Antimicrobial resistance in the Asia Pacific region: a development agenda

World Health Organization
Western Pacific Region

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Abbreviations

AMR	antimicrobial resistance
ASEAN	Association of Southeast Asian Nations
FAO	Food and Agriculture Organization of the United Nations
G7	Group of Seven
G20	Group of Twenty
GASP	Gonococcal Antimicrobial Surveillance Programme
GHIT Fund	Global Health Innovative Technology Fund
GLASS	Global Antimicrobial Resistance Surveillance System
JANIS	Japan Nosocomial Infections Surveillance
NAUSP	National Antimicrobial Utilization Surveillance Programme
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
R&D	research and development
SDGs	Sustainable Development Goals
TB	tuberculosis
UHC	universal health coverage
UNDP	United Nations Development Programme
WHO	World Health Organization

Executive summary

Antimicrobial resistance (AMR) is a serious public health concern with economic, social and political implications that are global in scope, and cross all environmental and ethnic boundaries. As a global threat, AMR risks the achievements of modern medicine, and has the potential to impact overall global development. It is important, therefore, to elevate AMR beyond health as part of a larger development agenda in the context of the Sustainable Development Goals (SDGs).

This report provides in-depth technical discussions in areas that have direct implications to the containment of AMR as a development agenda. The report is organized in five chapters which served as the technical background documents for the Biregional Technical Consultation on AMR in Asia, 14-15 April 2016. More information from the meeting is available in the WHO Meeting Report: Biregional Technical Consultation on Antimicrobial Resistance in Asia. The meeting was the first time senior officials from the Ministry of Health and Ministry of Agriculture across Asia came together to tackle AMR.

Chapter 1 discusses the importance and challenges of AMR and frames the containment of AMR as a development agenda. It also provides an overview of the recommendations from the Biregional Technical Consultation on AMR and the supporting technical discussions.

Chapter 2 highlights priorities for an integrated approach for addressing AMR by strengthening universal health coverage (UHC). It focuses on the use of drugs in outpatient settings. The chapter gives particular consideration to low- and middle-income countries with pluralistic health systems, where government provision and health markets combine and where people seek treatment for a large proportion of common infections in weakly regulated markets.

Chapter 3 describes the priorities for building robust systems for the containment of AMR. The chapter introduces six key elements that are critical to provide for robust, integrated and coordinated national systems for AMR: 1) governance, regulation and standards for AMR; 2) comprehensive, integrated national surveillance; 3) antimicrobial stewardship and reduced antibiotic use; 4) systematic infection prevention and control programmes; 5) research and development; and 6) education, communication and stakeholder engagement.

Chapter 4 advocates containment of AMR as a major policy objective in the context of the SDGs. AMR implies a health, social and economic problem that low- and middle-income countries and the world at large cannot afford.

Chapter 5 presents arguments to recognize the containment of AMR as a global public good, and discusses some policy directions and interventions to support regional actions to help tackle the problem. The rapid spread of AMR will ultimately deteriorate the health status of the population, with consequent losses in national income and tax revenues. AMR spans all countries as intensified global trade and travel contribute to its spread.

Without the containment of AMR, precious public goods in the form of antimicrobials are being jeopardized, leading to detrimental effects on human and animal health, the environment and ultimately in achieving the SDGs. It is imperative that global stakeholders collectively work towards preserving the efficacy of antimicrobials (current and new) to ensure that infections (in human and animals) can be effectively treated and to ensure food security and sustainable farming to ultimately support progress towards the SDGs.

Introduction

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1. Introduction

Antibiotics have long been regarded as one of the most significant medical achievements of the 20th century. These medicines have saved countless lives, including those of individuals living with diseases such as cancer or diabetes, and those undergoing surgical procedures. Unfortunately, this very success has accelerated the development of antibiotic resistance and, more broadly, antimicrobial resistance (AMR). Globally, the combined use and misuse of antibiotics and other antimicrobial medicines have accelerated the development of AMR to record high levels. The drivers of the spread and emergence of AMR are depicted in Figure 1.

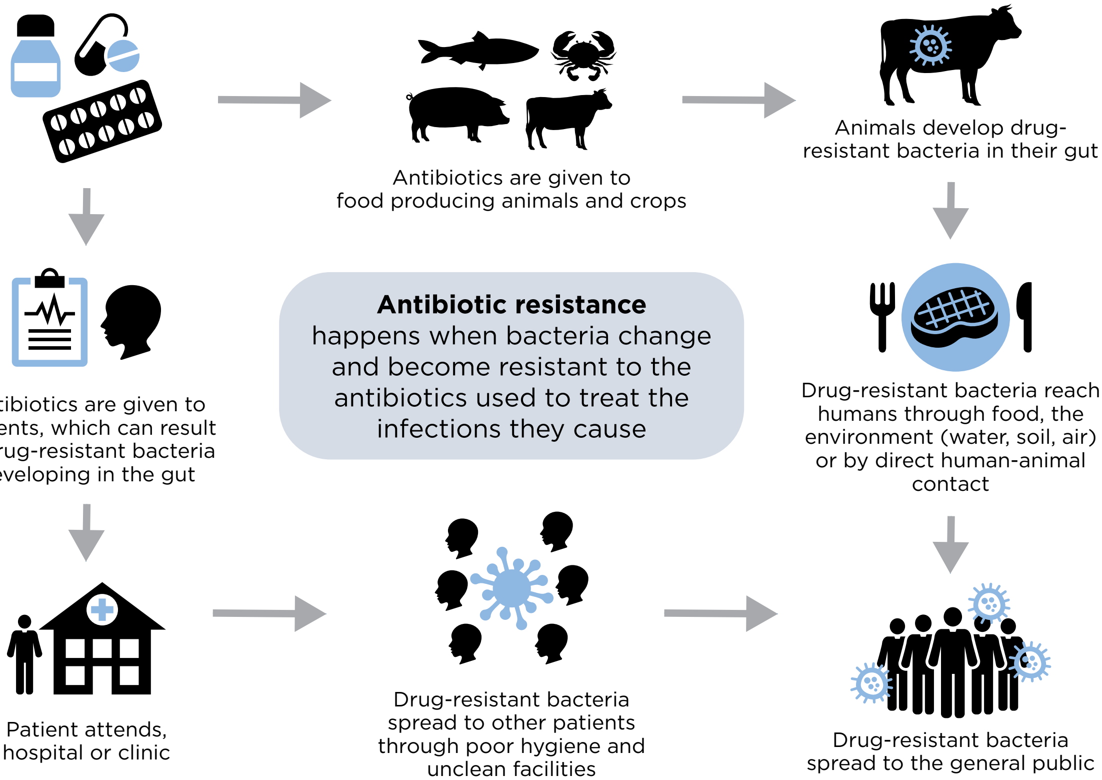
The 2014 *Antimicrobial resistance: global report on surveillance (1)* indicated that high levels of resistance have been observed in all six World Health Organization (WHO) regions to common bacteria that cause hospital- and community-acquired infections. A wide variety of infectious microorganisms are exhibiting resistance to single and multiple antimicrobials. The emergence of untreatable infections such as drug-resistant gonorrhoea *(2)* and the recent detection of plasmid-mediated colistin resistance mechanisms (MCR 1) in Enterobacteriaceae *(3)* highlight the need for containment efforts.

A systematic review on reported data of resistance to eight major bacteria in the Western Pacific Region and the calculated associated economic burden due to resistance estimated an economic cost of US$ 1.35 trillion in the Region over the next 10 years.[1]

The containment of AMR requires multisectoral, collaborative actions at the global, regional and national levels. In 2015, the results from a WHO survey highlighted gaps and challenges required for containment activities for AMR. The WHO *Worldwide country situation analysis: response to antimicrobial resistance (4)* showed that only a few countries have a multisectoral national action plan, although some did report having a national focal point for AMR or a national coordinating mechanism for AMR.

[1] World Health Organization unpublished data, 2016.

Figure 1. Illustration of the key drivers in the spread and emergence of AMR

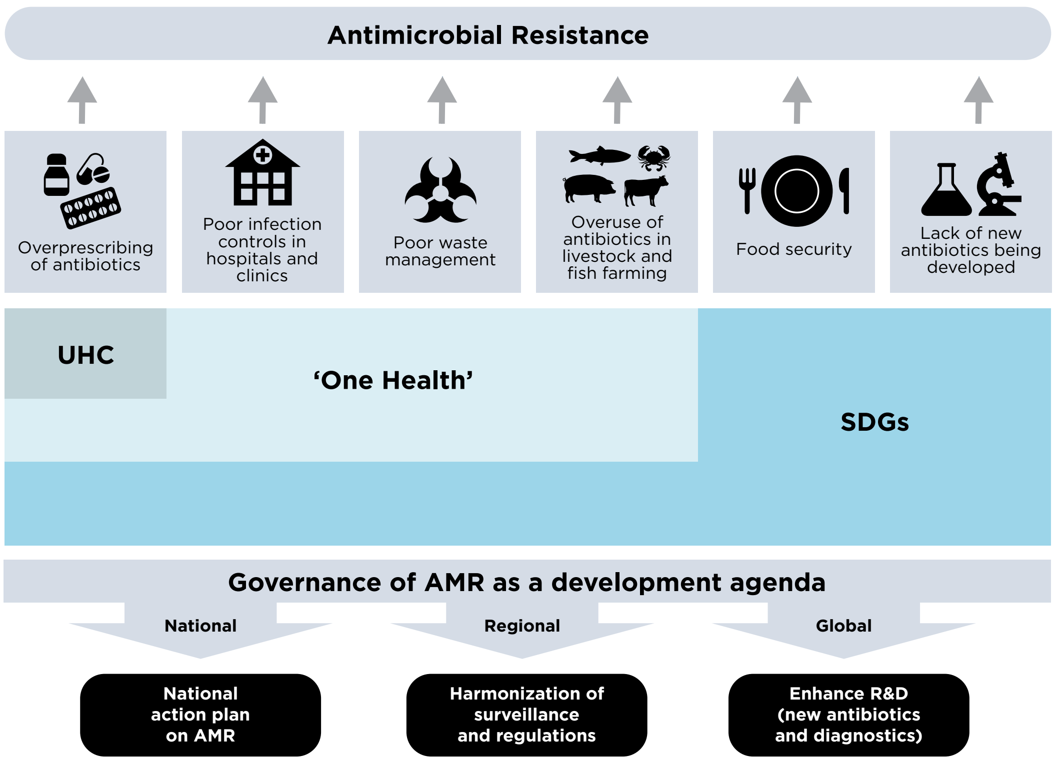


Source: World Health Organization, 2015.

1.1 Antimicrobial resistance as a development agenda

The spread and emergence of AMR threatens our ability to treat infections and ultimately the achievement of the Sustainable Development Goals (SDGs). Addressing this threat requires a whole-of-government political commitment and strategies to engage the general public, professionals and policy-makers across all sectors. Continued momentum to take action on AMR is imperative to ensure that antimicrobials remain effective for future generations. The Biregional Technical Consultation on Antimicrobial Resistance in Asia, which was held on 14-15 April 2016 focused on elevating AMR as a development agenda in the context of UHC, One Health and the SDGs (Figure 2). The meeting was the first time senior officials from the Ministry of Health and Ministry of Agriculture across Asia came together to tackle AMR.

Figure 2. Illustration to demonstrate the need for multisectoral approaches for the containment of AMR within the larger scope of achieving the SDGs



Without the containment of AMR, precious public goods in the form of antimicrobials are being jeopardized, leading to detrimental effects on human and animal health, the environment and ultimately in achieving the SDGs. It is imperative that global stakeholders collectively work towards preserving the efficacy of antimicrobials (current and new) to ensure that infections (in human and animals) can be effectively treated and to ensure food security and sustainable farming to ultimately support progress towards SDGs.

Box 1. Recommendations from the Biregional Technical Consultation on AMR in Asia, 14-15 April 2016, Tokyo, Japan

1. Promoting awareness and advocacy:

A. Accelerate advocacy for a whole-of-government political commitment to ensure sustained efforts are maintained to contain AMR at the local, national, regional and global levels;
- Organize ongoing public campaigns to increase awareness and change behaviour on sanitation, hygiene, infection prevention and control practices, and the responsible use of antimicrobials;
- Hold annual antibiotic awareness week campaign activities in all countries to deliver messages that address the challenges across the human, animal and agricultural sectors;
- Mandate inclusion of AMR stewardship into education programmes for personnel working in human and animal health, and agriculture sectors; and
- Seize opportunities through various policy entry points to stimulate ongoing political commitment such finishing the MDGs and progressing towards achievement of the SDGs.

2. Containing AMR through actions towards Universal Health Coverage (UHC):

A. Build resilient national health systems with clear accountability frameworks and mechanisms for implementing and monitoring actions to contain AMR at all levels;

B. Integrate strategies to slow the spread of AMR in national policies and plans for UHC development;
- Improve regulatory controls and health financing mechanisms (including quality assurance from manufacturers to authorized retailers and reducing financial incentives that contribute to inappropriate use) to ensure equitable access to quality antimicrobials to all who need them;
- Implement antimicrobial stewardship programmes with full national coverage to improve prescribing practices of health-care providers and ensure the rational use of antimicrobials;
- Develop and disseminate guidelines for diagnosis and treatment of common infectious diseases that take into account findings of surveillance of AMR;
- Develop and implement strategies to strengthen infection prevention and control in health-care and community settings; and
- Reduce the burden of infection through improved hygiene and sanitation, especially within poor and vulnerable populations.

3. Emphasize 'One Health' coordination mechanism in the implementation of national action plans:

A. Ensure harmonized multisectoral action across human and animal health, agriculture, food security and the environment with a clearly defined national governance mechanism that engages all relevant stakeholders and balances their interests and needs;

- Enact and enforce regulation of antimicrobials and control of the supply chain (including safe disposal and environmental controls) for humans, animals, agriculture and aquaculture;
- Develop and strengthen reliable, quality-assured surveillance systems to monitor the trends of drug-resistant pathogens and antimicrobial use in humans and animals;
- Limit the use of critically important antimicrobials for human health in food systems by improving the stewardship of antibiotics by animal health providers and promote sustainable agricultural practices;
- Optimize and expand vaccination programmes that can contribute to preventing AMR;
- Promote a concerted multisectoral food chain approach through using internationally recognized standards and guidelines such as the Codex Alimentarius and the OIE Standards and Guidelines; and
- Regulate production and domestic/international distribution channels of active pharmaceutical ingredients for antimicrobials and medicated feed;

B. Establish effective monitoring and evaluation through strong accountability and mechanisms to oversee the implementation of multisectoral national action plans.

4. Securing regional collaboration across Asia Pacific:

A. Harmonize standards and methodologies for surveillance of AMR and antimicrobial consumption across countries and strengthen human and animal health networks to share data and take appropriate policy action;

B. Share national experiences of successful regulatory practices to preserve the effectiveness of antimicrobials as a global public good in human and animal health;
- Enforce prescription or veterinary-equivalent-only sales of antimicrobials in human and veterinary medicine;
- Strengthen regulation on the use of critically important antimicrobials, based on scientific risk assessments, and phase out the use of antimicrobials as growth promoters in animals in the absence of risk analysis;

C. Strengthen regional capacities and mechanisms to enhance research and development for new diagnostics, vaccines and antimicrobials that utilize innovative financing approaches; and
- Increase commitments for research and development and innovation to facilitate investments, through a combination of incentives for new antimicrobials, diagnostics, vaccines and other interventions in human and animal health.

Chapters 2 to 5 of this document provided an in-depth technical discussion in four main areas for the containment of AMR as a development agenda which provided the technical background papers for the Biregional Technical Consultation on AMR in Asia. More information on the meeting can be found in the WHO *Meeting Report: Biregional Technical Consultation on Antimicrobial Resistance in Asia*. The recommendations from the meeting (Box 1) provide priority action areas for implementation of the *Communiqué of Tokyo Meeting of Health Ministers on Antimicrobial Resistance in Asia*, 16 April 2106, which was signed by 12 ministers of health across the Asia-Pacific.

Chapters:

Chapter 2 highlights priorities for an integrated approach for addressing AMR by strengthening universal health coverage (UHC). It focuses on the use of drugs in outpatient settings. The chapter gives particular consideration to low- and middle-income countries with pluralistic health systems, where government provision and health markets combine and where people seek treatment for a large proportion of common infections in weakly regulated markets.

Chapter 3 describes the priorities for building robust systems for the containment of AMR. The chapter introduces five key elements that are critical to provide for robust, integrated and co-ordinated national systems for AMR: governance, regulation and standards for AMR; comprehensive, integrated national surveillance; antimicrobial stewardship and reduced antibiotic use; systematic infection prevention and control programmes; research and development (R&D).

Chapter 4 advocates containment of AMR as a major policy objective in the context of the SDGs. AMR implies a health, social and economic problem that low- and middle-income countries and the world at large cannot afford.

Chapter 5 presents arguments to recognize the containment of AMR as a global public good, and discusses some policy directions and interventions to support regional actions to help tackle the problem. The rapid spread of AMR will ultimately deteriorate the health status of the population, with consequent losses in national income and tax revenues. AMR spans all countries as intensified global trade and travel contribute to its spread.

