

Evidence brief for policy

EVIPNet Europe

Number 6

Strengthening Romania's health system to address antimicrobial resistance



Evidence-informed Policy Network (EVIPNet) Europe

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ABSTRACT

This report is the first evidence brief for policy produced in Romania within the framework of the WHO European Evidence-informed Policy Network. It was prepared by the Public Health Research Centre of the Department of Public Health and Management, in partnership with the (1st) Department of Microbiology, from the Carol Davila University of Medicine and Pharmacy in Bucharest.

The working group identified, selected, appraised, and synthesized relevant research evidence on the problem, three options for tackling it and considerations in implementing them. The three options are: (1) consolidate and coordinate the legal framework for antimicrobial resistance in Romania, focusing on two layers (first, the legal framework for antimicrobial resistance control at national level, and second, a national antibiotic stewardship programme at the operational level); (2) align funding arrangements to facilitate antimicrobial resistance control, antibiotic stewardship programmes and infection prevention and control programmes; and (3) develop and implement programmes to provide information, improve education and strengthen communication among medical professionals and the public.

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LIST OF ABBREVIATIONS

AMR	antimicrobial resistance
AMSTAR	Assessing Methodological Quality of Systematic Reviews
ASP	antimicrobial stewardship programme
ATC	(WHO) Anatomical Therapeutic Chemical classification system
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
CME	continuing medical education
DDD	defined daily dose
EARS-Net	European Antimicrobial Resistance Surveillance Network
EBP	evidence brief for policy
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESPAUR	English Surveillance Programme for Antimicrobial Utilisation and Resistance
EU	European Union
EVIPNet	(WHO) Evidence-informed Policy Network
GP	general practitioner
HAI	healthcare-associated infection
ICU	intensive care unit
IPC	infection prevention and control
MDR	multidrug-resistant
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NAP	national action plan
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PHE	Public Health England
PPP	purchasing power parity
SARI	Strategy for the Control of Antimicrobial Resistance in Ireland
SURE	Specialist Unit for Review Evidence
TARGET	Treat Antibiotics Responsibly, Guidance, Education, Tools
WHO	World Health Organization

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The Evidence-informed Policy Network (EVIPNet) Europe (www.evipnet.org) – a regional arm of the global EVIPNet – promotes the use of health research in policy-making in countries of the WHO European Region. EVIPNet Europe promotes partnership at the country level between policy-makers, researchers and civil society to facilitate policy development and implementation through the use of the best available scientific evidence.

Through its Public Health Research Centre of the Department of Public Health and Management and the Department of Microbiology, the Carol Davila University of Medicine and Pharmacy in Bucharest is supporting research in public health, the use of evidence for both clinical practice and health management, and its practice and applicability within the health system in Romania.

The Ministry of Health of Romania incorporates the Public Health and Medical Assistance and Programmes General Directorate and coordinates the National Institute of Public Health's Centre for Communicable Diseases Surveillance and Control, as well as being responsible for determining rules and preparing legislation related to health care provision at national level.

AUTHORS

(affiliated with the Carol Davila University of Medicine and Pharmacy)

- » Dr Bogdan Cristian Pană, senior specialist in public health and senior lecturer at the Department of Public Health and Management
- » Professor Dr. Alexandru Rafila, Head of the Department of Microbiology I
- » Dr Dragoş Florea, senior specialist in microbiology and senior lecturer at the Department of Microbiology I
- » Dr Eugenia Claudia Bratu, senior specialist in public health and senior lecturer at the Department of Public Health and Management

MERIT-REVIEWERS

- » Professor Dana Galieta Mincă, Professor in public health and Head of the Department of Public Health and Management, Carol Davila University of Medicine and Pharmacy
- » Dr Florentina Ligia Furtunescu, Associate Professor of the Department of Public Health and Management, Carol Davila University of Medicine and Pharmacy
- » Dr Corneliu-Florin Buicu, Associate Professor of the Department of Public Health and Management, Tirgu-Mures University of Medicine and Pharmacy; Chairperson, Committee for Health and Family, Chamber of Deputies, Romanian Parliament.

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DISCLAIMER



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KEY MESSAGES

The problem

Antimicrobial resistance (AMR) is a priority public health issue in Romania. The country faces some of the highest levels of AMR worldwide, and has one of the highest levels of antibiotic consumption in the human health care sector in Europe. In the absence of efficient policies to stop the global spread of AMR, 33 000 people die every year as a result of infections with antibiotic-resistant bacteria.

Healthcare-associated infections (HAIs) are also a problem, but these remain underdiagnosed and underreported. Another part of the problem is the lack of awareness and understanding of AMR among health care providers, patients and the general public.

In terms of AMR control in Romania, various different initiatives and action plans are under way or in preparation.

What we know from the evidence about the three options for addressing the problem

- **Option 1 is to consolidate and coordinate the legal framework for AMR.**
 - The effect of AMR policies seems to be variable. Antimicrobial stewardship programmes (ASPs) are generally associated with improvements in microbial outcomes, including institutional resistance patterns without significant adverse impact on patient outcomes. ASPs in hospitals decrease total antimicrobial consumption and cost, as well as the use of restricted antimicrobial agents (including in intensive care units (ICUs)), the use of broad-spectrum antibiotics, and hospital lengths of stay. The national or subnational infection prevention and control (IPC) programmes are also cost-effective.
- **Option 2 is to align funding arrangements to facilitate AMR control, ASPs and IPC programmes.**
 - Mixed policies for AMR control could save 1524 lives per year in Romania. ASPs require careful evaluation and budget calculation in terms of costs associated with: implementation, materials (antimicrobials), operational requirements, length of stay, morbidity/mortality, and other hospital-related and societal costs.
- **Option 3 is to develop and implement programmes to provide information, improve education and strengthen communication (among health service providers and the general public).**
 - Inclusion of information on appropriate use of antibiotics in undergraduate and postgraduate curricula, accompanied by continuing medical education, has the potential to improve antibiotic prescribing practices and can require additional

financing. Interventions can also improve clinical outcomes. Multifaceted interventions would be more effective than a single approach in the improvement of antibiotic use and prescribing practices. Involving health care providers in designing interventions is a key element of intervention success and sustainability. On the other hand, educational interventions targeting patients have different levels of effectiveness in reducing the use of antibiotics. When the strategies involve the patient in decision-making on antibiotic use for the treatment of acute infectious respiratory diseases, antibiotic use is reduced by 40%.

