diseases in people, animal health, animal productivity, national economy and other indicators at the regional/national level requires standardized indicators and sustainable capacity for monitoring AMR and antimicrobial use. At a local level, the impact could probably be determined by targeted research studies, and meta-analyses of such available global data could prove useful.

Capacity to respond to AMR: National capacity to respond to problems due to AMR is not uniform at either country or local level. Capacity at farm level is lacking in many countries, for reasons such as a lack of effective organizational structure, trained personnel, and sufficient knowledge about the risks involved. To improve this situation, instruments to guide the characterization and evaluation of institutional and operational capabilities, measure advancement, and propose strategic actions for technical cooperation have been developed by the Pan American Health Organization (PAHO)[d].

Application of modern technologies: Available technologies could be better harnessed to analyse local situations and risk factors, and for effective communication including the improvement of existing communication networks to disseminate already available information. The possibility of developing new vaccines, particularly against the infections for which most antibiotics are being used, such as gastro-intestinal infections in pigs and calves, mastitis in cattle and *E. coli* infections in poultry, could be explored. Another possible option is the development and evaluation of probiotics, which are probably valuable alternatives to antibiotics in the control of gastro-intestinal infections in food animals.

Selection of appropriate interventions: Different commodity groups in different settings may require different interventions. For example an intervention to reduce resistance in 180-day swine system may not be directly applicable to a 42-day broiler chicken system, and interventions suited to extensive agriculture are unlikely to be of equivalent efficacy in intensive settings. Thus, the choice of interventions could be based on a process of identification, analysis and prioritization of needs and options which could include the introduction and/or enforcement of regulations on the use of antimicrobials in animals; measures to improve animal health; promotion of prudent antimicrobial use; strengthening hygiene in the food chain; and specific targeted measures in areas with a higher risk of AMR development or serious consequences.

Capacity building activities including staff training are still needed in many places. Public education on issues related to the use of antibiotics in food-producing animals may be needed to raise awareness of the potential harm and unclear benefit from their use in agriculture and aquaculture.

[d] http://www.paho.org/English/AD/DPC/VP/fos-program-page.htm

Chapter 5.

Infection prevention and control in health-care facilities

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Infection prevention and control in health-care facilities

As the centres where the most serious illnesses are treated, hospitals are unfortunately also where antibiotic-resistant infections are particularly likely to develop and spread. Infections acquired in hospitals and other health-care facilities (nosocomial infections) caused by resistant bacteria exert a heavy toll in terms of illness and mortality, as well as added direct and indirect costs. The key to limiting the risk lies in the meticulous application of measures for the prevention and control of infection.

Summary

The hospital environment favours the emergence and spread of resistant bacteria. In Europe, the death toll from health care-associated infections (HAI) caused by multidrug-resistant bacteria is estimated to exceed 25 000 per year and the death rate may be higher in other parts of the world. In addition to human suffering, the consequences of AMR also result in higher direct and indirect financial costs.

Infection prevention and control (IPC) measures are designed to prevent the spread of pathogens, including those with AMR, within and between health-care facilities, and from facilities to the community, and also vice versa. This was emphasized in the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance and in the 2011 World Health Day policy briefs. Interventions to bring about system change in individual health-care facilities involve organizational structures, human resources, guidelines, protocols and practices, monitoring and evaluation, infrastructure, and linking to public health services. In addition to the standard IPC measures, there are specific recommendations concerning AMR pathogens.

Many facilities and countries have progressed well in implementing recommendations on IPC and there have also been several welcome innovations recently in the field of IPC, as outlined in this chapter. WHO has led and coordinated the development of guidance on core components of IPC, based on evidence-based principles. However, there are considerable differences within and between countries in the extent to which IPC measures are implemented. Health-care facilities in some countries lack even the basic elements of IPC. Situation analyses at national and facility levels would help to define the current status, to set realistic goals for the local context, and to develop strategies for progressive improvement.

The gaps and challenges include: lack of data related to HAI and inadequate laboratory capacity in many parts of the world; lack of uniform standards, data collection methods and definitions; insufficient information on the effectiveness of specific interventions and the resources needed for effective and sustained implementation. This chapter examines the situation and options for action to improve it.

1. Infection prevention and control within health-care facilities to contain AMR

Bacteria which develop resistance to antibiotics can spread in the health-care facility environment and beyond. The spread of resistant pathogens in hospitals and other facilities contributes significantly to the increasing global burden of AMR. Infection prevention and control measures are designed to reduce the

spread of microorganisms within and between health-care facilities, and from there to the wider community, thereby preventing further infections and antimicrobial resistance spread. Preventing infections due to resistant bacteria is the ultimate goal of all AMR containment activities.

There is considerable evidence that resistant organisms evolve, survive, spread and cause infections within health-care facilities. For example, MRSA was recognized initially in a few hospitals; subsequently it became endemic in many health facilities around the world, and some strains are now also causing infections in the community. The spread of resistant bacteria is facilitated by the transfer of patients between wards within a hospital and between different hospitals (or other facilities), and more widely by travel, including medical tourism.

The health and economic burden due to AMR infections in hospitals varies between different countries and regions. In Europe, the death toll from multidrug-resistant bacterial hospital infections is estimated to exceed 25 000 per year. Infections due to selected multidrug-resistant bacteria in the EU are estimated to result in extra health-care costs and productivity losses of at least €1.5 billion each year.[8] In the USA, health care-associated infections are implicated in more than 99 000 deaths per year.[137] Although most available data on HAI and AMR infections come from high-income countries, the burden is likely to be even greater in low-income countries, as reported in several published studies. Pooled data show the prevalence of HAI in such settings to be 15.5 per 100 patients (95% CI 12·6–18·9) and the incidence in adult intensive care units as 47.9 per 1000 patient-days (95% CI 36·7–59·1). Methicillin resistance was found in more than 50% of *S. aureus* isolates, although this varies widely.[138]

In individual health facilities, several factors may contribute either to the spread or to the containment of AMR: these include infrastructure of the hospital, policies, protocols and practices, staffing numbers, skill-mix and health-care worker behaviour. Other patient-related factors, such as severity of illness and predisposing medical conditions, would be difficult to modify, whereas factors relating to health-care workers' performance and attitude, work processes and institutional infrastructure can be influenced successfully, provided there is support from local and national political decision-makers.

The long-accepted standard measures to prevent and control infections in health facilities also form the essential basis for preventing the spread of AMR, but they may need to be supplemented with additional measures. To ensure that standards are implemented and maintained, multimodal and multidisciplinary interventions may be needed to bring about a system change in individual facilities and in health-care worker behaviour. There are also some special considerations related to resistant pathogens, such as additional isolation standards and specific barrier precautions. AMR pathogens colonize far more people than they actually infect, and successful IPC strategies need to include measures for colonized patients in order to reduce the development of infections.[139,140]

IPC can bring added benefits through preventing infections, which reduces the need for antibiotic therapy and hence reduces antimicrobial use.

2. WHO guidance on infection prevention and control to contain AMR

The importance of IPC is recognized in the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance, which recommends the establishment of IPC programmes in all hospitals (Appendix 1).[1] The need for coordination of IPC activities at hospital levels and the education of staff is stressed.

The growing evidence for the spread of AMR infections in health-care facilities, between facilities and across borders has revealed many deficiencies in infection prevention and control in facilities around the world. In recent years WHO and many other agencies have focused on the need to identify priorities in IPC and to stimulate actions to improve the existing situation. Consequently the strategies to enhance IPC were further elaborated in the World Health Day 2011 policy briefs (Appendix 2),[2] which emphasize the need for IPC in all health facilities, addressing the essential components such as infrastructure and organizational aspects, laboratory support, human resources, protocols and practices, surveillance, monitoring and evaluation, and linking these to public health services.

3. The present position regarding these recommendations

Many facilities around the world have made good progress in implementing recommendations on IPC, but there are still marked differences in the level of implementation within and between countries. The reasons for these differences may include the degree of commitment, the financial situation, human resource availability, access to materials, as well as historical and cultural factors. Since 2005, through the First Global Patient Safety Challenge, WHO has appealed to Member States to pledge their support for the implementation of measures to reduce hospital infections in their countries, and thus far at least 125 have made such pledges, but their progress in implementation is yet to be mapped[a].

Progress related to the elements needed for IPC are summarized in the following sections using the concepts *core elements of IPC* (the long-accepted measures such as hand hygiene, environmental cleaning, sterilization, disinfection, and others) and measures where evidence for impact on AMR has been assessed at least in some studies.

3.1 Implementing IPC core elements in health-care facilities worldwide

Many recommended interventions are to be implemented at the health facility level, but central government authorities and policy-makers have a critical role in facilitating and ensuring that this takes place. Application of the core elements of IPC in each facility is the essential first step in infection prevention and control and also in preventing the spread of resistant microorganisms. As outlined in the 2011 World Health Day policy brief (Appendix 2) and in the WHO *Core components for IPC programmes*,[141] several fundamentals need to be addressed, including infrastructure and design of facilities, organizational structure, equipment and instruments, staff numbers and training, protocols and practices. Several nations/subnations around the world, especially in high-income countries, already meet many of the recommendations and have appropriate practice guidelines and standard operating procedures in place as relevant for each facility, and these are being implemented meticulously in many cases. IPC is also applied increasingly in primary and ambulatory care.

The roles, responsibilities and activities of national authorities in implementing functioning IPC programmes at facility levels have been proposed by WHO and EU Expert groups (Table 5.1).[141-143] National authorities have important leadership roles in developing policies, recommendations and guidelines, in making the necessary trained personnel available, in facilitating implementation in all health-care facilities, and in monitoring progress and providing feedback. Protocols and tools are already available from different sources, but choosing those most appropriate and modifying them to meet local needs would need coordination and support from the central authority.

[a] http://www.who.int/gpsc/statements/en/index.html

Table 5.1 Roles and activities at national and facility levels, as proposed by WHO and EU expert groups

Level	Activity
National	• Funded and functioning programme to improve IPC in all facilities • A functioning national advisory committee for IPC • National guidelines available for improving IPC specifically addressing AMR • A national standard for human resource requirements for improvement of IPC • Oversight on employment of designated IPC personnel, access to accredited microbiology laboratories, facilities for detailed testing and characterisation • Annual reports evaluating surveillance data on HAI and AMR • Official statement on the legal accountability of hospitals for IPC • Control mechanisms to ensure that reimbursement regulations for hospitals are not contradictory to the aim of improving IPC and reducing AMR • IPC indicators included in national health-care quality improvement • Audit of individual facilities, on the basis of indicators, and summary prepared • IPC education in relation to AMR included in medical and nursing curricula
Health Facility	• A functioning IPC programme and a multidisciplinary IPC committee • Local policies and practice protocols available on standard precautions, isolation precautions, screening for resistant organisms • Appropriate facility infrastructure to support and operate IPC and AMR interventions • Regular education programmes on IPC in general and in relation to AMR • An ongoing programme for promotion of IPC methods, e.g. hand hygiene • Monitoring compliance with IPC methods and regular feedback to HCW • Annual progress report issued on AMR pathogens, infections and HAI rates • Access to an accredited microbiology laboratory

HAI: Health care-associated Infection, HCW: Health-Care Worker, IPC: Infection Prevention and Control
Source: adapted from [141-143] with permission from the World Health Organization and Elsevier.