Antimicrobial resistance and universal health coverage

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2. Antimicrobial resistance and universal health coverage

For decades, governments and private companies in Asia have invested significant efforts and resources to make antimicrobial drugs widely available and convince people to use them. As a result, there are very few localities where someone with the symptoms of an infection cannot obtain antimicrobial agents for a price. Most countries have experienced dramatic reductions in deaths from common infections such as childhood pneumonia and postnatal sepsis, at least amongst the better off. There is an almost universal belief in the efficacy of antimicrobials and the demand for them is high. In many countries, access to antimicrobial treatment is now viewed as effectively a citizen's entitlement.

The emergence and spread of pathogens resistant to antimicrobials poses a big challenge to policy-makers, who need to oversee the transformation of a health system that evolved to provide easy access to these drugs into one that provides *access to appropriate antimicrobial treatment whilst reducing the risk of the emergence and spread of resistance*. They also need to persuade health workers, producers and distributors of antimicrobials and the general public that the right of access to the benefits of antimicrobials needs to be complemented by responsibility for preserving their efficacy. As factors influencing the supply and demand for antimicrobials are interdependent, strategic leadership is essential.

2.1 Universal health coverage and antimicrobial resistance

The strategies of the WHO Regional Offices for South-East Asia and the Western Pacific for addressing AMR emphasize the need for action to improve health system performance. Both regions have agreed strategies for making progress towards UHC, which can be defined as "all people having access to quality health services without suffering the financial hardship associated with paying for care". This paper argues that strategies for slowing the emergence of AMR should include measures to make substantial progress towards UHC. It also argues that countries need to clarify and make explicit how UHC strategies should take into account the challenge of AMR. The paper focuses on the use of antimicrobials for outpatient treatment of infections, as primary care is the most basic aspect of UHC. This does not imply that measures to improve the control and treatment of infections by hospitals are not also very important.

Table 1. Health system attributes and universal health coverage actions for addressing AMR

Health system attributes	Questions to be considered in addressing AMR	Actions for addressing AMR
Equity	Is there equitable access to measures to prevent and treat infections?	• Reduce the excessive burden of infectious disease amongst the poor by strengthening basic public health and prevention. • Ensure access to appropriate antibiotics at an affordable cost, including by the poor. • Ensure that measures aimed at reducing inappropriate use of antimicrobials do not interfere with access to them by the poor.
Quality	Are antimicrobials of sufficient quality and are they used appropriately?	• Regulate the quality of antimicrobials. • Include AMR in medical curriculum and training programmes. • Ensure that guidelines for treatment of infections take into account surveillance findings. • Ensure that advice on antimicrobial use provided to health-care workers and through advertisements in the media reflects best-practice guidelines and acknowledges the threat of AMR. • Increase access to low-cost diagnostic technologies for more accurate diagnosis.
Efficiency	Are there unnecessary expenses from overuse of antibiotics and the need to treat resistant infections with expensive drugs?	• Alter financial incentives that encourage overuse of antimicrobials. • Reduce need for expensive treatment of infections with resistant organisms.
Accountability	Are health-care workers and the general community adequately informed about how to use antimicrobials and reduce the risk of resistance?	• Provide information on surveillance findings. • Provide information on appropriate treatment for different infections.
Sustainability and resilience	Can a social coalition be created to preserve the long-term efficacy of antimicrobial drugs?	• Strengthen public health services and immunization to reduce exposure to infections. • Establish partnerships for management of antimicrobials. • Carry out awareness and educational campaigns to change understanding of health-care workers and the population on appropriate use of antimicrobials. • Invest in R&D of new drugs and new approaches for providing effective treatment of common infections.

There is tension between the objectives of reducing the risk of serious illness and death by treating infections and of preserving the efficacy of antimicrobials around the world and for future generations. The first refers to decisions that provide an immediate benefit to individuals and the second to decisions that can increase the risk of an untreated infection for these individuals whilst ensuring long-term benefits for others. This tension is made complicated by large inequalities between countries and between social groups in both the burden of infection and access to antimicrobial treatment. People are more likely to support actions to address AMR if they believe they are fair. For example, restrictions in access to antimicrobials should be accompanied by measures to ensure universal access to appropriate and affordable treatment of common infections, and investment in R&D of new antimicrobials should be complemented by investment in technologies and organizational arrangements to increase access to this treatment.

The way antimicrobial drugs are used reflects the overall performance of a country's health system. Table 1 identifies questions, relevant to AMR, associated with the equity, quality, efficiency, accountability and sustainability and resilience of the system. It also presents actions that can be taken to address these questions. The remainder of this section discusses these actions in more detail.

2.1.1 Population-level actions to decrease the burden of infections

The risk of emergence and subsequent transmission of antimicrobial genes can be reduced by several public health measures. These include reducing exposure to infections through contaminated water and food, reducing the susceptibility of people to infections as a result of reduced immunity due to malnutrition or untreated conditions such as HIV infection, and immunizing the population against common infectious diseases. These will involve actions to ensure access to clean water and achieve basic levels of sanitation and hygiene and sustained investment in disease prevention.

2.1.2 Ensuring access by individuals to effective and appropriate treatment of infections

Antibiotics are used in an array of different health system structures and markets. The following discussion focuses on low- and middle-income countries with pluralistic health systems, where government provision and health markets combine and where people seek treatment for a large proportion of common infections in weakly regulated markets (*5*). In these systems a wide variety of providers, in terms of their level of training and their relationship to the regulatory framework, supply antimicrobials. These arrangements have enabled people to obtain treatment for many infections and reduce mortality. However, there are problems with the use of substandard drugs, taking partial courses of treatment and overuse of antimicrobials. These problems are likely to result in treatment failure and encourage the emergence of resistance. The poor in these countries continue to experience a high burden of inadequately treated infections.

The simultaneous existence of insufficient access to antimicrobials and excess consumption creates special challenges for government action (*6*). When faced with the risk of serious illness, it makes sense for people to seek an antibiotic wherever it is available and take the risk regarding its efficacy and quality. Where it is difficult to get a specific diagnosis because of a shortage of skilled health-care workers or the high cost of care, it may make sense to take a combination of drugs that can treat potentially serious infections. Interventions need to ensure that people can obtain the appropriate antimicrobial (of acceptable quality) in the right dosage and at a price they can afford.

Enacting and enforcing laws that reserve the right to prescribe antibiotics to licensed health-care workers may not be realistic in many pluralistic health systems, where governments face a choice between denying many people access to life-saving drugs and turning a blind eye to nominally illegal practices. An alternative is for governments to strengthen their role as regulator and steward of the health sector and act to improve the performance of informal health workers and drug sellers in providing antibiotic treatment of common infections. This will require a combination of measures to ensure drug quality, encourage the use of treatment guidelines and alter incentives that encourage excessive use of antimicrobials.

2.1.3 Ensuring access to reliable information and advice

Access to reliable health-related information is an important element of strategies both to address AMR and to achieve UHC. Health workers, drug sellers and the general public make decisions about when and how to use antimicrobials in a complex health knowledge economy, which includes a number of actors *(7)*: health-care worker training institutes teach about the use of these drugs; government health services issue public health messages and organize special programmes, which sometimes recommend treatment without a specific diagnosis; companies that produce or distribute drugs provide information and advice to health-care workers and drug sellers aimed at increasing sales; advertising companies seek to influence the general public through the mass media; and the Internet and mobile phones have become important sources of health information and advice. Government regulators, organized professions and industry associations influence the behaviour of these actors.

Until recently, all these sources have emphasized the efficacy of antimicrobials in treating sickness and saving lives. The emphasis of policy debates has been on the right of access to these drugs. This has had a powerful long-term influence in many countries. Antibiotics have developed a reputation for being “strong” medicines with the capacity to cure a range of ailments *(8)*. Many patients expect to have access to these drugs. Trained and untrained health workers use antibiotics for any possible indication of infection, and they risk being accused of missing an infection if they deviate from this practice. Efforts to limit the use of antibiotics have to contend with these ingrained beliefs, norms and entitlements. Comprehensive and sustained public and medical educational programmes are needed that decouple antibiotics from their “cure-all” and risk-free associations.

A number of measures will be needed to align the knowledge economy with current scientific knowledge. Antibiotic guidelines for treating common infections need to be produced to take into account prevalent patterns of AMR (antibiograms). These guidelines should be incorporated into training courses and also supplied to formal and informal providers of health advice and antimicrobial drugs. The general public also needs access to basic information on when to use antimicrobials. Two important sources of information on antimicrobials are the publications that pharmaceutical companies produce and distribute and advertising on the mass media. Agreements will be needed to provide impartial advice on the use of antimicrobials. These agreements can take the form of voluntary standards or government regulations. In addition, it will be important to ensure that messages about the appropriate use of antimicrobials and the danger of AMR enter political discussions.

Efforts to improve surveillance for drug resistance are a cornerstone of the WHO Global Action Plan on Antimicrobial Resistance. Alongside the strengthening of surveillance systems, there needs to be sustained action to develop mechanisms for feeding evidence on resistance into up-to-date treatment advice. Such information needs to be made available to the public in a transparent and accountable way to foster public awareness and trust.

2.1.4 Drug systems

The organization of the value chain for production, distribution and supply of antimicrobials to patients strongly influences both the degree to which people have access to effective treatment of infections and the risk of emergence of AMR. In many countries there are serious problems with counterfeit and substandard products. The way antimicrobials are packaged also influences the way they are taken. For example, it would be possible to produce combination therapy products and package them in full courses of treatment.

The distributors of these drugs influence the people to whom they supply by providing information and advice – which cannot be considered impartial – and offering financial incentives to achieve a high volume of sales (*9*). The influence of sophisticated pharmaceutical marketing strategies, extending into the public, private and informal sectors, is considerable, often outweighing the influence of public health authorities. Strategies to reduce the proliferation of misleading information and perverse incentives throughout the supply chain are needed.

Measures to improve the governance of the value chain will involve government and private companies (*10*). Governments need to set basic quality standards for drugs. They may also set standards concerning treatment antibiotic guidelines and the contents of promotional and advertising materials. Effective interventions need the involvement of the pharmaceutical sector and leaders of the medical profession. They will need to support the enforcement of agreed regulations and professional and industry quality standards.

2.1.5 Treatment protocols

Over the years, the international community has supported a number of initiatives to ensure treatment of infections where people do not have easy access to a medical doctor. They have typically applied a syndromic approach in which people with symptoms of a childhood infection or of a sexually transmitted infection are treated with an antibiotic without a definitive diagnosis. Some initiatives have advocated prophylactic use of antibiotics by high-risk groups, such as sex workers. These initiatives have contributed to the now widespread public perception of the efficacy and strength of antimicrobials and to the high level of demand for them. The growing problem of

AMR is raising questions about these treatment strategies. Should we move towards combination therapies for different common infections to slow down the emergence of resistance? Is it possible to develop inexpensive and practical ways to diagnose and treat infections?

The precedent of the widespread adoption of artemisinin combination therapy for malaria suggests a similar strategy for the treatment of common infections with combination antibiotic therapy (*11*). However, the emergence of artemisinin-resistant malaria raises questions about the long-term sustainability of this approach. The alternative is to develop practical approaches for diagnosing and offering specific treatment for infections. One potentially important development is of low-cost diagnostic tests that could be used at scale. New tests are needed that can identify a specific pathogen or, at a minimum, distinguish between bacterial and viral infections, and also provide information on susceptibility to antimicrobials. This needs to be linked to the development of appropriate ways of organizing their use in countries without high levels of access to the formal health-care system (*12*). There are significant challenges to the development, regulatory approval and clinical integration of diagnostic tests that use new technologies. There is a key opportunity for private, non-profit and academic institutions to collaborate on this issue.

Research is needed to establish appropriate treatment guidelines for common infections in a context of changing patterns of AMR (*13*). Promotion of sequential use, cycling strategies or mixing strategies of different antibiotics have all demonstrated positive effects on the reduction of AMR (*14*). There is also a need to look more thoroughly at the scientific and societal perspectives of drug combination therapy as a means of combating drug resistance. As a first step, the scientific community will need to strengthen its assessment of appropriate usage, defining parameters for deciding which antimicrobials are effective in which areas of the world and useful at various levels of the health-care system. The findings need to be continuously reviewed and updated based on dynamics of use and evidence of emerging resistance.

2.1.6 Finance

The UHC strategies of the WHO Regional Offices for South-East Asia and the Western Pacific emphasize the need to reduce the financial burden of health care on poor families. Out-of-pocket payments by individuals account for a substantial share of total health expenditure in a number of countries. They account for 70% of total health expenditure in India, and 70% of those payments are for drugs. This section focuses on ways that strategies for health finance can take AMR into account. Many countries are increasing the contribution of the government and health insurance to total health expenditures. If a scheme covers outpatient treatment of infections, it can substantially reduce the financial barriers to access to antimicrobial treatment. This is likely to lead to increases in the use of these drugs. This can save lives, but it can also lead to excessive use. This is a particularly high risk if the payment of health workers and the facility is linked to the volume of drugs they supply. Measures to reduce the cost of antimicrobials to patients need to be complemented by actions to ensure that these drugs are used appropriately by providing treatment guidelines, monitoring the quality of treatment, altering the pattern of incentives and supporting surveillance for AMR.

In countries where the poor rely heavily on informal providers of health care and drugs, it may take a long time to provide universal health insurance. Other measures will be needed to increase access to effective treatment of common infections. One option is for government, donor agencies and philanthropic organizations to reduce the cost of antimicrobials through more effective procurement from manufacturers or supplying drugs at a subsidized price. This might involve programmes to address common infections such as childhood and postnatal infections. The provision of subsidized antimicrobials would need to be linked to measures to ensure they are used well by providing training and treatment guidelines and by measures to ensure the quality of drugs.

The Group of Seven (G7) and Group of Twenty (G20) are considering substantial investments in efforts to address AMR. A large proportion of these funds will be allocated to R&D of new antimicrobials. The plan is that the use of any new drugs would be severely limited to preserve their efficacy. It is important that there is also investment in measures to increase access to effective treatment of common infections. This will include development of new technologies and organizational arrangements to improve health system performance; it will also include funding the measures outlined above to reduce financial barriers to access to treatment and reduce exposure to infection and susceptibility to infections. This kind of combined investment strategy addresses the multiple factors that contribute to the emergence of resistance and acknowledges the need to ensure universal access to antimicrobials. It will increase the likelihood of winning wide political support. Without high levels of support, it may be difficult to prevent the production and commercial use of new antimicrobials that are developed.

2.1.7 Partnerships

The achievement of progress towards UHC, while containing AMR, hinges on partnerships and coalition building. The activities of a large number of stakeholders need to be aligned to the cause of providing *access to appropriate antimicrobial treatment whilst reducing the risk of resistance*. For a partnership to survive, each partner must believe that the benefits it derives from the effort of creating and maintaining it outweigh the potential losses from the constraints to pursuing its narrow interests. The way a partnership balances the interests of the different members reflects the governance arrangements put in place and the relative power of the different partners (*15*). Currently, powerful actors such as pharmaceutical companies, especially the generic manufacturers who supply cheap medicines to private providers, have not been sufficiently persuaded that entering into partnerships aiming to limit sales of antibiotics is in their economic interest.

The implementation of a sustained effort to induce systemwide changes in the use of antibiotics will require informed and committed coalitions at national, regional and global levels. Partnerships between the public and private sector, and the formal and informal sector, are especially important. Collaboration is also needed between those responsible for health prevention and heath provision. This may go beyond traditional health system boundaries, for instance involving municipal governments and utilities responsible for town planning, water and sanitation. Activities will need to build agreement on the importance of addressing AMR within the context of UHC and on the core elements of a strategy for achieving these goals. It will be important to ensure that the perspectives of poor and powerless people are taken into account so they are not required to bear unnecessary risks of treatment failure or high costs. One core aim of this kind of coalition would be to establish basic standards of conduct for health-care workers and for drug companies that emphasize the needs of patients and of the community. This may require new business and financial models to address existing incentives. These coalitions will need to be able to monitor progress in ensuring access to treatment and reducing inappropriate use of antibiotics. The government will need to build its capacity to play an effective role in this process.

2.2 Systems approach to addressing AMR

The discussion in the previous section illustrates the complex nature of the problem of both ensuring access to the benefits of antimicrobials and preserving the efficacy of these drugs. The different health system attributes are highly interdependent and stewardship requires a multilevel systems perspective (*6*). Interventions aimed at improving a health system attribute can have unintended consequences. For example, measures to improve quality by making antibiotics available only on a doctor's prescription may reduce equity by decreasing access to treatment by the poor. Also, strategies that focus disproportionately on one aspect of the system, such as ensuring access to treatment of infections, will have limited impact if basic public health and disease prevention are neglected.

AMR is affected by the use of antibiotics in human and animal health systems, and strategies for addressing it require a "One Health" approach. Bearing this broader context in mind, the system focus for UHC is on the suppliers and users of antibiotic drugs for human health and the local, national and global actors who influence them. Figure 3 shows drivers of AMR in the context of UHC (*16*).

Actions that are not based on an understanding of the interdependencies relevant to antibiotic supply and use may have relatively little impact. For example, qualified doctors often blame patients or the informal sector for inappropriate antibiotic use, when their practices are frequently no better. "Patient demand" is often noted to be a major factor in influencing inappropriate prescribing by health-care workers. However, observations of clinical interactions have not always confirmed this (*17*). Other factors that influence the decisions to use antibiotics need to be considered, such as perverse financial incentives and inadequate understanding of appropriate treatment guidelines.

