

POLICY BRIEF 32

Averting the AMR crisis

What are the avenues for policy action for countries in Europe?

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Keywords:

ANTI-BACTERIAL AGENTS

DRUG RESISTANCE, MICROBIAL

DRUG RESISTANCE, BACTERIAL

HEALTH POLICY

BIOMEDICAL RESEARCH

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This policy brief is one of a new series to meet the needs of policy-makers and health system managers. The aim is to develop key messages to support evidence-informed policy-making and the editors will continue to strengthen the series by working with authors to improve the consideration given to policy options and implementation.

What is a Policy Brief?

A policy brief is a short publication specifically designed to provide policy makers with evidence on a policy question or priority. Policy briefs

- Bring together existing evidence and present it in an accessible format
- Use systematic methods and make these transparent so that users can have confidence in the material
- Tailor the way evidence is identified and synthesised to reflect the nature of the policy question and the evidence available
- Are underpinned by a formal and rigorous open peer review process to ensure the independence of the evidence presented.

Each brief has a one page key messages section; a two page executive summary giving a succinct overview of the findings; and a 20 page review setting out the evidence. The idea is to provide instant access to key information and additional detail for those involved in drafting, informing or advising on the policy issue.

Policy briefs provide evidence for policy-makers not policy advice. They do not seek to explain or advocate a policy position but to set out clearly what is known about it. They may outline the evidence on different prospective policy options and on implementation issues, but they do not promote a particular option or act as a manual for implementation.

Averting the AMR crisis: What are the avenues for policy action for countries in Europe?

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Print ISSN 1997-8065

Web ISSN 1997-8073

Foreword

Antimicrobial Resistance (AMR) is one of the major challenges of our time. Without effective antimicrobials, common infections will become life-threatening and treatments such as surgical procedures and chemotherapy would not be possible. The most recent studies show that over 33 000 people die every year in the European Union (EU) due to infections from antibiotic-resistant bacteria. The economic impact is also significant – AMR costs the EU an estimated 1.5 billion euros per year in healthcare costs and productivity losses.

International and national efforts to combat AMR have grown steadily over the last two decades. Right from the start the EU has been part of these efforts, reflecting its longstanding ambition to lead by example when tackling AMR and to make the EU a best practice region.

As early as 1998, the European Commission established the European Antimicrobial Surveillance System (EARSS) and in 2001 the Community Strategy against AMR was published. The EU Council's recommendations on the prudent use of antimicrobial agents in human medicine followed in 2002. Subsequently, the importance of the prudent use of antimicrobials in animal health has also been recognized and reflected in regulation and official policy documents. For example, the use of antibiotics for promoting growth has been banned in all EU countries since 2006. Moreover, the 2018 EU Regulation on veterinary medicines now bans the prophylactic use of antibiotics in groups of animals, restricts metaphylactic use of antimicrobials in animals and provides for the possibility to restrict the use of certain antimicrobials to human use only. At the same time, it includes the obligation for EU Member States to collect data on the sale and use of antimicrobials in animals. The new EU Regulation on medicated feed also foresees a complete ban on the preventative use of antimicrobials via medicated feed, as well as further restrictions for veterinary antimicrobials. Guidelines for the prudent use of antimicrobials in veterinary medicine which support these efforts and encourage appropriate antimicrobial use were produced in 2015. The European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA) and the European Food and Safety Authority (EFSA) have been instrumental in supporting these efforts and developing a holistic approach to tackling AMR that goes beyond the human health sector.

In 2011, the European Commission issued a “Communication on an Action Plan against the rising threats from AMR” (COM(2011)748 final). This was updated through the adoption of the 2017 EU One Health Action Plan against AMR, which aims to (i) make the EU a best practice region, (ii) boost research, development and innovation and (iii) shape the global agenda. Today, there is a broad consensus that the drivers of AMR are interlinked and lie across the human, animal and environmental health sectors.

This ‘One Health’ perspective was recognized in the Global Action Plan on Antimicrobial Resistance adopted by the World Health Organization (WHO) in 2015, which asked for all countries to develop national action plans (NAPs) by 2017. Although meeting this ambitious target has proved challenging, today, the development of NAPs is underway in almost all countries and many have already adopted their plans.

Over the years, EU Council Presidencies have been used as important platforms to advocate for EU-wide action against AMR. In 2009, the Swedish Presidency made antimicrobial development a priority. In 2012 and 2016, Denmark and the Netherlands championed the ‘One Health’ perspective during their Presidencies. In 2016 Council Conclusions on the next steps under a ‘One Health’ approach to combat antimicrobial resistance were adopted under the Netherlands Presidency. Now, the Romanian Presidency seeks to encourage solidarity and consistency between Member States by improving the implementation of AMR NAPs with a particular focus on infection prevention and control and antimicrobial stewardship.

As a first step, there is a need to outline what works and in what context for policy-makers. This policy brief meets this demand by providing an accessible summary of the evidence available regarding key policy avenues to tackle AMR. It was prepared by the European Observatory on Health Systems and Policies in support of the Romanian EU Council Presidency and brings together expertise from the London School of Economics and Political Science, the Organisation for Economic Co-operation and Development (OECD) and WHO. It draws significantly on the forthcoming study *Challenges in Tackling Antimicrobial Resistance: Economic and Policy Responses* (produced by the Observatory and OECD in collaboration with the European Commission). It also capitalises on the extensive experience of many EU Member States in tackling AMR by showcasing examples of effective policies in action.

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Acknowledgments

This publication was produced as a collaboration between the European Observatory on Health Systems and Policies, the London School of Economics and Political Science (LSE), the Organisation for Economic Co-operation and Development (OECD), and the WHO Regional Office for Europe (WHO/Europe). It is being published to support the Romanian EU Presidency conference on combating AMR. It draws significantly on the forthcoming study *Challenges in Tackling Antimicrobial Resistance: Economic and Policy Responses* co-produced by the Observatory and the OECD with financial support from the European Union. It responds to the growing evidence regarding policy options across a multitude of contexts to combat AMR. The brief was reviewed by Danilo Lo Fo Wong and Ketevan Kandelaki, both from the Division of Health Emergencies and Communicable Diseases, WHO/Europe.

Acronyms

ABS	antibiotic stewardship
AMC	(WHO) Antimicrobial Medicines Consumption (Network)
AMR	antimicrobial resistance
AMRFF	Antimicrobial Resistance Funders Forum
AMU	antimicrobial use
AQP	Antibiotic Quality Premium
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
FAO	Food and Agricultural Organization (of the United Nations)
GARDP	Global Antibiotic Research & Development Partnership
GDP	gross domestic product
GLASS	Global Antimicrobial Resistance Surveillance System
HAC	hospital-acquired condition
HAI	healthcare-associated infection
HAI-Net	Healthcare-associated Infections Surveillance Network
IACG	Interagency Coordination Group (on Antimicrobial Resistance)
ICM	intersectoral coordinating mechanism
IPC	infection prevention and control
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	low- and middle-income country
MER	market entry reward
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NAP	national action plan
OIE	World Organisation for Animal Health
OTC	over-the-counter
PCU	population correction unit
PPP	purchasing power parity
PSI	patient safety indicator
SPHeP-AMR	Strategic Public Health Planning for AMR
StAR	(Swiss) Strategy on Antibiotic Resistance
STAR-PU	specific therapeutic group age–sex weightings related prescribing units
TB	tuberculosis
USD	United States Dollar
UV	ultraviolet

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How do Policy Briefs bring the evidence together?

There is no one single way of collecting evidence to inform policy-making. Different approaches are appropriate for different policy issues, so the Observatory briefs draw on a mix of methodologies (see Figure A) and explain transparently the different methods used and how these have been combined. This allows users to understand the nature and limits of the evidence.

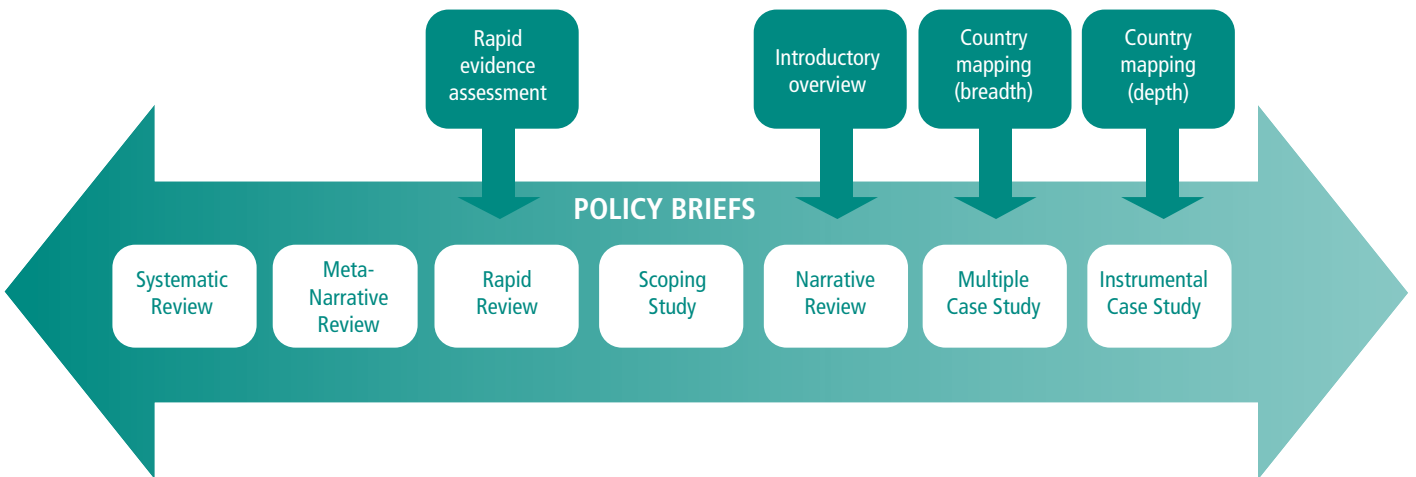
There are two main ‘categories’ of briefs that can be distinguished by method and further ‘sub-sets’ of briefs that can be mapped along a spectrum:

- **A rapid evidence assessment:** This is a targeted review of the available literature and requires authors to define key terms, set out explicit search strategies and be clear about what is excluded.

- **Comparative country mapping:** These use a case study approach and combine document reviews and consultation with appropriate technical and country experts. These fall into two groups depending on whether they prioritize depth or breadth.
- **Introductory overview:** These briefs have a different objective to the rapid evidence assessments but use a similar methodological approach. Literature is targeted and reviewed with the aim of explaining a subject to ‘beginners’.

Most briefs, however, will draw upon a mix of methods and it is for this reason that a ‘methods’ box is included in the introduction to each brief, signalling transparently that methods are explicit, robust and replicable and showing how they are appropriate to the policy question.

Figure A: The policy brief spectrum



Source: Erica Richardson

Key messages

- Antimicrobial resistance (AMR) has serious adverse effects on human, animal and environmental health, healthcare systems, agriculture and national economies. With growing AMR rates, these costs are projected to increase dramatically if no action is taken.
- International and national efforts to combat AMR have grown steadily over the last two decades and culminated in the adoption of the Global Action Plan on Antimicrobial Resistance in 2015, which asked for all countries to develop national action plans (NAPs) by 2017.
- However, what has been done so far does not match the recommended scale of actions, and progress with developing NAPs has been inconsistent. Countries have thus been under mounting political pressure either to develop their first AMR NAP or to revise their current plan in line with international guidance.
- Since the drivers of AMR are multifactorial, AMR NAPs should also be multifactorial, involving a broad range of sectors, including human, animal and environmental health sectors, and utilizing a 'One Health' approach.
- Drawing on guidance from the World Health Organization (WHO), Food and Agricultural Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE), key avenues of action to consider in an effective AMR strategy include:
 - (1) Increasing awareness of AMR
 - (2) Strengthening surveillance and monitoring, and moving towards national 'One Health' surveillance systems
 - (3) Strengthening antimicrobial stewardship in human health
 - (4) Strengthening infection prevention and control (IPC) in human health
 - (5) Strengthening IPC and reducing inappropriate antibiotic use in animals
 - (6) Limiting the exposure of antimicrobial-resistant pathogens to the environment
 - (7) Fostering R&D of new antimicrobial therapies, diagnostics and vaccines
- Countries will vary in their points of departure and contexts, and their policy responses will therefore differ. However, all these avenues are important and, while some countries may need to prioritize certain avenues initially, all countries should aim towards a comprehensive AMR NAP.
- Introduction of particular measures within some of these avenues may be obstructed by financial, regulatory and other barriers. However, a recent model developed by the Organisation for Economic Co-operation and Development (OECD) has shown that many policies targeted to tackle AMR are highly cost-effective. Countries should work together to overcome these barriers by sharing their experiences and examples of good practice.
- While the development of a NAP is an important step in governing the efforts to fight AMR, pursuing their successful implementation remains the biggest challenge. Good governance of AMR policies is thus a key determinant for success and should be at the forefront of any efforts to address the AMR challenge.

Executive summary

The health and financial impacts of AMR are huge and will increase dramatically if nothing is done

Antimicrobial resistance (AMR) is a naturally occurring mechanism by which microorganisms such as bacteria become resistant to antimicrobial medicines. This threatens our ability to treat infections and to undertake life-saving treatments such as surgical procedures and chemotherapy. It also comes at significant cost to healthcare systems and national economies. For example, hospital costs of treatment for a resistant infection are estimated to be USD10 000–40 000 higher than for susceptible infections. With growing AMR rates, these costs are projected to increase dramatically if no action is taken.