In many parts of the world, implementation of even the most basic recommendations poses tremendous challenges. Differences between countries in the existence of effective IPC practices within their facilities contribute to glaring inequities related to health-care delivery. These differences extend as far as IPC measures related to environmental hygiene and sanitation, which are proven to be important in reducing AMR spread and infections.[144]

Overcrowding, inadequate infrastructure, insufficient trained personnel, limited access to commodities needed for IPC, and limitations in financial resources are all barriers to the implementation of IPC recommendations. With such wide variations in the levels of IPC implementation, situation analyses at national and facility levels would help to obtain an overview of the current situation, so that realistic goals could be set according to the needs and opportunities

within the local context, with strategies for progressive improvement.

Education of health-care workers in IPC is being carried out in many countries with positive effects. WHO provides guidance on IPC elements to be included in education programmes for health-care providers in the *Patient Safety Curriculum Guide: Multi-Professional Edition*.[145] Another positive measure is the education of patients on infection prevention, which is being undertaken in some countries.[146] Many national and international professional societies also play an important role in knowledge sharing and in promoting IPC as part of medical and nursing curricula.

3.2 Implementation of measures and impact on AMR pathogens

The measures for which the impact on AMR pathogens has been studied include hand hygiene, contact precautions, screening measures, readmission alert systems, patient placement, decolonization, education and environmental cleaning. They have been used with varying degrees of success to stop outbreaks and decrease the disease burden due to resistant pathogens.[139] Evidence for the effectiveness of individual measures to contain AMR is limited, because studies to determine their comparative effectiveness cannot be carried out for ethical and practical reasons. Most of the evidence for impact of IPC measures comes from experience with MRSA-related interventions, and to a much lesser extent from glycopeptide-resistant enterococci. There is relatively little published information on IPC measures specific for Gram-negative resistant organisms, although this situation is changing rapidly.[139,140]

Implementation of a selection of these measures for AMR reduction is discussed in the following sections.

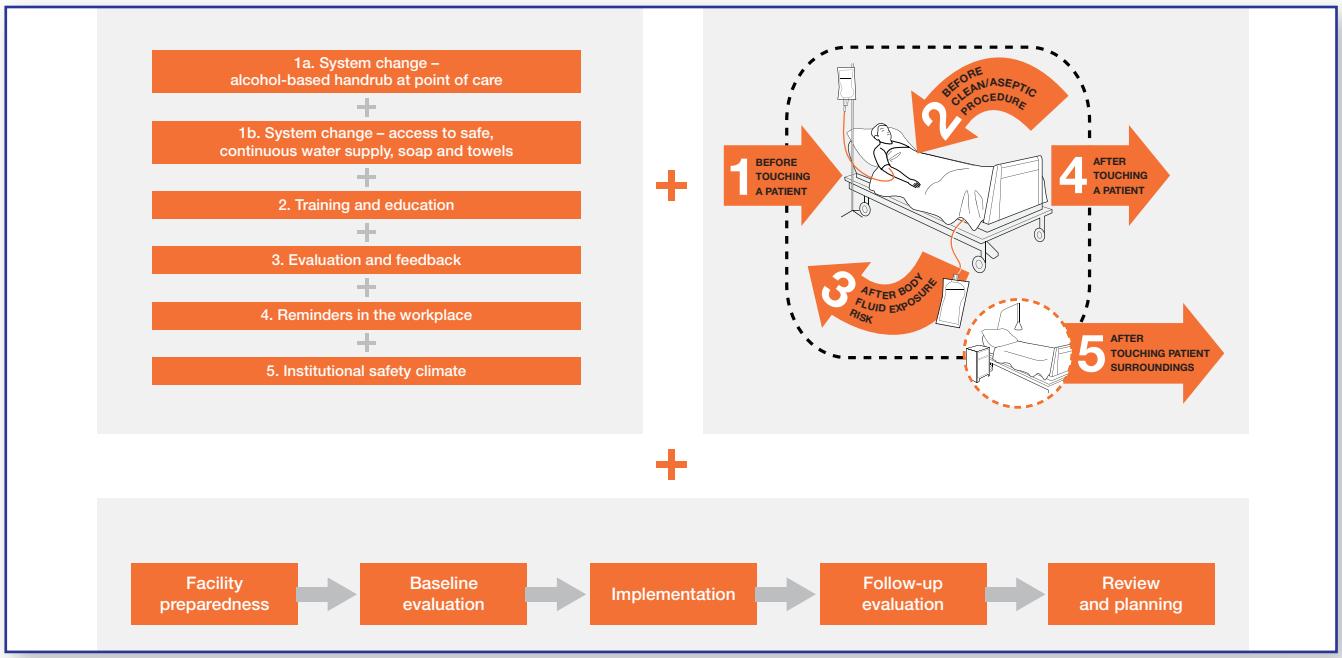
Hand hygiene

Transmission of resistant pathogens from patient to patient via the hands of health-care workers is a common occurrence, particularly in hospitals. Hand hygiene therefore remains one of the most effective, yet simple and cost-effective means for reducing the transmission of infections. Several reports confirm that improvement in hand hygiene greatly reduces the transmission of MRSA and other resistant organisms, and also saves costs and the use of additional resources. Guidelines consistently recommend hand hygiene as an essential method of controlling the spread of infections including those with AMR.[147] The WHO Patient Safety Programme designated the improvement of hand hygiene in all health-care facilities worldwide as the main element of the first Global Patient Safety Challenge.[b] The WHO *Guidelines on Hand Hygiene in Health Care* and the accompanying tools are examples of resources to promote hand hygiene, measure compliance and document progress in implementing a multimodal strategy[c].

The "My Five Moments for Hand Hygiene" concept proposed under this Challenge helps staff to understand the indications for hand hygiene during routine patient care and is intended to improve compliance. The multimodal strategy has five components (Figure 5.1).[148,149] Also under this Challenge, a network of over 45 national/subnational campaigns and programmes promoting hand hygiene in health care is coordinated. While they differ in their scope and range of activities,[150] the number of participating programmes is increasing and their scope and coverage are expanding. Large-scale actions to improve hand hygiene have been shown to reduce the numbers of infections with resistant bacteria (Box 5.1).

[b] http://www.who.int/gpsc
[c] http://www.who.int/gpsc/5may/tools/en/index.html

Figure 5.1 The WHO multimodal strategy for improving hand hygiene



Source: Ilustration reproduced from [148] with permission from Elsevier. Remainder reproduced from [149] with permission from the World Health Organization.

Box 5.1 Experience from Geneva, Switzerland and Victoria, Australia

The first multimodal intervention was conducted from 1995 to 2000 at the University of Geneva Hospitals, Switzerland. A decrease of almost 50% in health care-associated infections and methicillin-resistant *Staphylococcus aureus* (MRSA) transmission occured in parallel with a sustained improvement in compliance with hand hygiene. More than 20 000 opportunities for hand hygiene were observed. Although recourse to handwashing with soap and water remained stable, the frequency of hand antisepsis with alcohol-based handrub substantially increased during the study period ($p<0{\cdot}001$). The prevalence of overall nosocomial (hospital-acquired) infection decreased from 16·9% to 9·9% ($p=0{\cdot}04$), MRSA transmission rates decreased (from 2·16 to 0·93 episodes per 10 000 patient-days; $p<0{\cdot}001$), and the consumption of alcohol-based handrub increased from 3·5 to 15·4 L per 1000 patient-days ($p<0{\cdot}001$). This multimodal intervention model was used in 2005 by the WHO Global Patient Safety Challenge *Clean Care is Safer Care* as a basis for the global promotion of hand hygiene.[151]

In the state of Victoria, Australia, a centrally coordinated, multimodal, multi-site hand hygiene culture-change pilot programme (HHCCP) for reducing rates of MRSA bacteraemia and disease was carried out over a 24-month period (October 2004 to September 2006) in six health-care institutions. Subsequently, the efficacy of an identical programme implemented throughout Victoria's public hospitals over a 12-month period (between March 2006 and July 2006) was assessed. The mean rate of hand hygiene compliance improved significantly at all pilot programme sites, from 21% at baseline to 48% at 12 months and 47% at 24 months. Mean baseline rates for the number of patients with MRSA bacteraemia and the number of clinical MRSA isolates were 0.05/100 patient days per month and 1.39/100 patient days per month, respectively. These were significantly reduced after 24 months to 0.02/100 patient days per month for bacteraemia (i.e. 65 fewer patients with bacteraemia) and 0.73/100 patient days per month for MRSA isolates (i.e. 716 fewer isolates). Similar findings were noted 12 months after the statewide roll-out, with an increase in mean hand hygiene compliance (from 20% to 53%) and reductions in the rates of MRSA isolates and bacteraemia.[152]

Several hospital-based studies also confirm the importance of hand hygiene in preventing infections due to resistant pathogens. The cost-effectiveness of hand hygiene promotion has been demonstrated at facility levels and estimated at national levels (Box 5.2).[153-155] However, poor compliance with hand hygiene is still a problem in most parts of the world, for varying reasons, and continuing efforts are required.

Box 5.2 **Cost-effectiveness of hand hygiene promotion**

An eight-year study at the University of Geneva Hospitals, Geneva, Switzerland, estimated total costs associated with health care-associated infections (n=37 887) to be SFr 132.6 million (range, SFr 79.6–185.6 million) using conservative cost estimates of an average of SFr 3500 per health care-associated infection. Extra annual costs generated by 260 nosocomial infections equaled the budget for the hand hygiene promotion campaign and showed that the programme was already cost-saving if less than 1% of the reduction in infections was due to improved hand hygiene practices.[153]

The use of an alcohol-based handrub, together with education and staff performance feedback, reduced the incidence of MRSA infections and expenditures for teicoplanin (an antibiotic used to treat MRSA infections) in hospitals in England. For every £1 spent on the alcohol-based handrub, £9–20 were saved on teicoplanin expenditure.[154]

An economic analysis of the "clean**your**hands" promotional campaign in England and Wales concluded that the programme would be cost beneficial if hospital infection rates were decreased by as little as 0.1%.[155]

Isolation of AMR infected patients

The isolation of patients colonized or infected with resistant organisms and the application of specific contact precautions are key recommendations that are followed in many facilities.[139] Evidence on the effectiveness of different isolation policies and screening practices for MRSA indicate that concerted efforts including isolation can reduce MRSA colonization and infection in hospital inpatients, even when the infection is endemic.[156] However, isolation of MRSA patients in single rooms is not always feasible in many settings. Grouping a number of similarly affected patients in the same bay or part of the ward, with or without their own nursing staff, is an alternative, but more needs to be done on monitoring effectiveness and investment in isolation facilities.[157] Guidance is available on personal protective equipment,[139] but practice is probably far from satisfactory in many parts of the world.