There are no blueprints for implementing multilevel changes at scale in complex and rapidly changing contexts. These changes include measures to address immediate problems, such as inadequate access to treatment and problems with drug quality, and the longer-term need to change attitudes and create more effective mechanisms to govern and manage antimicrobial use. It is important to employ a learning approach to the management of this kind of system change. Governments, in partnership with WHO regional offices, will need to take the lead. This could involve: (a) undertaking studies of the factors influencing the performance of specific aspects of the system in different contexts; (b) experimentation with promising interventions with the aim of applying lessons at scale; (c) monitoring responses to policy initiatives to identify unexpected outcomes; and (d) reflexive approaches to planning and stewardship that involve all actors in building common understandings of the challenge and of potential pathways of development.

National action plans need to take into account regional and global interdependencies. The dense transportation links in Asia and the movement of very large quantities of goods and people mean that AMR genes can travel very quickly between countries. Also, the behaviour of international pharmaceutical companies and international media influence national systems. Countries with larger national incomes and higher levels of economic and social organization have a stake in the success of measures by relatively low-income countries to reduce their burden of infectious diseases and increase access to effective treatment. Measures to address AMR will need to be built on the foundation of strong regional and global agreements to actions that address the concerns of all countries and all social groups.

2.3 Priority actions for integrating a concern for AMR in universal health coverage

This section outlines actions that governments and key stakeholders can undertake to strengthen efforts to address AMR. These actions need to be part of a strategy that takes into account interactions between different parts of the health system. Implementing these actions requires leadership that is committed to making substantial improvements in current patterns of use of antimicrobials and has the capacity to learn from experience what works and what does not. The change from a system aimed at increasing use of antimicrobials to address problems of infection to one aimed at ensuring access to effective and affordable treatment of infections, and also at reducing the risk of AMR, is a long-term project.

Countries with relatively weak management and regulatory arrangements will need to address serious problems with current patterns of antimicrobial use through a range of measures, including:

- improved access to appropriate and affordable treatment of infections, especially for the poor;
- enactment and enforcement of regulations to ensure the efficacy and safety of antimicrobials;
- development and dissemination of guidelines for the treatment of common infectious diseases that take into account findings of surveillance of AMR;
- realignment of incentives within drug value chains and delinking health worker income from the volume of antimicrobial drugs supplied;
- improvements in basic public health and disease prevention;
- measures to reduce financial barriers to access to antimicrobial treatment of infections, linked with measures to encourage rational use of these drugs;
- organization of a public information campaign to increase awareness of how to use

- antimicrobial drugs and of the challenge of AMR;
- creation of partnerships, across the plurality of providers of drugs and information, that foster shared visions, interests and commitments;
- building capacity for iterative learning, especially for the rapid uptake and integration of surveillance and scientific information into treatment guidelines;
- strengthening the government capacity to play a role as regulator and steward of the health system, incorporating oversight of the private and informal sector.

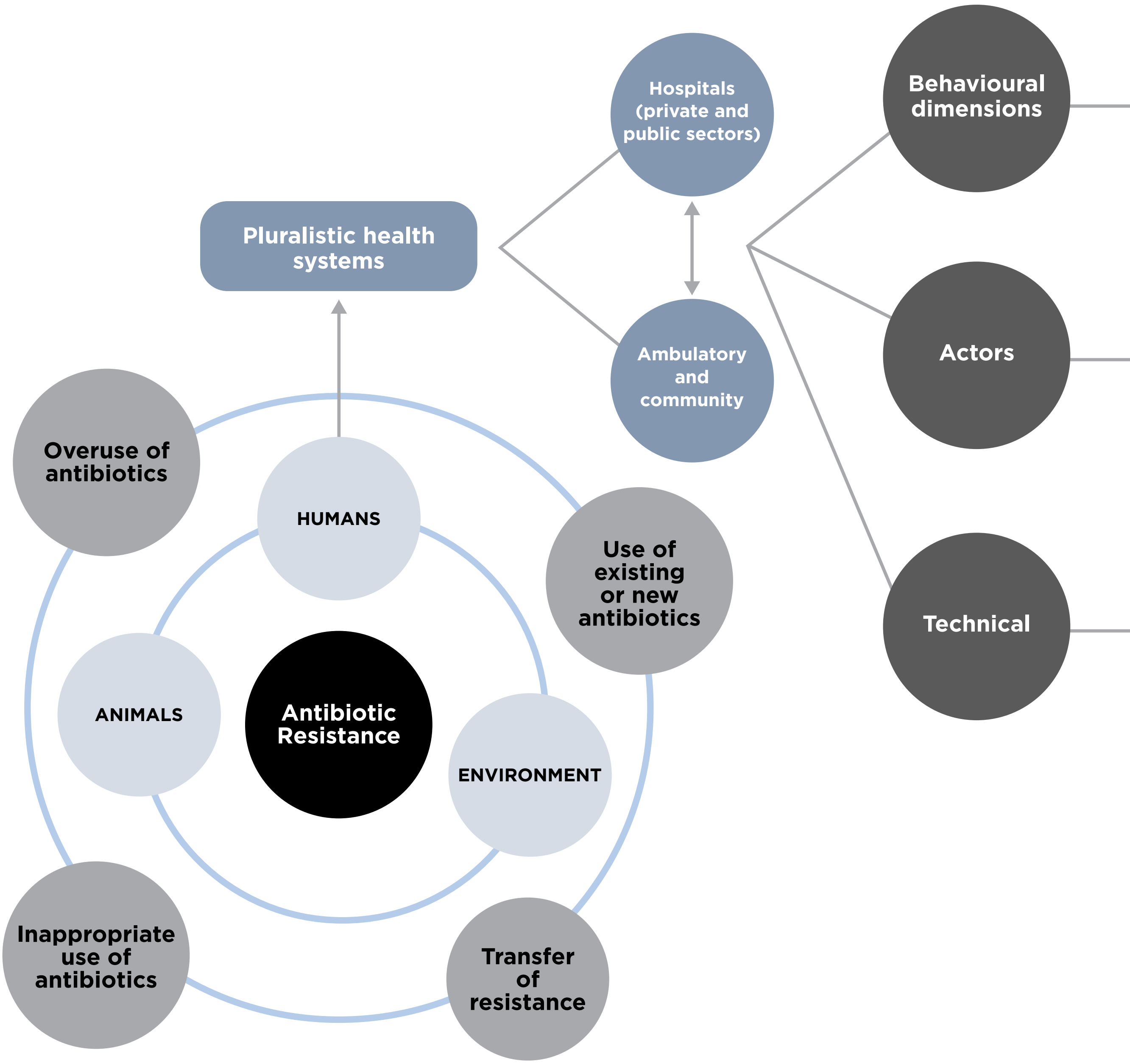
Other countries can give more emphasis to measures that enable accurate diagnosis of infections and more specific treatment. They need to alter the understanding of health-care workers and the general public about the appropriate use of antimicrobials and the measures needed to preserve their efficacy. They also need to invest in R&D of new drugs and new strategies for diagnosis and treatment of infections.

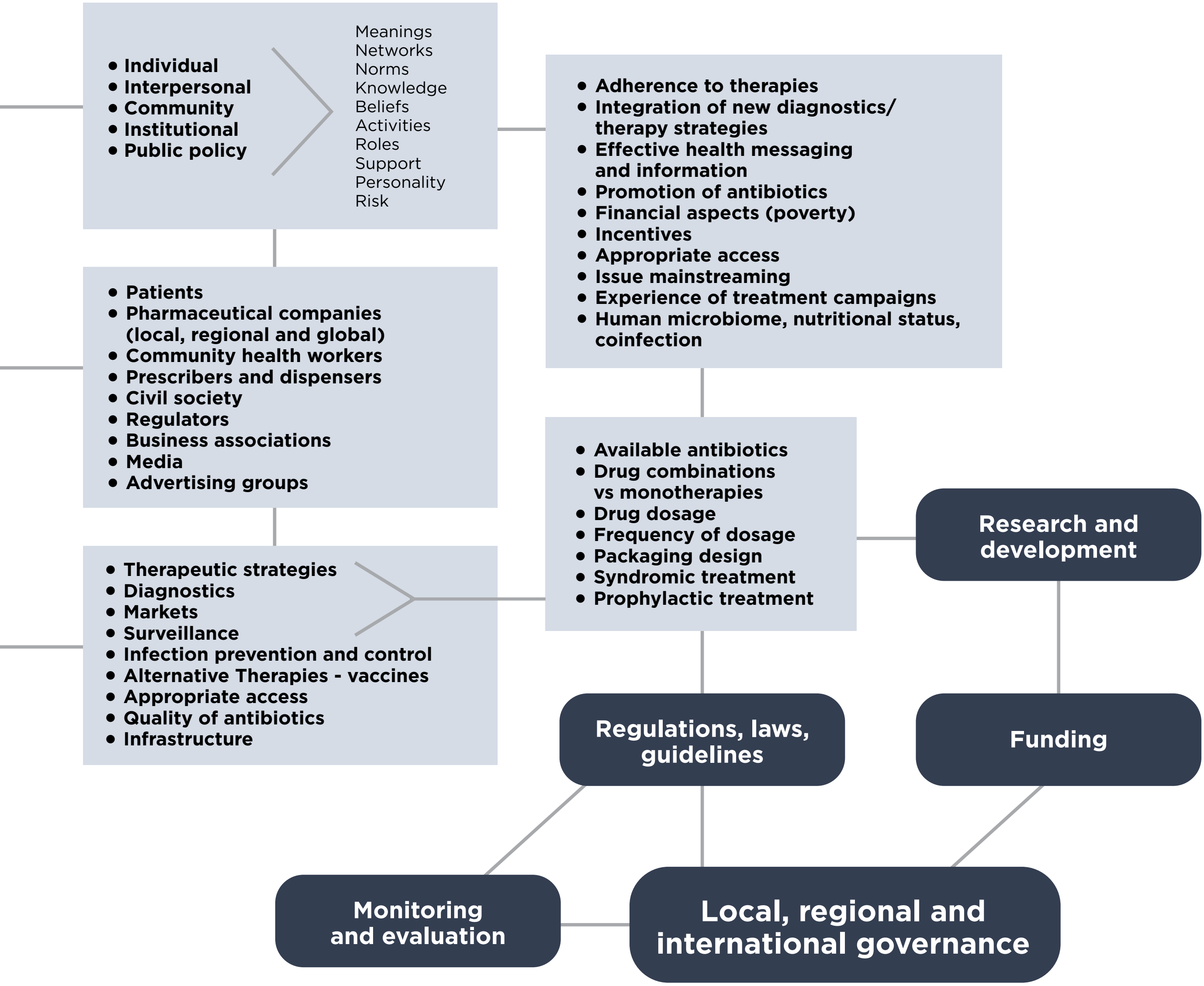
Measures to address AMR will need regional and global responses aligned with the regional action agenda (Western Pacific Region) and strategy (South-East Asia Region) and the Global Action Plan on Antimicrobial Resistance, which address the concerns of all countries and all social groups. Actions need to be formulated and implemented with the involvement of health professional bodies, training institutes and the pharmaceutical industry, as well as governments. The actions will need to address immediate problems and engender a long-term and sustained change in popular understanding of the role of antimicrobials and in the systems that govern their use.

Key policy implications

- Investment in (a) R&D of new antimicrobials; (b) innovative technologies and organizational arrangements to provide access to appropriate and affordable treatment of infections; and (c) support for the management of system changes in low- and middle-income countries.
- Strengthening of surveillance of AMR and the development and wide distribution of appropriate treatment guidelines.
- Establishment of codes of good practice regarding provision of information on antimicrobial use and marketing them to health workers and drug sellers.
- Measures to reduce financial barriers to effective and affordable treatment of infections through health insurance or subsidizing the cost of drugs for the poor.

Figure 3. A complex system: human drivers of antibiotic resistance in pluralistic health systems





Local epidemiological context:
e.g. prevalence rates, population demographics, drug-pathogen interactions

Building robust systems for antimicrobial resistance

3

3. Building robust systems for antimicrobial resistance

AMR is a critical health issue, with urgent action being called for by WHO *(18, 19)*. Some resistant bacterial pathogens that were originally primarily the concern of hospitals are now seen with increasing frequency in the community, and patients are arriving in hospitals carrying resistant bacteria acquired in the community setting. These bacteria produce infections that are difficult to treat and have an impact on clinical care. AMR contributes to increased patient illness and death, the complexity of treatments and the duration of hospital stay (*20*, *21*).

Scientifically, AMR is a complex and important issue; no one action alone will provide an effective response. The situation is exacerbated by the ability of many bacteria to share genetic material and pass on resistance genes, and the inadvertent transportation of resistant bacteria through international travel and, in some cases, medical tourism.

Socially, the evolving threat that AMR presents to human health is demonstrated by evidence showing that AMR, including multidrug resistance, is increasing among many pathogens responsible for infections in health-care facilities and in the community (*22*, *23*). Moreover, the frequency of resistance to antibiotics used to treat human pathogens is rising at varying rates in different parts of the world; the highest rates are reported in Asia, Africa and South America (*20*).

All antibiotics in common use for human health have been impacted by the development of resistance. While some antibiotics were able to be used for several decades before resistance was seen, for others the time difference for the development of resistance has been much shorter. Those antibiotics for which the development of resistance was slower, such as vancomycin, were highly valued because of their continued ability to treat infections that had become impervious to other commonly used antibiotics. The increasing level of vancomycin resistance is now an example of the significant concern being experienced as some types of bacteria, such as vancomycin-resistant enterococci, have changed their profile from being of little concern in human health to a cause of significant morbidity and mortality, particularly in hospital settings (*24*).

Antibiotics are regarded as basic and essential components of contemporary health care for all, globally. They are used to provide essential prophylactics for complex surgery, intensive care, organ transplants, survival of people with suppressed immune systems and the elderly (*19*, *25*). And yet, it is the use of antibiotics that is the key contributor to the development and spread of AMR. However, there is clear evidence that demonstrates that the rate of spread and extent of occurrence of AMR, albeit natural phenomena, are dependent on the appropriate and inappropriate use of antibiotics.

Some issues of particular concern include:

- inappropriate use of antibiotics, such as taking antibiotics to treat upper respiratory tract infections that are caused by a virus;
- lack of compliance with appropriate antibiotic therapy, such as missing doses or ceasing a course of antibiotics before cure, in which case bacteria are exposed to less-than-effective doses of the active agent, which facilitates their ability to develop and spread resistance;
- treatments that are prolonged beyond cure, leading to resistance in commensal bacteria, which can be transferred to pathogenic bacteria;
- prolonged use of prophylactic antibiotics after surgical procedures; and
- use of antibiotics in primary industries.

Existing efforts to address AMR have focused largely on human health. However, as AMR extends across both animal and human health, achieving real progress requires a national response employing a whole-of-system perspective, with a joint, coordinated response across governments, industries, educators, health and veterinary professionals, and the community. Responding effectively to the challenges of AMR involves a combination of monitoring and surveillance, targeted activity on specific organisms, regulation, research and education.

3.1 Contemporary responses to antimicrobial resistance

3.1.1 Moving beyond the single disease approach towards One Health

Approaches by countries should consider a collaborative effort to change those practices that have contributed to the development of resistance and implement new initiatives to reduce inappropriate antibiotic usage and resistance.

The One Health approach to action provides an opportunity to find common ground across sectors and develop a unified management plan. The approach should be predicated on key strategic principles that are empirically driven, including at the practice level. With respect to AMR and antibiotic usage, fundamental practices such as the "five Rs" (reduce use, refine use, replace antibiotics, regulate, research), underpinned by risk assessment and outcome effectiveness measures, are critical (*26*).

3.1.2 Internationally integrated national approach

WHO has been active in AMR and antibiotic usage for many years. In 1988, WHO announced the Global Strategy for Containment of Antimicrobial Resistance (*27*) to contain the spread of antimicrobial-resistant bacteria and prevent new antimicrobial-resistant bacteria from emerging.

This strategy called on Member States to implement programmes to prevent AMR, including through surveillance, education and policy development. Programmes were encouraged to extend surveillance to neighbouring countries or regions where appropriate, including countries that are less developed. A number of reports have followed (*1*).

The first WHO report on AMR surveillance clearly demonstrated the need for an improved and coordinated global effort, including sharing of surveillance data to better understand the overall morbidity and mortality of AMR, and the economic burden and societal impact of resistance (*1*). The control of other disease-specific programmes, such as tuberculosis, HIV and malaria, has been possible through engagements of governments, public health authorities, laboratories and surveillance bodies to inform strategic planning and action. The same sustained effort by governments is required to address AMR. Long-term commitment and resources to guide interventions and to measure the impact on the population are needed, and actions should be undertaken at national level to achieve containment and prevention of AMR.

The following sections describe the responses that can be undertaken at national level to address AMR, and provide examples of how the responses have been put into action.

3.2 Building effective and efficient systems for surveillance and reporting of AMR: guiding objectives

For internationally integrated national health systems for AMR and antibiotic usage to be effective and efficient, they must be guided by core scientific and social objectives that are mutually agreed and acted upon by all stakeholders. The prevailing AMR systems should (*24*):

- strengthen the capacity to conduct effective AMR surveillance activities and improve the flow of surveillance information;
- integrate bacterial isolate and resistance data from multiple databases to provide standardized reporting, and comparative and validated information sets;
- improve the use of information to detect changes in resistance patterns over time, and between geographical areas and institutions;
- improve the use of information to support rapid detection and response to emerging threats;
- provide guidance to public health authorities in responding to community and hospital outbreaks of resistant organisms;
- monitor the impact of interventions undertaken to reduce the levels of AMR;
- evaluate the impact of therapy and infection control interventions on infection rates and cure rates;
- strengthen laboratory capacity and performance through quality activities and review of reporting;
- provide timely AMR data that constitute a basis for policy decisions at both state and national levels;

- provide the capacity to link AMR data from health-care settings with information from other systems associated with antibiotic use, and veterinary and food industries; and
- initiate, foster and complement scientific research within countries in the field of AMR;
- provide advice to regulatory authorities on the availability and accessibility of antimicrobials based on the potential for resistance selection.