Considerations for the implementation of the three options

Evidence shows that all these actions can be implemented and produce results in different settings. The prerequisites to facilitate or sustain the process are:

- » the need for change and a willingness to change on the part of (key players within) the health care system;
- » understanding that there is a need among health professionals for protocols and procedures to improve quality;
- » increasing attention to health information among the general population.

EXECUTIVE SUMMARY

This evidence brief for policy (EBP) focuses on priority AMR challenges currently faced in Romania, as well as the best possible interventions available to address them by the human health care sector, tackling the problem of antibiotic misuse in human medicine.

The problem

AMR is the ability of a microorganism to resist the action of one or more antimicrobial agents. Although by definition AMR includes resistance to antibiotics, antiviral or antifungal agents, in most documents (including this report), this term refers more specifically to antibiotic resistance.

AMR is a priority public health issue in Romania, as well as worldwide. In the absence of efficient policies to stop the global spread of AMR, 33 000 people die every year due to infections with antibiotic-resistant bacteria (ECDC, 2018a).

Romania faces some of highest levels of AMR in Europe. Additionally, AMR results in increased costs for health care systems due to the risk of prolonged hospital stays, as well as the need for more expensive and complex therapeutic interventions to address infections produced by multidrug-resistant (MDR) microorganisms.

Many studies have proved that AMR is directly correlated with antibiotics consumption. Romania has one of the highest levels of consumption of antibiotics in Europe, as reported to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).

HAIs are also a problem, but they are underdiagnosed and underreported. The public only become aware of the problem of HAIs when major incidents are reported by the mass media.

Another part of the problem is the lack of awareness and understanding of AMR among health care providers, which stems from inadequate education and training programmes; and among patients and the public more generally, which stems from a lack of education and programmes intended to raise awareness of the challenges associated with AMR in the country.

The 2017 and 2018 data on AMR control in Romania from the Global Database for Antimicrobial Resistance Country Self-Assessment (WHO, OIE & FAO, 2017, 2018) shows the status of various initiatives and action plans that are under way or in preparation. Such programmes are at varying stages of implementation in different countries across Europe, as shown in this report.

The various causes of AMR in Romania call for interventions at different levels. This EBP frames the information to show that the problem of AMR – and related increasing HAIs – is associated with challenges related to a number of existing health system arrangements, including:

- » a lack of **national oversight** and **strategic guidance** to address AMR;
- » poor **coordination** and **regulation** related to the **surveillance** of AMR;

- » **financial arrangements** that act as a **barrier**, making it difficult to develop and implement AMR-reduction efforts; and
- » a lack of **awareness** and **understanding** of AMR among health care providers and patients.

Options for addressing the problem

The authors propose three options, which collectively address the above-mentioned challenges.

1. Consolidate and coordinate the legal framework for AMR in Romania, by focusing on two layers:
 - » elaborating or enhancing the legal framework (various types of regulation; different administrative levels) for AMR control at national level; and
 - » developing a national ASP at the operational level (outpatient and inpatient clinical settings with oversight of antibiotic use).
2. Align funding arrangements to facilitate AMR control, ASPs and IPC programmes.
3. Develop and implement programmes to provide information, improve education and strengthen communication among medical professionals and the public more generally.

These options may be implemented together or individually, or some of their elements may be used to create new options. The options are presented, along with notes from the authors regarding what is known from among the best available evidence relating to the benefits, harms, costs, need for local adaptations or stakeholders' views and experiences, in order to promote informed discussion.

For policy **option 1 (consolidate and coordinate the legal framework for AMR)**, several elements were identified for consideration, listed below according to the two layers of focus.

For the first layer (**elaborating/enhancing the legal framework for AMR control at national level**), the following points were pinpointed.

- » Developing a national strategy and national action plan (NAP) are essential priorities, establishing strategic guidance and steps to facilitate the elaboration of a robust set of national guidelines for critical actions relating to AMR control.
- » Strategic objectives that are appropriate for a Romanian national strategy and NAP overlap with general objectives mentioned in the literature and WHO's Antimicrobial resistance manual for developing national action plans (WHO, OIE & FAO, 2016).
- » According to the evidence, NAPs are coordinated at national (central) level, using a multisectoral approach, and are supported by the relevant agencies and organizations.
- » Data are transparent and public (in some countries) in order to create accountability.
- » Financial penalties exist for inadequate reporting and for non-compliance with NAPs.
- » Several NAP models are described in the literature.

For the second layer (**developing a national ASP at operational level in outpatient and inpatient clinical settings with oversight of antibiotic use**), the identified points included those listed here.

- » ASPs are coordinated programmes to guide the implementation of interventions to ensure appropriate antimicrobial prescribing.
- » ASPs have been included in the European Centre for Disease Prevention and Control (ECDC) guidelines (ECDC, 2017), among key elements to be introduced in a national strategy.
- » According to the global evidence, other measures (such as audit and feedback, guideline implementation and decision support) substantially impacted patient outcomes, including mortality, length of stay, readmission or incidence of *Clostridium difficile* infection.
- » The evidence identified also shows that hospital ASPs result in significant decreases in antimicrobial consumption and costs, and their benefit was found to be higher in critical care settings.

For policy **option 2 (align funding arrangements to facilitate AMR control, ASPs and IPC programmes)**, similarly, various elements were identified for consideration.

- » Sustainable financial arrangements, dedicated to AMR, are part of the policy package recommended by WHO.
- » The national or subnational IPC programmes that exist in high-income and upper-middle-income countries are effective.
- » Stewardship programmes are the most recommended and used models of intervention and consequently mostly analysed from economic perspective.
- » The following three packages of interventions are considered to have a health and cost-saving impact:
 1. actions in hospitals (including improving hand hygiene, implementing ASPs and ensuring enhanced environmental hygiene in the health care setting);
 2. community actions (including delayed prescription practices, mass media campaigns and the use of rapid testing);
 3. mixed interventions (namely, a package of interventions combining antimicrobial stewardship actions, enhanced environmental hygiene standards in the health care setting, mass media campaigns, and the use of rapid testing).
- » According to the data, in Romania the fiscal savings could be around US\$ 0.5 PPP (purchasing power parity) and 1524 lives could be saved per year with the careful implementation of such interventions.