There is broad agreement on what needs to be done to combat AMR but efforts so far have not been commensurate with the recommended scale of actions

International and national efforts to combat AMR have grown steadily over the last two decades, culminating in the adoption, in 2015, of the Global Action Plan on Antimicrobial Resistance, which asked for all countries to develop national action plans (NAPs) by 2017. The 'One

Health' perspective, which includes the imperative to coordinate actions across the human, animal and environmental health sectors to combat AMR has also gained acknowledgement and is now widely accepted. New initiatives have been started to strengthen the antibiotic pipeline and diagnostic development. Although the ambitious goal of all countries developing a NAP within two years of the adoption of the Global Action Plan has proven to be a challenge for countries with limited resources or capacity to plan across sectors, results from the second global self-assessment survey on the progress of countries indicate that almost all countries have initiated the process of NAP development and many have adopted their plans.

Countries are expected to develop or revise their AMR NAPs in line with international guidance

Countries have been under mounting political pressure either to develop their first AMR NAP or revise their current plan in line with international guidance. To aid policy-makers, this brief provides a summary of the essential policy areas and priority interventions, endorsed by the World Health Organization/Food and Agricultural Organization of the United Nations/World Organisation for Animal Health (WHO/FAO/OIE) tripartite, to consider when formulating a national strategy to combat AMR. A selection of specific measures is also provided.

Policy avenues	Examples of measures
<p>(1) Increasing awareness of AMR <i>To reduce inappropriate use of antibiotics</i></p>	<ul style="list-style-type: none"> • Public awareness campaigns at national, regional and local levels, including initiatives such as educational campaigns within schools (e.g. the European Union (EU)'s e-Bug programme), and the Antibiotic Guardian Programme for the general public and health professionals (Public Health England). • Education and training measures for professionals in the human, animal and environmental health sectors; a dedicated Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance was published by the WHO in 2018.
<p>(2) Strengthening surveillance and monitoring, and moving towards national 'One Health' surveillance systems <i>Surveillance is key from the conception of AMR NAPs through to their implementation and evaluation</i></p>	<ul style="list-style-type: none"> • AMR surveillance systems should seek to cover the human, animal and environmental health sectors, in line with the 'One Health' approach. • National surveillance systems should contribute to international surveillance systems, such as EARS-Net, ESAC-Net, HAI-Net, CAESAR, WHO AMC, ESVAC, GLASS.
<p>(3) Strengthening antimicrobial stewardship in human health <i>To reduce inappropriate prescribing, especially in primary care where most antibiotics are prescribed</i></p>	<ul style="list-style-type: none"> • Primary care: Interventions to alter the prescribing behaviour of physicians through (a combination of) non-financial measures such as guidelines, outreach visits, audits, computerized reminders and financial incentives; use of point-of-care tests to rule out viral infections; shared decision-making between the clinician and patient, in conjunction with delayed prescribing; patient education during consultations. • Hospital care: Interventions to alter the prescribing behaviour of healthcare professionals, including: educational (e.g. use of educational meetings, materials and outreach visits); persuasive (e.g. outreach visits); restrictive (use of rules and guidelines); environmental restructuring and enablement (use of physical reminders or laboratory improvements). Interventions usually involve multiple techniques.
<p>(4) Strengthening infection prevention and control (IPC) in human health <i>To reduce healthcare-associated infection (HAI) rate (about 30–40% of HAIs are caused by resistant organisms)</i></p>	<ul style="list-style-type: none"> • Combination of (vertical and horizontal) IPC measures that include both physicians and nurses (e.g. hand hygiene campaigns) and could be encouraged with financial incentives and/or penalties (related to HAI rates). • Evidence-based guidelines on core components of IPC programmes were published by the WHO in 2016.

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Policy avenues	Examples of measures
<p>(5) Strengthening IPC and reducing inappropriate antibiotic use in animals <i>To reduce prevalence of resistant pathogens in animals</i></p>	<ul style="list-style-type: none"> • Restricting the use of non-therapeutic antimicrobials and antimicrobials that are critically important for human use. • IPC measures such as implementing higher biosecurity, improved husbandry methods, use of vaccination.
<p>(6) Limiting the exposure of antimicrobial-resistant pathogens to the environment <i>To reduce spread of pathogens through the environment</i></p>	<ul style="list-style-type: none"> • Monitoring and regulation of the environment and environmentally related activities or products that influence the spread and development of AMR pathogens.
<p>(7) Fostering R&D of new antimicrobial therapies, diagnostics and vaccines <i>To replace antibiotics rendered ineffective by AMR, reduce unnecessary use of antibiotics and prevent infections</i></p>	<ul style="list-style-type: none"> • R&D in antibiotics: Pull and push incentives to boost returns from newly discovered antibiotics or to subsidize the cost of R&D, with recent reports recommending the use of market entry rewards (MERs) or an Options Market for Antibiotics (OMA); recent supranational funding initiatives include Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research & Development Partnership (GARDP). • R&D in diagnostics: Incentives to develop a simple rapid test to distinguish between bacterial and viral infections, including harmonization of regulatory standards and procedures to reduce duplication of clinical studies, minimizing delays and reducing the costs of meeting regulatory standards; application of health technology assessment (HTA) to diagnostics. • R&D in vaccines: Stimulate research and use of vaccines; the value of vaccines in combatting AMR should be incorporated into decisions on vaccine development and use. • Coordinating research: The approach to AMR research should be multidisciplinary and holistic to avoid gaps in research and/or duplication of efforts; organizations such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) support coordinating research activities globally but national coordination is also important.

Countries will of course vary in their points of departure and contexts, including in their ability to mobilize the resources necessary to combat AMR. Their policy responses will therefore differ. However, ultimately, all these avenues are equally important and, while some countries may need to prioritize certain avenues initially, all countries should aim towards a comprehensive AMR national action plan.

Surveillance is key in all stages of developing national AMR NAPs, including in monitoring progress of their implementation

Comprehensive surveillance is key during the conception, implementation, monitoring and evaluation of AMR NAPs. Surveillance data is useful initially to establish the extent of AMR and antimicrobial use (AMU) to inform the development phase of AMR NAPs. Thereafter, it is a key element in the feedback and accountability mechanisms for relevant stakeholders which will improve the likelihood of the successful implementation of the NAP. Surveillance is also essential for the ongoing monitoring and evaluation of NAPs as well as the effectiveness of specific policies. The importance of AMR surveillance systems cannot be overestimated.

Good governance of AMR policies should be at the forefront of any efforts to combat AMR

The implementation of particular measures within some of these avenues may be obstructed by financial, regulatory or other barriers. Yet, the biggest obstacle in fighting AMR is not just developing NAPs but also pursuing their successful implementation. Good governance of AMR policies should therefore be at the forefront of any efforts to address the AMR challenge. Common principles of good governance that are applied to health systems, such as strategic vision, participation, coordination, responsibility, accountability, sustainability, monitoring and evaluation, are also relevant to AMR NAPs. Examples of how these principles can be effectively applied are to be found in countries across Europe, including the United Kingdom, the Netherlands and the Nordic countries. These should be widely shared across countries to facilitate cross-country learning and to support collective action in addressing this global challenge.

Policy brief

Introduction

The discovery of antibiotics 90 years ago has revolutionized the treatment of communicable bacterial diseases and facilitated significant developments in areas of medicine such as surgery, obstetrics and oncology [1,2]. Concerns regarding resistance to antibiotics were raised almost immediately, with Sir Alexander Fleming, the discoverer of penicillin, noting in an interview as early as 1945:

In such cases, the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.

(New York Times, 1945)

AMR is a naturally occurring mechanism by which microorganisms such as bacteria become resistant to antimicrobial medicines. Resistance can be intrinsic¹ or acquired and occurs if selective pressure – through the use of antibacterial medicines – kills off susceptible bacteria, while creating a survival advantage for those bacteria with the ability to resist the killing effect of the respective antibiotic(s). We now understand that resistant pathogens can disseminate across the human, animal and environmental sectors, meaning there are wide implications for all aspects of society.

AMR² increasingly threatens our ability to treat infections and to undertake life-saving treatments such as surgical procedures and chemotherapy. The dangers emerging from this alarming development of increasingly resistant microorganisms have previously been mitigated by the discovery of novel classes of antibiotics. However, for the last 30 years this has not been the case, with very few novel antibiotics discovered [4,5]. To date, rising rates of AMR are already responsible for a significant health and economic burden, which, without swift action, is projected to dramatically increase.

The world community is taking the problem seriously, as demonstrated by a history of increasing efforts to combat AMR (see Figure 3 in 'Global action to date'). These efforts culminated in the launch of the Global Action Plan on

Antimicrobial Resistance, which asked for all countries to develop NAPs by 2017 [6,7]. However, progress has been inconsistent. Also, developing NAPs is only the beginning, and the ability of countries to implement these plans can be challenged by the absence of sufficient human and financial resources, low health system capacity, and weak governance and coordination. The UN Interagency Coordination Group on Antimicrobial Resistance (IACG) recently concluded that the biggest obstacle is not just developing the NAPs but also pursuing their successful implementation, suggesting that governance of AMR policies is a key determinant for success [8].

Aim and scope

The aim of this brief is to present key policy options that can be effective in combating AMR in Europe. The brief is meant to serve as a succinct, accessible overview of the policy avenues necessary to build a national strategy to combat AMR. This document does not supplant the need to look more deeply into the evidence for each of the discussed policy options, nor are the options discussed comprehensive or suitable for every type of setting. It begins with an overview of estimations of the health and economic impacts of AMR as well as an outline of global action to date. What follows is a description of several essential AMR policy areas and priority interventions to consider, and then an exploration of the importance of governance to facilitate the successful implementation of AMR NAPs.

Methods

The selection of policy responses reflects the breadth of objectives and recommendations contained within recent international guidance such as the 2015 WHO Global Action Plan on Antimicrobial Resistance [6], the 2016 World Organisation for Animal Health (OIE) Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials [9], and the 2016 Food and Agriculture Organisation (FAO) Action Plan on Antimicrobial Resistance [10]. These plans have overlapping, complementary goals and objectives (see Table 1). They also underscore the need for a holistic and multisectoral 'One Health' approach to controlling and preventing AMR, which has been generally accepted since the beginning of this decade.

¹ The intrinsic antibiotic resistome (antibiotic resistance genes) is a naturally occurring phenomenon that predates antibiotic chemotherapy and is present in all bacterial species [3].

² While this brief will focus on antibacterial resistance (ABR) more specifically, the term AMR will be used throughout, because the strategies discussed here concern AMR more broadly.

Table 1: Overview of the objectives of WHO/FAO/OIE action plans and strategies

2015 WHO Global Action Plan on Antimicrobial Resistance	2016 OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials	
<ol style="list-style-type: none"> 1. Improve awareness and understanding of AMR through effective communication, education and training. 2. Strengthen the knowledge and evidence base through surveillance and research. 3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures. 4. Optimize the use of antimicrobial medicines in human and animal health. 5. Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions. 	<ol style="list-style-type: none"> 1. Improve awareness and understanding. 2. Strengthen knowledge through surveillance and research. 3. Support good governance and capacity building. 4. Encourage implementation of international standards. 	
	<th data-bbox="799 479 1463 546">2016 FAO Action Plan on Antimicrobial Resistance</th>	2016 FAO Action Plan on Antimicrobial Resistance
	<ol style="list-style-type: none"> 1. Improve awareness of AMR and related threats. 2. Develop capacity for surveillance and monitoring of AMR and AMU in food and agriculture. 3. Strengthen governance related to AMU and AMR in food and agriculture. 4. Promote good practices in food and agricultural systems and the prudent use of antimicrobials. 	

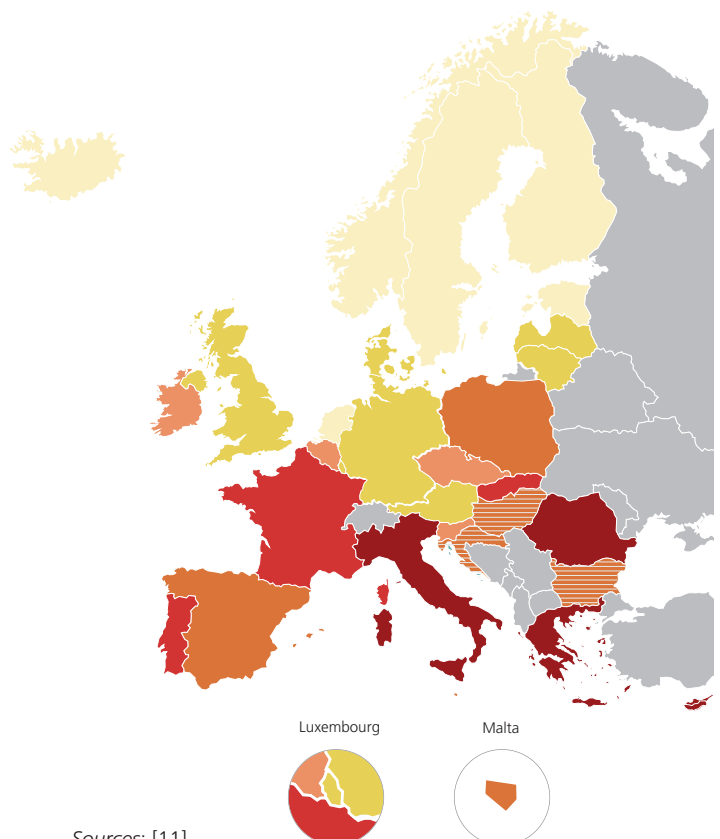
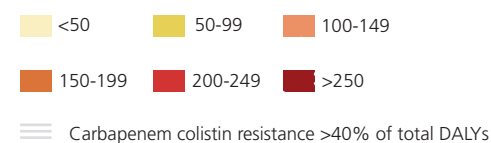
Sources: Based on [6,9–10].