Moreover, to be effective and efficient, national systems for AMR and antibiotic usage should vertically integrate with international approaches and systems. Doing so maximizes economies of scale and the traction of whole-of-society responses to AMR. Too often the efficacy of one or more national systems is eroded by the structure and processes (or lack thereof) of other national or regional jurisdictions. Global cooperation, with local tailoring of technical, scientific, governance, policy, financial and jurisdictional levers and constraints, is required. Fundamental to the success of future strategies is prudent, collaborative agreement on the ownership of, access to, and utility of data that are gathered, generated and stored.

3.3 Guiding elements

AMR extends across both animal and human health, and to achieve real progress any response must take a whole-of-system perspective and be jointly developed, coordinated and workable across governments, industries, educators, health and veterinary professionals, and the community.

Governments must recognize that responding effectively to the challenges of AMR will involve a combination of regulation, monitoring and surveillance, targeted activity on specific organisms, research and education. Implementation of an internationally integrated national AMR strategy is required, which in itself must be multifaceted and must address a range of dimensions of AMR. Using the Australian response as a model, any such strategy should comprise the following key elements (*28*):

Element 1: Governance, regulation and standards for AMR
Element 2: Comprehensive, integrated national surveillance
Element 3: Antimicrobial stewardship and reduced antibiotic use
Element 4: Systematic infection prevention and control programmes
Element 5: Research and development
Element 6: Education, communication and stakeholder engagement

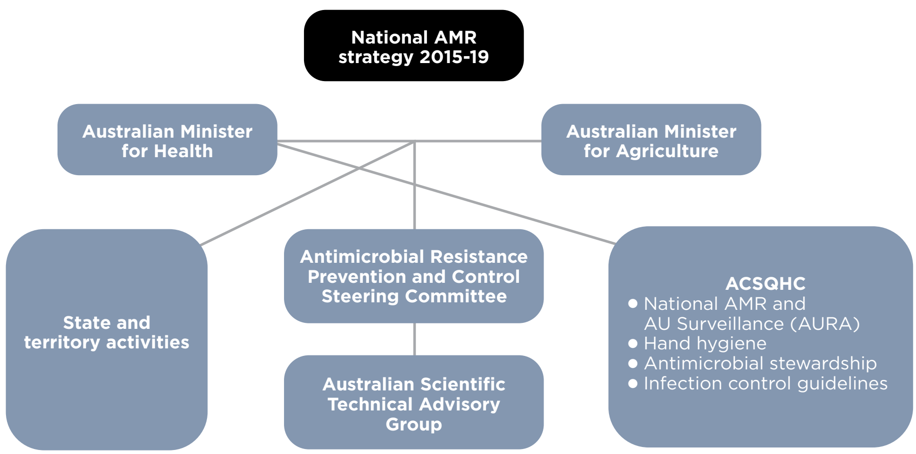
Element 1: Governance, regulation and standards for AMR

Effective and efficient governance is required to bring about internationally integrated national AMR programmes. In practice, this should occur formally at the highest levels of government through establishment of an AMR prevention and containment steering group to undertake leadership, oversight and coordination of a jurisdiction’s efforts to prevent and contain AMR. The steering group aims to provide accountability for the implementation of the national AMR strategy and ensure alignment with the WHO Global Action Plan, thus supporting global and regional efforts to prevent and contain AMR, in the recognition that no single country can manage the impact of AMR on its own.

The work of any such group is underpinned by a One Health approach, which provides a coordinated, collaborative, multidisciplinary and cross-sectoral approach in the development of health strategies for people, animals and the environment (*29*). In Australia, governance of the National Antimicrobial Resistance Strategy 2015–2019 is the responsibility of the highest level of government (Figure 4). The Australian Antimicrobial Resistance Prevention and Containment Steering Group, which is led by the Secretaries of the Australian Government Departments of Health and Agriculture and includes the Chief Medical Officer and Chief Veterinary Officer, oversees implementation and reports publicly on AMR (*28*). The Australian National Antimicrobial Resistance Strategy objectives are:

- increasing awareness and understanding of AMR;
- implementing effective antimicrobial stewardship practices to ensure the appropriate and judicious prescribing, dispensing and administering of antimicrobials;
- developing nationally coordinated One Health surveillance of AMR and antimicrobial usage;
- improving infection prevention and control measures to help prevent infections and the spread of AMR;
- agreeing on a national research agenda and promoting investment in new therapeutic and diagnostic products;
- strengthening international partnerships and collaboration on regional and global efforts to respond to AMR; and
- establishing and supporting clear governance arrangements at all levels to ensure leadership, engagement and accountability for actions to combat AMR.

Figure 4. Governance and regulation of AMR in Australia



In 2013, the Australian Commission on Safety and Quality in Health Care introduced the National Safety and Quality Health Service Standards, which require every Australian hospital and day procedure service to implement infection prevention and antimicrobial stewardship programmes. It is anticipated that the standards will play a significant role in helping to improve the appropriateness of antimicrobial usage in Australian hospitals. Hospital accreditation criteria for antimicrobial stewardship in Australia include:[2]

- have an antimicrobial stewardship programme in place;
- provide prescribing clinicians with access to current therapeutic guidelines;
- undertake monitoring of antimicrobial use and resistance;
- take action to improve the effectiveness of antimicrobial stewardship.

Element 2: Comprehensive, integrated national surveillance

Effective surveillance is the cornerstone of efforts to control AMR. At the local level, the data are used to formulate recommendations for rational antibiotic use, to develop standard treatment guidelines, and to ensure that health-care providers comply with recommendations. At a national level, data on resistance and use can inform policy decisions, such as development or revision of essential medicines lists, and identification of priorities for public health action to reduce the impact of AMR, such as education campaigns or regulatory measures. Conversely, lack of surveillance can lead to misdirected and inefficient policies, waste of limited resources, inappropriate therapy and ultimately human suffering and death through the inability to provide an effective drug to patients in need (*24*). Box 2 outlines some of the barriers to a system of surveillance.

Box 2. Barriers to a system of surveillance

Many of the barriers to a coordinated system of surveillance and reporting, and the limitations of existing antimicrobial containment initiatives, are known. The surveillance of AMR pathogens may be sporadic, largely due to technical and financial constraints. More informal networks may collect selective information, albeit with considerable delay. A lack of information technology (IT) infrastructure is frequently cited as a barrier to the implementation of comprehensive AMR surveillance and antibiotic usage programmes. Lastly, while several networks provide guidance for reporting AMR, none have successfully functioned as an early warning system (*30*).

Information on the prevalence and trends of AMR is needed at the local, national and international levels to guide policy and detect changes that require intervention strategies. Such monitoring programmes should be continuous and standardized, enabling comparison between countries as well as over time. The main aspects to be considered in establishing a monitoring system include animal or food groups to be sampled, the number of samples to take and the strategy for collection, bacterial species to be included, methods for susceptibility testing, antimicrobials to test, breakpoints to use, quality control, data to be reported, analysis and interpretation of data, and reporting (*31*). Box 3 provides some recommendations for a surveillance programme, and Box 4 summarizes the experience on surveillance in the Western Pacific Region.

[2] National Safety and Quality Health Service Standard 3.14.3 specifies that monitoring of antimicrobial usage and resistance is undertaken in eligible health services.

Box 3. Recommandations for a surveillance programme

WHO recommended that the programme's priorities be based on local epidemiology, and existing resources and infrastructure; the specific features would be largely dependent on the types of infections seen most frequently and the local health-care setting. At a national level, priority objectives included monitoring infection and resistance trends; developing standard treatment guidelines; assessing resistance-containment interventions; and setting up an early alert mechanism for novel resistance strains and prompt identification and control of outbreaks (*32*).

To support surveillance at multiple levels, the WHO Collaborating Centre for Surveillance of Antibiotic Resistance developed and supported WHONET software to manage and share microbiology testing. WHONET is used in more than 110 countries to support local and national surveillance in more than 1700 laboratories (clinical, public health, food and veterinary). In most of these countries, the WHONET software is used as a core component of the national surveillance programme (24).

AMR surveillance systems that demonstrate high levels of uptake and produce information that is useful at both local and national levels for driving developments in policy and practice across broad networks and geographies typically exhibit most, or all, of the following features (*24*):

- centralized coordination and direction setting, involving clinical experts and policy-makers;
- standardized data sets derived from pathology laboratory systems;
- quality-assured laboratory services providing the data;
- structured data submission and management protocols;
- a defined set of organisms, antibiotics and specimen sites for which data are gathered (which may be narrow or broad);
- a high level of participation from pathology laboratories in all sectors;
- a centralized database that receives laboratory data, preferably online;
- a centralized data-processing location that is resourced to undertake analysis and facilitate reporting;
- publicly available online access to reports and information that address a range of priorities and purposes;
- defined funding support, usually from government;
- the ability to link with data from other systems, such as those monitoring antimicrobial use, and AMR in animal and food sources;
- the ability to demonstrate trends across time, between geographical locations and between population groups, such as inpatients and outpatients;
- the ability to promptly detect and support investigation of emerging threats;
- outputs that support policy development at a national level, and guideline development and modification at a local level; and
- regular reports that measure and report on the impact of interventions.

Box 4. Surveillance in the Western Pacific Region

The Western Pacific Region WHO-coordinated surveillance programmes have been active. The Regional Programme for Surveillance of Antimicrobial Resistance was operated by the WHO Regional Office for the Western Pacific from 1990 to 2000, and involved 14 laboratories in 13 countries reporting on 26 species of bacteria across all sample types (*33*).

A new working group has been formed to focus on AMR and, in October 2011, the Regional Committee for the Western Pacific asked Member States to take urgent action, including the monitoring and assessment of AMR across the Region (*34*).

Implementation of the global policy in the Region is constrained by a lack of laboratory capacity to confirm AMR, and weak surveillance systems to detect it in a number of Member States. However, some accomplishments have been made, including:

- developing a training package on the rational use of antimicrobials for countries that are a part of the Association of South-East Asian Nations (ASEAN);
- conducting national advocacy workshops on AMR;
- increasing public advocacy on the rational use of antimicrobials; and
- providing technical support for pilot implementation of a minimum training package.

Future plans include finalizing an AMR Technical Strategic Framework, supporting joint ventures to help countries develop comprehensive multidisciplinary national plans to address AMR, and mobilizing resources to support implementation of the AMR Technical Strategic Framework (*35*).

Laboratory considerations

To enable data comparison, it is critical that uniform testing and reporting standards apply across medical and veterinary diagnostic laboratories to ensure methods are calibrated against the ISO reference standard where possible. At present, there is variation between the data sets held in surveillance systems, which may make data comparison at a national level difficult. Different susceptibility testing standards are used in Australian medical and veterinary diagnostic laboratories.

These standards are not always concordant on what is considered “susceptible”, “intermediate” or “resistant”, meaning that resistance in a bacterium identified in one laboratory may be reported differently in another laboratory. This variability in standards is particularly pronounced in veterinary laboratories. Quality assurance of all participating laboratories and harmonization of the laboratory information and surveillance systems are fundamental.

The importance of a One Health approach to AMR requires the examination of issues beyond human factors and dimensions. Animal and agricultural dimensions are major considerations. A significant knowledge gap exists in understanding the extent to which resistant bacteria are present in the wider global and regional food chain and the risks the presence of resistant bacteria, whether pathogens or indicator organisms, pose in food. The 2007 study, *Pilot*

Surveillance Program for Antimicrobial Resistance in Bacteria of Animal Origin (*36*), found that antibiotic resistance was present in some indicators and pathogenic bacteria in food of animal origin in Australia, but overall the impact at population level on human health was likely to be small. More surveillance data and research are required to better understand the pathways and extent of transmission of resistant organisms through foods of animal and non-animal origin and the risks this may pose to human health.

Element 3: Antimicrobial stewardship and reduced antibiotic use

Reducing antimicrobial usage is one element of a comprehensive national approach to preventing and containing the spread of AMR. Reducing inappropriate antimicrobial usage requires collaboration between experts, regulatory authorities and producers, and integrated monitoring of the effects of interventions is essential. Therefore, a One Health approach, which encourages collaboration between medical and health professions, veterinarians, farmers, food safety specialists and other experts, is critical in the monitoring and control of activities when addressing transmission of zoonotic and commensal AMR bacteria (*37*).

The appropriate and judicious use of antimicrobials is essential to slowing the emergence of resistance. Antibiotic use contributes to the development of resistance by increasing the selection of resistant strains. Inappropriate and injudicious use exacerbates the problem.

Antimicrobial stewardship is one of the most important and effective interventions in promoting appropriate use. In general terms, the programmatic effective and efficient use of antimicrobials in clinical settings is known as antimicrobial stewardship. It is a systematic programme within a health-care institution to optimize antimicrobial use among hospital patients in order to improve patient outcomes, ensure cost-effective therapy and reduce adverse sequelae of antimicrobial use, including AMR (*38*).

In some countries antimicrobial stewardship is maturing in the hospital sector but stewardship strategies need to be developed and enhanced for antimicrobial use in the community, including residential facilities for the care of older people. R&D in stewardship initiatives, include what does and does not work, would benefit from regional and global attention.

Antimicrobial stewardship refers to coordinated actions designed to promote and increase the appropriate use of antimicrobials and is a key strategy to conserve the effectiveness of antibiotics. In health-care settings, antimicrobial stewardship programmes have been shown to improve the appropriateness of antibiotic use; reduce institutional rates of resistance, morbidity and mortality; reduce health-care costs, including pharmacy costs; and reduce the adverse consequences of antibiotic use, including toxicity (*39*).

Studies have demonstrated that changing the way antibiotics are used in humans does result in a decrease in the level of resistance seen in bacteria of interest to human health. A study published in the United States in 2012 showed the association between a seasonal increase in antibiotic use in winter each year over a nine-year period, with a corresponding increase in antibiotic resistance in a range of bacteria, lagging the antibiotic consumption trend by a month (*30*).

Some European countries have banned the use of certain types of antibiotics in food animals, and other changes in practice have been achieved through widespread but voluntary changes in farming practices. This seems to have resulted in a significant reduction in the level of AMR in important bacteria (*40*). An encouraging feature of these studies is the demonstration that decreasing antibiotic use leads to a decrease in the level of resistance seen.

Antimicrobial stewardship programmes do not currently exist for all settings in which antibiotics are used. Setting-specific, evidence-based guidelines and other resources and approaches are needed to encourage the development and implementation of antimicrobial stewardship in primary health-care settings, residential facilities for the care of older people, kennels and catteries, veterinary practices, aquaculture enterprises and farms.

Stewardship programmes covering antibiotic use in animals and food production may have significant public health value in preventing the emergence of resistant strains and their spread to humans.

The Codex Alimentarius Commission, under WHO and FAO, provides recommendations on the responsibilities of regulatory authorities, the veterinary pharmaceutical industry, veterinarians, and wholesale and retail distributors and producers (*37*). In Australia, the Australian Veterinary Association and the International Dairy Federation have provided guidelines for the appropriate selection and use of antibiotics. There is significant scope to increase work in these areas. Box 5 summarizes how antimicrobial use in humans and animals is captured in Australia, and Box 6 presents examples of national antimicrobial surveillance initiatives in Australia.

Box 5. How data on antimicrobial use is collected in Australia

Australia currently has a mix of voluntary, incentive-based and legislative mechanisms to collect data on the quantity of antibiotics sold in, or imported into, Australia for use in humans and animals. For example, the volume of antibiotics dispensed for human use by community pharmacies under the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme is reported through the Drug Utilization Subcommittee of the Pharmaceutical Benefits Advisory Committee. Hospital antimicrobial usage is captured through the National Antimicrobial Utilisation Surveillance Program, with approximately 80% national representation of principal referral hospital beds. The quantities of antimicrobials sold for veterinary use are recorded and reported by the Australian Pesticides and Veterinary Medicines Authority, with data submitted voluntarily by registrants.

The overall accountability for antimicrobial management control lies with the hospital administration, which is responsible for ensuring an antimicrobial management programme is developed and implemented, and outcomes are evaluated.

Hospital management support is needed, including:

- providing dedicated resources for stewardship activities, education, and measuring and monitoring antimicrobial use;
- establishing a multidisciplinary antimicrobial stewardship team with core membership (wherever possible) of either an infectious diseases physician, clinical microbiologist or nominated clinician (lead doctor), and a clinical pharmacist;
- ensuring that antimicrobial stewardship resides within the hospital's quality improvement and patient safety governance structure, and clear lines of accountability exist between the chief executive; clinical governance; drug and therapeutics, and infection prevention and control committees; and the antimicrobial stewardship team.
- Three strategies considered essential for effective antimicrobial stewardship in Australia are:
- implementing clinical guidelines that are consistent with national prescribing guidelines, taking into account local microbiology and antimicrobial susceptibility patterns;
- establishing formulary restriction and approval systems that include restricting broad spectrum and later generation antimicrobials to patients in whom their use is clinically justified;
- reviewing antimicrobial prescribing with intervention and direct feedback to the prescriber, at a minimum, include intensive care patients.