For policy **option 3 (develop and implement programmes to provide information, improve education and strengthen communication)**, the following elements:

- » Education on AMR and the prudent use of antibiotics at the level of health service providers and the general population is found to be important for implementing AMR policies.
- » Introducing specific training modules for medical professionals is mentioned as a suggestion to improve the process of preparing human resources at undergraduate and postgraduate levels.

■ EVIDENCE BRIEF FOR POLICY

- » Further aspects for consideration are the dissemination of information, along with strengthening education programmes and physician–patient communication.
- » Evidence shows that including appropriate antibiotic use in undergraduate and postgraduate curricula, accompanied by continuing medical education (CME) in the field of antibiotic therapy, have the potential to improve antibiotic prescription practices.

Considerations for the implementation of the three options

The three options presented are the results extracted from an extensive search of worldwide published evidence relating to both the problem and potential solutions to the problem. While these results are backed by science and input from experts in the field, they nonetheless need to be implemented in facilities at health care system level, with the involvement of a variety of actors/stakeholders, within the available budget framework and in full consideration of day-to-day care constraints.

Potential barriers to implementation exist in the overall complexity and relative novelty of the problem. Successful implementation of the options requires (mainly human and organizational) resources to be mobilized, the necessary legal and regulatory framework to be established, operational procedures to be implemented and information disseminated to all care providers. The population also needs to be adequately informed, to enable them to embrace a new approach to dealing with antibiotics.

INTRODUCTION

Background and rationale

AMR is a priority public health issue in Romania and worldwide, with a number of studies and reports published that highlight the growing magnitude of the problem. Furthermore, as increasingly more countries continue to grapple with the issue, discussion focuses on the best possible solutions available to policy-makers and stakeholders in order to keep AMR under control.

With the growing awareness of AMR in Romania and an increasing level of political will to address the problem, this report was prepared in order to support decision-makers and ensure debates are underpinned with the best available evidence relating to the benefits, harms, costs, need for local adaptations or stakeholders' views and experience. The intention is to contribute to the improvement of surveillance and control policies and programmes for AMR in Romania.

Box 1. Background to the EBP

This policy brief mobilizes both global and local research evidence about a problem, three options for addressing it, and key implementation considerations.

Seven steps were taken in preparing the evidence brief. These comprised:

1. convening a working group of representatives from the Public Health and Microbiology departments at the Carol Davila University of Medicine and Pharmacy in Bucharest;
2. undertaking training on searching for relevant evidence and writing an EBP report;
3. developing and refining the terms of reference for the EBP, particularly the framing of the problem and the options for addressing it;
4. identifying, selecting, appraising, and synthesizing relevant research evidence on the problem, options to address it, and implementation considerations;
5. interviewing key informants about local implementation considerations;
6. drafting the text to present, concisely and in accessible language, the global and local research evidence; and
7. finalizing the EBP based on the input of several merit-reviewers.

How this EBP was prepared

This report is the first EBP produced in Romania within the framework of the WHO EVIPNet Europe (WHO, 2015a; WHO Regional Office for Europe, 2019). It was prepared by the Public Health Research Centre of the Department of Public Health and Management, in partnership with the (1st) Department of Microbiology, from the Carol Davila University of Medicine and Pharmacy in Bucharest. Experts from the National Institute of Public Health were also involved (Box 1).

During the development process, policy-makers, stakeholders (including managers in relevant fields, health care providers and researchers with AMR knowledge in the Romanian context) as well as researchers and international experts on the subject were engaged to continuously review the EBP, either as members of the project steering committee or as one of the 14 key informants that were interviewed as part of its development. These individuals provided their insights into the problem, the options for addressing it and various implementation considerations, which were used by the authors to iteratively revise the EBP during its various development stages.

The authors combined these insights with a review of the best available global research evidence (prioritizing systematic reviews), along with local data and studies, to inform how the problems were defined and the options framed, along with challenges or barriers to and opportunities for implementing the proposed solutions (see Box 2). The search for evidence focused on systematic reviews that helped to answer key questions about the policy options considered (concentrating, for example, on their benefits, harms, costs and cost-effectiveness) and the implementation strategies that would be needed to support their adoption in Romania. Other relevant study findings, key publications from major international organizations, government reports and unpublished literature were also used. For instance, the information related to the costs and benefits of each option is primarily drawn from the scientific literature, but not exclusively: reports issued by representative organizations and institutions were also used. Since each policy option offers multiple alternatives for implementation design, the exact content of interventions would need to be decided before the direct and indirect costs and benefits specific to the country situation could be calculated. This would need to be the focus of further work on policy development.

The authors approached the review of the scientific evidence in a systematic and transparent way, trying to be as impartial as possible when considering hierarchies of evidence, relevance and implications of the findings. They also conducted surveys with key policy-makers, stakeholders and researchers from Romania, who are likely to be involved in decisions addressing AMR in the country, or who will be affected by such decisions.

The EBP is intended as an input into a broader set of deliberations related to how Romania can best address AMR challenges, and details about additional related work being pursued to complement this report is outlined in Box. 2.

Box 2. Mobilizing research evidence

For the development of this EBP, various sources were used: international and local reports, and database information from Medline/PubMed, Cochrane Library, Health Systems Evidence, Health Evidence and Google Scholar databases. Relevant grey literature was found by reviewing the websites of leading international and national organizations, such as the National Institute of Public Health, WHO, ECDC, and the United States Centers for Disease Control and Prevention (CDC). The most challenging aspect of the search was obtaining accurate and comprehensive data from within the Romanian health system. Therefore the data used from local reports were double-checked, as were international reports referring to Romania's surveillance of infectious diseases, HAIs, AMR and antibiotic consumption.

The search strategy was stratified separately by three dimensions (problems, policy options and implementation) using specific keywords: antibiotic, antibacterial, antimicrobial, misuse, overuse, inappropriate use, stewardship, guideline, hospital acquired infections, prescribing, education, training, financing, cost, benefit, financial evaluation, reimbursement, implementation, strategy, and feasibility.

Priority was given to research-based evidence, in particular meta-analysis and systematic reviews, recently published and locally applicable sources (i.e. research conducted in the country).