Screening of patients for AMR bacteria

Screening of all patients for resistant bacteria on admission to hospital has produced mixed results. Conflicting results about the efficacy and cost-effectiveness of active surveillance by bacterial examination in reducing AMR have been published. Furthermore, there is conflicting evidence on whether rapid molecular identification methods, such as the polymerase chain reaction (PCR), provide better results than the conventional screening methods.[158] The development and application of screening tests is a rapidly evolving field, and interpretation of the published results could be context-dependent.[159-161]

When screening focuses specifically on high-risk patients (those with previous AMR organism carrier status, patients admitted to intensive care units, patients with open wounds, and the room mates of AMR carriers), there is evidence that screening combined with other measures such as hand hygiene, contact precautions, and staff education can reduce the transmission of resistant pathogens. A policy termed "Search and Destroy" for MRSA, consisting of a range of interventions, including isolating and screening of high-risk patient groups, screening of low-risk groups, strict isolation of carriers, and treatment of people carrying MRSA, has been implemented successfully in the Netherlands and several other European countries. As patients often carry MRSA and glycopeptide-resistant enterococci for more than a year, computer-based "readmission alert systems" are used effectively by some hospitals to prevent delays in recognition of readmitted MRSA carriers.[162]

3.3 Surveillance of AMR

Surveillance of AMR enables the identification of trends in local endemic patterns and the emergence of unusual AMR, such as an increase in numbers, or the emergence of new resistant strains. Based on this information, antibiotic stewardship programmes in health-care facilities can help reduce the unnecessary use of antibiotics. Surveillance systems for AMR are discussed in detail in Chapter 2 and antibiotic stewardship in Chapter 3.

Surveillance for HAI and sharing data through networking at national or subnational levels are integral to health services in many high-income countries. For example, the US Centers for Disease Control and Prevention (CDC) currently supports over 3000 hospitals to report on HAI through its National Healthcare Safety Network.[d] The "Hospitals in Europe Linked for Infection Control through Surveillance" (HELICS) network (subsequently transferred to ECDC) collected, analysed and disseminated data on HAIs.[e] The Canadian Nosocomial Infection Surveillance Programme (CNISP), initiated in 1994, has 49 sentinel hospitals from nine provinces as participants.[f] Such systems are lacking in many low- and middle-income countries. The International Nosocomial Infection Control Consortium (INICC) collects and pools rates of HAI and AMR from 36 low- and middle-income countries (Box 5.3).

Box 5.3 The International Nosocomial Infection Control Consortium (INICC) HAI and AMR surveillance system

Through the analysis and feedback of voluntarily collected surveillance data, INICC promotes evidence-based infection control in hospitals in low- and middle-income countries, and in hospitals without sufficient experience in HAI surveillance, prevention and control. Regularly updated data serve to show trends in the situation of bacterial resistance related to specific types of nosocomial infections.[g] [163,164]

3.4 Innovations in IPC

In recent years investment in research and development to improve IPC practices and antibiotic stewardship has increased. As a result, there have been several advances including in new diagnostic tools, innovative hospital design and engineering, and also new approaches to enable better use of available resources, such as "care bundles" and medical care checklists.

New methods for detecting pathogens such as MRSA, glycopeptide-resistant enterococci and *C. difficile* have become available and others are being further developed. However, these methods vary in their sensitivity, specificity, time to result, and impact in different health-care settings. Near-patient molecular test methods are beginning to appear, and in the long run they are likely to be more cost effective than their laboratory-based predecessors. However, since molecular methods do not necessarily detect resistance in vivo, reliable standard phenotypic tests still have a vital place in diagnosis and screening.

Advances in molecular methods have made it possible to trace the sources of outbreaks, by linking infections due to the same bacterial strains or bacteria carrying similar AMR genetic elements. Using such methods, several resistance genes and mechanisms are being described, enabling a better understanding of the epidemiology of AMR, the factors favouring the emergence of AMR, multiple drug resistances which are genetically linked, the transferability of genes carrying AMR, and other aspects. These methods have also provided the evidence for AMR spread within and across hospitals and within regions and across international borders; the account of carbapenemase spread is an example (Chapter 1).[19]

[d] http://www.cdc.gov/nhsn/
[e] http://helics.univ-lyon1.fr/home.htm
[f] http://198.103.98.45/nois-sinp/survprog-eng.php
[g] http://www.inicc.org/english/eng_index.php

Interactions with engineering and design experts to review health-care infrastructure, devices and equipment have resulted in a number of improvements, such as better antimicrobial delivery systems, new approaches to wound dressing, improved intravenous and urinary catheters and faecal incontinence devices, better designed isolation cubicles which can be assembled within a room, improved cleansing methods and decontamination procedures, alcohol-based handrub, and innovative product delivery and monitoring devices, all of which should contribute to reducing the transmission of microorganisms in health-care facilities. There is still further scope for innovation and improving the uptake of effective products.

3.5 National coordinated IPC programmes and networks

Many countries have national strategies to combat AMR, and these usually include an IPC component. Some of them are already successful, as summarized in Table 5.2. Strategies that have been implemented at national levels include infection reduction target setting, legislation, accreditation, visits of "improvement teams" and various types of inspection and feedback. Penalties for non-compliance are imposed in some settings and include withholding of patient treatment reimbursements if patients have contracted a HAI, fines, and closure of hospital wards, units or services.

Table 5.2 Examples of large-scale campaigns to reduce AMR pathogens in health-care facilities and/or the community, incorporating IPC interventions

Country	Agency	Measures	Results
Australia	Ministry of Health	- Multi-site hygiene culture-change programme - Subsequent statewide roll-out and national promotion campaign	MRSA bacteraemia and the number of clinical MRSA isolates was significantly reduced after 24 months.[152]
Belgium	Belgian Antibiotic Coordination Committee (BAPCOC)	Campaigns to decrease antibiotic consumption in hospitals and the community (2004), and to improve hand hygiene and prevent HAI (2005, 2007, 2009)	Compliance with hand hygiene increased; percentage of resistant infections and antibiotic use decreased.[165]
England	Department of Health; National Patient Safety Agency; Health Protection Agency	- Legislation on HAI and IPC - Mandatory reporting of MRSA bacteraemia rates - Establishment of reduction targets - Chief Executive held responsible for the data - National Hand Hygiene campaign - Many others, e.g. care bundles, visits by improvement teams	The target to decrease MRSA bacteraemia rate by 50% was achieved in 2008.[166] *C.difficile* infection was decreased by 54% between 2007/08 and 2009/10.[167]
France	Ministry of Health[h]	- Media campaigns to decrease antibiotic usage - Admission screening and isolation - Reporting on mandatory indicators, beginning in 2004 and reporting of alcohol-based handrub consumption in 2005	There was a 41% decrease in MRSA infections.[168] (see also Chapter 3)
Malaysia	Ministry of Health	National MRSA monitoring and promotion of the WHO Global Strategy for the Containment of Antimicrobial Resistance	Percentage of MRSA isolated decreased from 29.5% in 2003 to 22% in 2010 (personal communication, MoH).

Source: Compiled and adapted from [152,165-168]

[h] http://www.sante.gouv.fr/programme-national-de-prevention-des-infections-nosocomiales.html

There are many other national and international initiatives to reduce infections in hospitals, including the following examples. The WHO Regional Office for the Eastern Mediterranean (EMRO) has initiated a "Patient Safety Friendly Hospital Initiative", with IPC as one of the core elements.[i] The WHO "African Partnerships for Patient Safety" programme, which builds north-south twinning partnerships and south-south knowledge transfer partnerships between hospitals in various African and European countries, incorporated hand hygiene improvement as one of its first activities.[j] The WHO Patient Safety programme "Safe Surgery Saves Lives" included IPC aspects as well as rational use of peri-operative antibiotics in their Surgical Safety Checklist.[k] All of these WHO-initiated programmes have led to increased national and international efforts to promote IPC.

3.6 Regulations and incentives related to IPC

In a number of countries, adherence to IPC recommendations is supported by legal provisions and regulations, and through incentives linked to reimbursement of hospital expenses. Many countries and agencies have included elements of IPC in hospital accreditation protocols. In the USA, hospitals are required to have IPC programmes as a condition for accreditation. France and other European countries require all health-care facilities to have an IPC committee to define and implement an IPC programme.[169] In some countries, reporting of HAI is mandatory. In Germany, a new infection prevention act came into force in 2011. Brazil has regulations requiring all facilities to provide alcohol-based handrub.[l] China has issued a directive whereby one health-care professional proficient in surveillance and infection control is recommended for every 200 to 250 beds.[170]

Target setting[171] as practised in some countries involves selecting at least one resistant indicator organism for mandatory surveillance (e.g. MRSA) based on the AMR situation in the country. Summarized data for these 'alert' organisms are monitored over time and published periodically, giving political decision-makers, the public and the media an opportunity to evaluate progress and the impact of any intervention, including IPC measures. Such data are also being used by individual health-care facilities for endorsing the quality of service provided.

Health-care financing systems with a universal or ceiling budget could, in principle, have strong incentives to reduce HAI-associated costs by investing in preventive measures. However, when Germany introduced a Diagnosis Related Groups (DRG) financing system in 2001, the AMR situation did not improve. The main reason may be that adequate local data on additional costs for HAI and AMR were not available to allow informed decisions by hospital managers. In health-care provision systems which depend, even only partially, on fee-for-service reimbursement mechanisms, there may be little incentive to reduce the transmission of pathogens in health-care facilities, as any additional diagnostic procedure or intervention and treatment for a colonized or infected patient generates income for the provider.

4. Gaps and challenges

Inadequate infrastructure and human resources: Deficiencies in infrastructure and limited access to commodities represent a major barrier to implementing IPC recommendations in health-care settings in many countries. There are examples of inadequate hospital buildings, understaffing, inadequate clean water supplies and lack of reliable microbiology support in many parts of the world. Addressing these deficiencies requires commitment and financing from national/subnational authorities. Until these major gaps are corrected, optimal global IPC will not be achieved.

Lack of sufficiently trained and dedicated personnel to manage IPC in each health-care facility is another major barrier in many countries.[141] IPC as a clinical discipline has only recently gained visibility and

[i] http://www.emro.who.int/pakistan/pdf/psfhi.pdf
[j] http://www.who.int/patientsafety/implementation/apps/en/index.html
[k] http://www.who.int/patientsafety/safesurgery/en/index.html
[l] http://new.paho.org/bra/index.php?option=com_content&task=view&id=1601&Itemid=463

although every health-care worker may have an obligation to take steps to prevent infections, often the overall responsibility for implementing IPC does not fall clearly within the remit of any one clinical specialty. This may result in a lack of ownership and therefore of accountability for IPC within health-care facilities.

Incorporating the principles of IPC in basic medical and nursing curricula, and a system for training of experts in IPC and AMR, would help meet the education gap. Ongoing education of all health-care personnel and regular audits and feedback to staff help maintain standards and compliance.