Box 6. Examples of national antimicrobial surveillance initiatives in Australia

The National Antimicrobial Utilisation Surveillance Program (NAUSP) collects, analyses and reports data on use of antimicrobials at the hospital level. Participating hospitals receive bimonthly reports of their own data, and national reports are prepared annually. Although submission of data to NAUSP is voluntary, the programme represents more than 90% of principal referring hospitals, and 82% of mid-sized hospitals.

There is a wide variance in average antimicrobial usage rates between hospitals. However, overall there has been a slight decline in use since 2010 (*41*).

The National Antimicrobial Prescribing Survey is an audit performed by hospitals to assess antimicrobial prescribing practices and appropriateness of prescribing within the hospital. Data are reported nationally from this programme every year, and hospitals are able to interrogate their own data within the audit tool.

The Aged Care National Antimicrobial Prescribing Survey is a pilot programme based on the National Antimicrobial Prescribing Survey model and is an audit of antimicrobial prescribing and appropriateness of prescribing in residential facilities for care of older people (*42*).

Critical to the success of the element on responding to AMR is access to quality-assured affordable medicines, and regulated and consistent availability of essential antimicrobials through strengthened procurement and supply management systems. Finally, although antibiotics have become the dominant treatment for bacterial infections and will continue to play a key role, there are other opportunities to tackle bacterial infections, including the role of vaccines, phage and other alternative therapies that could replace or accompany antibiotics.

Element 4: Systematic infection prevention and control programmes

Infection control programmes and plans

Health-care agencies and professionals must develop and implement strategies to prevent and control health care-associated infection through formal governance and management systems. These operate within the quality assurance framework. Patients may present with an infection or acquire an infection or colonization during or following care, which must be promptly identified, managed and treated. Patients must be fully informed about their treatment and care *(43)*.

Systematic structure and process in infection control, through formal programmes and plans, enable institutions to meet their infection prevention and control obligations within their broader corporate missions and goals. Programmes and plans must incorporate all practice contexts in the local health-care setting, and provide a strategic evidence base to guide work practices. This ensures institutions and their people are held accountable for quality and safety, and make efforts to reduce the incidence of preventable health care-associated infection.

Programmes and plans are tailored to the local environment, and their scope takes into account patient demographics, the epidemiology of infection and the availability of resources. They underpin the infection control committee's agenda, and assist the infection control committee to steer activity. Elements of programmes and plans should include:

- governance and systems for infection prevention, control and surveillance
- infection prevention and control strategies
- managing patients with infections or colonizations
- antimicrobial stewardship
- cleaning, disinfection and sterilization
- communicating with patients and carers.

These elements build on and extend the organizational strategic plan through risk management, allowing organizations to prioritize infection prevention activity. It informs the development of appropriate professional and programme performance measures, demonstrating professional and public accountability of the infection prevention programme. The process requires leadership and input from key stakeholders. Stakeholders include organizational administrators, clinicians, ancillary staff, the community, and patients and carers. Their input is required to set policies, guidelines, targets and performance measures. Performance measures monitor the performance of stakeholders. Stakeholder involvement allows clarity for clinicians and service providers, who are held accountable for their actions and outcomes. It also enhances stakeholder buy-in. Infection control professionals must have appropriate skills and knowledge for their health-care settings. When clinicians and service providers comply with infection control principles and standards, and report risk factors and situations with the potential for infection transmission, good outcomes are achieved (*43*).

Example of a comprehensive national infection prevention response

Australia has a comprehensive national programme for infection prevention and control through the national health care-associated infection programme of the Australian Commission on Safety and Quality in Health Care. These programmes are aligned with the Commonwealth's Strategic Plan to Combat Antimicrobial Resistance. The programmes include the following:

- The National Hand Hygiene Initiative was established in 2008 and is based on WHO's Five Moments for Hand Hygiene. The National Hand Hygiene Initiative is a world-leading programme standardizing hand hygiene across the country, providing education to health workers, and obtaining feedback on compliance rates through auditing. The National Hand Hygiene Initiative is a core feature of Australia's infection prevention and control practice. Since data were first collected in 2009, the national compliance rate for hand hygiene in hospitals has risen from 63.5% to 81% in 2014.[3] Data for each hospital are publicly reported and this has become an accepted performance measurement for hospitals.
- Public reporting of *Staphylococcus aureus bacteraemia* (SAB) (*44*) and hand hygiene (*45*) rates for every public hospital are published on the MyHospitals website.[4] Australia now has one of the lowest national SAB rates reported.
- The *Australian guidelines for the prevention and control of infections in health care* and related education modules and other resources assist effective implementation. The evidence-based guidelines were released in 2010 and are currently undergoing revision (*46*).
- The National Antimicrobial Stewardship Programme sets the standard and core elements for antimicrobial stewardship in hospitals. The Antimicrobial Stewardship Clinical Care Standard addresses prescribing of antibiotics at the patient and prescriber level. Work is being undertaken to provide guidance on antimicrobial stewardship programmes to areas outside hospitals.
- Standard 3 of the National Safety and Quality Health Service Standards sets out the mandatory requirements for public and private health service organizations, day procedure centres and dental practices to comply with preventing and controlling health care-associated infections (*47*).

Capacity-building with a focus on training and competency assessment of the workforce includes hand hygiene compliance; aseptic technique assessment; master classes for nurses and antimicrobial stewardship leaders; a suite of educational modules for infection prevention and control; and modules for beginning antibiotic prescribers.

Standard and transmission-based precautions

Infection prevention and control is critical in the control of all infectious organisms, but particularly so in limiting the spread of resistant organisms where there may be limited or no antimicrobial treatments available. Preventing infection and its spread through the application of standard and

[3] Hand Hygiene Australia data: www.hha.org.au/LatestNationalData.aspx.
[4] http://www.myhospitals.gov.au.

transmission-based precautions is core to breaking the chain of infection, thus reducing the need for antibiotics and the opportunity for organisms to develop resistance and share resistance genes. Infection prevention and control practices, such as hand hygiene, the use of personal protective equipment, equipment disinfection, environmental cleaning and vaccination, are recognized as an essential part of an effective response to AMR.

Resistant organisms can be transmitted between livestock animals and production workers, through the food chain, between companion animals and their owners, and between humans in the community and health-care facilities. Evidence-based infection prevention and control programmes are required across all sectors and settings, recognizing that some settings pose a higher risk of infection than others. Over time, the availability of surveillance data, findings from research and the development of new technologies will inform new approaches and improvements in infection prevention and control.

Element 5: Research and development

Limited systematic coordination of research effort has contributed to gaps in our understanding of how AMR develops and spreads and how best to prevent and contain it. A strong R&D agenda is needed to advance the discovery of new therapies and diagnostic technologies to better prevent infectious disease, treat resistant infections, and support the development, refinement and implementation of evidence-based practices to limit the emergence and spread of AMR.
The following R&D needs have been identified, for example (*48*):

- Basic and molecular microbiological research is needed to advance the development of novel therapeutics, including antimicrobials, adjunct treatments, combination therapies and vaccines, and to support the redevelopment of existing antimicrobials.
- Rapid and point-of-care diagnostic technologies are needed to reduce inappropriate and unnecessary antibiotic use. Existing systems are not in widespread use and there is a need to identify and minimize the barriers to their uptake.
- A better understanding is needed on how resistance develops and can transfer between species and settings, including across different health-care settings, between animals and their carers, in food processing and the environment, in order to better target intervention strategies.
- Health services research is needed to identify and refine best-practice antimicrobial stewardship and infection prevention and control approaches.
- Social research into key messaging to promote behaviour change is needed to support improved prescribing practices and the use of antimicrobials.

Element 6: Education, communication and stakeholder engagement

An examination of key success factors in response to the AMR threat in a number of European countries with comparable health systems and similar challenges, and of the strategies of the United States of America and South Africa, identified that a coordinated and harmonized approach to communication, education and stakeholder engagement at local, national and global levels is critical to successfully combating AMR (*49*).

Education is important for all prescribers and dispensers of antimicrobials to ensure they prescribe and dispense appropriately, consider alternatives to antibiotics for the treatment and control of bacterial diseases, and have appropriate support to assist in communicating with patients, farmers and clients effectively. Education and awareness initiatives must also convey the importance of infection prevention and control practices in limiting the spread of resistant organisms.

Moreover, there are critical whole-of-society approaches that must underpin the success of national programmes for AMR. These include transparency and accountability across the system, advocacy and communications, media engagement, and formal and informal education. At the individual and community levels, awareness and action, through health literacy and consumer engagement, are critical, and act as important vehicles for discourse and dialogue with an empowered and civilized society.

As AMR affects the whole community, the audience includes all citizens. More specifically, wide-ranging audiences should be considered, as a large proportion of people are not well informed and do not understand the issues of AMR. Even where prescribers and consumers appreciate the need for conservative use, they may not know what to do about it. Messages need to stress judicious use of antibiotics and infection prevention, containment and control in animal and human sectors (for example, “every prescription matters”, “save our antibiotics”, “we are running out of weapons to fight infections”). More technical issues include the need for vaccines and improved diagnostic methods (especially in veterinary laboratories). Collaboration between human and veterinary laboratories may promote rapid diagnosis and better prescribing in animals.

Messages should be action oriented, with a focus on what can be done now (for example, four top actions). They should resonate, have value, and reinforce positive achievements, and should raise awareness of risks while keeping risks in proportion – this is particularly important for stories to the media, to avoid “scare stories”. They need to be simple but carry authority and generate media interest. To reinforce this, under the One Health umbrella, messages can be developed that are tailored to the needs for different groups, have emotional appeal, and are designed to promote action (for example, for consumers: “Don’t pay for antibiotics that you don’t need”). Professional groups respond better to messages that are tailored to the reality of their practice. Commercial sectors (particularly farmers and veterinarians) require supporting data and communication to justify action with financial implications (such as sale of antibiotics by veterinarians) (*26*).

Engagement with key stakeholders should be planned and purposeful, as a national system for the surveillance and reporting of AMR and antibiotic usage grows and evolves. As is the case in the Australian context, effective and continuing collaboration between interdisciplinary stakeholders from various jurisdictions, public and private alike, enables the creation of a systematic environment for One Health AMR systems.

3.4 Conclusion

AMR is a leading worldwide threat to the well-being of patients, and the safety and quality of health care. AMR is developing at an alarming pace and threatens many current medical practices, such as major abdominal surgery, cancer chemotherapy, organ transplantation, joint replacement and neonatal care. The world is now facing the very real possibility of a return to non-treatable infections, severe limitations on medical procedures and escalating health-care costs.

Improving national AMR and antimicrobial use surveillance is a critical next step in an expanded strategy for the prevention and containment of AMR. The surveillance will provide ongoing data to give an accurate picture of what is happening across the country, and provide information about trends in and changing patterns of resistance and the impact on patients. National coordination in the context of human health is central to AMR management and, in time, should extend to other organisms and contexts, such as veterinary usage and surveillance of bacterial resistance in animals, agriculture and food. Linking data on animals, agriculture and food with those on humans is fundamental to the comprehensive prevention and containment of AMR.

Surveillance and reporting of AMR and antibiotic usage is central to the prevention and containment of AMR. Data generated through surveillance of AMR and antibiotic usage are complementary and fundamental to everyday practices. At the local level, the data are used to formulate recommendations for rational antibiotic use and standard treatment guidelines. At a national level, data on resistance and antibiotic use inform policy decisions, such as antibiotic guideline development or revision, and identify priorities for public health action, such as education campaigns or regulatory measures. Without comprehensive and coordinated surveillance systems, efforts to prevent and contain AMR may be misdirected and inefficient, whereby poor practices such as inappropriate therapy result in wasted limited resources, and harm and human suffering through the inability to provide an effective drug to patients in need.

Antimicrobial resistance in the context of the Sustainable Development Goals

4

4. Antimicrobial resistance in the context of the Sustainable Development Goals

The Millennium Development Goals dealt with only developing countries and only development issues, while the Sustainable Development Goals deal with all countries and sustainable development. The spread of AMR both in low- and middle-income countries and in high-income countries endangers the continuity of such international mid-term and long-term sustainability efforts. AMR is not considered as a disease, and thus lacks the global attention it deserves.

From the aid and development perspective, AMR strikes the poor hardest. Lack of access to clean water and sanitation, and to affordable and effective antibiotics, significantly affects women and children in low-income countries as well as in the poorer sections of middle- and higher-income countries. AMR implies a health, social and economic problem that low- and middle-income countries and the world at large cannot afford.

4.1 The Sustainable Development Goals and AMR

4.1.1 Sustainable Development Goal 2: zero hunger

Achieving adequate food for all requires sustainable, equitable, accessible and resilient food systems. This is coupled with complementary policy development and implementation across all relevant sectors consistent with the right to adequate food and the fundamental right of everyone to be free from hunger.

To mitigate hunger, food and agriculture systems, including crops, livestock, forestry, fisheries and aquaculture, need to be addressed comprehensively through coordinated public policies, taking into account the resources, investment, environment, people, institutions and processes with which food is produced, processed, stored, distributed, prepared and consumed. Smallholders and family farmers play an important role in reducing malnutrition and should be supported by public policies to that end.

Responsible public and private investment in agriculture and other related sectors and appropriate market regulation are essential for overcoming hunger and malnutrition. Food systems need to contribute to preventing, addressing and mitigating human and zoonotic infectious diseases as an overarching approach to halt or reduce the severity of risk and probability of disease occurrences relating to AMR.

4.1.2 Sustainable Development Goal 3: good health and well-being

Several of the targets under Sustainable Development Goal 3 – Ensure healthy lives and promote well-being for all at all ages – will not be possible to achieve without effective antimicrobials, for example in the areas of maternal mortality ratio, newborn and under-5 child mortality, communicable disease epidemics, and a significant number of noncommunicable diseases. AMR can thus restrict the attainment of human potential and reduce productivity, resulting in a high burden of negative social and economic consequences for individuals, families, communities and States. Health systems will not be sustainable without effective antimicrobials and antibiotics.

AMR is a problem on a global scale, as resistance originating in one part of the world has the ability to spread rapidly. Intensified human mobility and food trade accelerate the spread of resistant bacteria across national borders, across different bacterial species and from bacteria in animals to those in humans. Responding to outbreaks of resistant infections involves coordinated efforts across national borders and at various levels of health systems, with the assistance of international agencies.

Along with the scale of the issue there is also the great diversity of social, economic, political and cultural contexts in which AMR emerges or spreads. While legal regulation of antimicrobial sales or usage has worked well enough in certain parts of the world, in other parts such restrictions are difficult to implement in practice. Non-prudent use of antimicrobials in just a few regions of the world is enough to overturn achievements in containing AMR elsewhere. In many countries antibiotics are available without any prescription, regulation is weak and counterfeit medicines sometimes account for a very large proportion of the market.

4.1.3 Antimicrobial resistance

AMR is a global threat that spans all countries, even those with relative low consumption of antimicrobials. AMR is increasingly becoming an important public health, economic and societal challenge that requires a comprehensive One Health approach. Progress is needed on these fronts in order to tackle the threat, and this cannot be limited to action on human use. Experts recognize that, in the future, the spread of AMR may follow patterns similar to those of epidemic outbreaks developing into pandemics. Studies looking at the effect of pandemic outbreaks have concluded that the areas of travelling and leisure, and finance and banking, may experience substantial losses. Trade and agriculture are among the sectors of the wider economy that are most likely to be affected by AMR.

4.1.4 One Health approach to AMR

As complex challenges are faced in the 21st century, a One Health approach, involving the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, plants and the environment, is essential.

One Health is a concept that acknowledges that human health is interconnected with the health of animals, agriculture and the environment. It has been known for many years that diseases can pass between animals and humans, and that use of antimicrobials can further drive resistance. Achieving synergy through a One Health approach therefore requires closer collaboration between human and veterinary health professionals.

It is evident therefore that a One Health approach is needed to effectively tackle the threat of AMR. In May 2014, by resolution WHA67.25, the World Health Assembly called for the development of a global action plan on antimicrobial resistance, and strengthened collaboration between FAO, WHO and OIE to combat AMR within the context of a One Health approach. Both FAO and OIE actively contributed to the development of the draft global action plan, which was approved by the World Health Assembly in May 2015. The Global Action Plan on Antimicrobial Resistance reinforces the need for collaboration on AMR between FAO, OIE, WHO and other intergovernmental organizations, partners and stakeholders and calls upon FAO to support the implementation of a number of AMR prevention and control measures in the agriculture, livestock and fisheries sectors. The development of the Global Action Plan reflects a global consensus that AMR poses a profound threat to human health.

The Second International Conference on Nutrition, in Rome, November 2014, produced the Rome Declaration on Nutrition, which recognized that food systems need to contribute to preventing and addressing infectious diseases, including zoonotic diseases, and tackling AMR; and endorsed a Framework for Action with recommended actions on food safety and AMR. The Framework for Action recommended raising awareness among relevant stakeholders on the problems posed by AMR, and implementing appropriate multisectoral measures to address AMR, including prudent use of antimicrobials in veterinary and human medicine; and further recommended development and implementation of national guidelines on prudent use of antimicrobials in food-producing animals according to internationally recognized standards adopted by competent international organizations to reduce non-therapeutic use of antimicrobials and to phase out the use of antimicrobials as growth promoters in the absence of risk analysis, as described in the Codex Code of Practice CAC/RCP61-2005. There are encouraging signs that some governments are adopting a broad One Health approach to tackling the issue of resistance, but it is an approach that needs to be replicated by others.