The health and economic impact of AMR

AMR prevalence rates have been on the rise in recent years. Between 2007 and 2015, it is estimated that the annual burden of infections with selected antibiotic-resistant bacteria of public health importance more than doubled across European Union/European Economic Area (EU/EEA) countries [11]. If this trend continues, simple infections may no longer be treatable, with extensively drug-resistant strains of bacteria such as tuberculosis (TB) and gonorrhoea already emerging [12,13].

AMR has adverse effects on both health outcomes and the cost of healthcare. Clinicians often decide the type of antibiotic treatment in the absence of microbiological test results. If a resistant infection is present, the chosen treatment may be ineffective, resulting in wasted resource and a delayed commencement of effective treatment [14]. Additional diagnostic tests will often need to be undertaken to identify the appropriate treatment – again, at increased cost. The severity of resistant infections is often greater than that of treatment-susceptible infections, and this can be intensified by the delayed start of effective treatment. The appropriate treatment for resistant strains is often second-line treatment, which is more costly than front-line options. Treatment of resistant infections often also relies on broad-spectrum antibiotics, which can be less safe and less effective than narrow-spectrum counterparts. Increased severity leads to poorer outcomes and an increase in treatment failure and fatality. There is also a higher risk of complications and a greater chance that patients will require (longer) hospital stays, surgery and time in intensive care or isolation [15]. Modelling analysis of the health burden in disability-adjusted life years (DALYs) of selected antibiotic-resistant bacteria of public health importance across the EU/EEA in 2015 showed that the burden was greatest in infants (aged <1 year) and people aged 65+, and was highest in Romania, Italy and Greece (Figure 1).

Figure 1: Estimates of the burden of infections with selected antibiotic-resistant bacteria of public health importance in DALYs per 100 000 population, EU/EEA, 2015



Sources: [11].

These all come at significant cost to patients (including non-monetary costs), healthcare systems and the wider economy. For example, hospital costs of treatment for resistant infection are estimated to be USD 10 000–40 000 higher than those for susceptible infection [16–20]. In Europe, about 6% of patients develop HAIs, of which 30–40% may be caused by resistant organisms [21]. In 2007, it was estimated that in 31 European countries there were more than 8000 deaths and €62 million of excess costs caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) and resistant *Escherichia coli* [22,23]. The adverse health effects of AMR can also have a serious economic impact by reducing the size of the working population and affecting labour market participation and productivity. Rand Europe [24] estimated that by 2050 a situation of 100% resistance to *E.coli*, *Klebsiella pneumoniae*, *S.aureus*, human immunodeficiency virus (HIV), TB and malaria in OECD countries would lead to a loss of 10.2 million working-age people per year, compared with a loss of 2.1 million per year under current levels of resistance (Figure 2).

KPMG estimated that a doubling of infection rates for MRSA, *E.coli*, *K.pneumoniae*, HIV and TB due to AMR would lead to 700 million deaths by 2050, at a cumulative cost of \$14 trillion to the global economy [26]. Further modelling by the World Bank using two scenarios, a low-impact and a high-impact scenario, again emphasized the cost of inaction but across many dimensions (Box 1).

More recently, the OECD has published individual analyses evaluating the impact of AMR on health and healthcare expenditure for 33 OECD and EU/EEA Member countries. The OECD model estimated that, on average, AMR causes around 67 000 deaths per year across the included countries and costs their healthcare systems \$3.5 billion annually [27] (see also Box 4).

Box 1: World Bank projections of AMR impact by 2050

- **GDP:** In an optimistic scenario of comparatively low impacts, unchecked AMR will likely reduce annual global gross domestic product (GDP) by 1.1% by 2050. In the case of high AMR impacts, by 2050, drug-resistant infections could cut annual global GDP by 3.8%.
- **Poverty:** AMR is projected to lead to a pronounced increase in the incidence of extreme poverty. By 2050, of the additional 28.3 million people falling into extreme poverty in the high-AMR scenario, the vast majority (26.2 million) would live in low-income countries.
- **Livestock:** Livestock production in low-income countries would decline the most, with a possible 11% loss by 2050 in the high-AMR impact scenario.
- **Trade:** By 2050, the volume of global real exports could fall below base-case values by 1.1% in the low-AMR scenario and by 3.8% in the high-AMR scenario.
- **Healthcare costs:** In the high-AMR scenario, healthcare expenditures in 2050 would be as much as 25% higher than the baseline values for low-income countries, 15% higher for middle-income countries, and 6% higher for high-income countries.

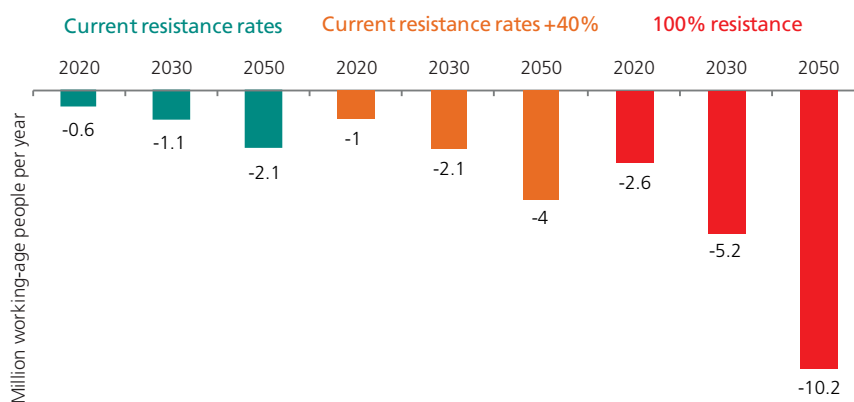
Source: [25].

Global action to date

In 1998, due to concerns regarding the rapid emergence and spread of many human pathogens resistant to available antibiotics, the first WHO resolution on antimicrobial resistance was published [28,29]. Following this, some (mainly OECD) countries began to publish AMR NAPs [7,8].

In 2009, the Swedish EU Presidency made antimicrobial development a priority. High unmet need, as well as potential policies and incentives to promote antimicrobial research, were highlighted as priorities at an expert conference in Stockholm [30]. Following this meeting, the Swedish Prime Minister, Fredrik Reinfeldt, proposed to the US President, Barack Obama, the formation of a Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

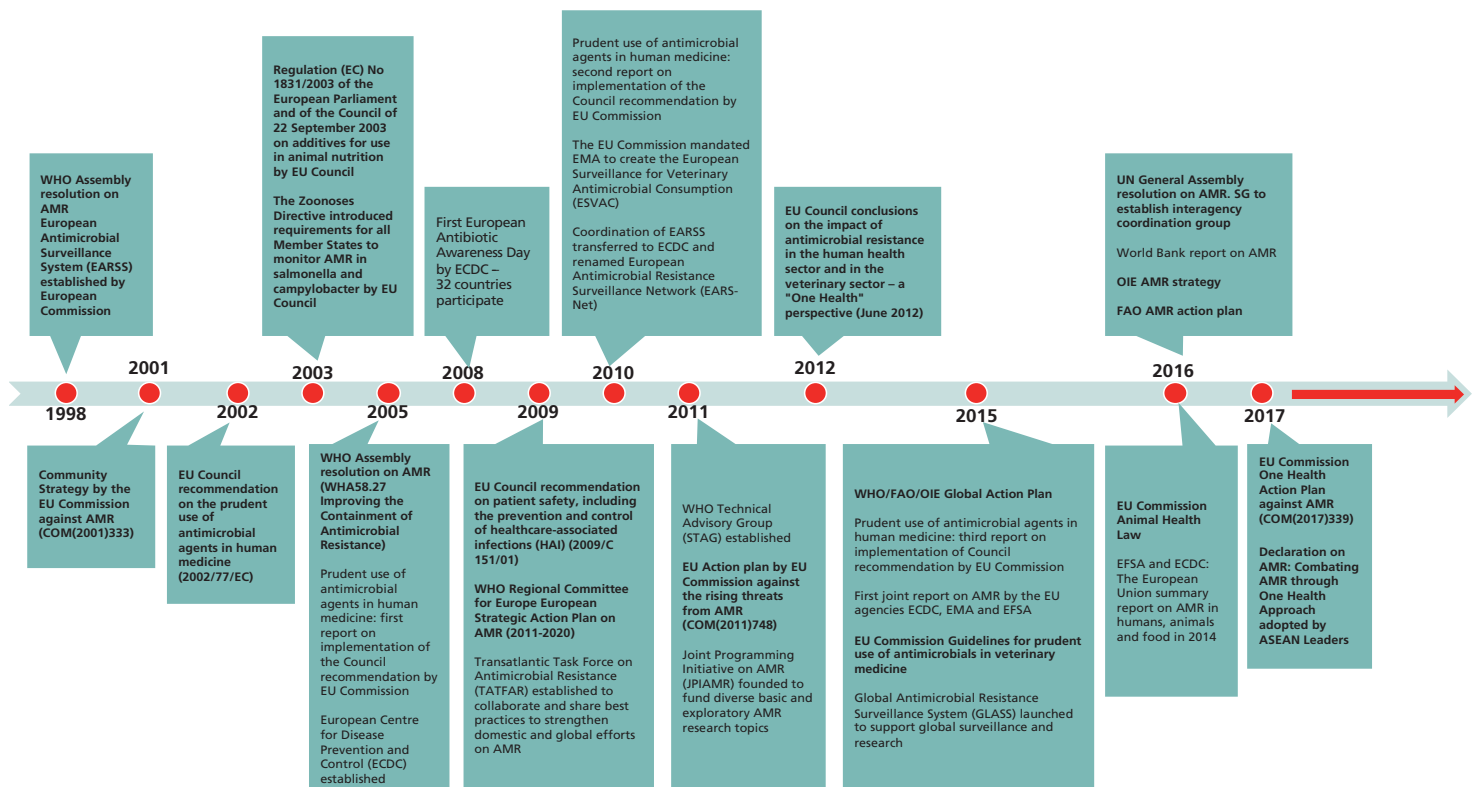
Figure 2: Estimated annual working-age population loss in OECD countries in various resistance scenarios



Source: Adapted from World Bank [25].

Note: Resistance rates of *E.coli*, *K. pneumoniae*, *S. aureus*, HIV, TB and malaria.

Figure 3: Timeline of international AMR key events and policies



Source: Authors.

Note: AMR policies are marked in bold; ASEAN = Association of Southeast Asian Nations; ECDC = European Centre for Disease Prevention and Control; EFSA = European Food Safety Authority; EMA = European Medicines Agency.

between the EU and the United States to encourage global research and address resistance [31]. Slowly, the 'One Health' perspective, which includes the imperative to coordinate actions across the human, animal and environmental health sectors to combat AMR, has gained widespread acknowledgement, with one significant milestone being the European Council conclusions on a 'One Health' perspective in 2012 [32].

Later in 2014, G7³ leaders committed to working with the WHO to develop a global action plan on AMR. To follow this up, the United Kingdom established the independent review on AMR, which in 2016 outlined the severity of the threat AMR poses to health and the global economy, proposing several measures necessary to improve antibiotic stewardship and promote the development of new antibiotics, vaccines and diagnostics [33].

Efforts were renewed with World Health Assembly resolutions in 2014 and 2015, which peaked in the launch of the Global Action Plan on Antimicrobial Resistance, which asked for all countries to develop NAPs by 2017 [6,8,34]. In 2016, a mapping exercise of international initiatives to encourage antibiotic drug discovery commissioned by the Dutch EU presidency noted that, despite progress, there

appeared to be a lack of global coordination across all initiatives, which risked duplicated effort, funding gaps in the value chain and overlooking important AMR goals [35]. In 2016, the tripartite collaboration of the WHO, FAO and OIE reported that only 53% (79/149) of countries had developed an AMR NAP. However, results from the second global self-assessment survey on the progress of countries indicate that almost all countries have initiated the process of NAP development and many have adopted their plans: by May 2017, 79 out of 154 countries (51%) reported they had a plan, with a further 50 reporting having a plan under development.

Later in 2016, the UN General Assembly agreed a political declaration on AMR, which accepted the WHO Global Action Plan on Antimicrobial Resistance as a blueprint; recognized and underlined the severity of the AMR threat to health and society in general; and committed to work at national, regional and global levels to develop and implement multisectoral NAPs in accordance with the 'One Health' approach [36]. In 2017, leaders of the G20 endorsed actions to combat AMR, including the establishment of a new international R&D Collaboration Hub [37]. Figure 3 summarizes the major WHO, EU and UN AMR key events and policy milestones.

³ Canada, France, Germany, Italy, Japan, the United Kingdom and the United States.

Besides the actions taken by international bodies, many nations have made further concrete steps to restrict the unnecessary use of antibiotics in both humans and animals. New initiatives, such as CARB-X and GARDP, have been started to strengthen the pipeline of new antibiotic drugs urgently needed as resistance grows, and diagnostic development has been stimulated by several schemes, such as the Longitude Prize (see below).