Inadequate data on AMR infections: Most of the data on infection rates in hospitals due to resistant organisms are from high-income countries. Although a national overview of infection rates is a useful measure and can inform bench-marking, summaries of data from individual facilities are essential to stimulate local actions. Even well-functioning AMR surveillance systems may not collect data to measure the magnitude of harm to patients, or the additional resources needed for managing AMR bacteria HAI. Although AMR bacteria, including MRSA and extended-spectrum beta-lactamase-producing strains, are also transmitted outside hospitals, much less is known about their transmission in the community.

The lack of standardized methods and universally applicable standards for measuring HAI[138, 141] makes it difficult to assess the current situation, and could potentially invalidate comparisons between and within facilities or attempts to measure the effectiveness of different interventions. Accepted methods mostly require laboratory support and careful steps to validate the standards and processes used to collect clinical data.

Choosing interventions and implementing sustainable changes: Choosing and prioritizing the most appropriate interventions for an individual facility is not always a simple matter. The effectiveness of specific interventions is highly context-dependent, and strategies may vary according to the existing situation. In highly endemic facilities with limited resources, it may be possible to reduce AMR infection rates significantly by the effective introduction of only a few IPC interventions (e.g. improving hand hygiene, reducing device usage). In settings where basic IPC measures are already in place, the priority may be to ensure sustained compliance with recommendations. This could be achieved through a combination of measures such as 'care bundle' approaches and interventions targeting human behaviour change.

Behaviour can be influenced by the level of knowledge about an issue and the importance placed on certain interventions. Behaviour change is an area which could benefit from more research, particularly to understand factors which influence and sustain individual and organizational change. The *WHO Guidelines on Hand Hygiene in Health Care*[147] include the evidence for some factors which influence the implementation of hand hygiene recommendations.

The assessment of gaps, feasibility and efficacy of interventions, and the stepwise introduction of a series of interventions can be facilitated by appropriate tools. The HARMONY project showed that interactive tools based on a template approach enabled experts on antimicrobial stewardship to review their own policies and processes to facilitate the design of a hospital antibiotic policy.[172] Similar tools could also help in assessing existing IPC practices and in elaborating policies. An assessment tool is being developed by WHO to enable facilities to identify gaps in IPC.

Lack of information on costs and cost-effectiveness: National budgets allocated to health care vary, even in high-income countries, and the situation is worse where resources are limited. Data on cost-effectiveness in diverse settings are therefore crucial for policy decision-making. However, there is insufficient information on health care-associated as well as societal costs of interventions and the savings due to their impact.

The costs for specific interventions may vary considerably, depending on many local factors such as differing material, personnel, and bed costs. To quantify the savings resulting from the interventions, a variety of local issues need to be taken into account, including the pre-intervention burden, the effectiveness of interventions, potential direct savings for health-care systems (e.g. shorter hospital stays, fewer readmissions, less need for tests, less use of antimicrobials) as well as savings for social security systems and/or increased productivity.

Need for innovations to reduce the transmission of pathogens: Both the private and public sectors need encouragement to explore new technologies to reduce the transmission of pathogens and infections

in health-care facilities. “New” products need to be tested quickly for feasibility and potential impact in different health-care settings.

Mathematical modeling could be applied to estimate cost–benefits of interventions in different settings with differing resource levels and health-care delivery systems. Such models may be useful for determining the types of interventions best suited for individual facilities. The credibility of mathematical models depends on the quality and applicability of the data informing them. Additional efforts to gather appropriate data are necessary and consensus in this area needs to be explored with multi-disciplinary groups.

There is also a pressing need for innovative approaches that are feasible and readily applicable in low-resource settings.

Chapter 6.

Fostering innovation to combat antimicrobial resistance

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Fostering innovation to combat antimicrobial resistance

With an inexorable increase in antimicrobial-resistant infections, a dearth of new antibiotics in the pipeline and little incentive for industry to invest in research and development in this field, innovative approaches are crucial for the development of new products to counter the rise of AMR. Innovation is under way, with successful initiatives in scientific collaboration, funding mechanisms and regulatory provisions. Other opportunities for innovation exist in all of these areas. An enabling environment for innovation depends on support from policy decision-makers.

Summary

Innovative strategies and technologies are needed to alleviate the dearth of new antibiotics and other products for limiting AMR, ranging from scientific to financial and regulatory aspects. Various innovative approaches are being pursued but more are needed. Innovation flourishes in an enabling environment, and this chapter examines what can be done to create conditions that would foster innovation in this field.

While antimicrobial medicines are the mainstay of treatment for bacterial infections, diagnostics and vaccines play important complementary roles by promoting rational use of such medicines and preventing infections that would require antimicrobial treatment. New products coming on to the market have not kept pace with the increasing needs for improvements in antimicrobial treatment. Setting priorities for research and development (R&D) involves making strategic choices and identifying complementary technologies. This chapter considers the current status of innovations, especially in drug discovery, and identifies the main gaps and challenges.

Both scientific and financial aspects pose challenges for R&D. Strengthening infrastructure, from specimen banks for diagnostics to broader compound library access for drugs, as well as human resources, has facilitated collaborative research. Carefully weighed financing mechanisms—*push* and *pull* incentives— are being used to spur greater R&D into new technologies. Push incentives that de-link the return on investment from volume-based sales, such as the public funding of clinical trials and providing services that help bring promising compounds to trials, are being explored. Such incentives could also reduce the inappropriate use of antibiotics by preventing the need to sell large volumes to improve return on investment. Strategies such as pooled procurement and Advanced Market Commitments can help to create markets that reassure the private sector of returns on investment. Target Product Profiles are being used increasingly to help align public health goals with economic incentives, especially in pharmaceutical R&D, to facilitate public sector return on investment. Innovations such as pooling of building blocks of knowledge and open access repositories show promise.

Regulatory requirements have an important role in directing R&D and there is a need for clear guidance to the industry. Strategic and judicious use of intellectual property rights, which can be either an incentive or an obstacle, is discussed. New opportunities could result from supporting greater participation of developing countries in R&D, including small biotechnology firms and academic institutions. To meet the twin challenges of enhanced innovation and affordable end-products, there is a need to pilot alternative approaches to pharmaceutical R&D, and for concerted action by a broad range of stakeholders.

1. The need for innovations in several domains

The increasing health and economic threats posed by resistant infections call for improved and new products, technology, and ideas to counter AMR. Innovations are needed in many different areas, notably in drug discovery, vaccine development and diagnostics. Non-antibiotic therapies such as immuno-modulators and other agents may add to advancements in addressing AMR.

Antibiotics, in addition to the treatment of a broad range of common infections, ensure the successful application of modern medical advances, from organ transplants to cancer chemotherapy. Logically, therefore, for effective treatment, antimicrobials should keep a step ahead of resistant pathogens. In reality, however, a growing range of bacteria are rapidly developing resistance to more and more antibiotics, rendering them useless for treating many infections. Bacteria resistant to almost all known antibiotics have already emerged and are causing infections. Over the past 30 years, only two truly novel classes of antibiotics have entered the market: the oxazolidinones (linezolid) and cyclic lipopeptides (daptomycin), and resistance has been documented for both of these compounds.

Effective vaccines reduce the prevalence of disease and thereby also reduce the need for antibiotics. Several studies have shown significant reduction in resistant *S. pneumoniae* following the introduction of multivalent pneumococcal conjugate vaccines in infants and children, not only in the vaccinated children but also in the population as a whole (due to reduced transmission of infection). This exemplifies how developments in vaccines and the strengthening of immunization programmes contribute indirectly to the control of AMR.

Rapid point-of-care diagnostic tools for case management of individual patients could play a valuable role by removing clinical uncertainty and reassuring patients that some conditions do not require antibiotics. Without such tools, patients may be under-diagnosed, but over-treated. For example, an improved diagnostic tool for acute lower respiratory infection could theoretically save over 400 000 unnecessary antibiotic treatments per year in developing countries.[173] Diagnostic tools could also assist in the selection of an effective antibiotic in cases where resistance has rendered first-line treatment ineffective, and in surveillance and infection prevention and control.

A spectrum of technologies with applications in many domains from health-care delivery systems to food safety measures, have an impact on the development and spread of AMR. Innovations are needed in these areas, as well as improvements in technology and better use of available tools, including in resource-constrained settings. The continuing growth in trade in animal and agricultural products provides greater opportunities for the spread of infectious agents, and regulatory agencies face increasing challenges in rapidly detecting pathogens, especially in goods crossing national borders. Improved diagnostic tools could allow more prompt and sensitive detection of pathogenic organisms, including those with AMR, and raise awareness of the globalization of this problem.

Innovations in drug formulation can improve patients' adherence to treatment or enhance the effectiveness of antimicrobials. For example, in patients with both tuberculosis and HIV infection, the use of fixed-dose formulations of multiple antimicrobial components facilitates compliance with the full course of treatment. Innovations to encourage patients' compliance with treatment and optimizing treatment regimens can help to limit the risk of resistance.

2. WHO guidance on innovations to contain AMR

Encouragement of cooperation between industry, government bodies and academic institutions in the search for new drugs and vaccines is one of the recommendations in the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance. Other recommendations on fostering innovations address aspects such as incentives to advance R&D, fast tracking market authorization, and partnerships to promote access to new products (Appendix1).[1]

A decade later, the global strategy recommendations remain valid and on World Health Day 2011, WHO renewed the call for global and national commitments to develop diagnostics, drugs and vaccines for infectious diseases. The core actions identified in the 2011 WHD policy briefs include improving the use of current diagnostics and antimicrobials, creating incentives for new product development, enabling rapid regulatory processes for new tools, and ensuring equitable access (Appendix 2).[2]

3. The present position regarding these recommendations

Setting R&D priorities involves consideration of a number of factors which in turn affect progress in innovations. These include, as explained below, (i) the predicted reduction in disease burden; (ii) the expected number of treatments averted; (iii) the opportunity costs for bringing a new technology to market; (iv) the scientific likelihood of achieving a 'breakthrough' invention; and (v) the likelihood of adapting the product for public health purposes, particularly in resource-limited settings.

The reduction in the burden of disease could depend on the prevalence of the disease, the level of attributable morbidity and mortality, and its responsiveness to medical intervention. The effects of a product could range from total avoidance of the illness (prevention by vaccination) to mitigation of the severity and course of the disease (treatment with drugs). Reliable diagnostic tests can reduce unnecessary treatment, which reduces costs, and facilitate the selection of optimal therapy, which is critical when more costly second-line treatments are needed.

Both the financial costs of R&D and the time from laboratory to point-of-care are considerable; they differ for diagnostics, drugs and vaccines and also within these categories. Large multinational companies are likely to view the opportunity costs quite differently from small firms, product development partnerships, or government-owned pharmaceutical companies. In 2004, a study of 63 projects on drug development for neglected diseases found that half were carried out by multinational companies, on a "no profit, no loss" basis. The other half were mainly done by smaller companies on a commercial basis, motivated by smaller profits than multinationals would expect, and in collaboration with Product Development Partnerships (PDPs).[174] While it is estimated to cost over US$ 800 million for a U.S. multinational pharmaceutical company to bring a new drug to market, a public-private partnership has put the cost of developing a new drug for treating tuberculosis at about US$ 76–115 million, including the costs of failure.[175] The much lower PDP estimate indicates that alternative approaches might usefully be explored, particularly for the development of products that would offer little financial incentive for the multinationals.