Meta-analysis is statistical analysis that usually combines the results of multiple scientific studies for a particular problem to produce a common conclusion on the effect.

Systematic reviews are a type of literature review that uses systematic methods to collect secondary data, critically appraise research studies, and synthesize studies. Systematic reviews formulate research questions that can be broad or narrow in scope, and they identify and synthesize studies that directly relate to the question.

A summary of the systematic reviews identified and used in this EBP, with a view to developing the options, are listed in the annexes.

Each review was also assessed in terms of its quality (given an Assessing Methodological Quality of Systematic Reviews (AMSTAR) rating of 0–11) and local applicability (according to the proportion of studies conducted in the country).

The quality of evidence was classified as follows:

Evidence quality AMSTAR rating (points)	High 8–11
	Medium 4–7
	Low 0–3

Scope of this report

This EBP focuses on priority AMR challenges currently faced in Romania, as well as the best possible interventions available to address them by the human health care sector, tackling the problem of antibiotic misuse in human medicine. The authors are aware that the issue is wildly complex, and that key aspects of the problem – as well as the solutions to address them – are being dealt with in a range of non-health sectors (e.g. agricultural, veterinary, environmental). However, it was decided to focus on the issues most relevant to the health sector to ensure that a sufficiently targeted approach was possible within the (time-) constraints faced by the team. It is the full intention of the authors that this report be used as an input into intersectoral discussions, adding value from the health perspective (that is, enabling an holistic and multisectoral, One Health approach).

THE PROBLEM OF AMR

AMR is a growing problem around the world

AMR is the ability of a microorganism to resist the action of one or more antimicrobial agents to which they were previously susceptible. Although by definition AMR includes resistance to antibiotics, antiviral or antifungal agents, in most documents (including this report) the term refers to antibiotic resistance (Box 3). AMR is a major threat to human health, negatively affecting patient safety and contributing to prolonged illness, disability and death.

Development of AMR is a natural phenomenon caused by mutations in bacterial genes or, more frequently, by the acquisition of resistance genes from other bacteria (ECDC, 2018d).

Even though AMR may occur naturally over time, the misuse of antibiotics is accelerating this process globally. The misuse of antibiotics in the human health sector means their inappropriate use (when they are not the most appropriate treatment; when they're not taken as prescribed by patients; or when they are overused) and has severe consequences.

These consequences include potentially severe side-effects, limited therapeutic alternatives, and increased morbidity and mortality. In human health the misuse of antibiotics is prevalent worldwide – mainly in hospitals, but also in ambulatory settings.

The spread of AMR is enhanced by poor diagnostic and treatment protocols and inadequate measures of IPC. Deficient IPC activities also represent a major driver for the occurrence of HAIs. Since HAIs are often produced by antimicrobial-resistant microorganisms, the issues of AMR and HAI are closely interrelated.

With increasing resistance – even to last-line antibiotics – and a lack progress towards the development of new antimicrobials since the late 2000s, the risk of losing many antimicrobial treatment alternatives is cause for even more concern. The lack of options for antimicrobial treatment will significantly increase mortality due to infections and minimize the benefits of other therapeutic interventions, such as surgery, intensive care and immune suppression procedures. In the absence of efficient policies to stop the global spread of AMR, 33 000 people die every year due to infections with antibiotic-resistant bacteria. (ECDC, 2018a; OECD, 2018b) and this number will continue to rise without significant developments.

In addition, AMR results in increased costs for health care systems due to the risk of prolonged hospital stays, as well as the need for more expensive and complex therapeutic interventions to address infections produced by MDR microorganisms. This is even more critical for people with medical conditions associated with impaired antimicrobial response, such as patients from oncology, transplant or ICUs.

Box 3. Definitions

An **antimicrobial** is any substance of natural, semi-synthetic, or synthetic origin that in in vivo concentrations kills or inhibits the growth of microorganisms by interacting with a specific target.

Antibacterial agents are antimicrobials acting against bacteria.

An antibiotic is a substance produced by, or derived (chemically produced) from a microorganism that selectively destroys or inhibits the growth of bacteria.

AMR is the resistance of a microorganism to an antimicrobial agent that was originally effective for treatment of infections caused by this microorganism.

An **MDR organism** is a microorganism that is not susceptible to at least one agent in each of three or more antimicrobial categories (or two or more antimicrobial categories for *Mycobacterium tuberculosis*).

Antimicrobial therapy: empiric antimicrobial therapy is based on a reasonable informed clinical judgement regarding the most likely infecting organism; **documented antimicrobial therapy** is when the identity and antimicrobial susceptibility of the infecting organism is known, as the result of appropriate diagnostic or reference testing.

Antimicrobial prophylaxis is the use of antimicrobials for the prevention of infections.

Prudent antimicrobial use is use of antimicrobials which benefits the patient, while at the same time minimizing the probability of adverse effects (including toxicity and the selection of pathogenic organisms, such as *C. difficile*) and the emergence or spread of AMR. Other terms that have been used with the same purpose include: judicious, rational, adequate, correct and optimal.

Antimicrobial stewardship is an organizational or health care system-wide multidisciplinary approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness.

ASPs are coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing.

Source: ECDC, 2017b.

Romania faces some of highest levels of AMR in Europe

While Romania lacks robust data on AMR rates, the available data suggest that the country is facing some of the biggest AMR-related challenges in Europe. The most relevant available data at national level are those reported annually to the European Antimicrobial Resistance Surveillance Network (EARS-Net). These data are based on reports from a limited number of hospitals, which provide AMR levels in defined bacteria isolated from patients with invasive infections (blood culture, cerebrospinal fluid culture). For most of the reported bacteria and antibiotic combinations, the levels of AMR in Romania are among the highest in the European Union (EU)/European Economic Area (EEA) (Table 1) (ECDC, 2018d)).

According to an EARS-Net report with data up to 2017 (ECDC, 2018d), the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) strains in Romania was the highest at that point among EU Member States since 2014 and was 2.6% higher than the EU/EEA mean. The emergence of vancomycin-resistant *Enterococcus faecium* is worrying: showing a progression from 2.9% in 2012, to 10.9% in 2013, 39% in 2016 and still maintaining at high value in 2017 at

34.4%. Although slightly decreasing towards the end of the period studied, the proportion of Enterobacteriaceae strains resistant to carbapenems – a major last-line class of antibiotics to treat such bacterial infections – is still more than three times higher than the EU/EEA mean: 0.4% for *Escherichia coli* and 22.5% for *K. pneumoniae* (Fig. 1). All major classes of carbapenemase have been detected in *K. pneumoniae* isolates from Romania (OECD, 2018a).