Yet, what has been done so far does not match the scale of actions required to address AMR that have been recommended in recent reports [38]. For example, while there has been some progress in addressing the financing of early-stage research, nothing has been done to implement proposals for incentivizing late-stage research and clinical trials. Much also remains to be done to eliminate inappropriate antibiotic use in both humans and animals. The limited availability of rapid point-of-care diagnostics is a key barrier to reducing inappropriate use, given the natural risk aversion of health professionals. Finally, AMR does not respect borders, and countries in Europe cannot coordinate their actions in isolation from the rest of the global community. They should seek to support other countries in their actions to combat AMR with financial and technical expertise, in particular low- and middle-income countries (LMICs), whose specific contexts have led to the emergence of a disproportionately high prevalence of resistant pathogens (Box 2).

Box 2: Prevalence of AMR in low- and middle-income countries

Challenges common to LMICs, such as weak healthcare systems, lack of sustainable healthcare funding, prevalence of over-the-counter (OTC) sales of antimicrobials, plus unhygienic living conditions, contribute to a high burden from infectious disease and foster the occurrence and spread of resistant bacteria.

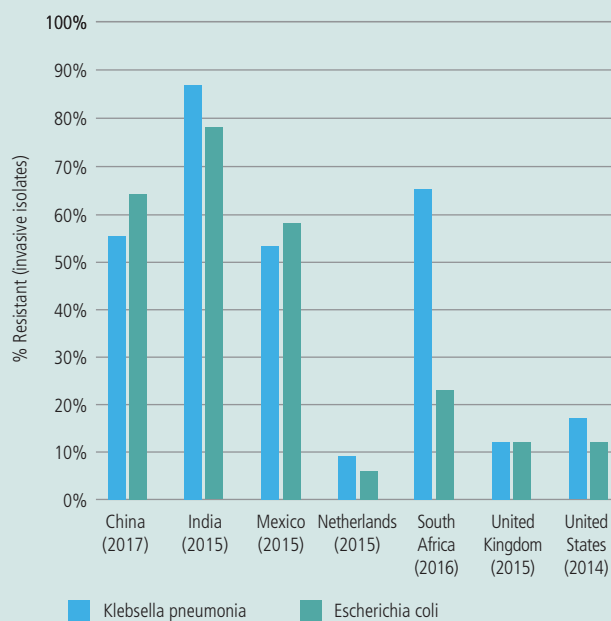
The indicative data shown in Figure 4 suggest an inverse relationship between the prevalence of AMR and a country's per capita income [39]. Between 2000 and 2015, antibiotic use in high-income countries (HICs) rose by just 6%, while in LMICs it increased by 114% [40]. A recent cross-country comparison focusing on 47 LMICs also suggested a strong correlation between out-of-pocket (OOP) health expenditure and AMR, particularly in settings that require a co-payment on drugs in the public sector [41].

The available data for LMICs suggests resistance patterns that surpass those for HICs for most pathogens under AMR surveillance – a phenomenon that has been described as a north-to-south and west-to-east gradient [42]. Overall, data on AMR for LMIC settings is scarce and often biased towards the critically ill patient population due to sample selection, for example from intensive care or neonatal units [20,43]. The difficulties in finding high-quality, representative data on AMR are linked to underlying health system challenges in LMICs, such as the limited availability of high-quality and affordable diagnostic consumables and high-quality microbiological laboratory support, and, not least, health workforce capacity to perform and interpret the diagnostic tests needed to identify bacterial pathogens and establish their susceptibility patterns. Consequently, treatment of infections in LMIC settings is largely driven by empiric algorithms and guidelines, which are often not standardized across clinical settings, and – again due to the lack of reliable local data – not informed by evidence [44,45].

Today, antimicrobial consumption in LMICs is growing at a higher rate compared to HICs; at the same time, access to a core set of life-saving antimicrobial medicines is not yet ensured for all segments of the

population. The high and often unrestricted use of antimicrobials in humans and animals in LMICs places a financial burden and drives resistance in these settings. OTC sales of antimicrobials and self-medication have been reported as a common occurrence in LMICs, and antimicrobials are still frequently used as growth-promoters in the animal health sector, even where these practices have been officially banned [46]. Weak health sector governance and lack of regulatory frameworks and enforcement of policy and legislation in LMICs contribute greatly to these practices in LMICs [47]. Patients in resource-limited countries may also suffer the most from the consequences of the increasing prevalence of AMR, as second- and third-line antibiotics to treat resistant bacteria are not widely available. These therapies are often difficult to obtain in LMICs as a result of high cost and low availability.

Figure 4: Cross-country comparison of E.coli and K.pneumoniae resistance patterns



Source: Adapted from [48].

What are the options? Essential AMR policies and priority interventions

To date, 23 EU countries report that they have completed an AMR NAP and countries are adopting a broad range of policies to tackle AMR [49]. However, given that the health and economic impact of AMR is potentially huge, recent comparative reviews of AMR NAPs find that the quality and comprehensiveness of AMR NAPs is inconsistent [50]. To aid policy-makers, the following section includes a summary of the essential policy areas and priority interventions to consider when formulating a national strategy to combat AMR. As the drivers of AMR are multifactorial, the response should be multifactorial, and any national strategy to combat AMR should weight these avenues equally. These options have been endorsed by the WHO/FAO/OIE tripartite in their respective AMR action plans (see Table 1).

1. Increasing awareness of AMR

Participation in the European Antibiotic Awareness Day (EAAD) initiated in 2008 and the World Antibiotic Awareness Week (WAAW) initiated in 2015 has been strong, however ongoing and repeated efforts are needed to raise public awareness. Eurobarometer results from 2018 showed that 57% of Europeans were unaware that antibiotics are ineffective against viruses [51]. This is a slight improvement from 2013, when 60% of Europeans were unaware that antibiotics are ineffective against viruses [52]. Therefore, it is essential that any national strategy to combat AMR includes actions to increase awareness of AMR among the public as well as for professionals who may be in a position to prescribe antibiotics.

Patient pressure and expectations in primary care have been identified as a trigger for clinicians to prescribe antibiotics in the absence of a clear indication; therefore, it is not surprising that several countries have experienced a reduction in the number of antibiotic prescriptions following AMR awareness campaigns [53]. Nevertheless, the most effective messages and interventions remain unclear as it is difficult to compare interventions due to variations in measurement [54–56]. It has also been suggested that future AMR campaigns should be multimodal in nature and that their design needs to incorporate behavioural science to consider the messages and modalities that will be most cost-effective in reducing antibiotic prescribing, whilst also maximizing the impact on people's knowledge, attitudes and behaviour [57]. It is recommended that campaigns should be implemented at national, regional and local levels to ensure widespread coverage and, when possible, involve an integrated evaluation plan.

Increasingly, countries are focusing on educational campaigns within schools, to target the very young. For example, the e-Bug programme led by Public Health England and involving a consortium of 28 international partner countries, provides interactive exercises which educate children on communicable diseases generally as well as infection prevention measures such as handwashing techniques [58]. Another important strategy that has gained momentum is the Antibiotic Guardian movement developed by Public Health England, which asks both the public and professionals to sign up to be advocates of restricting antimicrobial usage [59,60].

For professionals, it is important that they receive dedicated and continuous education on responsible antimicrobial prescribing and IPC, and that there is an environment conducive to using and adopting standards, facilitating control policies, and implementing guidelines sufficiently [54]. Acknowledging the need to provide guidance in this area, WHO recently (2018) published a dedicated Competency Framework for Health Workers' Education and Training on Antimicrobial Resistance [61].

In the health sector, medical students, physicians, pharmacists, nurses, midwives, dentists and technicians need to be trained in order to build the capacity required to implement guidelines and objectives [62]. It is equally important for professionals from the animal and environmental health sectors, such as veterinarians,

veterinary nurses, farmers, as well as professionals working in sensitive parts of the food industry or environmental agencies, to be trained [63]. Findings from the most recent 'Global monitoring of country progress on addressing antimicrobial resistance: Self-assessment questionnaire 2017–18' indicate that there is still room for improvement in Europe: currently 48% of EU/ EEA countries report having fragmented, ad hoc or limited pre- and in-service training for healthcare workers on AMR. The same was reported by 41% of respondents for training activities in the veterinary sector [49]. Results from the latest global survey find that in 38% of EU/EEA countries awareness campaigns on antibiotic resistance in humans are rather limited and/or small-scale in scope and reach; in non-human health sectors this was reported by 44% of respondents [49].

2. Strengthening surveillance and monitoring, and moving towards national 'One Health' surveillance systems

Comprehensive surveillance is key during the conception, implementation, monitoring and evaluation of AMR NAPs. Surveillance data is useful initially to establish the extent of AMR and AMU to inform the development phase of an AMR NAP. Thereafter, it is a key element in the feedback and accountability mechanisms for relevant stakeholders which will improve the likelihood of the successful implementation of the NAP. Surveillance is also essential for the ongoing monitoring and evaluation of NAPs as well the effectiveness of specific policies. The importance of AMR surveillance systems cannot be overestimated.

While not always the case currently, countries should aspire towards developing a national AMR surveillance system that adopts a 'One Health' approach across animal, human and environmental health [64]. Some countries, such as Denmark, Norway, the United Kingdom, Sweden and Canada, have already begun to publish joint annual AMR surveillance reports, which cover AMR rates of different organisms across both human and animal health, as well as recent data regarding antimicrobial usage [65–69]. Across Europe, many human health surveillance systems are well established and financed, and, due to EU financing and guidance regarding the monitoring of resistant isolates from food animals, national surveillance for animal health is becoming increasingly harmonized [70,71]. Surveillance systems in the environment remain inconsistent, although a recent report from the United Nations Environment Programme (UNEP) provides data sources and exposure pathways for AMR and AMU in the environment, which could be used to identify entry points for integrating environmental surveillance into existing systems [72].

These national surveillance systems must also link into international surveillance systems such as the European Antimicrobial Resistance Surveillance Network (EARS-Net), European Surveillance of Antimicrobial Consumption Network (ESAC-Net), European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR), WHO Antimicrobial Medicines Consumption (AMC) Network, Healthcare-associated Infections

Surveillance Network (HAI-Net) and the Global Antimicrobial Resistance Surveillance System (GLASS). To meet the standards of these systems, the provision of adequate laboratories, equipment and technical expertise, as well as regular external quality assessment, is necessary.

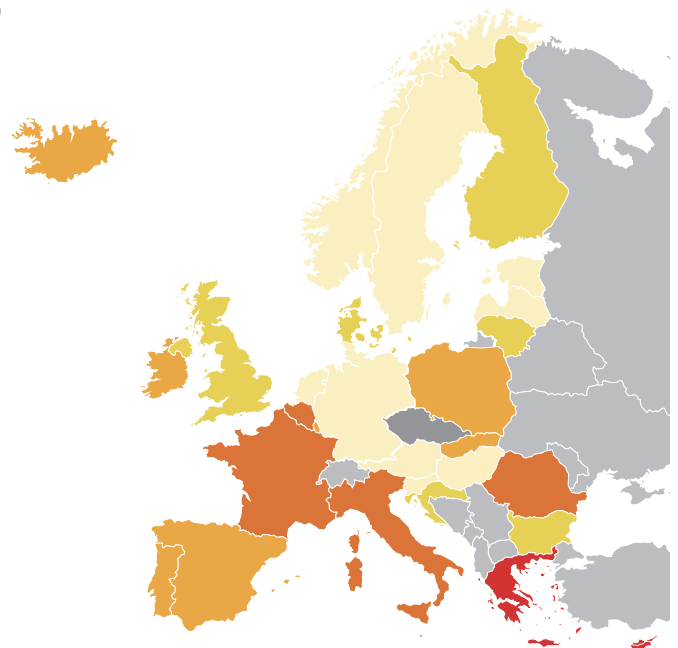
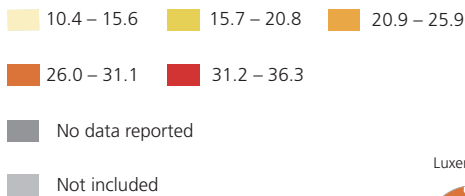
3. Strengthening antimicrobial stewardship in human health

Antibiotic stewardship (ABS) can be defined as ‘the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance [73].’

In 2016, the EU/EEA population-weighted mean consumption of antibiotics for systemic use in the community was 21.9 defined daily doses (DDD) per 1000 inhabitants per day, ranging from 10.4 in the Netherlands to 36.3 in Greece (Figure 5a). In the hospital sector the mean consumption was 2.1 DDD per 1000 inhabitants per day, ranging from 1.0 in the Netherlands to 2.9 in Malta (Figure 5b). Whilst the majority of antimicrobials are prescribed in the community, antimicrobial use in hospital patients tends to be high-volume use by relatively small populations, exerting a higher selection pressure. It has been estimated that on any given day an average of 35% of hospitalized patients in EU/EEA countries receive at least one antibiotic (country range 21–55%) [74].