Scientific potential for achieving a breakthrough invention is often unpredictable. Over a decade of R&D efforts focusing on the high-throughput screening of compounds have yielded disappointing results. Between 1995 and 2001, GlaxoSmithKline conducted 70 such screening campaigns which yielded only five leads, a success rate four-fold lower than in other therapeutic areas.[176] The low yield obtained by high-throughput screening has led to suggestions that screening of natural products might prove more fruitful. Other opportunities could come from recent developments in genome research which may help bring in the next generation of anti-infective agents. Knowledge of bacterial genomics and protein expression has provided novel targets for high-throughput screening against compound libraries and yielded some promising leads, but so far these have not resulted in the successful development of new antibacterial agents for reasons including toxicity. In another approach, some important advances could be made through the modification of existing medicines to improve efficacy and compliance with treatment.

It is important to consider whether technologies are likely to be adapted to meet public health needs, particularly in resource-limited settings. Available new health technologies are not always used in developing countries for reasons such as unaffordable start-up and maintenance costs, lack of infrastructure including water, electricity, refrigeration, and lack of trained staff. Characteristics of a diagnostic test that would facilitate its use in developing countries have been proposed (Box 6.1).[177]

Box 6.1 ASSURED: Characteristics of the ideal diagnostic test for the developing world

- **A**ffordable by those at risk of infection
- **S**ensitive (few false-negative results)
- **S**pecific (few false-positive results)
- **U**ser-friendly (simple to perform by persons with little training)
- **R**apid (to enable treatment at first visit) and Robust (does not require refrigerated storage)
- **E**quipment-free
- **D**elivered to those who need it

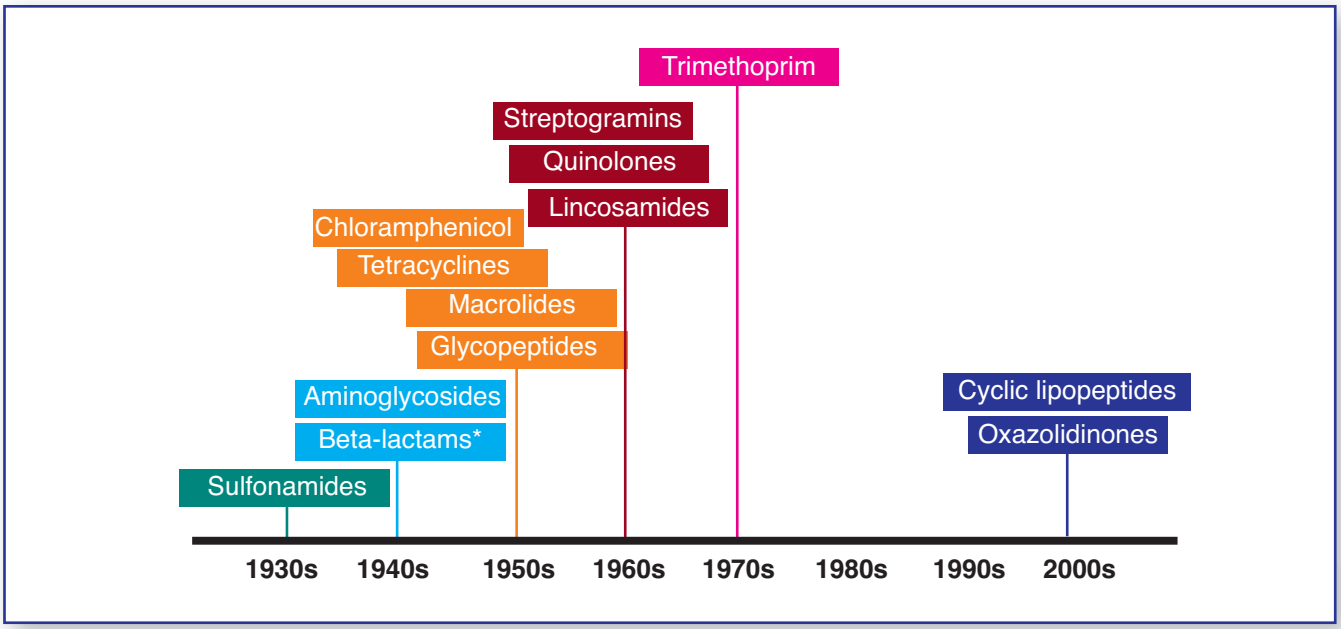
3.1 Overview of the drugs, diagnostics and vaccines pipeline

Mapping of the R&D pipeline, both across technologies that might combat AMR and across the range of different pathogens, is far from complete. The distance from laboratory to point-of-care will be shorter or longer for the development of different products, and this has to be taken into account in R&D prioritization. The R&D pipeline for drugs is perhaps better understood than for other products. The number of new medicinal products, including antibiotics, brought successfully to market has not kept pace with the increase in expenditures on pharmaceutical R&D.

Drug R&D

As the number of infections that are treatable with existing antibacterial drugs progressively decreases, the dearth of new candidate compounds is a matter of much concern. Only two truly novel classes of antibiotics have been developed over the past 30 years (Figure 6.1) and both are for the treatment of Gram-positive bacterial infections, which represent only a part of the whole spectrum of bacterial pathogens that are becoming resistant.[178]

Figure 6.1 Discovery of new classes of antibacterial drugs (1930s to 2000s)



* Penicillins were the first beta-lactams. This class includes cephalosporins and carbapenems, developed in the 1960s and 1980s, respectively.
Source: Reproduced with data from [178]. Modified with permission from Thomson Reuters (Professional) Ltd

The future pipeline also appears bleak. Only five (1.6%) of the drugs in the R&D pipelines of 15 pharmaceutical companies, which together produced 93% of antibiotics placed on the market between 1980 and 2003, were antibacterials.[179] A more comprehensive and recent analysis also found disappointingly few truly novel candidates: of 90 potential systemic agents, only four had activity against Gram-negative bacteria, which are of greater concern than MRSA in some situations, and none had a novel mechanism of action.[8]

The return on investment on R&D is likely to be relatively low for antibiotics. Compared to many other medicines, particularly those prescribed for long-term use, antibiotics have a smaller commercial market. Antibiotics for primarily hospital-based use command a higher average price and have greater market growth prospects than those for community use, which currently accounts for over 60% of total antibiotic sales.[180]

The *net present value* of a drug candidate is used to estimate the expected returns from a drug under development compared to the estimated R&D investment. The higher the net present value, the greater the likely returns on investment. On this basis, potential returns from a musculoskeletal drug are over an order of magnitude greater than those predicted for an injectable antibiotic.[181] Certain intrinsic features of antibacterials affect the net present value, for example an uncomplicated urinary tract infection is usually cured with a short treatment course, whereas anti-hypertensive treatment may be for life. Bacterial resistance itself contributes to shortening the effective market life-span of an antibiotic. Extrinsic factors that influence the net present value include differences in disease burden between developed and developing countries, the level of therapeutic competition, and the limits on reimbursement. In 2009, 60% of the US$ 1.3 billion global sales of meropenem, a broad spectrum antibacterial drug, were in industrialized countries, including the USA, Europe, and Japan. In contrast, less than a fifth of the estimated global sales of first-line TB drugs – a smaller market in the range of US$ 261–418 million – were from high-income countries. Beyond these calculations on returns, gains for a company's reputation, the opportunity to enter into emerging

markets, and collaboration with PDPs which help with the regulatory systems of developing countries, could also influence a company's prioritization of R&D projects. Public health needs could enter this equation in the form of policy interventions to diminish the financial risks associated with R&D, or as enhancements in the likelihood of returns on investment.

The prominent role played by smaller firms (Box 6.2) raises important issues such as differences in opportunity costs and therefore differing incentives that could be used to take candidates through the pipeline. A company with a diverse portfolio of drug candidates is positioned differently to consider trade-offs in investing in a musculoskeletal drug compared to an antibacterial drug. In contrast, a smaller company's future may depend on the success of a single drug. Rescuing and repurposing existing drugs could entail lower R&D costs, and picking up drugs shelved for other reasons could also prove useful (e.g. Cubicin®).

Box 6.2 **The potential role of small companies in antibiotic R&D**

In November 2003, Cubicin® (daptomycin) produced by Cubist Pharmaceuticals Inc was approved in the USA. Daptomycin is the first of a new class of antibiotics, the lipopeptides. Administered in the hospital setting, this drug targets *S. aureus*, including MRSA, and other Gram-positive bacteria causing complicated infections. Eli Lilly first discovered daptomycin, but discontinued its development because of concerns over toxicity when administered in high dose therapy. Licensed from Eli Lilly in 1997, daptomycin was then successfully developed by Cubist.

Several factors may have contributed to this success of a small company. It targets the smaller hospital market, where the prescriber is more clearly identifiable, and therefore only a small workforce is needed to promote the drug. Secondly, the rise of hospital infections with MRSA led to a growing market potential for antibiotics with MRSA as the target. Also, concern over the dearth of new-class antibiotics may have helped with the regulatory process of the U.S. Food and Drug Administration (FDA).[182]

The pharmaceutical market is mature and prospects for further growth are limited. Market penetration by generic products is high and newly developed antimicrobials are likely to face competition from the large numbers of those already approved and widely used. While R&D programmes may favour broad-spectrum antimicrobials, public health authorities could seek to limit their use in order to counter the development of resistance. Discouraging the use of a newly developed antimicrobial for first-line treatment is usual practice, and in many cases this measure has a negative impact on sales.

Diagnostics R&D

The pipeline for new diagnostics differs from that of drugs in several key respects. The global market for diagnostics in 2008 was US$ 41 billion, most of which related to infectious diseases.[183] In contrast, the worldwide market for medicines in the same year was US$ 758 billion (Figure 6.2).[184] For diagnostics, the time required for the development process from laboratory to point-of-use is shorter, and typically the R&D costs are lower, than for drug development. But with a lower net present value, diagnostic products command a smaller share of investment and returns. Innovations are needed to increase the use of existing diagnostics, as well as for the development of new technologies.

Lessons can be drawn from experience in international coordinated actions to improve TB diagnostics and their utilization. Of the billion-dollar worldwide market for TB diagnostics, one third is outside the established market economies.[185] Sputum microscopy remains the mainstay of TB diagnostics in resource-limited settings. By expanding reference laboratory capacity and facilitating the roll-out of new diagnostic tools that can be deployed in more peripheral settings, WHO and the Stop TB Partnership Global Laboratory Initiative (GLI) hope to improve the efficacy and reach of TB diagnostic tools.[186] Recently, WHO revised its policy guidance to include new technologies for TB diagnosis, such as molecular line probe assays and fluorescent light emitting diode (LED) microscopy.

WHO also endorsed Xpert® MTB/RIF, a new rapid test for diagnosing TB and identifying TB with rifampicin resistance, which was developed by Cepheid with support from the Foundation for Innovative New Diagnostics (FIND). Obviating the need for lengthy in vitro culture, the results can be obtained in under two hours.[187] In exchange for support for R&D, FIND has secured concessionary pricing of these tests in resource-limited settings. The Xpert system also opens up opportunities to add on other diagnostic tests to the instrument, e.g. for sexually transmitted diseases.