A major concern is the near-constant detection since the mid-2010s of multidrug resistance in most isolates of *K. pneumoniae* (55.4%) and other gram-negative bacteria, mainly those found in HAI: *Pseudomonas aeruginosa* (59.1%) and *Acinetobacter baumannii* (81.3%) (Popescu, Şerban & Niculcea, 2018). Most isolates of *P. aeruginosa* are resistant to ceftazidime (55.9%), carbapenems (63.4%), or at least three antimicrobial groups; that is, they can be classified as MDR bacteria (59.1%), representing the highest levels in the EU and more than four times higher than the EU/EEA mean (Table 1).

Table 1. Antibiotic resistance in key indicators (types of bacteria), Romania and EU/EEA countries, 2014–2017

Antibiotic-resistant bacteria (antibiotic)	2014		2015		2016		2017		
	% R	EU rank	% R	EU rank	% R	EU rank	% R	EU rank	% R EU/EEA mean
<i>Staphylococcus aureus</i> (Methicillin R)	56.0	1	57.2	1	50.5	1	44.4	1	16.9
<i>Enterococcus faecium</i> (Vancomycin R)	25.0	4	25.0	4	39.0	3	34.4	4	14.9
<i>Escherichia coli</i> (3rd generation Cephalosporin R)	29.4	3	26.8	5	23.4	6	18.7	7	14.9
<i>E. coli</i> (Carbapenem R)	0.7	1	1.9	1	1.0	1	0.4	3	0.1
<i>E. coli</i> (MDR)	14.4	3	13.5	3	11.7	4	9.7	7	6.3
<i>Klebsiella pneumoniae</i> (3rd generation Cephalosporin R)	73.8	2	70.7	2	68.0	3	62.5	6	31.2
<i>K. pneumoniae</i> (Carbapenem R)	31.5	3	24.7	3	31.4	3	22.5	3	7.2
<i>K. pneumoniae</i> (MDR)	56.3	2	49.8	3	55.2	2	55.4	2	20.5
<i>Pseudomonas aeruginosa</i> (Ceftazidime R)	59.1	1	65.9	1	44.2	1	55.9	1	14.7

Table 1. (Contd)

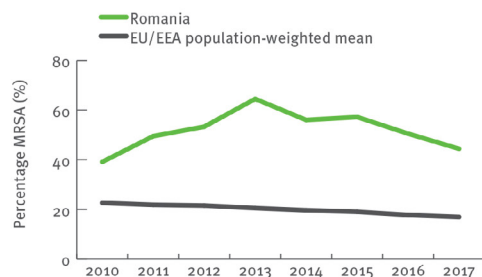
Antibiotic-resistant bacteria (antibiotic)	2014		2015		2016		2017		
	% R	EU rank	% R	EU rank	% R	EU rank	% R	EU rank	% R EU/EEA mean
<i>P. aeruginosa</i> (Carbapenem R)	58.5	1	66.3	1	51.6	1	63.4	1	17.4
<i>P. aeruginosa</i> (MDR)	59.6	1	63.0	1	42.9	1	59.1	1	13.3
<i>Acinetobacter spp.</i> (Carbapenem R)	81.3	4	81.5	3	85.0	3	87.4	4	33.4
<i>Acinetobacter spp.</i> (MDR)	76.9	3	76.9	3	82.9	2	81.3	3	28.4

Note. % R: percentage of resistant isolates.

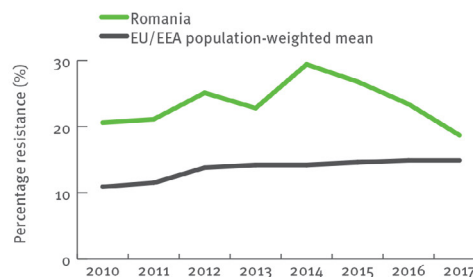
Sources: ECDC EARS-Net data from 2018 (ECDC, 2018d; ECDC, 2019).

Fig. 1 Surveillance of AMR in Romania and the EU, 2010–2017

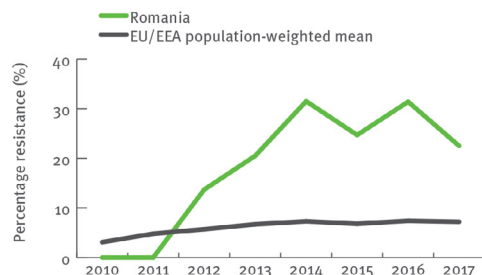
Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), Romania and EU/EEA population-weighted mean, 2010–2017



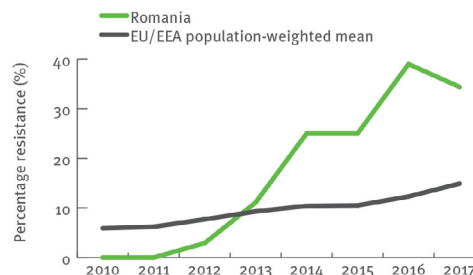
Escherichia coli. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, Romania and EU/EEA population-weighted mean, 2010–2017



Klebsiella pneumoniae. Percentage (%) of invasive isolates with resistance to carbapenems, Romania and EU/EEA population-weighted mean, 2010–2017



Enterococcus faecium. Percentage (%) of invasive isolates with resistance to vancomycin, Romania and EU/EEA population-weighted mean, 2010–2017



Sources: CARMIN-ROM study 2016 (Popescu, Șerban & Niculcea, 2017); ECDC EARS-Net reports (ECDC, 2018d; ECDC, 2019).

Romania has among the highest levels of antibiotic consumption in Europe

Many studies have proved that AMR is directly correlated with antibiotic consumption. Antibiotic use, definitions and common measures are presented in Box 4 (Bell et al., 2014; WHO, 2001, 2005; McDonnell et al., 2017; Axtente et al., 2017).