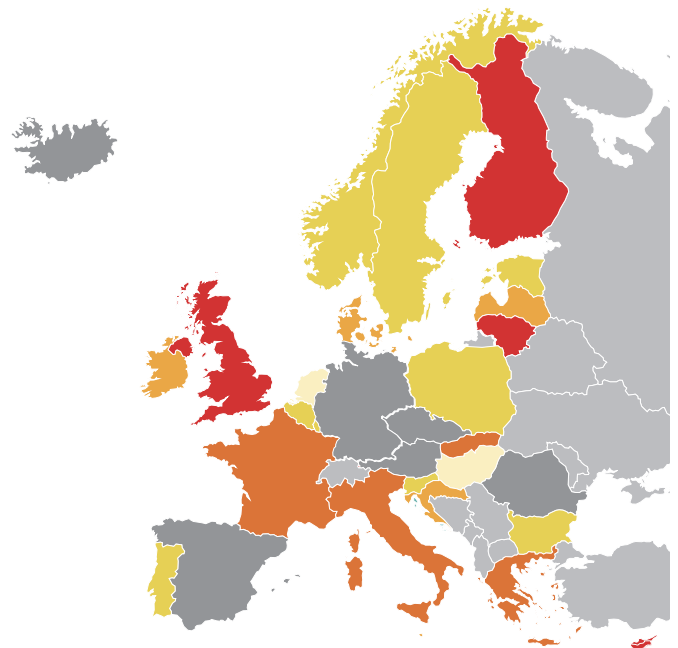
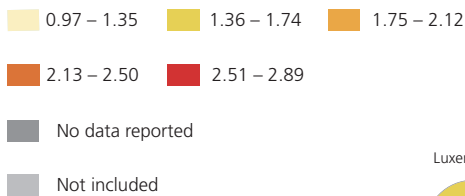
Figure 5: Consumption of antibiotics for systemic use (ATC group J01) in EU/EEA countries, in DDDs per 1000 inhabitants per day, 2016

a) Consumption in the community



Notes: Cyprus and Romania provided total care data, i.e. including the hospital sector; Spain provided reimbursement data, i.e. not including consumption without a prescription and other non-reimbursed courses.

b) Consumption in the hospital sector



Notes: Finland: data include consumption in remote primary healthcare centres and nursing homes; Portugal: data refer to public hospitals. Population was adjusted, based on hospital catchment area information provided by the country.

Source: [75].

Governments are adopting a broad range of policy approaches to decrease the ineffective use of antimicrobials, usually as part of their NAP. A recent OECD survey (2016) showed that about 60% of OECD countries have produced a strategy to rationalize the use of antimicrobials, while an additional 37% are in the process of developing one [76]. Recent models from the OECD concluded that the implementation of ABS programmes could result in a 51% reduction of deaths from AMR and €2.3 billion saved [76].

Antimicrobial stewardship in the community

In HICs, most antibiotics are prescribed not in hospitals but in primary care in the community; in England, for example, three quarters of antibiotics are prescribed in general practice and just 11% in hospitals [77], with an estimated 8.8–23.1% of antibiotic prescribing in primary care considered to be inappropriate [78]. Common infections, such as throat, urinary, skin or tooth and especially respiratory tract infections (RTI), are responsible for the biggest share of antibiotic prescriptions in non-hospitalized patients. For the majority of RTIs and sore throats, which are caused by viral agents and are self-limiting in nature, antibiotics have only been shown to reduce the length of symptoms by a few hours [79,80].

Stewardship strategies in primary care focus on the use of evidence-based guidelines and algorithms, delayed prescribing, and recommendations to discourage the use of broad-spectrum antibiotics wherever possible when narrower options are available and likely to be effective (e.g. in the case of urinary tract infections; UTIs) [81]. Interventions focusing mainly on changing the prescribing behaviour of clinicians through the use of guidelines, outreach visits, clinical audit, as well as computerized reminders, have all been shown to be effective [82]. A multifaceted approach combining several measures is preferable to focusing on single interventions. Many healthcare systems also utilize financial incentives to encourage appropriate antibiotic use, such as the Antibiotic Quality Premium (AQP) in England in 2015/16, which contributed to a 3% reduction in antibiotic prescribing rates for uncomplicated RTIs [83] (Box 3). Shared decision-making between the clinician and patient, based on the best available evidence and patient preferences, is an essential tool for reducing antibiotic use and has been shown to be highly effective [84]. Shared decision-making can often be utilized in conjunction with delayed prescribing strategies [85,86], although both strategies rely upon good communication and well-informed patients who appreciate the importance of tackling AMR. A further option is to provide patient educational materials during consultation [86].

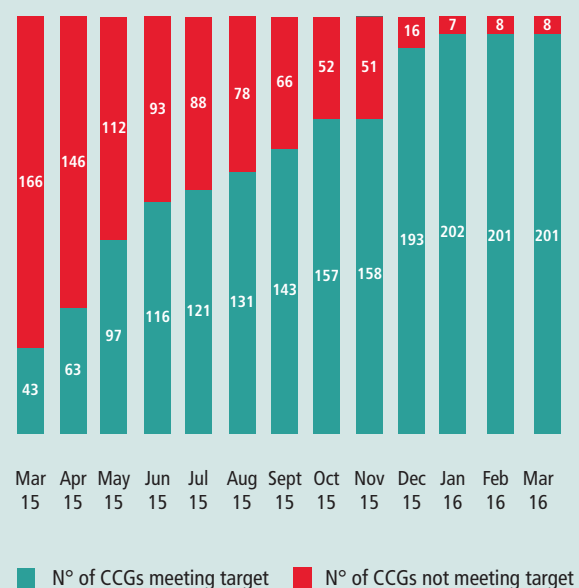
Effective interventions also focus on rapid, affordable and easy-to-use diagnostic tools. Point-of-care tests, such as for C-reactive protein, can be effective in ruling out viral infections, but appropriate tests are often not available [87]. Evidence on the cost-effectiveness of these strategies is currently limited, due to uncertainties about the impact of reduced antibiotic use on AMR, and of the value that should then be attached to AMR reduction.

Box 3: The United Kingdom Antibiotic Quality Premium (AQP)

In 2015, NHS England introduced the AQP, which forms part of the world's largest healthcare incentive scheme to reduce AMR, offering financial incentives in both primary and secondary care with the aim of reducing inappropriate use of antibiotics [88]. The AQP is worth 10% of the greater quality premium programme. Initially, practices were rewarded up to a maximum of £5 per patient if they reduced the number of antibiotic prescriptions by 1% (weighted at 50% of the overall measure) and/or reduced the proportion of broad-spectrum antibiotics, cephalosporins, quinolones and co-amoxiclav by 10% or to below the median for England (weighted at 30%) [89]. Secondary care providers are rewarded if 10% or more of their activity being commissioned by the relevant clinical commissioning groups (CCG) have validated their total antibiotic prescribing data as certified by Public Health England (weighted at 20%) [89].

Early results from this programme are promising in terms of improving antibiotic prescribing practices. The number of CCGs complying with antibiotic targets rose sharply over the first year of the programme (fiscal year (FY) 2015/16). Targets were calculated relative to a 2013/14 baseline (Figure 6). After this impressive achievement, the AQP was expanded in 2017 to include a wider array of incremental targets, such as reducing gram-negative bloodstream infections (BSI) across the whole health economy by 10–20%, and the reduction of inappropriate antibiotic prescribing for UTIs in primary care by 30% [90].

Figure 6: Antibiotic Quality Premium monitoring dashboard, March 2016



Source: Adapted from [92].

Notes: Number of CCGs meeting (green) and not meeting (red) antibiotic comparator targets over the course of FY2015/16 [91]. Specific therapeutic group age–sex weightings related prescribing units (STAR-PU) are weighted units adjusted for sex, age and therapeutic area to allow analysis of prescribing data.

Antimicrobial stewardship in the hospital sector

ABS programmes in hospitals primarily focus on changing the prescribing behaviour of healthcare professionals. The strategies can be broadly split into five categories: educational, persuasive, restrictive, environmental

restructuring and enablement [93]. Educational techniques involve the use of educational meetings and the dissemination of educational materials, whereas persuasion techniques involve outreach visits to review and recommend actions to stimulate change. Restrictive techniques use rules and guidelines to alter behaviour, whereas structural techniques involve the use of physical reminders or laboratory improvements. Lastly, enablement uses techniques such as audit and feedback, and decision support tools [93]. A recent systematic review found that both enablement and restrictive techniques consistently improve the effectiveness of ABS interventions, although often ABS interventions involved multiple techniques [93]. Overall, it was found that ABS interventions improve hospital antibiotic prescribing, reduce the length of hospital stays and do not affect mortality [93]. However, current evidence on what works and what is cost-effective is often of low quality and more research is needed to build a stronger case for investment in ABS [94,95]. Recent efforts in this area include the cost-effectiveness model developed by the OECD, which aims to assess and compare the health and economic impact of a number of AMR control policies relative to a business-as-usual scenario in which there are no interventions (Box 4).

Box 4: The OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model

The SPHeP-AMR model was used to assess the performances of six selected policies (stewardship programmes, improved hand hygiene, enhanced hospital hygiene, rapid diagnostic tests, delayed prescriptions and mass media campaigns) if they were scaled up and implemented at national level in 33 countries. All six policies tested in the OECD model appeared highly effective in reducing mortality due to AMR. For example, upscaling stewardship programmes, improved hand hygiene and enhanced environmental hygiene policies to national levels (under a 70% adherence assumption in the targeted population) would reduce the annual AMR mortality by on average 54–58% across the included countries.

For most control policies, implementation costs would be largely offset by the savings generated, including for relatively expensive strategies, such as enhanced hospital hygiene, stewardship programmes and rapid diagnostic tests. Improved hand hygiene would represent a particularly good investment, as its average annual implementation across the countries considered was estimated to be around USD PPP 8500 per 100 000 persons for a net return of approximately USD PPP 140 000.*

Combining multiple policies in a broader policy package would generate overall effects (in terms of disease burden and healthcare expenditure) close to the sum of the effects of the individual component policies. For example, a policy package including all three healthcare-based policies would save on average USD PPP 1.2 million per 100 000 persons per year. A community-based policy package and a mixed policy package, would result, respectively, in average reductions in healthcare expenditure of approximately USD PPP 275 000 and USD PPP 920 000, per year.

*United States Dollar (USD) purchasing power parity (PPP) is used to equate currencies between countries, based on the currency's purchasing power for a select basket of goods in each respective country.

Source: [27].

4. Strengthening infection prevention and control (IPC) in human health

Although antibiotic use in hospitals is small relative to total use, the impact of AMR on critically ill patients, the associated extra healthcare costs and the opportunities for cross-infection through patient or caregiver contact mean that the health and economic impacts of AMR in hospitals are disproportionate. Data collected by the HAI-Net indicate that, on any given day, one in 18 patients in a European acute care hospital has a HAI [21]. The excess costs associated with resistant HAIs have not been comprehensively studied, but the available evidence suggests that the major costs arise from extended hospital stays and blocked beds that are needed to isolate infected patients.

Effective IPC requires a combination of actions such as standard hygiene measures (i.e. hand washing), the isolation of infected patients, environmental cleaning, as well as active screening of incoming patients [96]. IPC teams within hospitals should include nurses and physicians, and be supported by laboratory and data analysis [97]. IPC activities can be further broken down into horizontal or vertical measures. Horizontal measures are general approaches across a whole institution, such as hand hygiene campaigns, whereas vertical measures address specific problems, such as catheter-associated bloodstream infections [98]. Although there is no clear consensus over which strategy is the more effective, it is likely that a combination of both should be taken [98]. To encourage consistent implementation of IPC practices across providers, many countries have utilized financial incentives and/or penalties associated with HAI rates. One example from the United States is considered further in Box 5.

Box 5: Hospital-Acquired Condition (HAC) Reduction Program in the United States

Since its inception in FY2015, the HAC Reduction Program has involved adjusting payments through Medicare to hospitals that rank in the worst performing 25% of hospitals with respect to risk-adjusted HAC quality measures. These hospitals are subject to a 1% payment reduction. The total HAC score is calculated using both standardized infection ratios (SIRs) and the patient safety and adverse event composite, known as patient safety indicator (PSI) 90. The SIRs are calculated using observed-to-predicted numbers of HAIs, such as catheter-associated urinary tract infections (CAUTI) and MRSA bacteraemia. The PSI 90 is calculated by collating data on adverse events, such as pressure ulcer rates and postoperative sepsis rates. Table 2 shows how the HAC Reduction Program has evolved over time in response to specific priorities [99].

Whilst it is still too early to judge the effectiveness of this programme (first results are expected in 2019), between the FY2015 and FY2016 programmes the average score across eligible hospitals improved on two measures (PSI 90 Composite and central line-associated bloodstream infections (CLABSI)), with a slight increase in the average CAUTI score.

Table 2: HAC Reduction Program measures

Measure	FY2015	FY2016	FY2017
Patient safety indicator (PSI) 90 Composite	X	X	X
Central line-associated blood-stream infection (CLABSI)	X	X	X
Catheter-associated urinary tract infection (CAUTI)	X	X	X
Surgical site infection (SSI) (colon and hysterectomy)		X	X
MRSA bacteraemia (presence of bacteria in the blood)			X
<i>Clostridium difficile</i>			X

Source: Adapted from [92].