The development of new diagnostic tests relies on the availability of biospecimens that are needed to evaluate these tools. For tuberculosis, an open-access collection of over 41 000 samples from adult patients in 13 countries has been assembled in a TB Specimen and Strain Bank by the Special Programme for Research and Training in Tropical Diseases (TDR). Responding to concerns over the quality of tests, FIND, TDR, and the WHO Regional Office for the Western Pacific (WPRO) supported an evaluation of rapid diagnostic tests for malaria. Such evaluations are much needed and enable purchasing decisions to be based on test performance as well as price.

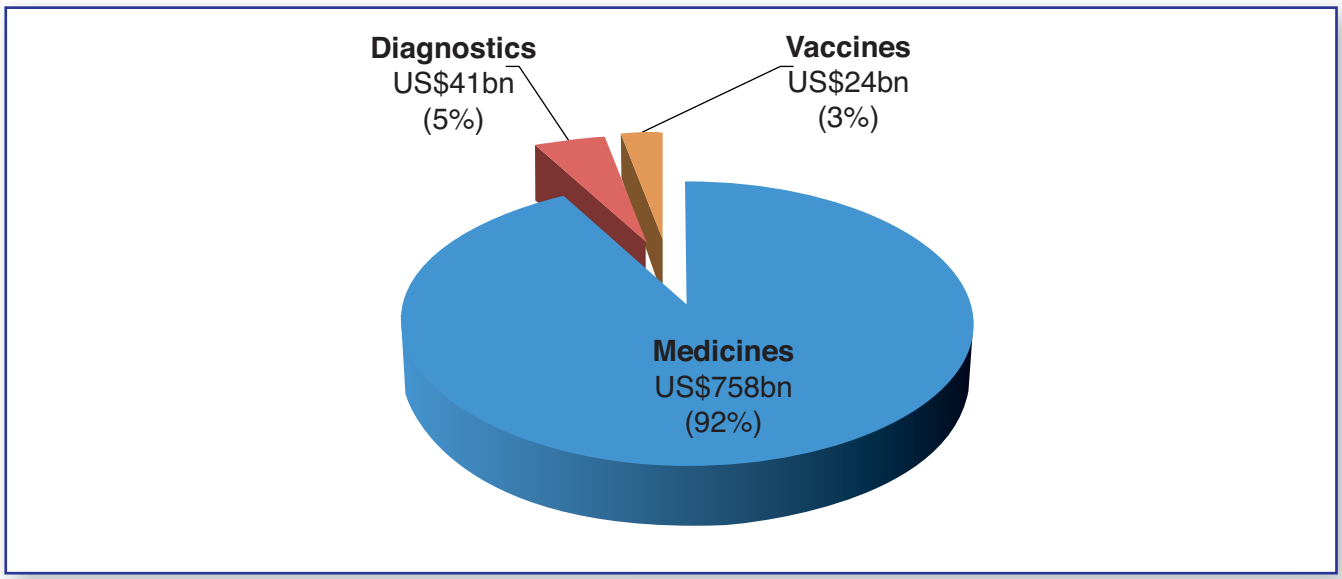
Vaccines R&D

The worldwide market for vaccines was estimated at US$ 24 billion in 2008.[188] Five multinational companies – GlaxoSmithKline, Merck & Co, Novartis, Sanofi Aventis, Wyeth (now part of Pfizer) – account for 85% of the value of this market. Several new vaccines, such as those against *S. pneumoniae,* rotavirus, and human papilloma virus (HPV), have been successful both clinically and in markets. Wyeth's Prevenar® (pneumococcal septavalent conjugate vaccine), an antibacterial vaccine, reached an annual sales record of US$ 2.7 billion in 2008.[189] Recently, 10-valent and 13-valent pneumococcal vaccines from GlaxoSmithKline and Pfizer respectively have been licensed. Information on many activities that are taking place in vaccine development can be accessed through the WHO web pages.[a]

Nevertheless, the track record still reveals significant scientific challenges facing the development of new vaccines. A recent update of R&D efforts on anti-staphylococcal vaccines and immunoglobulins shows much enthusiasm for attacking the pathogen with toxin-based or virulence factor-based interventions. However, 5 out of 7 projects have so far failed or been terminated. A wide range of R&D cost estimates for new vaccine development exists, and these vary considerably by disease area and vaccine complexity. The recently approved meningococcal conjugate vaccine adapted to strains endemic in sub-Saharan Africa received a seed grant of US$ 70 million from the Gates Foundation and additional funding as the programme has begun to scale up for distribution and delivery. The Roll Back Malaria Initiative, on the other hand, estimates the R&D costs at approximately US$ 800 million per new malaria vaccine. Thus, significant financial resources are always needed to bring new vaccine candidates to market.

[a] http://www.who.int/vaccine_research/en/index.html

Figure 6.2 Global markets of medicines, diagnostics, and vaccines in 2008 (US$ billion)



Source: Data obtained from [183]

3.2 Creating an enabling environment for R&D and innovations to improve access

The dearth of diagnostics, drugs and vaccines for neglected diseases in the developing world has triggered a renewed look at alternative approaches in many areas to improve product development and access to available products. Creating an enabling environment could be a critical factor in stimulating innovation, particularly where paying markets are small and resources limited.

Clear market signals to stimulate and streamline R&D

Market signals on both the demand and supply sides could potentially enlist greater public and private sector engagement in R&D. Improving the demand side signal could be an option not only to improve procurement and quality of products, but also to stimulate development to meet demand. Pooling the procurement needs of many purchasers could enable suppliers to more easily foresee the likely demand in a market. Such efforts could also ensure greater stability of forecasted demand, increase purchase volumes, and provide an opportunity to harmonize regulatory and quality issues among purchasing agents. Pooled procurement could also exert monopsony (consolidation of purchasing power) influence, which can shape how the products perform and how they are priced and marketed.

As an example, the WHO's procurement service for diagnostics evaluates diagnostic test kits prior to their inclusion in the Bulk Procurement Scheme. Reviewed annually, test kits have to meet certain standards of performance. Negotiating with manufacturers, WHO has secured assay tests at half the open market price under the Bulk Procurement Scheme. This procurement service started in 1990 to assist Member States in accessing high quality HIV test kits at reasonable cost, but now covers diagnostics for a range of conditions, from malaria to hepatitis B and C. In 2007 the service procured 13 million test kits for priority diseases, making substantial savings for 45 Member States, mostly low-income countries, which procured test kits under this arrangement.[b]

Established in 2000, the Global Alliance for Vaccines and Immunization (GAVI) is a public-private partnership

[b] http://www.who.int/diagnostics_laboratory/procurement/en/

which works with procurement partners and seeks to ensure access for low and lower-middle income countries to new and underutilized vaccines. GAVI prioritizes its investments in a portfolio of vaccines on the basis of various factors, from vaccine readiness and cost, to cases and deaths averted. Using Advance Market Commitments (AMC) as a strategy, GAVI guaranteed a viable market to pneumococcal vaccine manufacturers provided they could develop a vaccine meeting a predefined Target Product Profile (TPP). Following this, WHO developed a TPP for pneumococcal conjugate vaccine candidates where a vaccine product must meet 13 required attributes, including serotype formulation, projected public health impact, safety, and suitability for use in developing country health systems.[190] With support from GAVI, the Pneumococcal Global Serotype Project created metrics that assess whether a pneumococcal vaccine matches regional serotype coverage.

TPP could also be an effective instrument in the product development process and for R&D funding agencies and product development partnerships. In this context, a TPP can provide a clear description of where R&D might meet an important public health need. The U.S. FDA uses TPP as a basis for communication between pharmaceutical companies and the agency's staff as well as with review panels.[191] TPP could also be used to solicit inputs for decisions, from various stakeholders including sponsors, research personnel, health-care workers, patients, regulatory agencies, and policy-makers in disease-endemic countries. TPP could therefore be a useful approach to bring new health technologies for combating AMR to market.

Capacity strengthening at various levels to enhance innovation

Strengthening infrastructure for R&D, including the training of research scientists, may be needed in many areas of the world for each stage of product development across health technologies and also for the roll-out of new products. Antimicrobial R&D efforts could take a lesson from the WHO Stop TB strategy to ensure that key infrastructure and a trained workforce are available in developing countries.

While pharmaceutical companies in industrialized countries are increasingly conducting clinical trials in developing countries, more needs to be done to involve disease-endemic countries in R&D, especially upstream in the drug discovery and pre-clinical phases. Launched in October 2008, the African Network for Drugs and Diagnostics Innovation (ANDI) seeks to promote and sustain the R&D innovation for drugs and diagnostics in disease-endemic settings. ANDI hopes to strengthen south-south research ties and to facilitate the creation of partnerships between the public and private sectors.[192]

Creating a trusted platform for testing and evaluating diagnostics could help respond to the lack of capacity in many parts of the world. TDR obtains clinical samples from disease-endemic countries for its specimen banks for TB and malaria, and has carried out series of evaluations on diagnostic tests for visceral leishmaniasis, malaria, sexually transmitted infections, and CD4 counts for HIV/AIDS. By examining commercially available diagnostic tests using predefined criteria, these evaluations help set standards for quality diagnostic tests and provide guidance for international and national level procurement.

Policies to create an enabling environment

Of the various factors central to an enabling environment for pharmaceutical innovation, three are probably particularly noteworthy for antibiotic R&D: (i) potential regulatory impediments to bringing health technologies to market; (ii) strategic use of intellectual property rights that might help relieve upstream bottlenecks in R&D, such as access to compound libraries; and (iii) open innovation, including open source drug discovery. These aspects are discussed below.

Regulatory issues potentially shape the enabling environment for innovation, particularly for drugs. Since 1964, antimicrobials have had among the highest rates of regulatory agency approval and shortest approval times for any therapeutic class. Therefore regulatory restrictions would not appear to be the principal factor preventing antimicrobial R&D.

However, providing clear guidance on the regulatory process would benefit companies submitting products for registration. Regulatory reforms could also be envisaged to decrease the costs of clinical trials or reduce the time required for conducting them. Options could include the review of sample size requirements,

a fast track process for approvals, and providing incentives such as FDA priority vouchers or extended market exclusivity, as explained below.