The One Health approach features strongly in the plans of many developed countries of Europe, Asia and Oceania, and approaches include addressing AMR issues such as waste water management through setting up an interministerial AMR working group, and supporting research on zoonoses through renewed research agreements between ministries. Further national plans entail various monitoring activities, including monitoring resistance of zoonotic pathogens beyond those identified for obligatory monitoring by countries.

4.1.5 Improved surveillance

Surveillance and monitoring of AMR is necessary to assess and determine the trends and sources of AMR in bacteria; detect the emergence of new AMR mechanisms; provide the data necessary for conducting risk analyses as relevant to animal and human health; provide a basis for policy recommendations for animal and human health; provide information for evaluating antimicrobial prescribing practices and for prudent use of recommendations; and assess, determine and evaluate effects of actions to combat AMR. FAO and OIE have issued various guidelines on surveillance of resistance and prudential use of antibiotics in animals. Globally, only half of countries in the world (97 countries) have put in place a surveillance system to monitor antibiotic-resistant microorganisms (*50*). While the majority of countries in the regions of South-East Asia (100%), Western Pacific (70%), Europe (62%) and the Americas (57%) have implemented surveillance systems, only 40% of world countries implement effective actions aimed at tackling AMR (*50*).

The general aspects of surveillance of AMR at targeted intervals or continuing monitoring of the prevalence of resistance in bacteria from animals, food, the environment and humans constitute a critical part of animal health and food safety strategies aimed at limiting the spread of AMR and optimizing the choice of antimicrobial agents used in therapy. Monitoring of bacteria from products of animal origin intended for human consumption collected at different steps of the food chain, including processing, packing and retailing, should also be considered. The national AMR monitoring and surveillance programmes should be scientifically based.

FAO has a unique role in supporting producers and value chain actors as important partners in addressing AMR risks within the broader framework of improved food safety and sustainable agriculture. Promoting prudent and responsible use of antimicrobials in agriculture and supporting primary producers in adopting good animal husbandry, as well as biosecurity practices to reduce the need for antimicrobial drugs in animal production, are essential components.

The main objectives of strengthening AMR surveillance and antimicrobial usage monitoring are to build country capacities to generate national data on AMR prevalence and trends to inform risk-based management decisions.

The Codex *Guidelines for risk analysis of foodborne antimicrobial resistance (CAC/GL 77-2011*) *(51)* provide a structured risk analysis framework to address the risk to human health associated with the presence in food and animal feed, including with regard to aquaculture, and the transmission through food and animal feed of AMR microorganisms or determinants linked to non-human use of antimicrobial agents.

There remain too many knowledge gaps on AMR dynamics, epidemiology and mechanisms of development and spread in different agriculture production and agro-ecological systems, in the environment and in humans. These gaps will require further study and research in coming years, and the issues will be better understood with the benefit of improved molecular techniques.

There are limited national, state, and federal capacities to detect and respond to urgent and emerging antibiotic resistance threats, even for critical pathogens. Currently, there is no systematic international surveillance of antibiotic resistance threats; also, data on antibiotic use in human health care and in agriculture are not systematically collected. In addition, there are knowledge gaps regarding patterns of antimicrobial use in agriculture and release during manufacturing, and what this means for resistance and, ultimately, human health. This needs to change if meaningful progress is to be made.

The OIE suggests continued collection of basic information that will help to give an indication of trends in the use of antimicrobial agents in animals over time and potential associations with AMR in animals. This information may also assist in risk management to evaluate the effectiveness of efforts to ensure responsible and prudent use and mitigation strategies.

The quality of surveillance and the effectiveness of responses to foodborne diseases and food poisoning outbreaks can be improved through information sharing and exchange of expertise.

4.2 Current global scale of uses of antimicrobials in agriculture and livestock production

The use of antimicrobials in food production globally is difficult to estimate; however, it may be as great as the use in human medicine. In some parts of the world antimicrobial use in animals is far greater than in humans. In the United States alone, more than 70% of medically important antibiotics are used in animals (*52*).

The projected use of antimicrobial agents in food animals is a result of the increase in human population, from 7 billion to roughly 10 billion by 2050 *(53)*. With increasing global incomes and prosperity, the demand for meat and other animal products is predicted to nearly double in the next 35 years. According to FAO, meat consumption will increase by 73% and dairy consumption by 58% over the 2011 levels (*53*).

Growth promotion has no counterpart in human antibiotic use. It accounts for the majority of uses in animals and is the focus of most legal and regulatory efforts to reduce antibiotic consumption in livestock and poultry. Growth promotion is accomplished with ultralow doses of antibiotics mixed with feed by the manufacturers or farmers.

The relative use in agriculture without better policies is likely to grow even more due to the increase in economic growth and wealth, accompanied by a trend towards the food and consumption preferences of the developed world. Consumption of antimicrobials by meat-producing animals to produce meat products in the BRICS countries (Brazil, Russian Federation, India, China and South Africa) alone is expected to double between 2010 and 2030 (*52*). In China, already the largest producer and user of antimicrobials in the world, the livestock sector could consume a third of the antibiotics produced worldwide by 2030 (*54*).

Antimicrobials have been used to treat infections in animals for as long as they have been widely used in humans. Currently more antimicrobials are used in poultry, swine and beef lot cattle to promote growth and prevent disease than are used by the entire human population.

Urgent steps are needed to reduce the dependence on antimicrobials, thus helping countries optimize production systems. The feasibility of reducing dependence on antimicrobials has already been demonstrated by several high-income countries. However, information on antimicrobial use in animals is scant in high-income countries, and even less available in low- and middle-income countries.

Significant amounts of the antimicrobials used by people and animals eventually find their way into the environment, particularly in surface and ground water and in soil. AMR bacteria arise and spread in animals and in the environment and may cause human disease. The situation is particularly acute where clean water and adequate sanitation are not available.

4.2.1 Livestock

Estimates of total annual global antibiotic consumption in agriculture vary considerably, due to poor surveillance and data collection in many countries, ranging from around 63 000 tonnes to over 240 000 tonnes (*52*). However, it is clear by any measure that use is widespread, on a scale at least equivalent to use in humans, and is projected to increase. It is estimated that global consumption of antibiotics in agriculture will increase by 67% from 2010 to 2030 (*52*). The antimicrobials are used for different purposes, some to protect or improve the health of the animals, and others to stimulate quicker growth and maximize profits.

The most inappropriate use is growth promotion, because it does not serve to maintain the health of the livestock. As with any antibiotic use, this increases the chances that resistant bacteria will develop. Not long after antibiotics were first used widely in human medicine it was discovered that they had the effect of promoting more rapid growth when given to farm animals at low levels, helping them reach their full market weight more quickly. However, there is evidence to suggest that use of antibiotics at low or "subtherapeutic" levels fosters the development of resistant bacteria; one recent study showed that subtherapeutic use of antibiotics in agriculture resulted in huge increases in the number of antibiotic resistance genes, relative to an antibiotic-free site in a similar region (*52*). This clearly raises concerns from a human health perspective and indeed many countries have already banned the use of antibiotics for these purposes, with the notable European Union ban in 2006, and the United States has recently moved towards voluntary relabelling of antibiotics to reduce their use as growth promoters.

Chicken and pigs consume most of the antibiotics used in food animals around the world. The amount of antimicrobials used in aquaculture worldwide is also significant. Antimicrobials are also used in beef cattle in Argentina, Brazil and the United States, where animals are finished in large feedlots. Most antimicrobials used in animal production are similar to those used in the human population. The top three classes of antibiotics used in 2009 for animals were macrolides, penicillins and tetracyclines, all of which are critically important in human medicine. In aquaculture at least a dozen antimicrobials, including a large amount of quinolones, are used. These antimicrobials not only produce resistance in farmed fish but also transmit resistant bacteria to wild fish populations and the environment.

Among the Organisation for Economic Co-operation and Development (OECD) countries, European Union Member States, Mexico, New Zealand and the Republic of Korea have bans on the use of antibiotic growth promoters, while some other OECD countries, such as Australia, Canada, Japan and the United States, had not banned the use of antibiotic growth promoters as of 2014. Non-OECD countries that are major meat producers, such as Argentina, Brazil, China, India, Indonesia, the Philippines, the Russian Federation and South Africa, have not banned the use of growth promoters. The greatest uncertainty about current use patterns in livestock is in the low-income countries. More effort is needed to investigate the current practices of antimicrobial use in animal production and to provide appropriate guidance for increasing production without the use of antimicrobials. There is growing evidence to suggest that antibiotics used as growth promoters do not have as much economic benefit as previously thought. Two countries that have made large strides in reducing antibiotic use in their livestock sectors in recent years, while retaining their commercial competitiveness, are Denmark and the Netherlands.

In Asia, Japan's response to rising rates of AMR in the livestock sector is based on a three-pronged approach. First, Japan has based the development of specific policies and risk management measures in the area taking the risk analysis principles of the code of practice developed by the Codex Alimentarius Commission as a reference point. Risk management measures are continuously conducted and reinforced in accordance with the risk level. Second, in response to international concern about the impact of AMR on public health, Japan has established the Japanese Veterinary Antimicrobial Resistance Monitoring System, which monitors levels of AMR in zoonotic and animal pathogenic bacteria and the quantities of antimicrobials used in animals, and collaborates with its health counterparts for AMR surveillance in the human health sector. Japan has published prudent use of guidelines for veterinary use of antimicrobials to keep animals healthy by observing high hygiene standards and to prevent infectious diseases through vaccinations or other means. The guidelines stipulate that critically important antimicrobials (for example fluoroquinolones and cephalosporins) be preserved for human health, and their use should be sought when other treatment options have failed.

A global target is needed for the reduction of antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for human health.

4.2.2 Aquaculture

In aquaculture, antibiotic doses can be higher proportionately than those in livestock farming. Not only can residues of antibiotics remain in fish products, but the antibiotics used in fish feed can remain in the aquatic environment for an extended period of time through excretion, exerting selective pressure and spreading rapidly through water systems. Indeed, some estimates suggest that 70–80% of antibiotics given to fish are excreted into water (*52*). Use of antibiotics in aquaculture and its impact on the environment is a growing concern amongst scientists, yet quantifying the amount of use and how much is being disseminated into the environment is very difficult. Use of antimicrobials in aquaculture in Norway fell by 99% between 1987 and 2013, despite the industry's output growing more than 20-fold over that time (*52*). This has happened because there has been increased availability and use of effective vaccine, and better farm hygiene and selection of more suitable farm sites, with good water exchange and stricter usage oversight.

4.2.3 Crops

It is estimated that the amount of antibiotics used for crops is relatively low in comparison to the quantities used in livestock and aquaculture, with estimates ranging from 0.2% to 0.4% of total agricultural antibiotic consumption (*52*). For this reason direct use of antibiotics on crops is not a priority area to find major reductions, but should not be ignored. Fungal diseases tend to pose much larger threats to crops and therefore, fungicides are used in significant quantities. They are commonly used on cereals and grapes in particular. Fungal infections contribute to the deaths of almost 750 000 people each year (*52*). The number of patients relying on antifungals to stay alive has increased over the last two decades, as advances in modern medicine have allowed many more patients with weakened immune systems to survive. This increased use in humans alongside the use of fungicides in agriculture has meant that resistance is becoming an increasing problem.

4.3 Antibiotic-resistant bacteria in the environment

According to a United States Food and Drug Administration 2011 report, 93% of medically important antibiotics were administered via feed or water in agriculture in the United States (*55*). Scientific studies also suggest that 75–90% of tested antibiotics are excreted from animals unmetabolized and enter sewage systems and water sources (*52*). Therefore, animal waste not only contains resistant bacteria, but also antibiotics that could then foster the emergence of resistance in bacteria beyond those in an animal's gut – including bacteria that may pose a greater risk to humans. This manure from farm animals is often used on crops as a fertilizer, which has been shown to create resistance. Animal waste and manure used as fertilizer can also release resistance genes and resistant bacteria into soil and ground water. Agricultural use of antibiotics has been connected to resistant bacteria found in surface water and high rates of antibiotic resistance have been found on farms.

As with the use of antibiotics in animals, most of the antibiotics consumed by humans are excreted and therefore pass into the environment. In addition, antibiotics can pass into the environment through inappropriate human disposal of antibiotics, for instance by flushing them down the toilet. Public awareness raising is necessary to help to change this behaviour.

In countries with less developed sanitation infrastructure, there is higher risk that the waste will not be treated and will sometimes be closer to communities. This increases the risk of exposure and the carriage of resistant bacteria by otherwise healthy individuals. Even in countries with advanced sewage systems, studies have revealed the presence of antibiotics downstream of sewage treatment plants. These may act as hotspots for resistance development, with antibiotics from human, animal and manufacturing units converging. This is usually due to the fact that even these countries do not have advanced systems to treat this water to ensure that traces of antibiotics are removed. However, reducing unnecessary use of antibiotics will clearly help to counteract this problem at source.

Antibiotic-resistant bacteria have also been found near wastewater treatment plants and in other water sources. Minimum standards are needed to improve waste management in antimicrobial production to avoid scenarios where very high concentrations of antibiotics are released into the environment.

In European countries moderate to high resistance to tetracyclines, sulphonamides and ampicillin in bacteria from poultry and swine production has been reported (*56*). Among low- and middle-income countries, Nepal reported a very high resistance level (greater than 90%) of *Salmonella* in poultry to several antimicrobials in 2010 (*57*). Similarly, in India, resistance to various antimicrobial agents was found for avian strains of *Pasteurella multocida* (*58*). Resistance to amikacin, carbenicillin, erythromycin and penicillin was also widespread. Similarly, *Staphylococcus* and other bacteria in poultry litter were highly resistant to streptomycin, erythromycin, tobramycin and ampicillin (*59*).

4.4 Impact of antibiotic use in animals and the extent of its impact on human health

There is growing evidence to suggest that antibiotics used as growth promoters do not have as much economic benefit as previously thought, particularly in countries with advanced farming techniques characterized by automation and a high level of biosecurity (*60*).

Proof that antimicrobial use in animals for growth promotion and treatment has a significant effect on human health is lacking. However, several lines of evidence connect antimicrobial use in livestock with effects in humans, including direct animal to human transmission of resistance; animal food to human transmission of resistance; foodborne outbreaks of infection; and parallel trends in antimicrobial use in animals and related AMR in humans.

Evidence of direct animal to human transmission has been demonstrated in several studies, for example, antibiotic-resistant bacteria (*Escherichia coli*) transmitted from animals (chickens) to poultry farm workers and their families (*61*). For example in 1985 an outbreak of a multidrug-resistant *Salmonella typhimurium* was linked to unpasteurized milk in the United States (*62*). In Denmark an outbreak of nalidixic acid-resistant *Salmonella typhimurium* was linked to pork (*63*). Similar findings have emerged from all over the world involving virtually all food animals (including fish) and a host of bacteria.

4.5 Global target to reduce antibiotic use in food production

There is a need to reduce global levels of antimicrobial use in agriculture to an agreed limit for each country within a global target, while giving individual countries the responsibility to decide how best to achieve this goal. An ambitious but achievable global target for reducing antibiotic use in agriculture would greatly assist in reducing use over the next 10 years. There are countries that have advanced farming systems with very low levels of antibiotic use, particularly in Scandinavia. Denmark has combined low usage with its status as one of the largest exporters of pork in the world. Reducing levels of use to that of Denmark (for example) – an average of less than 50 milligrams of antibiotics used a year per kilogram of livestock in the country – may be a good starting point for such a target. This would be feasible without harming the health of animals or the long-term productivity of farmers. Country-specific environmental and climatic issues need to be taken into consideration, using evidence from the academic literature and case studies. The exact level of the target would, however, need to be discussed and assessed by experts. Low- and middle-income countries may need more time to achieve such a target, while many of these countries may already be below the threshold.

There is growing consensus that specific medically important classes of antimicrobials, in particular the critically important antimicrobials classified by WHO as having highest priority for human medicine, should be restricted for use in animals.

Success can only be achieved by considering a range of interventions. These should take into account the key drivers of the real or perceived need for antibiotics, whether for use as therapy, prophylaxis (prevention) or growth promotion. Interventions will no doubt include improvements in infection control, better animal husbandry practices, greater use of vaccines and the adoption of diagnostic devices to ensure better-targeted and more appropriate veterinary prescribing. In manufacturing, the potential to prevent waste as well as to treat it, should be taken into account.

4.5.1 Behavioural interventions to tackle AMR

Behavioural interventions seek to complement measures on preventing emergence and spread of AMR. Behavioural interventions largely target prescribers, health-care workers, veterinarians and the general public through measures that provide relevant information and seek to set the correct behaviour as the default option. Interventions include education, introduction of dedicated AMR improvement teams, and compliance and feedback measures. Behavioural interventions tend to be introduced as bundles of interventions, hence the effectiveness of individual interventions is difficult to assess, though it has been found that these bundles may significantly reduce health care-associated infections or colonization rates.

4.5.2 FAO/OIE/WHO tripartite collaboration

In support of tripartite dialogue and partnership, FAO, OIE and WHO have developed a tripartite concept note (2010), which emphasizes sharing of responsibilities and coordinating global activities to address health risks at the animal–human–ecosystem interfaces (*64*). Technical focal points for AMR have been designated by each of the organizations and have jointly elaborated a tripartite work plan, which is aligned to the Global Action Plan on Antimicrobial Resistance. The work plan prioritizes advocacy, awareness, training, AMR surveillance, monitoring the use of antimicrobial agents, promotion of prudent use of antimicrobial agents and the development and implementation of the Global Action Plan. WHO, FAO and OIE are also collaborating in assisting countries in developing national AMR action plans.