In 2009, WHO published evidence-based guidelines on core components for IPC programmes to support countries and healthcare facilities in developing or strengthening IPC programmes and strategies. Updated guidelines were published in 2016 and cover eight components: (1) IPC programmes; (2) IPC guidelines; (3) IPC education and training; (4) Surveillance; (5) Multimodal strategies; (6) Monitoring/audit of IPC practices and feedback; (7) Workload, staffing and bed occupancy (acute healthcare

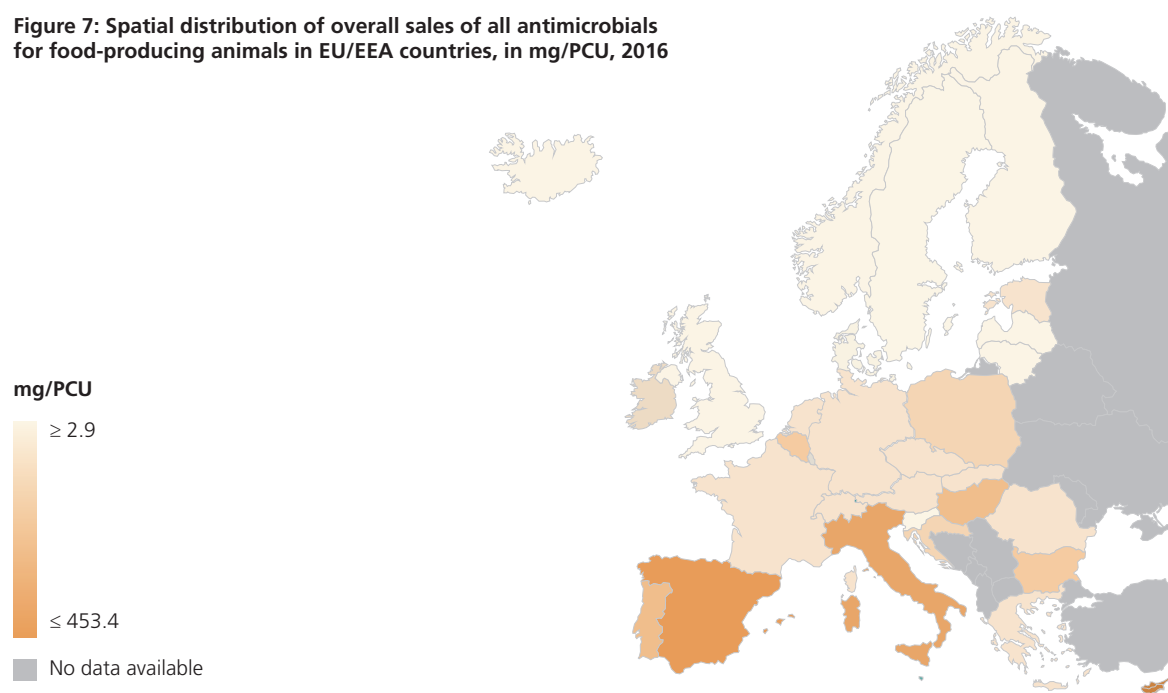
facilities only); and (8) Built environment, materials and equipment for IPC at the facility level (acute healthcare facilities only). In 2017, 14 HICs in Europe had functioning IPC programmes at national and health facility levels, according to the WHO IPC core component guidelines, as well as a mechanism in place to monitor compliance and evaluate effectiveness [100].

5. Strengthening IPC and reducing inappropriate antibiotic use in animals

The use of antibiotics in the food and animal sector generates resistance in bacteria that may affect both humans and animals. For example, resistance to colistin, which is commonly used as a last-resort antibiotic in humans, has been detected in pigs with *E.coli* [101]. Even low doses, such as those used for growth promotion, have an impact on AMR. The transmission of pathogens between humans and animals may occur in several ways – by direct contact or by transmission through the environment (see Figure A1 in the Appendix). In the livestock sector, antibiotic use extends beyond therapy to use for prophylactic and growth promotion purposes. Antibiotics have often been used to boost productivity by counteracting the adverse consequences of poor or 'intensive' farming conditions, as their benefits far outweigh their costs.

The global use of antibiotics in animal production is excessive. For example, in the US, it has been estimated that food and agriculture production accounts for an estimated 70% of total antimicrobial consumption in the country [102]. A global study estimated that the volume of antimicrobials used in agriculture is expected to increase by 67% by 2030, principally because of increasing demand for

Figure 7: Spatial distribution of overall sales of all antimicrobials for food-producing animals in EU/EEA countries, in mg/PCU, 2016



Source: [104].

Note: Population correction unit (PCU) is a unit of measurement developed by the European Medicines Agency to monitor antibiotic use and sales across Europe. It considers the animal population as well as the estimated weight of each animal at the time of treatment with antibiotics.

food-producing animals and ‘intensive’ farming in countries with growing populations, such as the US, India, China and Brazil [102]. In Europe, on the other hand, an important step has been a ban on the use of antibiotic growth promoters in animal feed for all EU countries since 2006 (Regulation 1831/2003/EC7) [103]. Despite this, there is still significant variation in the sales of veterinary antimicrobials across Europe (Figure 7). Positively, recent trends in Europe across 25 countries have seen an overall decline in sales of veterinary antimicrobials by 20.1% between 2011 and 2016, although in six countries sales increased by more than 5% in this period (a range of 7.9–67.7%) [104].

Strategies to reduce AMU in animals should involve: preventing the use of non-therapeutic antimicrobials; IPC measures such as higher biosecurity; improved husbandry methods; use of vaccination; as well as restricting the use of critically important antimicrobials for human use [105–107]. In some cases, farmers’ attitudes and behaviour, such as the perception that improved husbandry methods and higher biosecurity are costly interventions, can act as barriers to implementation [108,109]. These can be overcome though, and countries such as Norway and Iceland have achieved impressive low sales of veterinary antimicrobials, with both countries recording sales below 5mg/PCU in 2016, compared to an EU/EEA average of 129.4mg/PCU [104]. Norway has cut the antibiotic use in salmon farming (one of the central foods consumed in that country and a principal export good) to almost zero [110], while the Netherlands has shown that antimicrobial use can be reduced (64% between 2011 and 2016) by improved monitoring and husbandry (see Box 6) [104].

Box 6: Vaccinating salmon in Norway and antimicrobial stewardship in livestock in the Netherlands

In the 1980s, Norway experienced an explosion of salmon farming. As a result, the bacterial fish disease furunculosis developed and led to widespread use of antibiotics in fish feed [110]. Norway’s government recognized the need to support the country’s fish farming industry without increasing the risk of AMR. In close collaboration between the government and the fish farming industry, an effective vaccination against furunculosis in salmon was developed, with no side effects for humans. By 1994, fish farmers across Norway had changed from antibiotics to vaccination. Norway also uses additional measures to prevent infections, such as keeping only one single generation of fish in each site, and emptying and disinfecting sites to prevent cross-contamination between old and new generations.

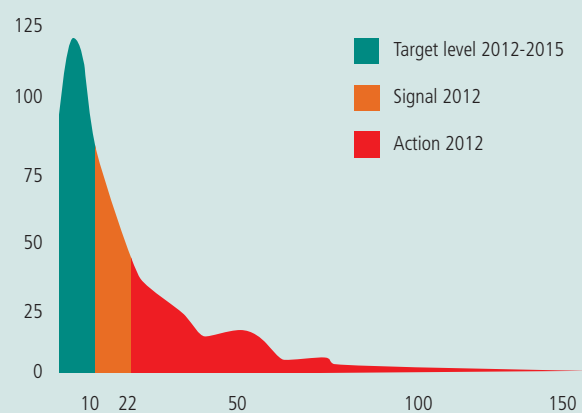
In the Netherlands, a policy was developed between 2008 and 2011 as a public–private partnership between livestock production sector stakeholders, the Royal Dutch Veterinary Association (KNMvD) and the government, with the aim of reducing AMU in livestock. Following the introduction of the national policy, veterinary antibiotic use was reduced by 58% and the use of antibiotics critical to human health was reduced to almost zero between 2009 and 2015 [111]. Key elements of the approach developed, which was strongly linked to pre-existing operational production chain quality systems, were [112]:

1. Transparency and benchmarking of antibiotic use per herd and per veterinarian.
2. Improvement of herd health with clear responsibilities for farmer and veterinarian, mandatory herd health plans, one contracted veterinarian per herd and mandatory periodical veterinary herd inspections.

3. Reduction targets for livestock production as a whole: –20% in 2011 and –50% in 2013 with reference to the amount of effective substance sold in 2009 (later set at –70% in 2015 by government decree).

The four major livestock sectors (pig, broiler, veal, cattle) are required by law to record herd use data and herd health plans in a central database, and veterinarians are required to enter prescriptions and the supply of medicines in a practice management system (PMS) [113]. An independent body, the Veterinary Medicines Authority (SDa), monitors and benchmarks the use of antibiotics based on the distribution of herds, according to the number of animal-defined daily doses per year (ADDD/Y) (Figure 8 shows a typical example of such a distribution), and supervises the follow-up of recommendations to reduce use.

Figure 8: Frequency distribution of ADDD/Y for Dutch farms with sows and piglets, 2012



Source: [112].

Note: ADDD/Y = average defined daily dose per year.

Veterinarians and farmers are classified by antibiotic consumption into ‘action area’, ‘signal area’ or ‘target level’. Those in the warning area (orange zone in Figure 8) are notified that their AMU needs attention and those in the action area (red zone) must implement improvement measures. Heavy users are reported to the inspection authority. In addition, measures to enforce compliance, including spot-checks by the inspection authority, permits for possession of raw materials for antibiotic production, and allowing only veterinarians to prescribe and administer antibiotics to livestock, were adopted into relevant law [112].

6. Limiting the exposure of antimicrobial-resistant pathogens to the environment

The barriers to combatting antimicrobial-resistant infections in the clinical setting have been studied and understood well, which has resulted in AMR NAPs and policies focusing on the clinical setting and lack of emphasis on the environment [56]. Yet, without a comprehensive ‘One Health’ approach, including actions within the environmental health sector, AMR NAPs are not complete and are at potential risk of being ineffective. The research on AMR and the environment has long focused on antibiotics in animal, human and manufacturing waste, without investigating other compounds that affect resistance [114]. Recent research, however, has extended the list of

resistance-driving chemicals to three classes. First, antimicrobials consisting of four subclasses (antibiotics, antifungals, antivirals and antiparasitics); second, heavy metals; and third, biocides (e.g. disinfectants and surfactants) [56]. The research also describes three main pathways through which these chemicals can enter the environment: municipal and industrial wastewater; land spreading of animal manure and sewage sludge; and aquaculture (see Figure A2 in the Appendix). The interactions and relationships between these chemicals and pathways contribute to the spread of AMR and should be considered in AMR policy.

One key approach to addressing AMR in the environment is to monitor and regulate the environment and environmentally related activities or products that influence the spread and development of AMR pathogens. The Environmental Agency of England, for example, monitors and regulates wastewater treatment plants (WWTPs); agriculture (i.e. land spreading of manure, sewage sludge, fertilizers, bioaerosols); animal husbandry (i.e. disposal of animal byproducts, slurry and manure); river water quality (i.e. impact of sewage effluent, fresh fish farms); coastal and bathing waters (e.g. impact of aquaculture); and groundwater quality (e.g. content of chemical crop treatments) [115–117]. These different locations can provide effective targets for intervention. For example, as WWTPs are a major pathway for the dissemination of AMR bacteria, treatment of wastewater with ozone, ultraviolet (UV), ultrafiltration or chlorination can drastically reduce their concentrations [114]. Switzerland is one country in Europe that has included targets for WWTPs in its AMR strategy [118]. The goal is to almost entirely remove antibiotics from the upgraded WWTPs (see Box 7). A number of countries, including Germany, France, Sweden and the Netherlands, are also presently looking into similar solutions to upgrade their WWTPs [119].

Box 7: Swiss Strategy on Antibiotic Resistance (StAR): upgrade of wastewater treatment plants

In 2015, the Swiss Federal Council adopted the Swiss National Strategy on Antibiotic Resistance (StAR) to ensure the long-term efficacy of antibiotics, while preserving human and animal health. Developed through a consultation process involving all interested stakeholders (across public health, animal health, agriculture and the environment), this strategy is in line with the WHO Global Action Plan on Antimicrobial Resistance and establishes a range of measures to monitor and contain antimicrobial resistance [118].

According to the StAR, an integrated approach to the ‘One Health’ principle regarding people, animals and the environment is necessary for preserving effective antibiotics. For example, antibiotics and other microscopic impurities in the water should be significantly reduced by improving WWTPs. Conventional biological WWTPs typically reduce the total number of antibiotic-resistant bacteria or mobile antibiotic resistance genes by more than 95%. Nevertheless, the number of antibiotic-resistant bacteria and antibiotic resistance genes released with treated wastewater is higher than that found in Swiss surface waters. WWTPs enrich water with antibiotic-resistant bacteria, resulting in a relatively high proportion of antibiotic-resistant bacteria

in the treated wastewater. The goal is to almost entirely remove antibiotics from the upgraded WWTPs and thus further alleviate the burden caused to bodies of water by antibiotic-resistant bacteria [119].

Defined as a measure in StAR and based on the revised Swiss Water Protection legislation, more than 70% of Swiss WWTPs will be upgraded by 2040, with treatment steps for the elimination of micropollutants, including antibiotics and antibiotic-resistant bacteria. Ozonation and powdered activated carbon (PAC) are currently the standard treatment options. In Switzerland, the municipalities are responsible for implementing this optimization.

With this upgrade, the discharge of micropollutants into surface waters will be reduced by two thirds. Groundwater, which is the most important drinking water source in Switzerland, will benefit from these improvements as well.

Note: This box was prepared by Karin Waefler, Project Leader for AMR at the Swiss Federal Council in Berne.