The sample sizes for clinical trials influence not only the cost, but also the time for recruiting and enrolling patients and are dependent on the study design. Debate about the most appropriate trial design is still ongoing. Regulatory authorities understandably seek to avoid repeating the circumstances that led to the withdrawal of telithromycin, an antibiotic for the treatment of community-acquired respiratory tract infections, after 53 cases of hepatotoxicity, including deaths, were reported. In an effort to abide by earlier agreements with industry sponsors, the U.S. FDA had approved telithromycin solely on the basis of non-inferiority trials.[193]

Recently the USA adopted the FDA Priority Review Voucher programme. In exchange for conducting R&D on treatments for neglected diseases and bringing the product through the regulatory process, a company receives a voucher that entitles it to receive priority review for another product. The benefit of reducing the time for the FDA to act on a new drug application gives the voucher value, and some have estimated the voucher's value at potentially more than US$ 100 million per product.[194] The first successful applicant to the programme was Novartis, which received FDA approval of Coartem®, but this was a drug added to the WHO Essential Medicines List in 2002 and already widely available in developing countries. However, the FDA priority voucher programme has been criticized on grounds that the voucher's value is not calibrated to the usefulness of the drug developed, and that there are no assurances that what the industry gains from the voucher will result in more affordable products or even more research.[195] A recent study has also raised concerns about safety problems associated with accelerated regulatory deadlines.[196]

Another innovative approach could be to involve regulatory agencies to encourage co-development of diagnostics with drugs, whereby the recruitment of patients with treatment-resistant infection might be made considerably more efficient.

Intellectual property rights policies can have an important influence on R&D. While judicious application of some policies could enhance the incentive for R&D, some approaches could prove to be obstacles. Policy proposals to encourage R&D range from extending market exclusivity on antibiotics to lowering intellectual property barriers to enable greater scientific exchange. But as a pull mechanism, intellectual property based incentives fail to de-link recouping R&D expenses from volume-based sales, and so such approaches could encourage inappropriate marketing and irrational use of antibiotics. Careful consideration is required before adopting such policies into practice.

Extending market exclusivity on a drug increases the potential for returns on R&D investment. However, delaying the entry of generic products into the market may result in monopoly pricing and so availability based on price. The U.S. Orphan Drug Act approach provides an extended market exclusivity period of seven years. The judicious application of this to antibiotics was proposed in the 2001 WHO Global Strategy for Containment of AMR (Appendix1). In September 2008, the U.S. Congress extended the market exclusivity to three years for "older" antibacterial drugs approved for a new indication, and to five years for a previously unapproved "older" antibacterial drug. With such measures already in place, the potential for incremental gain from this approach may be limited.

Intellectual property rights could also impede innovation and affordable access. A proliferation of patenting can create a situation where "multiple owners each have a right to exclude others from a scarce resource, while no one has an effective privilege of use".[197] For example, multiple building blocks of knowledge are required to develop a vaccine or to adapt it to microbial strains endemic in developing countries. An analysis of the patent holdings around ten key malarial antigens found that there were 167 patent families, held by 75 different assignees.[198] Royalty stacking from these multiple components can add significant cost to the final product: for example, Merck & Co pays 24%–26% royalties on worldwide sales of its cervical cancer vaccine, Gardasil®, to GlaxoSmithKline and other patent holders.[199]

Patent holdings may also present obstacles to the assembly of composite inventions, such as fixed-dose combination drugs for HIV/AIDS or malaria, or inflate their combined cost. For example, in 2003 Abbott raised the price of Norvir® (ritonavir) by 400%. This price increase pushed the price of non-Abbott drug combinations for HIV/AIDS upwards while Kaletra®, Abbott's combination, remained at the same price and captured a larger market share – although still

remaining out of affordable reach for many in the developing world.[200]

UNITAID recently launched the 'Medicines Patent Pool',[201] to enable effective cross-licensing and production of fixed-dose combination AIDS drugs, particularly for second-line therapy and pediatric formulations. If applied to antibiotics, pooling of patents could lower transaction costs and so allow decision-makers to target upstream (knowledge building blocks) or downstream (e.g. fixed-dose combinations) innovations.

Other modes of pooling building blocks of knowledge, from data to compound libraries, could also help to accelerate R&D not only for neglected diseases, but also for health technologies to combat AMR. The U.S. National Institutes of Health (NIH) Molecular Libraries Initiative pools compounds in a public repository. The European Rare Disease Therapeutic Initiative and the TDR programme have sought alternative approaches to tap into proprietary compound libraries. These initiatives could provide models for antibacterial compound libraries, thus lowering the entry barrier for academic research institutions and smaller firms to pursue these drug candidates.

Open Source Drug Discovery is another option for enabling innovation. Building on bioinformatics tools and web-based platforms, open source models create opportunities for scientists across organizations, disciplines and borders to collaborate and share information freely. Examples include the sharing of genetic sequencing data, as encouraged by the Bermuda Rules under the Human Genome Project, and innovation platforms such as the Indian Council on Scientific and Industrial Research's Open Source Drug Discovery initiative for Tuberculosis (Box 6.3), demonstrating the vibrant potential of online scientific collaboration. However, there are complexities related to regulations, the need for collaboration beyond virtual interaction (e.g. access to laboratory facilities), and a potentially complicated patent situation.

Box 6.3 **Open Source Drug Discovery**

Launched in 2008, the Open Source Drug Discovery (OSDD) project of India's Council of Scientific and Industrial Research (CSIR) is an on-line collaborative platform for projects on *Mycobacterium tuberculosis*, from gene sequencing to new drug development. Committed to an open source philosophy, the project requires those joining its efforts to grant back additions and modifications to the OSDD community under a "click-wrap license." A click-wrap license is an on-line agreement made by the user upon accepting the general conditions by clicking through. In the space of only a few years, the project has prioritized a potential drug target for TB, and enlisted hundreds of volunteers in re-annotating the TB genome within a span of four months. To date, more than 4500 participants from 130 countries are engaged in various work packages, including in silico screening, in vivo target validation, and lead molecules identification. As part of the initiative, CSIR has involved multiple universities, where local infrastructure will be upgraded and students will conduct experiments related to this initiative. This initiative is still at an early stage in its development, but it represents an important advance over previous open source efforts in biomedical R&D.

Financing innovation

Two types of financing options are explored in this section: (i) *push mechanisms* that pay for inputs of R&D and thereby lower the risks of R&D investments and (ii) *pull mechanisms* that pay for outputs of R&D and thereby offer greater assurance of a return on the investment or a paying market.

(i) Push mechanisms: Lowering the risks of R&D could entice more firms to pursue R&D for health technologies to combat AMR. These could take the form of public sector or philanthropic funding of different stages of R&D.

With a pledge of UK£91 million during a five year period, the Wellcome Trust's Seeding Drug Discovery Initiative attempts to advance R&D of novel small molecule drug candidates. Several projects funded under this initiative relate to AMR, for example GlaxoSmithKline received UK£4 million to develop compounds for the treatment of Gram-negative bacteria. From 2008, the Innovative Medicines Initiative (IMI), a joint European

Commission-pharma industry initiative[c], is channeling €2 billion over five years into developing new drugs in five disease areas, including infectious diseases.

The U.S. NIH has also announced plans to create the National Center for Advancing Translational Sciences (NCATS). NCATS will focus on "accelerating the development and delivery of new, more effective therapeutics." The Center will consolidate and build upon some already promising initiatives, complementing academic and private sector R&D efforts.

The increased public funding of clinical trials might also lower the barriers to bringing a new antibacterial drug to the market. In return, companies could be asked for disclosure of clinical trial data and for assurances of affordable pricing and rational use of their products.[202]

The Meningitis Vaccine Project has adapted the meningococcal conjugate vaccine to strains endemic in sub-Saharan Africa with support from a US$ 70 million Gates Foundation grant. The transfer of conjugate vaccine technology, which is also part of the project, builds capacity in a developing country. The Netherlands Vaccine Institute, through its work on an international technology platform for influenza viruses in collaboration with WHO, has shown that another push approach might be to provide expertise and training for vaccine production to multiple manufacturers in low- and middle-income countries.[d]

Other product development partnerships (PDPs) serve by mobilizing public and private sector resources for R&D, connecting needed inputs, and negotiating arrangements where private sector expertise or scale-up is required. The number of PDPs across the spectrum of health technologies has proliferated. FIND has made significant strides in advancing diagnostics for TB and in negotiating concessionary prices for such tests. PATH has worked on a broad range of diagnostics[e] specifically targeting low-resource settings; its efforts have been important in building local R&D and manufacturing capacity for diagnostics in developing countries. By lowering the risk–return ratio, PATH has also engaged the private sector to help ensure a more sustainable delivery of products. But there remain unmet needs for antibacterial drug and diagnostic development for a range of diseases, and overall there is still a gap in PDPs addressing these broader needs.

(ii) Pull mechanisms: Pull mechanisms lower the risks of market entry through a guaranteed purchase of the product. Pull mechanisms can take various forms such as third party payer, government reimbursement, or awarding prizes.

Prizes provide rewards after results are produced. This has the advantage of knowing with some certainty the results for which the public sector might pay, but there are also disadvantages that must be addressed in the design of the prize. Given the "winner-takes-all" nature of some prizes, competitors may not be willing to share their findings or the building blocks of knowledge on the way to winning the prize, although incentives built into the design of the prize competition could mitigate these shortcomings. However, the prospective competitors for a prize have to be sufficiently resourced – a potentially significant barrier – to complete the race to the finish line. Prizes might also need to be complemented by push mechanisms and other incentives that help lower the barrier to entry. If prizes can de-link financial incentives from the subsequent volume of sales of the product, this would realign economic incentives to encourage rational use of drugs better than incentives based on patent or market exclusivity.[203]

Perhaps a more recognizably traditional use of prizes is the one recently offered by the Global Alliance for TB Drug Development to stimulate simpler and safer methods for making a phase II trial of a TB drug candidate (PA-824). For prizes of US$ 20 000, 27 entities submitted proposals, and two won awards for their unique ideas that will be further tested by a contract research organization. Spurred by a proposal from Knowledge Ecology International and Médecins sans Frontières, momentum has built to consider how a prize might stimulate innovation of a low-cost, point-of-care, rapid diagnostic test for tuberculosis. The X Prize Foundation has received a planning grant from the Gates Foundation to develop an X Prize for diagnosing tuberculosis in the developing world.[204] In April 2009, Bangladesh, Barbados, Bolivia and Suriname submitted a proposal for establishing a prize fund for developing a low-cost, rapid diagnostic test

[c] http://www.imi.europa.eu/
[d] http://www.flusecure.eu/
[e] http://www.path.org/dxcenter/HomePage.php

for tuberculosis for consideration by the WHO Expert Working Group on R&D Financing.[205]

Another pull mechanism is the Advanced Market Commitment (AMC). Conceived as a financial incentive to encourage companies to bring their products through the final stages to market, the AMC guarantees the initial sale price of the vaccines developed to meet the TPP. Piloting this approach through GAVI, five countries (Canada, Italy, Norway, the Russian Federation, and the United Kingdom) and the Gates Foundation contributed a total of US$ 1.5 billion to bring to market a late-stage pneumococcal conjugate vaccine adapted to developing countries.

This pilot AMC project raises important issues that deserve resolution before replicating it for other pharmaceutical products. The pilot project focused on a vaccine already entering phase III clinical trials, hence its impact as a pull mechanism for products in earlier stages of development cannot be judged. Secondly, there are questions regarding which companies might participate in the AMC, and particularly whether there is room for the participation of manufacturers from disease-endemic countries who may not be ready to supply vaccines – on this issue GAVI kept the door open by awarding funds to manufacturers in tranches. Thirdly, some have questioned whether the AMC subsidy price plus the retail price of US$ 7.00 for the initial doses purchased was higher than what the public could afford. GAVI plans an evaluation of the AMC, which should inform the design of future AMCs.