Antibiotic exposure exerts selective pressure not only on pathogenic bacteria, but also on commensal and environmental bacteria. Altogether these represent a reservoir of antibiotic resistance genes from which pathogenic bacteria can acquire resistance through horizontal gene transfer (von Wintersdorf et al., 2016). The human gut microbiota are not only an important reservoir of antibiotic resistance genes, but also an environment in which these genes can spread across species (Francino, 2016).

Romania has among the highest consumption of antibiotics in Europe, as reported to the ESAC-Net (ECDC, 2018b). The consumption of antibiotics for systemic use, expressed as the DDD (defined daily dose; see Box 4) per 1000 inhabitants per day, showed an increasing trend from 2011 (30.9) to 2015 (33.3) and a decreasing trend in 2016 (29.5) and 2017 (29.1), resulting in Romania occupying one of the top positions for antibiotic consumption in the EU each year (ECDC, 2019).

Data provided by IMS Health Romania, a private operator on market research, only refer to “total consumption” and are adjusted using data from the National Health Insurance House database for reimbursed drugs. The decreasing trend reported in 2016–2017 is mainly based on decreased use of oral antibiotics, likely due to more stringent regulations about over-the-counter sales, as well as public information campaigns by the Romanian Ministry of Health (Popescu, Șerban & Niculcea, 2018).

Box 4. Antibiotic use: definitions and common measures

Systemic antibiotics are antibacterial drugs with a method of administration (oral or by injection) which allow their distribution into the circulatory system. These include:

- » **narrow-spectrum antibiotics** – antibacterial drugs active against a limited subset of bacteria;
- » **broad-spectrum antibiotics** – antibacterial drugs active against a wide range of bacteria.

The classification in narrow- versus broad-spectrum is not entirely consistent; some classes of antibiotics contain both narrow- and broad-spectrum agents.

The **DDD** is the assumed average maintenance dose per day of a drug used for its main indication in adults (WHO, 2019c).

Drug-specific quality indicators (ECDC, 2018b; Popescu, Șerban & Niculcea, 2018)

- » Consumption: total consumption of systemic antibiotics and its subgroups.
- » Relative consumption: consumption of narrow-spectrum beta-lactamase-sensitive penicillins, broad-spectrum combinations of penicillins including beta-lactamase inhibitors, third- and fourth-generation cephalosporins, and fluoroquinolones, as a percentage of total consumption.
- » Broad-to-narrow ratio: the ratio of the consumption of broad- to narrow-spectrum penicillins, cephalosporins and macrolides.
- » Seasonal variation: overuse of systemic antibiotics and of quinolones in autumn–winter, compared to spring–summer.

The quality of community-based antibiotic use is analysed according to 12 indicators defined by the ESAC-Net. In the last ESAC-Net report on Romania, dividing the data by antimicrobial consumption in the community sector and in hospitals was not possible, because the country reports data for total care, therefore total consumption is assimilated to the community sector. Also, the reported data do not allow the evaluation of two of the ESAC-Net quality indicators: seasonal variation of the total antibiotic consumption and of the quinolone consumption (Popescu, Șerban & Niculcea, 2018).

The quality of antibiotic use needs to be improved, as reflected by 10 available indicators (Table 2) (Popescu, Șerban & Niculcea, 2018; ECDC, 2018b).

- a. For **consumption** (expressed as the DDD per 1000 inhabitants per day): three of the four indicators rank in the top four among EU Member States and reflect overprescription (total consumption of antimicrobials for systemic use, along with consumption of penicillins, cephalosporins and quinolones), especially for antibiotics associated with a higher risk of AMR selection.
- b. For **relative consumption** (expressed as percentage of the total consumption of antibacterials for systemic use):
 - » beta-lactamase sensitive penicillins (J01CE), and narrow spectrum penicillins (the only indicator for with a higher value that indicates adequate prescription) have a relative consumption level in Romania that is close to the EU mean;
 - » relative consumption of a combination of penicillins, including beta-lactamase-inhibitors (J01CR), third- and fourth-generation cephalosporins (J01DD +J01DE), and fluoroquinolones (J01MA) ranks among the highest in the EU.
- c. Broad- to narrow-spectrum antibiotic consumption (expressed as DDD per 1000 inhabitants per day) continuously increased from 6.4 in 2011 to 8.4 (2012), 11.1 (2013), 11.9 (2014), 13.2 (2015), 16.6 (2016) and 19.9 (2017).

Table 2. Quality indicators for antibiotic use in Romania compared to other EU countries, 2017 (DDD per 1000 inhabitants per day)

	Quality indicator	Romania	Minimum value	Percentile			Maximum value
				25th	50th	75th	
Consumption	J01	29.1	10.1	14.5	20.3	23.8	33.6
	J01C	15.7	4.0	6.8	9.9	12.8	21.2
	J01D	5.0	<0.1	0.6	1.6	2.4	5.8
	J01F	2.9	0.5	1.8	2.8	3.2	5.5
	J01M	3.3	0.4	0.8	1.2	2.3	6.3

Table 2. (Contd)

	Quality indicator	Romania	Minimum value	Percentile			Maximum value
				25th	50th	75th	
Relative consumption (%)	J01CE%	2.2	<0.1	0.6	1.4	5.2	27.2
	J01CR%	33.1	0.1	14.4	22.7	34.0	44.9
	J01DD+DE%	4.4	<0.1	0.0	0.5	1.9	7.2
	J01MA%	11.2	2.3	4.8	7.3	9.1	18.6
Broad/ Narrow	J01B/N	19.3	0.2	4.8	17.1	49.2	266.5

Notes. Consumption of antibiotics, according to the WHO Anatomical Therapeutic Chemical (ATC) Classification system. J01: systemic antibiotics. J01C: penicillins. J01CE: beta-lactamase sensitive penicillins. J01CR: combination of penicillins, including beta-lactamase-inhibitors. J01D: cephalosporins. J01DD: third-generation cephalosporins. J01DE: fourth-generation cephalosporins. J01F: macrolides, lincosamides and streptogramins. J01M: quinolones. J01MA: fluoroquinolones.

Source: ECDC, 2018b.

HAIs are also a problem, but are underdiagnosed and underreported

The reported level of HAIs in Romania is based on data input to a passive surveillance system by most of the public and private hospitals. The reported incidence of HAIs at national level was less than 1% since 1989, and less than 0.25% between 2006 and 2014, with a slight increase in 2015 (0.33%) and 2016 (0.44%) (Popescu, Șerban & Niculcea, 2017, 2018; ECDC, 2018c; OECD & European Observatory on Health Systems and Policies, 2017).