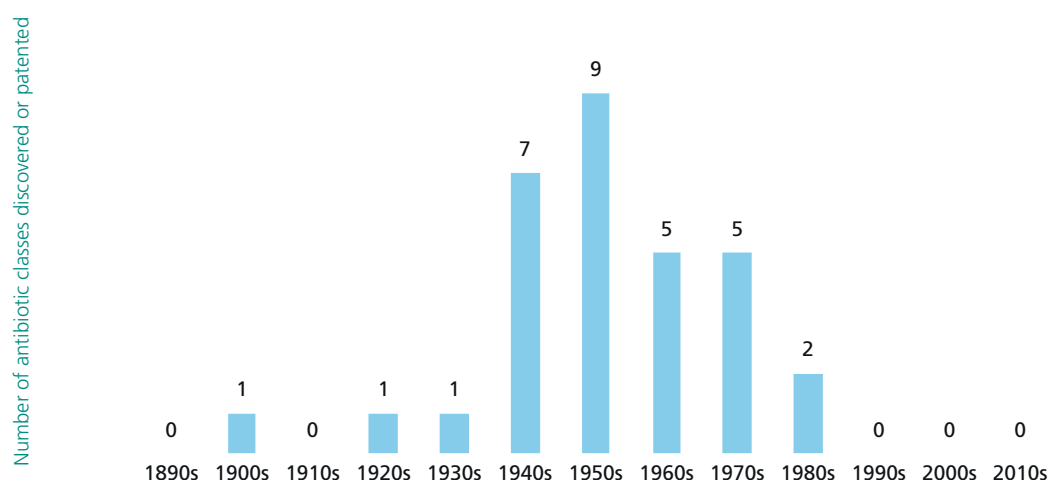
However, as measures have been suggested to avoid the discharge of AMR pathogens into the wastewater in the first place, such as: reducing antibiotic misuse in human and veterinary use; holding producers and factories accountable, especially in countries with weak local regulatory frameworks; reducing biocide use in personal care and household products; or capture, reuse and recycling of metals within the wastestream [56].

7. Fostering R&D of new antimicrobial therapies, diagnostics and vaccines

Regenerating the antibiotic pipeline

As AMR increases there is a need for new classes of antibiotics to replace those rendered ineffective by resistance [120]. A recent WHO review reports that the current pipeline of antibiotics and biologicals could lead to around 10 new approvals over the next 5 years, given past success rates and development times [121]. However, these new treatments will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat. More investment is needed in basic science, drug discovery and clinical development, especially for the critical priority Gram-negative carbapenem-resistant pathogens *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacteriaceae*. To highlight the need for more R&D, priority lists of pathogens to guide research and development of new antibiotics have been published [122]. Pharmaceutical companies find it less profitable to invest in antibiotic R&D compared to other disease areas (Figure 9). One reason is that a novel class of antibiotics is likely to be restricted in use, for stewardship reasons, reducing its revenue potential and market value.

Figure 9: Number of new classes of antibiotics discovered or patented each decade



Source: [123].

Some progress has been made in the effort to regenerate the antibiotic pipeline, including new initiatives, particularly to increase funding for early-stage and pre-clinical research. These include CARB-X, a non-profit public-private partnership dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria and GARDP, which aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists [124,125].

But there remains a large gap in funding, notably in the risky and expensive business of taking drug candidates through clinical trials to possible marketing approval [126]. This

particularly affects small and medium enterprises (SMEs) that are responsible for developing a large proportion of new drug candidates. Various forms of incentive have been proposed through changes in the regulatory or intellectual property regimes. These include a combination of pull and push incentive strategies, either to boost the return from newly discovered antibiotics or to subsidize the cost of R&D (Table 3). Currently, there is a significant mismatch between funding allocated to push and pull incentives. According to an OECD analysis it is estimated that 95% of current funding for antibiotic R&D consists of push incentives [127].

Recent reports have recommended the introduction of 'market entry rewards' (MER) (a pull strategy), which would

Table 3: Push and pull incentives for antibiotic development

Push incentive strategies	
<ul style="list-style-type: none"> Supporting open access to research Grants for scientific personnel Direct funding Conditional grants 	<ul style="list-style-type: none"> Funding translational research Tax incentives Refundable tax credits Product development partnership
Outcome-based pull incentive strategies	
<ul style="list-style-type: none"> End prize Milestone prize Pay-for-performance payments Patent buyout Payer licence 	<ul style="list-style-type: none"> Research tournament Advanced market commitment Strategic Antibiotic Reserve Service availability premium
Lego-regulatory pull incentive strategies	
<ul style="list-style-type: none"> Accelerated assessment and approval Market exclusivity extensions Transferable intellectual property rights Conservation-based market exclusivity Liability protection 	<ul style="list-style-type: none"> Anti-trust waivers Sui generis rights Value-based reimbursement Targeted approval specifications Priority review vouchers

Source: [128].

offer rewards of USD1–2 billion for the successful development of new antibiotics meeting prespecified criteria and would also delink the funding of the R&D from the revenues derived from sales [128,129]. This would remove the incentive for maximizing sales and assist good antibiotic stewardship. The impact of such schemes would be maximized if harmonized amongst countries with innovative potential for antibiotics. The Options Market for Antibiotics (OMA) model postulated by the London School of Economics and Political Science takes the MER one step further by combining the pull-based prize of a MER with push-based R&D funding under one mechanism [130]. The OMA, modelled on the principle of financial call options, allows payers to buy the right, in early stages of development, to purchase antibiotics at a discounted price if they ever make it to market approval. It also allows governments and non-governmental organizations (NGOs) to fund all stages of antibiotic R&D and ensure that successful antibiotics are then purchased at a fair price, rationed appropriately, and distributed equitably. Unlike with MERs, purchasers of options are rewarded with discounted prices for the significant risk they take with financing antibiotic R&D [130,131].

Incentivizing research and development of diagnostics

Diagnostics should play an essential role in facilitating the appropriate use of antibiotics by reducing the unnecessary use of antibiotics for non-bacterial infections. They are necessary for improved patient management and outcomes; effective AMR surveillance; and in mounting clinical trials. To be effective in primary care, diagnostics need to provide a result in 15–20 minutes. However, because of the wide variety of bacterial and other infections that can be responsible for similar symptoms, isolating the exact strain of an infection is difficult. A simple rapid test to distinguish between bacterial and viral infections would be very useful.

However, diagnostic developers face several obstacles to innovation, including regulatory and financial barriers. Approval processes for diagnostics are lengthy, costly and often not transparent, and there is wide variation between countries in their quality. There is an urgent need to harmonize regulatory standards and procedures to reduce duplication of clinical performance studies, to minimize delays and to reduce the costs of meeting regulatory standards. HTAs need to be applied so that the risks and benefits can be better understood by policy-makers as well as regulators and other stakeholders [132].

Diagnostic development has been stimulated by several schemes, such as the Longitude Prize [133]. However, access to finance is also a problem. Public funders do not generally view diagnostics as having a direct effect on health outcomes. There is therefore a need to develop a better business case for investment in diagnostic development to combat AMR, which would identify the health and economic cost of not having effective diagnostics [134].

Stimulating research and development in vaccines to combat AMR

Vaccination can help in reducing the number of infections through herd immunity and the transmission of infections,

with a consequent reduction in antibiotic use [135]. It can also reduce the inappropriate use of antibiotics for viral infections and their use to treat secondary bacterial infections often associated with influenza. It has been estimated that in 75 countries universal coverage with pneumococcal conjugate vaccine could halve antibiotic use in young children [136].

Hitherto, the value of vaccines in combatting AMR has not been a factor in decisions on vaccine development and use, which rely on the traditional financial and health benefits of vaccines. In principle, this value should be incorporated in such decisions. But there are difficulties in accurately assessing this value because of the multiple pathways by which vaccines could reduce AMR [137]. Moreover, it is not well understood how reductions in antibiotic use translate into reductions in AMR. Three pathways are important. First, how vaccine use translates into reductions in prescribing. Secondly, the epidemiological pathway that governs the direct impact of vaccine use on AMR. Thirdly, there is the pathway that assigns a value to AMR reduction, which involves developing counterfactual scenarios modelling the future health and economic costs of AMR and here there is a high degree of uncertainty. Thus, in practice, there are considerable challenges in quantifying the undoubted value of vaccines in the fight against AMR.

Research efforts must be coordinated

As AMR has achieved growing attention, research efforts to address the emergence and spread of AMR, as well as to incentivize the development of novel antimicrobials, have accelerated. Due to the complexity of AMR, these research activities are sponsored by multiple funding organizations. There is a need to coordinate the research activities funded by these organizations for many reasons. The very nature of AMR warrants a multidisciplinary and holistic approach to research and, without effective coordination, there is a risk that gaps and/or duplication of effort will occur. On the international level, organizations such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) have taken important steps in coordinating research activities. JPIAMR was formed in 2011 and now comprises 26 countries globally. It is funding €65 million of basic and exploratory research across six priority areas (Box 8).

Box 8: JPIAMR priority areas

- **Therapeutics:** Development of novel antibiotics and alternatives for antibiotics – from basic research to the market
- **Diagnostics:** Design strategies to improve treatment and prevention of infections by developing new diagnostics.
- **Surveillance:** Implementation of a publicly funded global antibiotic resistance surveillance programme.
- **Transmission:** Establish multidisciplinary research networks to investigate the dynamics of transmission and selection of AMR.
- **Environment:** The role of the environment and sewage as a source for the emergence and spread of AMR.
- **Intervention:** Designing and testing interventions to prevent acquisition, transmission and infection caused by antibiotic-resistant bacteria.

Source: [138].

A mapping exercise of the 19 countries signed up to JPIAMR demonstrated that approximately half of the research funding for AMR research projects is at EU level and half at national level [139]. Therefore, there is a need also to effectively coordinate AMR research projects nationally. Box 9 shows how the funding of AMR research is coordinated across 20 funding organizations in the UK.

Box 9: Coordinating AMR research in the United Kingdom

In the UK, the Antimicrobial Resistance Funders Forum (AMRFF) coordinates the efforts of 20 separate funders of AMR-related research (Figure 10). The aim of the forum is to ensure that research activities are not duplicated, to fill any gaps and to promote joint action to fund research [140]. The forum takes a holistic approach based around four key themes:

- **Theme 1:** Understanding resistant bacteria.
- **Theme 2:** Accelerating therapeutics and diagnostics development with collaboration between academia and industry.
- **Theme 3:** Understanding the complexity of the environment in AMR emergence and transmission.
- **Theme 4:** Understanding behaviour within and beyond the health-care setting.

AMRFF members fund research in the United Kingdom through multiple channels, including the AMR Cross Research Council Initiative, involving all seven United Kingdom Research Councils, and the Newton Fund, which develops partnerships to promote the economic development and social welfare of partner countries, and has focused on AMR in countries such as India, China and South Africa. Support is also channelled through individual organizations, where budgets are not necessarily ring-fenced for AMR, but researchers can apply and compete for funding domestically or internationally.

Figure 10: Organizations within the AMRFF



Several AMR projects have been funded through these channels. Through these activities, the AMRFF is appropriately positioned to map out research efforts across the UK and to facilitate information-sharing between organizations. As the AMRFF includes the central government departments, who are leading implementation and development of UK AMR strategy, there is a direct link between research and policy.

Facilitating successful implementation of ‘One Health’ AMR NAPs: governance is key

In 2018, the UN IACG on Antimicrobial Resistance concluded that developing a national AMR policy is not enough – the main challenge in tackling AMR is not writing the policy but its successful implementation [7]. Strengthening governance is a key strategy for any policy-maker attempting to address this challenge. A review of health system governance frameworks identified common principles of good governance, such as strategic vision, participation, coordination, responsibility, accountability, sustainability, monitoring and evaluation [141]. Although an AMR NAP should cover activities beyond the health system, these governance principles remain just as relevant.

Strategic vision should reflect good leadership, with oversight of the general direction of the national AMR strategy, as well as an awareness of any gaps or failures that need to be addressed. The United Kingdom and Sweden have set clear national targets to reduce AMU (Table 4); this is a positive example of overall strategic direction, which allows stakeholders to converge around a common goal.

Table 4: National antimicrobial usage quantitative targets in the United Kingdom and Sweden

United Kingdom: 2016 Antimicrobial Resistance Review: Government response
<ul style="list-style-type: none"> • Reduce inappropriate antibiotic prescribing in England by 50% by 2020 • Reduce antibiotic use in livestock and fish farmed for food to a multispecies average of 50mg/kg by 2018 from the most recent 2014 figure of 62mg/kg.
Sweden: 2009 Sweden Strategic Programme against Antibiotic Resistance
<ul style="list-style-type: none"> • No more than 250 prescriptions per 1000 inhabitants per year in outpatient care.

Sources: [142,143].