4.6 Conclusion

Antibiotic use in food animals began almost as early as it did in people and grew steadily with little oversight. Today in some countries far more antibiotics are consumed by animals than by humans. The vast majority of use in animals is for growth promotion and disease prevention as a substitute for hygiene and nutrition. The growing demand for meat and other animal products over the next few decades presages a potentially massive increase in antibiotic use, even greater than the increase in demand as intensive large-scale production replaces small-scale operations in low- and middle-income countries.

Some of the antibiotics used by people and animals contaminate ground and surface water and soil. The consequences of this antibiotic load in the environment are just beginning to be studied. Early research suggests that it adds to the total burden of antibiotic resistance in the world, although effects on humans cannot yet be measured.

Key policy implications

- Strengthening the existing national surveillance and monitoring systems should be a priority of countries, particularly increasing the number of microorganisms that are monitored, and expanding the monitoring of infections to and improving statistics on the consumption of antimicrobials.
- Countries should strengthen their ongoing efforts to facilitate the scale-up of practices of proven effectiveness and efficiency at national level, ultimately leading to total elimination of antimicrobials for growth promotion.
- There is a need for improvement of international collaboration and capacities for AMR-related surveillance control and antibiotic research and development.
- Use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.
- Optimization of the existing vaccination programmes can contribute towards preventing AMR.
- The genetic potential of animals and the health status of animal herds and flocks are more important than feeding suboptimal levels of antimicrobial agents.

Containment of antimicrobial resistance as a global public good

5

5. Containment of antimicrobial resistance as a global public good

AMR poses a profound threat to health and society, and has recently been recognized as a global health security risk. AMR leads to significant economic and societal costs, and involves sectors beyond human health, including animal health, agriculture and food security. For communities and countries, the rapid spread of antimicrobial drug resistance will translate into higher health-care costs, decreases in labour supply, productivity, and household incomes, and losses in national income and tax revenues.

AMR spans all countries as intensified global trade and travel contribute to the spread of AMR across communities, cities, countries, regions and the world (*50*, *65*, *66*). Efforts to contain AMR are beyond the capacity of any organization or nation alone, and require a global integrated approach and international cooperation and collaboration, with the involvement of all relevant sectors including human and animal health, agriculture, environment and research (*66*).

AMR represents a global failure in public policy global governance, research prioritization and the market system (*67*). Given the global scope and scale of AMR, this background document presents arguments to recognize the containment of AMR as a global public good, and proposes and discusses some policy directions and interventions to support regional actions to help tackle the problem.

The directions proposed have been extensively discussed in the policy and scholarly literature, and are considered fundamental enablers to contain AMR. In this document, they are recognized as intermediate public goods since they have the potential to slow the spreading pace of AMR. They include a regional surveillance system, a regional regulatory framework or platform, and a regional framework for research, development and innovation.

The production of these public goods will require a collective and coordinated regional multistakeholder action and commitment so that, if successfully produced, they will have the potential to yield significant and mutual external benefits, across multiple nations.

5.1 The concept of global public goods

Public goods are goods that – once provided or produced – anyone can benefit from, and consumption by one individual does not limit consumption by others. They range from street signs to a clean environment, and they are provided by nonmarket mechanisms, such as the state or, sometimes, voluntary organizations. Because the benefits of a public good are available to everyone (no one can be excluded), there are diminishing incentives for private sector provision. Consumption by one individual or group does not reduce availability for others, so a price is difficult to set in a market context.

One important argument for public subsidy of health is that there are strong societywide benefits from environmental health and disease control interventions. Reduced levels of infections and of the vectors of diseases are pure public goods.

As globalization progresses, it is becoming clear in many areas that matters that were once confined to national policy are now issues of global impact and concern. The most obvious example of this is in communicable disease, which is often a problem against which no single country can orchestrate a response sufficient to protect the health of its population. Public goods become global (or international public goods) in nature when the benefits flow to more than one country and no country can effectively be denied access to those benefits. Recognition of this led to the development of the concept of global public goods. The definition of global public goods used by the United Nations Development Programme (UNDP) is as follows:

A global public good is a public good with benefits that are strongly universal in terms of countries (covering more than one group of countries), people (accruing to several, preferably all, population groups) and generations (extending to both current and future generations, or at least meeting the needs of current generations without foreclosing development options for future generations).

Under this definition, this background document proposes the containment of AMR as a global public good. If successfully produced, societywide benefits will be universally available to countries, populations and generations.

5.2 Containment of antimicrobial resistance as a regional/global public good

The increasing ease of transmission of infectious diseases, including antimicrobial-resistant infections, between populations and across national boundaries, and the importance to future generations of the current development of resistance, only reinforces the regional and global nature of AMR. As a global public good, the containment of AMR is a desirable outcome or end state (or a final public good) that will benefit everyone, but that requires regional and global collective and collaborative actions beyond national efforts.

Preventing one person from getting antibiotic-resistant infections benefits the individual concerned, but also provides a significant positive externality to others by reducing their risk of antibiotic-resistant infections. The cumulative benefit for a nation, in terms of gains in production and income, resulting from improvements in population health may be substantial. For example, economic evidence confirms that a 10% improvement in life expectancy at birth is associated with a rise in economic growth of some 0.3-0.4 percentage points a year (*68*). Similarly, the reduction of antibiotic-resistant infections within one country reduces the probability of cross-border transmission to other countries in the region and across the world. Contrarily, negative externalities are also possible if AMR is not contained or not addressed simultaneously by all through international, concerted actions. For example, a hospital with weak or lacking antibiotic stewardship programme or infection control precautions may serve as an incubator for individuals colonized with antimicrobial-resistant organisms. These individuals may then become a source of infection for individuals in other hospitals and care and community settings, and other regions and countries (*69*). Similarly, if some countries introduce legal regulations on antimicrobial sales, their potential achievements in containing AMR will be overturned by others that do not introduce legal regulations. The case of Scandinavia in northern Europe is an example of collective, regional actions with positive externalities (Box 7).

Box 7. Scandinavia: collective regional action on AMR

The case of Scandinavia in northern Europe is an example of collective, regional action among four countries (Denmark, Finland, Norway and Sweden) to tackle AMR. Sweden banned antimicrobial growth promoters in animal production in 1986. Ten years later, antimicrobial growth promoters were gradually removed in other Scandinavian countries. All countries have also implemented optimal disease preventive management routines and guidelines on antimicrobial drug therapy in food animals. In addition, Sweden has a zero tolerance control policy for salmonella contamination, and Denmark does not allow economic incentives to veterinarians when prescribing antibiotics.

The result has been significant reductions in antimicrobial use in food animal production after the ban in Sweden (65%), Denmark (47%), Norway (40%) and Finland (27%). The current prevalence of AMR in animal bacterial populations is also considerably lower than in some other countries within the European Union. A considerable reduction in the animal reservoir of enterococci resistant to antimicrobials previously used for growth promotion has also been documented.

These collective actions have decreased the risk of human exposure via the food chain. This benefit will probably produce positive externalities to other countries outside northern Europe that have significant trade and travel with Scandinavian countries.

Source: Bengtsson and Wierup (70).

5.2.1 Antimicrobial resistance as a global public "bad"

AMR affects all areas of health, involves many sectors and has an impact on the whole of society. From that first case of resistant staphylococcus, the problem of AMR has snowballed to a serious public health concern with economic, social and political implications that are global in scope, and cross all environmental and ethnic boundaries (*71*). AMR is therefore a global public "bad". In health, AMR will have a direct impact on targets identified in the Sustainable Development Goals for maternal mortality, newborn and under-5 child mortality, communicable disease epidemics, and a significant number of NCDs (*65*). More broadly, health systems will not be sustainable without effective antimicrobials, specifically antibiotics (*65*). Resistance increases health-care costs as treatments become more expensive. This compromises efforts towards achieving universal health coverage, and towards reducing inequalities.

AMR strikes hardest on the poor (*70*). Antibiotic resistance, for example, is very high in low- and middle-income countries, where antibiotics are available without prescription, regulation is weak, and counterfeit medicines sometimes account for more than one third of the medicines market (*65*). This may lead to the emergence and rapid spread of antibiotic-resistant infections, and a consequent deterioration in health status. Poor health, in turn, reduces the capacity to work and has substantive effects on wages, labour force participation and job choice (*72*).

Disease – and therefore resistance – also thrives in conditions of civil unrest, poverty, mass migration and environmental degradation, where large numbers of people are exposed to infectious diseases, with little in the way of the most basic health care (*71*). Given these relationships, improvements in poverty, hunger and food security, and economic growth can all be compromised with increased rates of AMR.

The relationship between poverty and disease – particularly communicable disease – has been recognized for generations. Not only does disease reduce the productivity and incomes of people and nations, but the resultant poverty also impacts health through its effects on nutrition, education, housing and health care, creating a cycle of ill health and poverty that is hard to break.

In addition, as abuse, overuse and misuse of antimicrobials extend beyond human health to animal husbandry, aquaculture and agriculture, increases in resistance rates have the potential to offset gains in other critical sectors of society, including progress towards sustainable consumption and production.

5.2.2 Intermediate global public goods

Intermediate public goods contribute to the provision of final public goods. For example, international health regulations can be regarded as an intermediate public good since they contribute to stopping the cross-border movement of communicable diseases and thus reducing cross-border health risks. If successfully produced, intermediate public goods also provide societywide universal benefits for countries, populations and generations.

In some situations, however, producing truly intermediate public goods may be a major challenge. Vaccines, for example, are considered an intermediate (global) public goods, that is, they should be available to anyone everywhere. In practice, they are private (or access) goods, as not everyone has access to vaccines. Typically, those who have access are likely to be the better off, so that the benefits of providing public goods will tend to be skewed away from the poor. This situation challenges the fundamental public and universal nature of public goods.

For the containment of AMR, producing intermediate public goods (for example, a regional surveillance system) necessarily requires concerted and collective regional (and global) actions. This is important because any effort made by an individual country to contain AMR (for example, prohibition of over-the-counter antibiotics) will be offset if other countries do not take any actions to contain resistance. As a result, resistance rates in a region may continue to rise, even though one country may have made significant investments to tackle AMR. This behaviour is also known as the collective action problem (or the “free rider” problem), and threatens progress towards producing global public goods.

The free rider problem describes a situation when no individual is prepared to pay the cost of something that others may be expected to benefit from; instead, all hope that someone else will pay for it and they will benefit for free. In the case of AMR, countries may not have the proper incentives to supply or invest in public goods on their own since if others do it, they can benefit from them.

Concerted and collective regional actions are also important to maximize the impact of investments towards producing intermediate public goods. Countries with constrained resources and infrastructure (for example, laboratory capacity) can limit the overall outcome of AMR containment in the region. Collective and coordinated regional multistakeholder actions will allow recognition of these limitations and enable redirection of efforts and resources in ways that maximize the production of public goods (for example, by transferring knowledge and capacity to resource-constrained countries). Economically, this will be more efficient, as collective investments in public goods will yield a combined effect greater than the sum of individual, uncoordinated country investments.

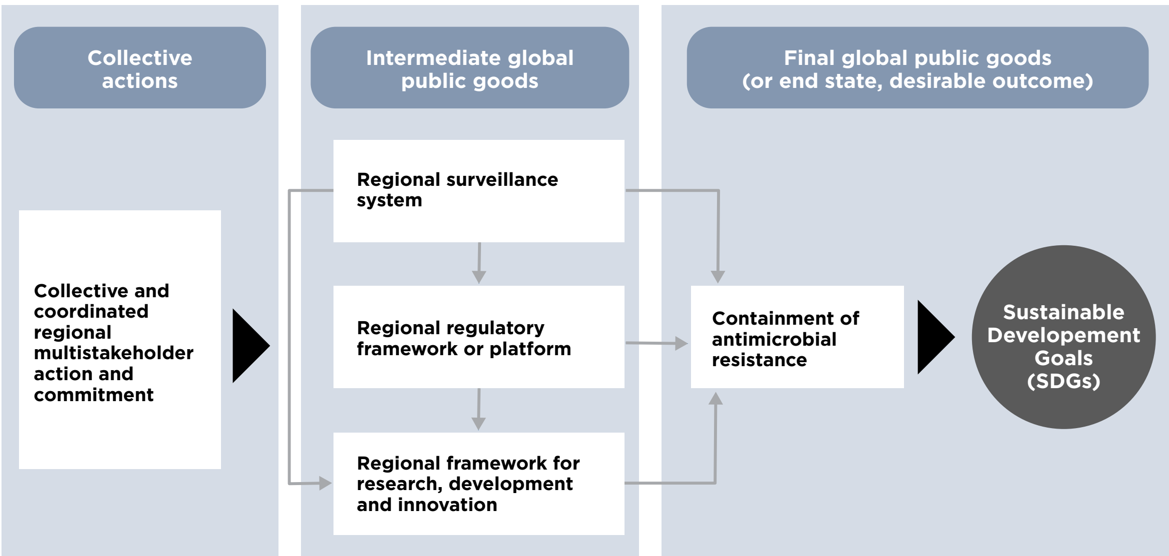
In this document, prioritization of three intermediate public goods is proposed in order to contribute to the containment of AMR. Their production will require collective and coordinated regional multistakeholder action and commitment so that, if successfully produced, they will have the potential to yield significant and mutual external benefits, across multiple nations. These goods have been extensively discussed in the policy and scholarly literature. For the purpose of this document, they have been classified under three main themes, with the goal of becoming regional public goods:

- regional surveillance system
- regional regulatory framework or platform
- regional framework for research, development and innovation.

As public goods, they are also desirable outcomes, although intermediate, as they have the potential to slow the spreading pace of AMR. The benefits of producing these public goods are also in alignment with the overall goal of the Global Action Plan on Antimicrobial Resistance adopted by the World Health Assembly in 2015, which is: to ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them.

Figure 5 summarizes the relationships between these three regional interventions, containment of AMR, and the Sustainable Development Goals. It also shows how these public goods relate to each other. For example, trends and patterns of antibiotic resistance and use gathered from a regional surveillance system can help direct R&D so that containment of AMR is maximized.

Figure 5. Intermediate and final global public goods



The following section describes these regional interventions, provides examples of successful initiatives implemented, and discusses some policy directions and interventions to support the production and implementation of them as intermediate public goods.

5.3 Regional surveillance system

A regional surveillance system is a fundamental enabler to inform policies and regulations at all levels of governance, and is key to direct research, development and innovation to contain the spread of AMR. It is the cornerstone for assessing the burden of resistance and for providing the necessary information for action in support of local, national and global strategies. A regional surveillance system can also inform if actions being taken are working, or need to be adjusted. For example, it can help assess whether infection prevention and control measures are effective in hospitals.

In the Global Action Plan on Antimicrobial Resistance, and in the two regional strategies (the Action Agenda for Antimicrobial Resistance in the Western Pacific Region and the Regional Strategy on Prevention and Containment of Antimicrobial Resistance in the South-East Asia Region), surveillance and research are the mainstays to strengthen knowledge and evidence that can support actions and investments with clear rationale of their benefits and cost-effectiveness.

In a recent review, surveillance was recognized as the single most important public health instrument for identifying public health events of global concern, particularly infectious diseases that are emerging (*73*). In the Berlin Declaration on Antimicrobial Resistance, the G7 health ministers acknowledged the lack of comparable data on the quantity and use of antibiotics and the prevalence of resistance. They also recognized that the availability of comparable international and national data is a precondition for targeted action within countries.

Surveillance of AMR, use of antimicrobials and the overall burden of infectious diseases should be performed at local, national and regional levels to guide clinical management and infection control, to monitor treatment guidelines, and to update national essential medicines lists and antibiotic guidelines.

For resistance, a surveillance system is essential to detect, analyse and track both resistant and non-resistant (susceptible) microorganisms, including geographical patterns, trends, early detection and outbreaks. The information collected is also relevant to monitoring the effectiveness of interventions targeting the containment of resistance, informing effective strategies and policies, and implementing activities at all levels of governance.

Surveillance of AMR is enhanced when linked to monitoring of antimicrobial use practices. Monitoring of antimicrobial consumption tracks how frequently and in what volumes antimicrobials are used, and is critical to assess the link between the use of antimicrobial agents and the development of resistant pathogens in humans and animals. It does require, however, a surveillance system built from a combination of data sources (for example sales and dispensing data, reimbursement systems, patient encounter-based and survey data, and health-care facility data) and a common, standardized methodology to produce reliable data and information that is

comparable across health-care settings and countries within the region.
The goal of tracking (and monitoring) antimicrobial use is to provide information to guide policy formulation and effective decision-making on the appropriate use of antimicrobials in order to contain the increasing burden of resistant microorganisms, including assessing health-care professional prescribing patterns and adherence to standard treatment and antibiotic guidelines. In France, for example, the 2002–2007 National Action Plan produced a 23% reduction in antibiotic consumption through a number of targeted interventions, including surveillance of antibiotic use (*74*). Box 8 presents an example of how monitoring of antibiotics use in China helped decision-making.

Box 8. Overuse of antibiotics in China

In China, overuse of antibiotics was found to be driven by financial incentives for physicians to prescribe more expensive antibiotics. Recent changes to control inappropriate use of antibiotics introduced physician reimbursement mechanisms that delinked sales of pharmaceuticals, while drugs were divided into three classes based on resistance rates, with only specialists allowed to prescribe drugs with high resistance.