With limited available evidence, the relative strengths and shortcomings of these different approaches are yet to be fully defined. Both push and pull mechanisms, and also the strategic use of public and philanthropic funding, could leverage additional private sector resources.

4. Gaps and challenges

The main gaps and challenges involved in combating antimicrobial resistance include the following:

Concerted action by stakeholders: Any government, UN agency, product development partnership, or NGO is unlikely to be successful in stimulating R&D if acting in isolation. Policies and actions to create an enabling environment for innovations in technologies and drugs to combat AMR require the concerted effort of various key stakeholders in both the public and private sectors.

Identifying gaps and setting priorities: Although numerous efforts are already being made to stimulate innovation, there are still many gaps in R&D across a range of health technologies for products targeting AMR containment. A priority-setting approach for R&D for health technologies that might, separately or in synergy, help combat AMR, could prove useful. Developing TPPs could help to organize and give focus to R&D. The co-development of diagnostics with drugs might accelerate clinical trial recruitment as well as lower R&D costs.

Alternative funding mechanisms: More could be done to improve funding mechanisms targeting R&D (push mechanisms) complemented by selected pull mechanisms coordinated and aligned around TPPs. Several options, including public co-financing, could be explored to ensure funding for R&D. This support can be tied to ensuring fair returns to the public, such as through lower prices and improved rational use, and help de-link return on investment from volume-based sales.

Involvement of developing countries in R&D: Initiatives to encourage and support institutions in developing countries, including small biotechnology firms and academic institutions, might bring new contributors to pharmaceutical innovation. They would face lower opportunity costs and be committed to scaling up products affordably. Specimen banks to facilitate diagnostics development, training in different aspects of R&D from medicinal chemistry to Good Manufacturing Practice (GMP), and technical assistance with the regulatory process are potential measures to build local infrastructure, so that disease-endemic countries can also participate in innovation.

Access to information: Obstacles in the diagnostics R&D pipeline also include deficiencies in the pooled knowledge of advances in biomarker research, the lack of access to clinical trial data, and other important scientific information. Broader access to compound libraries and research inputs, such as through open access repositories and open source collaboration, could lower the barrier to entry and enhance innovation.

Chapter 7.

The way forward: political commitment to enable options for action

Chapter 7.

The way forward: political commitment to enable options for action

The global health crisis due to antimicrobial resistance concerns us all. It is a question of whether or not there will be effective antibiotics to treat many important life-threatening infections in the future. AMR can be minimized, and despite knowledge gaps, the strategies and practical measures that work are well known and could be applied more widely. Mobilizing the necessary expertise and resources to mount a concerted effort to prevent and control AMR will depend on the commitment of policy decision-makers across the world.

The development of resistance by a growing number of pathogens to a growing number of antibiotics is a public health problem which has been steadily increasing for several decades. It has now reached a scale and distribution which led WHO to recognize AMR as a global public health crisis. AMR is both a medical and an economic problem, with consequences felt worldwide, including in lower-income countries where the burden of infectious diseases is generally greater and the availability, accessibility and affordability of medicines more limited. The preceding chapters of this book have examined the main contributing factors to the AMR problem and the strategies and measures needed to deal with them, highlighting the importance of governments in creating the enabling environment necessary to implement effective actions. Looking ahead, the overriding message from past experience is that AMR *can* be contained, if not totally prevented, and that a concerted effort could ensure that it will not constitute a significant public health threat in the long term.

The urgency of the AMR situation is now well recognized by most policy-makers, scientists, and professionals in relevant domains, and by civil society including patients' advocacy groups. Combating antimicrobial resistance was chosen by WHO as the theme for World Health Day 2011, to draw international attention to the urgency – "no action today, no cure tomorrow" – and call for political commitment and intensified efforts to apply the array of measures needed to alleviate the problem.[206] By setting out the main facets of the AMR situation – what drives it, what can be done about it – illustrated by practical experiences from around the world, this book seeks to encourage greater national and international efforts and further initiatives to counter AMR.

Experts agree that the recommendations made by WHO in the 2001 Global Strategy remain largely valid 10 years later, but their implementation is still far from universal or complete. To add impetus to national and international efforts, WHO has repeatedly called for action through a series of World Health Assembly resolutions[a]. All of these resolutions urged concerted efforts to tackle AMR at global level as a matter of urgency. The WHO regional offices have also sought to stimulate action through several regional resolutions and scientific forums.

International and national actions to address AMR have shown what can be done, often with good results, but usually these efforts have been limited in scope and lacking coordination. The reasons behind the lack of general worldwide determination to tackle AMR perhaps include a widespread assumption that

[a] 1998 «WHA 51.17 Emerging and other communicable diseases: antimicrobial resistance»; 2001 «WHA 54.11 WHO medicines strategy»; 2001 «WHA 54.14 Global health security: epidemic alert and response»; 2005 «WHA 58.27 Improving the containment of antimicrobial resistance»; 2007 «WHA 60.16 Rational use of medicines»; 2007 «WHA 60.20 Better medicines for children» (http://apps.who.int/gb and http://apps.who.int/gb/archive/).

scientific advancement will eventually resolve the problem by bringing in an endless supply of new and potent anti-infective medicines. But the reality is that there are only very few new antibiotics on the horizon, and this is not a priority for pharmaceutical companies, and so the effective lifespan of existing antibiotics must be prolonged by preventing and controlling AMR. As discussed in this book, there is broad international consensus on the key areas for action and the specific measures that need to be taken. As part of the six-point policy recommendations, the call to action on WHD 2011 highlights political commitment as a prerequisite for a comprehensive and coordinated multi-stakeholder effort against AMR. This book recognizes and stresses the crucial role of political commitment to lead and support concerted action in all relevant domains, for the benefit of populations worldwide. Decisions on interventions have to balance the need to provide effective antimicrobial therapy to patients today with the need to preserve the usefulness of medicines for future generations.

A number of strategies and measures have been implemented successfully, and not only in the wealthier countries, as shown by examples cited in this book. All of those require some level of political commitment, leadership and support. Sustaining and building upon these gains requires assured financial, human resources and infrastructure capabilities, as is true for most health programmes in many countries. A range of interventions are needed, but not all of them are necessary or relevant in all countries or settings. As local circumstances and current AMR statuses differ widely between and within countries, a country-focused situation analysis would be a logical initial step towards setting up a comprehensive anti-AMR programme. Prioritizing national strategies, measures and resources is essential and to this end, partnerships and closer collaboration could be fostered between policy-makers, academia, and appropriate professionals, managers, and interest groups. More collaboration is needed between disciplines within sectors as well. In the health sector, for example, between those involved in promoting the rational use of medicines and those in infection prevention and control. In producing this book, WHO seeks to stimulate thinking and policy action in this direction, by discussing the range of key issues and actions in one document, probably for the first time, to assist policy decision-makers, and raise awareness among all stakeholders concerned by AMR.

Interventions, such as those focussing on hospitals, pharmacies, medical and veterinary practices, are ongoing in many countries, but very few countries have nationally funded and coordinated comprehensive activities. These are mostly high-income countries with stronger management and infrastructure capabilities, which have progressed further in designing, implementing and sustaining AMR interventions and in networking and data collection. But where commitment, including from the political level exists, some less wealthy countries are also making important progress and showing the way for others. Strengthening health systems in countries where these are weaker is an issue for most public health initiatives, including national efforts to limit the development and spread of AMR. This would enable the countries to participate in, and benefit fully from, global efforts to deal with the problem. The commitment of policy decision-makers will be essential to ensure leadership and support for these efforts.

Although most of the large-scale actions described in this book have a ‘top down’ approach instated with government support, there are other successful examples where activities were initiated by a few motivated individuals and groups, and which were later developed stepwise to a nationwide scale. This is probably a useful model to follow, particularly where resources for large-scale national actions are not sufficient at the outset. It requires leadership and support from the political level fostering multi-stakeholder engagement and empowerment for action. To fill knowledge gaps regarding implementation, it is important to incorporate mechanisms to monitor and evaluate the impact, resource requirements and sustainability of the measures taken.

The role of WHO is to facilitate action worldwide through stimulating political commitment, advocating for action, shaping collaborations between different stakeholders, facilitating development of evidence-based guidance, norms and standards, and tools for countries to implement specific interventions and evaluations. WHO support is critical for strengthening global surveillance strategies and networks, and in defining an AMR research agenda.

Although there is more to be learnt about the impact of AMR on individuals, societies and countries, the need for additional information should not delay national or international anti-AMR initiatives, of which there are plenty of successful examples. And many more

opportunities for innovation could be exploited in areas spanning the spectrum from scientific discovery, R&D for new products, financing mechanisms, regulatory aspects, to marketing and service provision. Some very promising developments have already accrued from recent innovations in these areas.

Because AMR is a complex problem with many diverse contributing factors, tackling it effectively has to involve many individuals and groups in society. This may be perceived as a discouraging reality that could lead to apathy and inaction, with people feeling that their own individual effort is not worth making. On the contrary, efforts at all levels are essential and advocacy is needed to convince and encourage people, from patients to policy-makers, to make their special contribution, and to be part of the solution rather than part of the problem. Leadership by governments is, therefore, crucial to motivate, support and sustain these efforts, if the way forward is to be the way towards long-term availability of effective antimicrobial medicines.

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Appendices

Appendix 1

List of 2001 WHO Global Strategy for Containment of Antimicrobial Resistance recommendations

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

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.

* *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.

Appendix 2

2011 World Health Day six point policy brief

1. Commit to a comprehensive, financed national plan with accountability and civil society engagement

a. Provide stewardship and coordination
b. Cost plans and mobilize resources
c. Build Partnerships with civil society

2. Strengthen surveillance and laboratory capacity

a. Establish AMR surveillance and monitoring systems
b. Build laboratory capacity for rapid and reliable diagnostic testing
c. Engage in regional and global surveillance networks

3. Ensure uninterrupted access to essential medicines of assured quality

a. Reinforce the system for supply of essential medicines
b. Assure the quality of drugs according to international standards

4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care

a. Promote and enforce standard treatment guidelines
b. Enforce prescription-only use of antimicrobials
c. Promote education on antimicrobial medicines and their use
d. Reduce antimicrobial use in food-producing animals
    (i) Provide national leadership and promote intersectoral collaboration
    (ii) Create and enforce an enabling regulatory framework
    (iii) Strengthen surveillance and monitoring
    (iv) Promote education and training on antimicrobial use in food-producing animals
    (v) Reduce the need for antimicrobials through better animal husbandry
e. Work to reduce financial incentives that encourage irrational use of medicines

5. Enhance infection prevention and control

a. Ensure availability of IPC programmes across the spectrum of health care, that include core elements
b. Foster basic IPC standards in congregate settings
c. Promote standards IPC measures and provide education on IPC in the community setting

6. Foster innovations and research and development for new tools

a. Improve the use of current diagnostics and antimicrobials

b. Create incentives for new product development

c. Enable rapid regulatory processes for new tools and equitable access

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