This is in major contrast not only to the EU mean of 5.2% but also to the high levels of AMR and antimicrobial consumption in Romania, ranking among the first 5 among EU Member States (ECDC, 2018b). Moreover, an ECDC point prevalence survey performed in 10 Romanian hospitals in 2012 indicated a tenfold higher prevalence of HAIs (at least 2.8%, and adjusted over 5%, as reported in the re-validated data from five hospitals) (ECDC, 2013, 2018c; OECD & European Observatory on Health Systems and Policies, 2017). Based on these data discrepancies it is reasonable to conclude that HAIs are extensively underdiagnosed and/or underreported in Romania.

The slow ascending trend of total reported HAIs – from the lowest level (8105 cases) in 2010 to 9296 cases in 2013 and 16 175 cases in 2016 – might be partially the result of improved reporting, but a major factor is probably the implementation in September 2014 of a national reporting system for *C. difficile* infection, including HAIs. This argument is sustained by the sharp increase in digestive infections among all HAIs, from 15.2% in 2013 to 33.0% in 2015 and 35.2% in 2016 (Popescu, Șerban & Niculcea, 2018). The striking differences in the number of reported *C. difficile* cases between the 40 counties studied, with Bucharest and one county having together 30% of all cases, and two counties with no cases at all, also sustains the assertion that HAIs are underreported.

Box 5. Percentage of 49 WHO European Region Member States implementing various policies, actions or regulations to control AMR (April 2015)

- » 92% had quality standards.
- » 91% reported that they could enforce the quality standards, and therefore:
 - poor-quality and counterfeit medicines may not be a significant cause of AMR in those countries of the Region.
- » 89% had a national regulatory agency.
- » 79% reported having organized at least one campaign, and:
 - 50% of the EU population believed that antibiotics were effective against viral infections and therefore expected them to be prescribed for a common cold or influenza.
- » 70% had a national focal point.
- » 62% collected data from surveillance of antimicrobial-resistant bacteria.
- » 60% have a list of essential medicines.
- » 50% had an action plan to counteract AMR.
- » 47% had a national coordination mechanism for AMR
- » 40% had policies or strategies in place to counteract AMR.
- » 21% had issued a recent report on activities relevant to AMR.

Source: WHO, 2015b.

At public level the problem of HAI becomes visible only when major incidents are reported by the mass media. Such a major incident happened in Bucharest in 2015, when dozens of burn patients, victims of a fire at a nightclub, were colonized after their admission and developed HAIs with extensively drug-resistant and even pan-drug-resistant strains of Enterobacteriaceae and *A. baumannii* (ECDC, 2018c). Another recent incident, involving an outbreak of more than 30 cases of MRSA infection in neonates from a maternity ward, occurred in Bucharest in November 2018 (ECDC, 2018c).

Under-reporting of HAIs in Romania might be the result of several factors, as stated in the mission report of the ECDC team which visited the country in 2016 (ECDC, 2018c). These factors include:

- » the lack of intersectoral coordinating mechanisms to prevent, detect and combat HAIs;
- » the tradition of fighting HAIs based on administrative negative incentives;
- » use at hospital level of a system whereby epidemiologists are responsible for data reporting and statistics, instead of a control system operated by a multi-disciplinary infection control team with executive powers and adequate funding;
- » insufficient standards and proper protocols in hospital microbiology laboratories to adequately monitor HAIs;

- » insufficient availability of epidemiologists and clinical microbiologists properly trained for infection control activities;
- » the low use of hand disinfectants in clinical wards,
- » the impact of the media depicting the hospitals that report higher (and most probably closer to true) rates of HAI as being overly dangerous for patients.

Existing health system arrangements contribute to the increasing magnitude of the problem

Underpinning the range of problems outlined in the sections above are a number of health system arrangements that continue to contribute to the increasing levels of AMR in Romania, along with underreported HAIs, and high levels of antibiotic consumption. Specifically, four key areas are problematic, including:

1. a lack of national oversight and strategic guidance to address AMR;
2. poor coordination and regulation related to the surveillance of AMR;
3. financial arrangements that make it difficult to develop and implement AMR-reduction efforts;
4. a lack of awareness and understanding of AMR among health care providers and patients.

LACK OF NATIONAL OVERSIGHT AND STRATEGIC GUIDANCE

There is a lack of national oversight and guidance in the form of a consolidated plan for AMR in Romania. The global framework, international studies and the national situation are detailed in the following subsections.

On 7 April 2011, WHO introduced a policy package to combat AMR, which lists the critical actions by all stakeholders to stimulate change, including the key directives targeting action on AMR in the health sector (Leung et al., 2011). This was consolidated in the years that followed in the *Global action plan on antimicrobial resistance* (WHO, 2015a) and the European One Health Action Plan (EC, 2017a).

A worldwide country situation analysis was subsequently conducted in each of the six WHO regions to assess current practices to determine the structures already in place to control AMR. The report, released in 2015, showed that there is progress in each of the directions listed in the WHO policy package (Leung et al., 2011), but with large disparities in the WHO European Region (WHO, 2015b) (see Box 5).

Available data from 2017 and 2018 from the Global Database for Antimicrobial Resistance Country Self-Assessment (WHO, OIE & FAO, 2017, 2018) show the status of various areas of AMR control in Romania.

- » There is a coordination committee on AMR established with government leadership. (Government of Romania, 2018).
- » National AMR surveillance activities for common bacterial infections follow national standards, and a national reference laboratory participates in external quality assurance.
- » A national AMR action plan is under development.

- » No financing programme exists dedicated to AMR.
- » Limited or small-scale antibiotic resistance awareness campaigns target some, but not all, relevant stakeholders (e.g. general public, doctors, pharmacists, nurses, medicine sellers)
- » AMR is covered in ad hoc AMR training courses in some disciplines relating to human health.
- » Total sales of antimicrobials are monitored at national level and there is some monitoring of antibiotic use at subnational (local) level.
- » A national IPC programme and operational plan are available and some national guidelines for IPC in health care are available and disseminated (Popescu et al., 2016).
- » Selected health facilities are implementing the guidelines, with monitoring and feedback systems in place.
- » Practices to ensure appropriate antimicrobial use are being implemented in some health care facilities, and guidelines for appropriate use of antimicrobials are available.
- » National legislation covers all aspects of national manufacture, import, marketing authorization, control of safety, quality and efficacy, and distribution of antimicrobial products.