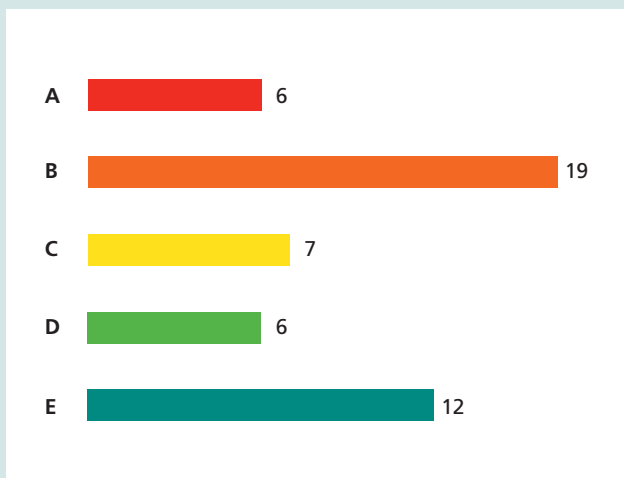
Effective leadership should also facilitate the inclusive *participation* and engagement of relevant stakeholders, including ministries, the medical and veterinary professions, research and academic institutions, agricultural organizations, and the food and pharmaceutical industries, during the conception and development of the NAP to

maximize its legitimacy. A 'One Health' approach means that effective *coordination between stakeholders* across the human, animal and environmental health sectors during implementation is essential to avoid initiatives and programmes operating in silos. Many countries now use a national intersectoral coordinating mechanism (ICM) for this purpose, which offers a formal platform for coordinating activities during regular meetings (Box 10). These began with the EU Council recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC) to establish a national ICM with responsibility for developing a national strategy. Subsequently, ICMs were also utilized to coordinate the implementation and then evaluation of NAPs [144].

Box 10: The importance of intersectoral coordinating mechanisms

Coordination between the human, animal and environmental health sectors is key to the success of any country's AMR NAP. For this purpose, in 2012, the European Commission and, in 2015, WHO recommended the formation of an ICM as a fundamental step when designing, implementing and evaluating an AMR NAP [145]. WHO has begun to monitor progress towards this goal but, in 2017, six countries still did not have a formal ICM (Figure 11).

Figure 11: Progress of WHO European region countries in developing AMR national ICMs, 2017 Survey



Source: [100].

Notes: A: No formal multisectoral governance or coordination mechanism exists; B: Multisectoral working group(s) or coordination committee on AMR established with government leadership; C: Multisectoral working group(s) is (are) functional, with clear terms of reference, regular meetings, and funding for working group(s); activities and reporting/accountability arrangements are defined; D: Joint working on issues such as agreement on common objectives, including restriction of use of critically important antimicrobials; E: Integrated approaches used to implement the AMR NAP.

Sweden provides a useful example of an ICM in operation. In 2012, the Swedish government commissioned the National Board of Health and Welfare and the Swedish Board of Agriculture to jointly run a national ICM, which involves cooperation between 20 authorities active

within public health, animal health, food and the environment [146]. A fundamental principle of the ICM is to offer a forum to facilitate cross-sectoral work. This is achieved through regular meetings, for example, there is an annual antibiotic forum held in conjunction with European Antibiotic Awareness Day. The purpose of the forum is to offer the opportunity for different stakeholders to meet to agree contacts, collaborate and exchange information. The stakeholders included represent animal healthcare, food production, care companies, pharmaceutical companies, interest groups (for animals, the environment and care), professional associations, higher education, universities, research, national agencies and authorities, municipalities, county administrative boards and county councils. The responsibilities and actions of the ICM have gradually grown and, in 2014, the national ICM was appointed to develop and improve a renewed Swedish AMR NAP [146].

Just as important as coordination between sectors is *coordination within sectors*. For example, coordinating activities across different levels of the healthcare sector, such as ambulatory, hospital and long-term care is particularly challenging. Sweden's approach to addressing this has been to develop regional networks known as Strama groups; this is explored further in Box 11.

Box 11: Coordination of AMR policies across the Swedish healthcare system

In addition to improving ABS in the hospital sector, recent reviews have highlighted the necessity to include different levels of the health sector in ABS efforts [33]. Often, ABS programmes are conducted solely in the hospital sector but, as most antibiotics are consumed in the community, it is important to consider both ambulatory and long-term care in NAPs. Resistant bacteria can spread between different healthcare settings, especially as patients transfer between ambulatory, hospital and long-term care. Effective coordination across the healthcare system is essential. This can facilitate the exchange of information, the dissemination of educational material and improved awareness between different healthcare professionals.

The Swedish programme to combat AMR (Strama) started as a voluntary network in 1995, consisting of several local Strama groups across different regions. Following the introduction of the 2011 Patient Safety Act, all 21 county councils were incentivized to create a local Strama group [147]. These multidisciplinary groups, led by the county medical officer for communicable diseases control, consist of different healthcare professionals from general practice, hospital medicine and long-term care, who are granted earmarked time to dedicate to Strama activities. The main objective is to evaluate the use of antibiotics and antibacterial resistance in the county and to improve prescribing patterns. They facilitate coordination and knowledge transfer between all levels of care locally whilst coordinating with the national Strama steering group and the Swedish public health agency, therefore acting as a mechanism to adapt national initiatives to local settings.

Local Strama groups undertake several activities, such as the monitoring of AMR/AMU data, outreach visits to primary healthcare centres, educational campaigns and updating guidelines. They also host workshops and seminars 1–2 times a year, which involve the dissemination of comparative prescription data to individual practices [148].

This approach has led Sweden to have some of the lowest outpatient use of antibiotics in Europe as the country aims to approach its long-term target of 250 prescriptions/inhabitants/year [149].

Without specific, measurable, achievable, relevant and time-bound (SMART) objectives within AMR NAPs, mechanisms to enforce *responsibility* and *accountability* are difficult to implement. Setting SMART objectives should be a by-product of strategic vision and are key to facilitating the monitoring and evaluation phase of a national action plan. Many countries have used this as a framework to structure objectives; one example from the Austrian NAP is showcased below (Table 5). A larger goal has been broken down into more specific measurable objectives, with priorities defined, responsibilities designated and clear deadlines outlined.

To improve the quality of governance of AMR policies, the interlinked nature of these governance principles should be acknowledged. They can form a cyclical process where progress is continuously *monitored and evaluated*, and priorities are realigned. Ongoing research to review existing and novel policy interventions is essential for this process. Without a thorough understanding of the drivers of AMR and policies in place to limit them, resistance will quickly develop against any potentially new antimicrobials discovered. The cyclical nature of continual improvement is key to improving *sustainability*, but it is also important that an AMR NAP is linked to a dedicated budget and to a transparent financial strategy. Without engaging with these processes, there is a risk that an AMR NAP will not lead to effective implementation and may become a solely symbolic effort which is not followed up or improved upon.

Table 5: Implementation plan for Goal 5: 'Promoting feedback systems for surveillance data' of the Austrian National Action Plan for Antibiotic Resistance

Measures	Status	Priority	Implementation	Responsibility
Facilitate access to online surveillance tools for IPC and ABS teams	Recommended	Medium	End of 2016	Hospitals
Feedback at the level of hospitals or hospital networks	Recommended	High	End of 2016	Hospitals
Agreement of quantitative targets	Recommended	Medium	Long-term	Hospital operator

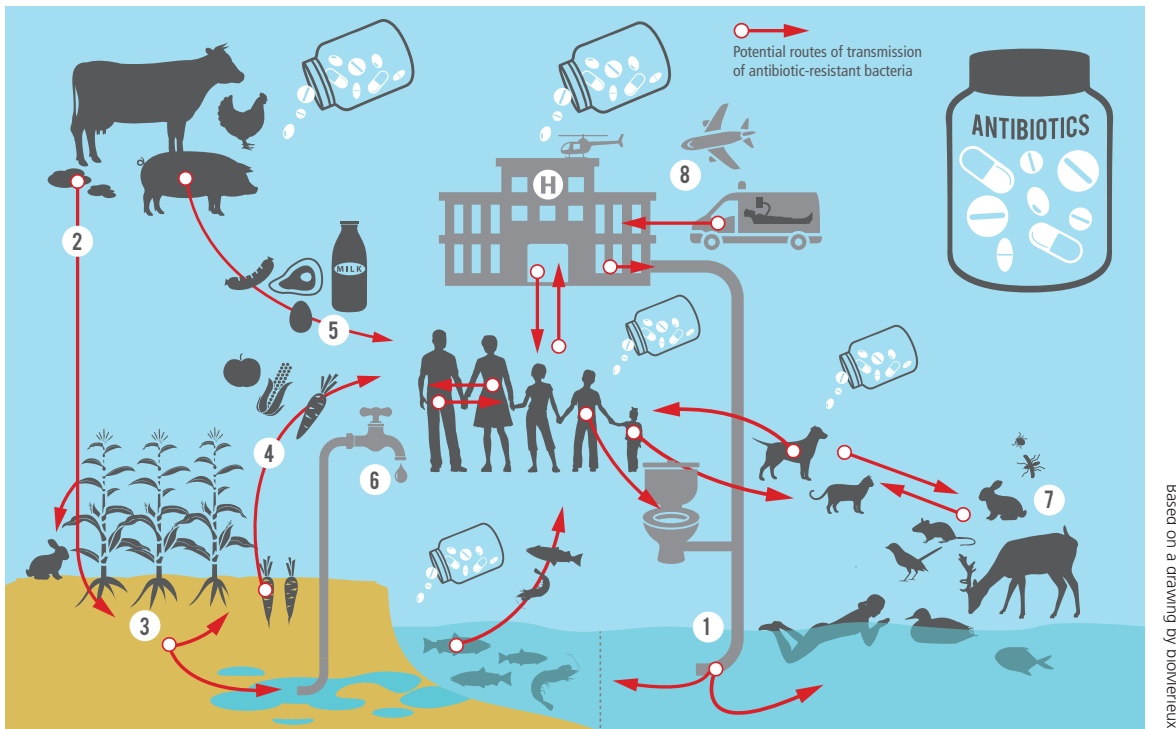
Discussion

AMR is global in nature and crosses national boundaries; the costs of inaction therefore affect all countries. The costs of action, however, must be carried by individual nations, which may be unwilling to invest in the absence of action by others. Nations also vary widely in their ability to mobilize the resources necessary to combat AMR. Moreover, the costs of action are immediate and more visible than the benefits, which are long-term and difficult to value economically. Several countries (such as the Nordic countries and the Netherlands) have demonstrated that successful action to reduce antibiotic use in both humans and animals is achievable at an affordable cost.

Collective global action critically depends on effective national policies. Without dedicated national efforts to tackle AMR across the entire 'One Health' spectrum, national surveillance data collection and sharing, committed funds for AMR research and AMR activities in general, as well as stringent governance of national AMR policies to ensure successful implementation, global collective action will not be able to deliver the desired outcomes – with potentially dire consequences for health and economies. Here, we have outlined key policy options that enable policy-makers both to direct action to addressing AMR nationally and to contribute to the efforts to tackle AMR globally. Ultimately, all these avenues are important and, while some countries may need to prioritize certain avenues initially, all countries should aim towards a comprehensive AMR NAP. The drivers of AMR are multifactorial, so the response to combatting AMR should also be multifactorial.

Appendix

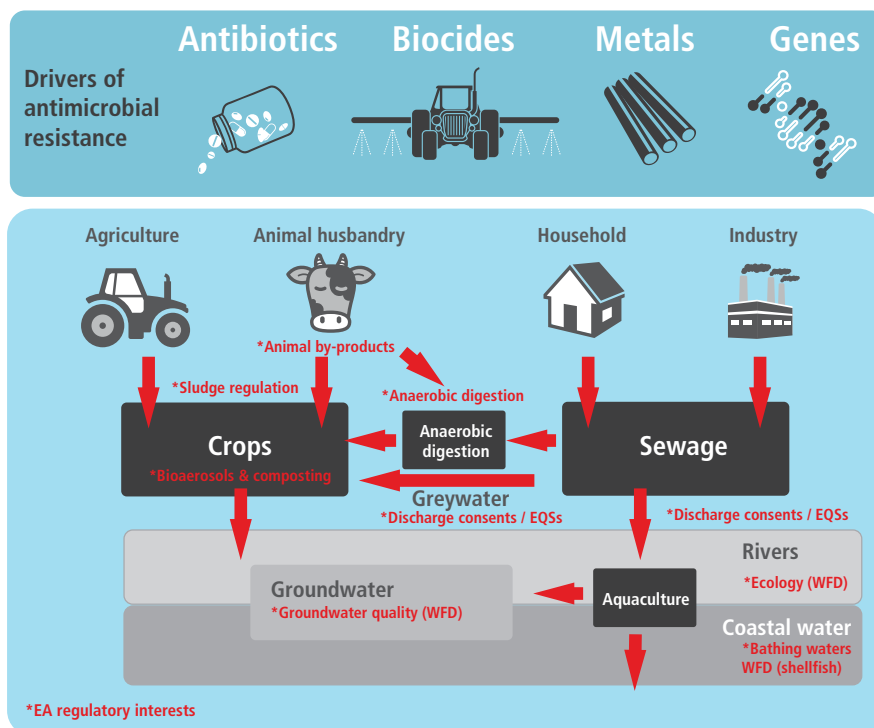
Figure A1: Summary of the pathways of transmission of resistant bacteria between animals, humans and the environment



Source: [151].

Notes: Common routes through which resistant bacteria can spread into the environment include water sanitation systems (1) and use of animal manure on cultivated crops (2&3). Uptake and spread of resistant bacteria can occur through the food chain (4&5); water distribution infrastructure (6); wildlife (7); and tourism, migration and food imports (8). At the healthcare facility level, resistant bacteria can spread by contact between patients or with healthcare staff, or through contaminated surfaces and medical devices (HAIs).

Figure A2: Relationship between the drivers of AMR and the environment



Source: [56].

Notes: EA = environmental agency; EQS = environment quality standards; WFD = water framework directive.

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In support of the Romanian Council Presidency



Print ISSN
1997-8065

Web ISSN
1997-8073