Source: Buckland Merrett 2013 (*74*).

Through surveillance networks, surveillance of antimicrobial resistance and use can complement each other to drive policy changes. The European Antimicrobial Resistance Surveillance Network and the European Surveillance of Antimicrobial Consumption Network have demonstrated that the integrated monitoring of resistance and use can prove the crucial factor driving political commitment to successful resistance-containment campaigns and actions.

For nearly three decades WHO, including the Regional Office for the Western Pacific, has been engaged in discussions, recommendations, and actions related to AMR. In 2015, a regional technical working group identified AMR surveillance priorities at local, national and regional levels, with the goal of establishing a regional surveillance network. The priorities focus on enhancing core laboratory testing capacity, establishing surveillance activities, and supporting the development of data systems, including the use of standards and methods for data collection, sharing and linkages.
In May 2014, the Sixty-seventh World Health Assembly passed resolution WHA67.25 on antimicrobial resistance. In monitoring consumption, Member States were urged to monitor the extent of AMR, including regular monitoring of the use of antibiotics in all relevant sectors. The resolution also urged the development of AMR surveillance systems in three separate sectors: (a) inpatients in hospitals; (b) outpatients in all other health-care settings and the community; and (c) animals and non-human usage of antimicrobials.

Box 9 presents the experience of the Japan Nosocomial Infections Surveillance (JANIS), which demonstrates the feasibility of developing an AMR surveillance system, and may be used as a benchmark case for the region to inform efforts towards developing a regional surveillance system.

Box 9. Japan Nosocomial Infections Surveillance

The Japan Nosocomial Infections Surveillance (JANIS) is an example of a surveillance system designed to provide basic information on the incidence and prevalence of hospital-acquired infections and antimicrobial-resistant bacteria in Japanese medical settings. JANIS was launched in 2000, and collects data from close to 1000 hospitals with more than 200 beds. The surveillance data after completion of analysis are fed back to the member hospitals and are made accessible on the Internet.

In 2013, participating hospitals reported more than 4.5 million specimens from close to 1.6 million patients. Escherichia coli infection rates, for example, increased from 11.00% in 2009 to 11.94% in 2013, and fluoroquinolone-resistant E. coli infection rates from 1.88% to 3.12%.

In order to contribute to the global efforts towards AMR surveillance, and to maximize the impact of coordinated activities, the pursuit of a regional surveillance system will require close coordination with the Global Antimicrobial Resistance Surveillance System (GLASS). GLASS is being developed to support the Global Action Plan on Antimicrobial Resistance, and aims to coordinate with the national action plans of countries. The goal of GLASS is to enable standardized, comparable and validated data on AMR to be collected, analysed and shared with countries, in order to inform decision-making, drive local, national and regional actions, and provide evidence for action and advocacy.

GLASS will combine patient, laboratory and epidemiological surveillance data to enhance understanding of the extent and impact of AMR on populations. In view of the challenges of collecting all these data, GLASS proposes that countries consider gradual implementation of the surveillance standards proposed on the basis of their priorities and resources.

5.4 Regional regulatory framework or platform

A regulatory framework is a key enabler to optimize the use of antimicrobial medicines in human and animal health. The Global Action Plan argues that more widespread recognition of antimicrobial medicines as a public good is needed in order to strengthen regulation of their distribution, quality and use, and encourage investment in R&D.

Health and pharmaceutical regulations shape the way in which antimicrobials are used. In the Western Pacific Region, many countries do not have a solid legal and regulatory framework to mandate, support and enforce the rational use of medicines. Countries with weak regulatory systems have limited capacity for ensuring drug quality, improving dispensing of medicines, restricting the use of antibiotics in animals, and controlling the movement of drugs in the supply system.

Ensuring the quality of all antimicrobials is essential for safe and effective delivery to patients. Through regulations, Member States can control the quality, safety and efficacy of drugs. Counterfeit, substandard or degraded antimicrobials are likely to drive drug resistance, as inappropriate drug concentrations affect bacterial eradication. Countries without systems for controlling the quality and assessing the safety and efficacy of drugs face an increased risk of exposure to substandard, inferior and counterfeit drugs that penetrate the market.

In many countries of the Western Pacific Region, antimicrobials are commonly dispensed by unauthorized people who lack the appropriate training. Over half of the Member States in the Region report that antimicrobials are sold over the counter without a prescription. In the South-East Asia Region, antimicrobial medicines are available without prescription in 64% of Member States. Enforcing regulations that prohibit over-the-counter sales is critical for promoting the rational use of antibiotics.

Antimicrobial use in food-producing animals affects human health due to the presence of active antimicrobial residues in foods, and contributes to the selection of resistant bacteria in animals that have the ability to spread to humans. The national regulatory authorities in 66% of Member States in the Region do not have mechanisms in place to enforce requirements for rational use of antimicrobials in animals. Likewise, there are legal provisions to reduce the use of antibiotics as growth promoters for food animals in only 32% of Member States. Enhanced collaboration between veterinary and human medicine would accelerate interdisciplinary and international action to contain AMR through a One Health approach.

The ability of prescribers and dispensers to provide appropriate, high-quality antimicrobial agents is determined by the consistent supply of the necessary antimicrobials. The role of government regulators is to ensure access to good-quality medicines and secure the supply chain from the manufacturer to the patient. Often, the drug supply chain is inadequately secured due to limited or inappropriate regulation related to the procurement, storage and sales of quality antimicrobials. Additionally, in the Western Pacific Region, with only 32% of Member States reported to manufacture antimicrobial medicines in their countries, it is necessary to strictly enforce importation requirements and inspect the quality of medications.

Investments in R&D will also require re-engineering of the current regulatory mechanisms governing the process of getting new antimicrobial medications to the market (*74*). The regulatory environment is often cited as a major constraint to development because of the high cost of meeting the requirements, relative to expected rewards.

5.5 Regional framework for research, development and innovation

Research, development and innovation are fundamental endeavours to contain the spread of AMR. A potential framework should facilitate investment in new medicines, diagnostic tools, vaccines, and other interventions in both human and animal health. The need for increased investment in R&D, in particular for the development of new antibiotics, has been widely recognized, with misaligned incentives at the core of the problem (*50, 65–67, 74, 75*).

In the case of antibiotics, for instance, a combination of factors, including scientific challenges, low prices, and the reservation of new products for "last line" defence against the growing problem of AMR, has reduced incentives for industry investment in R&D (*67, 74*).

The traditional business model, whereby the cost of R&D has to be evaluated against pricing, sales and return on investment, appears to be intrinsically unsuited to future development of critical antimicrobial agents (*67*). This has been described as a type of market failure (*74, 75*). The lack of investment in new antimicrobial medicines reflects, in part, fears that resistance will develop rapidly and that returns on investment will be limited because of restrictions in use. If newer antimicrobials become obsolete sooner, then profits extinguish, which makes investment in this area unattractive (*50*). In addition, a new antibiotic might be needed only in exceptional circumstances, which would necessitate some mechanisms to finance R&D other than sales revenues (*74*).

Thus R&D of new antibiotics is seen as a less attractive business investment than that of other medicines, such as those for chronic diseases, where drugs are taken by many people, every day, for long periods, and are patent protected for the first 10–15 years of their life (*74*).

The future development of critical agents should be regarded as a global public good, and business models should seek mechanisms that dissociate or delink the costs of R&D from the pricing of the products and return on investment, and that encourage rational use of antimicrobial agents (*50, 67, 74*). As a global public good, R&D should be stimulated through financial and non-financial mechanisms that ensure a fair level of contribution by each country, since every country in the world would benefit (*67*).

The policy and scholarly literature suggests and discusses several approaches to improving incentives for R&D and enhancing the resources devoted to it (*50, 67, 74*). They have been typically classified within pull and push mechanisms. In most mechanisms, governments have the potential to play a significant role through either direct funding or enabling policies and regulations. For example, governments may provide a special priority status to new classes of medications, such as antibiotics, with guaranteed review and approval time.

5.5.1 Pull mechanisms

Pull mechanisms aim to stimulate R&D by offering incentives such as guaranteed purchase of final products, milestone) prizes, special patent incentives or buyouts, advance market commitments, priority review and higher product prices (*74*). Pull mechanisms boost the reward at the end of the development process (*50*). The main advantage of this mechanism is that governments and funders assume no risk and are paid out only in the case of success.

Industry and developers assume the risk and uncertainty associated with developing new medicines, which means that small and medium enterprises are less likely to participate in R&D efforts. Examples include various kinds of guaranteed purchase schemes for vaccines, including an advance purchase commitment for pneumococcal vaccine (*74*). In general, pull mechanisms do not delink incentives from sales and some may actually compromise access to antimicrobial medicines.

5.5.2 Push mechanisms

Push mechanisms are research subsidies (or tax incentives) intended to encourage and finance R&D on particular topics or in particular areas (*74*). They target the early development phase of R&D and aim to lower costs associated with the uncertainty surrounding successful development (*50*). Funding can come from public sector research grant schemes and private sector funding schemes such as venture capital. The main advantage of push mechanisms is that they attract organizations of any size, as funding is provided up front. Governments and funders assume the risks, since resources are spent irrespective of results. Funding through push mechanisms is typically not enough to cover the most expensive part of the development process.

Collaborative models of push mechanisms include product development partnerships or setting up a global collaboration platform (*50*). Product development partnerships use public and philanthropic funds to engage the pharmaceutical industry and academic research institutions in undertaking R&D. Product development partnerships rely on their partners for financing and other in-kind contributions (for example laboratories and expertise), allocate resources to the most promising targets, coordinate partner activities for various stages of the R&D process, and manage the project portfolio. The main advantage of product development partnerships is that sponsors (for example governments) can set targets and priorities, and risk is spread over a number of projects. Governance may be a challenge given the multiple stakeholders involved. Box 10 presents an example of a collaborative partnership headquartered in Japan.

Box 10. Global Health Innovative Technology Fund (GHIT Fund)

An example of an innovative, collaborative partnership is the Global Health Innovative Technology Fund (GHIT Fund). The GHIT Fund is an international non-profit organization headquartered in Japan that invests in the discovery and development of new health technologies such as drugs, vaccines and diagnostics. The GHIT Fund is the world's first product development fund for global health R&D, built on the strength of contributions from partners in the public, private and civil sectors.

The GHIT Fund incorporates product development partnerships, overseas research, and other initiatives through a platform for global health R&D, and is considered a ground-breaking funding response to the failure of free-market mechanisms to facilitate R&D. In financial year 2013 alone, the GHIT Fund invested over US$ 17.5 million in more than 20 development partnerships between Japanese and international research institutions, and reinvigorated drug discovery for neglected and parasitic diseases by opening the door for product development partnerships to seven of Japan's major chemical compound libraries. In 2014, the GHIT Fund portfolio grew to US$ 33.5 million in grant investments to develop vaccines and drugs for neglected diseases.

A global collaboration platform would enable collaborative R&D through an open source platform. The platform makes information and ideas freely available, lower barriers to entry for all actors and enables entrepreneurial innovation to flourish. It involves linkage of research data across a range of disciplines and sectors, molecule libraries, clinical trial data and surveillance data into one freely accessible global repository. It also requires considerable investment and relies on strong governance, administration and political buy-in from a range of stakeholders. The main advantage of a global collaboration platform is that it lowers the marginal cost of information, duplication and waste, and risk spreads across sponsors and participants.

5.5.3 Push-pull mechanisms

Combined push-pull mechanisms comprise elements of both, and in some cases push mechanisms can only work if pull incentives are adequate (*74*). In fact, it has been argued that, in isolation, none of these incentives will achieve the desired results, and a hybrid approach is universally recommended (*50*). For example, in the case of orphan diseases, incentives to stimulate R&D can combine initial grants and tax credits as pushing mechanisms with market exclusivity and guaranteed purchase as pulling mechanisms. These combined financing mechanisms have to be large enough to encourage industry to develop drugs that eventually generate profits.

In a comprehensive review, the OECD concluded that a hybrid approach should balance the need to encourage and harness global innovation and entrepreneurial thinking against the notion of antimicrobial therapies as social goods and the concerns of preservation and need-based access (*50*). A mix of push and pull interventions is needed to ensure development and is supported along the entire value chain, from concept to approval, production and distribution.

Box 11 presents the OECD comprehensive approach to support research, development and innovation on AMR. This approach will require, however, significant financial investment, public money and the creation of a public (and international) institution or consortium, which has been unanimously endorsed in the literature.

5.5.4 Diagnostics and alternative approaches

Although the development of new medicines is the mainstay to address AMR, diagnostic tools and vaccines are also important complementary tools where R&D is needed. They are also intermediate public goods since they will contribute to the containment of AMR, if successfully produced. Better and faster point-of-care diagnostics tools can avoid, for example, unnecessary use of antibiotics, which is a well-recognized driver of AMR.

The development process for diagnostics tools is typically shorter and less costly than for new drugs, but the return on investment is also potentially lower than for drugs (*74*). It may also require a less complex set of either push or pull incentives and mechanisms. Advance purchase commitment by governments may be a strong, and possibly the most important, incentive needed to foster innovation in point-of-care tests that can detect, for example, the presence of acute respiratory bacterial infections, for which no tests are currently able to provide perfect diagnostic accuracy (*76*).

Box 11. OECD comprehensive approach to foster research, development and innovation

OECD proposes a comprehensive approach with the following elements:

1. A global collaborative research platform
Using an open source approach to engage the "global brain" in developing new antimicrobial therapies and conducting other complementary research is one of the more effective and efficient methods available.

2. Push levers such as milestone prizes and grants
Push levers should be deployed to enable small to medium enterprises and academia to participate in and contribute to this global collaborative. This should include a set of incentives aimed at diagnostics and other neglected research areas.

3. Patent buyouts for successfully developed products
These pull levers incentivize completion of development, are attractive to larger stakeholders and, most importantly, sever links between sales and development costs.

4. Funding of clinical trials and a single global approval process
The clinical trial process is a considerable disincentive for developers. This element of the OECD approach would not only lower this barrier but would also increase the depth and richness of the integrated data repository, access to which would, in turn, make the clinical trial process more efficient. Harmonized approval would expedite access to antimicrobial therapies for populations in need, regardless of ability to pay.

A spectrum of tools and technologies could have a regional impact, especially those suitable for settings in low- and middle-income countries. The goal of diagnostic tools is to improve rational use of antimicrobials, and thereby delay emergence or development of resistance. Experiences with tuberculosis have been exemplary, expanding reference laboratory capacity and facilitating the roll-out of new tools for remote locations, and the tuberculosis specimen and strain banks, which provide biospecimens needed to evaluate tools. New rapid diagnostics could also facilitate clinical trials of new antibiotics, permitting smaller, less expensive studies (*74*).

Vaccines are the ultimate means to reduce the widespread use of antibiotics by preventing infections in the first place *(74)*. Pneumococcal (and typhoid) vaccines present an example of the potential benefits that existing vaccines can have in relation to AMR. Introduction of this vaccine not only reduced pneumococcal disease amongst vaccinated and non-vaccinated individuals within the study region, but was also linked to a decrease in resistance and antibiotic use amongst the study population (*50*).

5.6 Conclusion and policy implications

AMR poses a profound threat to health and society, and has been recognized as a global health security risk. Efforts to contain AMR are beyond the capacity of any organization or nation alone, and require a global integrated approach and international cooperation and collaboration, with the involvement of all relevant sectors, including human and animal health, agriculture, the environment and research.

Given the global scope and scale of AMR, this background document presents arguments to recognize the containment of AMR as a global public good, and proposes and discusses some policy directions and interventions to support regional actions to help tackle the problem.

The overall directions proposed are presented as intermediate public goods, since they have the potential to slow the spreading pace of AMR. They have been classified under three main themes:

- regional surveillance system
- regional regulatory framework or platform
- regional framework for research, development and innovation.

For each of these public goods, the document describes their importance, outlines some potential courses of action, and provides examples that may serve as benchmark cases for the region to inform efforts towards producing these three public goods. For the regional surveillance system, in particular, activities will require close coordination with the Global Antimicrobial Resistance Surveillance System (GLASS), which aims to produce meaningful data and common standards at a global level to enable comprehensive monitoring and analysis of the occurrence and trends of resistance worldwide. In addition, the experience of the Japan Nosocomial Infections Surveillance (JANIS) demonstrates the feasibility of developing an AMR surveillance system, and may be used as a benchmark case for the region to inform efforts towards developing a regional surveillance system.

As public goods, they are also desirable outcomes. Their production will require collective and coordinated regional multistakeholder action and commitment so that, if successfully produced, they will have the potential to yield significant and mutual external benefits, across multiple nations. Box 12 briefly describes the policy implications of producing the three intermediate public goods discussed in this background paper to contain AMR.

Box 12. Regional policy implications

The containment of AMR is a long-term endeavour that will require long-term partnership and commitment among regional Member States and key stakeholders.

This endeavour will require concerted and collective action at the regional level to maximize the financing and investment needed to contain AMR.

Given the global and public nature of this problem, active government participation through either direct funding or enabling policies and regulations will be critical.

The containment of AMR will require Member States to focus on three intermediate public goods:

- a regional surveillance system to detect, analyse and track resistant and non-resistant (susceptible) microorganisms, and antimicrobial consumption;
- a regional regulatory framework or platform to optimize the use of antimicrobial medicines in human and animal health; and
- a regional framework for research, development, and innovation to facilitate investment, through a combination of incentives, in new medicines, diagnostics tools, vaccines, and other interventions in human and animal health.

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