For other sections of the Antimicrobial Resistance Country Self-Assessment, data were reported starting with the year 2018 for Romania.

POOR COORDINATION AND REGULATION OF AMR SURVEILLANCE EFFORTS

No coordinated efforts or mechanisms exist to allow the routine integration of existing AMR surveillance results into targeted public health interventions (in either the public or private sectors).

Incoherent and incongruent regulations, at various legislative levels create undesirable behaviours and outputs.

- » According to Law 95/2006 (art.168), hospitals are legally responsible for measures to control HAIs, and are required to cover the legal penalties if a related case is brought.
- » No audits or validation of HAIs reported by the hospitals have been carried out, but penalties exist for higher values of HAI than those agreed in the hospital management contract (Ministry of Health of Romania, 2010).
- » AMR detection and reporting are mandatory for hospitalized patients and environment samples, but not for healthy carriers of drug-resistant organisms.
- » In terms of AMR testing, surveillance and intervention, there is insufficient coordination and integration between the private and public sectors. Private laboratories are not required to report results related to AMR to the local/national public health authorities.
- » According to the Deontological Code of the Romanian College of Pharmacists (Romanian College of Pharmacists, 2009), a pharmacist is exceptionally allowed to dispense antibiotics, without receipt, in emergency situations, up to a 72-hour doses.

FINANCIAL ARRANGEMENTS HAMPERING THE DEVELOPMENT AND IMPLEMENTATION OF AMR-REDUCTION EFFORTS

With a per-capita health spending of €814 in 2015, Romania was in the bottom third of countries in the EU in terms of the amount of public funding provided for health care financing. This equalled 4.9% of gross domestic product and was well below the EU average of 9.9%. Out-of-pocket medical spending in Romania was at 21.3% of total health expenditure, with the highest share dedicated to pharmaceuticals (70.8% vs 44.2% in the EU in 2015) (OECD & European Observatory on Health Systems and Policies, 2017).

The challenges of the much-needed ongoing reforms combined with insufficient funding affect all aspects of health care delivery, including the ability to implement effective AMR and HAI control policies at national level. Evidence shows that weak regulation and misaligned financing models for health care can create perverse economic incentives for providers (Dar et al., 2016).

Providers are paid by the National Health Insurance House in various models, mainly: DRGs for hospitals, per service for outpatient care, and per capita and per service for family physicians. Alongside these mechanisms, national programmes for public health also exist, financed by the Ministry of Health, as well as programmes for financing drugs and devices with funding from the National Health Insurance House. Local authorities can finance investments and infrastructure for publicly owned hospitals, varying according to financial capabilities and willingness.

According to regulations (Ministry of Health of Romania, 2016), each health provider has to allocate a budget for their own programme for HAI surveillance and control. These allocations come under pressure at the provider level when the budgets are challenged by other cost categories, such as medicines, medical materials or personnel salaries.

LACK OF AWARENESS AND UNDERSTANDING OF AMR AMONG HEALTH CARE PROVIDERS AND PATIENTS

Another part of the problem is the lack of awareness and understanding of AMR among health care providers, which stems from inadequate education and training programmes, as well as among patients and the public more generally, which also stems from lack of education and the fact that very few programmes intended to raise awareness of the challenges associated with AMR exist in the country. Taken together, this can result in suboptimal prescribing patterns, poor patient management, and behaviours among both medical professionals and their patients that contribute to (rather than reduce) AMR and its precursors (e.g., inappropriate antibiotic use). For example, it is known that poor antibiotic practices are common in health systems around the world, to varying degrees, and that this heavily contributes to AMR (Box 6). This is likely the result of lack of awareness and knowledge among both providers and patients, resulting in behaviours that are not optimal for addressing AMR. It is estimated that 50% of antibiotic consumption is unnecessary (Axtente et al., 2017; Ghiga & Stålsby Lundborg, 2016). In the subsections that follow, health care providers and patients (and the general public) are discussed in turn.

Health care providers' awareness and understanding

Health care providers' insufficient knowledge is problematic in that it can lead to inappropriate antimicrobial prescribing behaviours. In particular, the behaviour of health care providers in

antibiotic prescribing depends on the existence and availability of guidelines, protocols and regulations to enforce them, but knowledge about these standards of care is also important. In Romania, this is lacking.

Insufficient knowledge and expertise about AMR can result in inappropriate antimicrobial prescription and use practices; for example, prescription of antibiotics to treat viral illnesses; broad-spectrum antibiotics prescribed where a narrow-spectrum antibiotic would be preferable; or inappropriate use, in terms of inadequate dosing, wrong duration of the course of antibiotics, etc. (Fridkin et al., 2014; Pulcini & Gyssens, 2013). The pattern of antibiotic use in Romania shows a rising trend towards broad-spectrum antibiotics, instead of narrow-spectrum ones. The overuse of these systemic antibiotics and lower usage rate of narrow-spectrum antibiotics are associated with suboptimal prescribing practices, and heavily influenced by (lack of) knowledge about and the latest updates regarding AMR (Pulcini & Gyssens, 2013).

Box 6. Inappropriate use of antibiotics

There are several forms of inappropriate use of antibiotics, including:

- » unnecessary antibiotic treatments (e.g. for viral infections);
- » inefficient antibiotic treatment, due to inappropriate dosage or length of treatment;
- » use of more antibiotics than necessary (overuse) or unnecessary combinations of antibiotics;
- » treatment with antibiotics without confirmatory laboratory testing to confirm the causative agent and its susceptibility (empiric treatment);
- » unnecessary prophylactic treatment with antibiotics;
- » self-medication, by the patient, for example when left-over antibiotics are available.

Furthermore, antibiotics are prescribed by health care providers in many situations without first confirming the need for their use. For instance, based on the results of the latest *Eurobarometer* study on the knowledge, attitudes and behaviour of the population in the field of AMR, only 40% of the Romanian respondents who had taken antibiotics in the last year declared that they had taken a test to find the cause of the disease before taking the antibiotic (EC & Kantar Public, 2018). Additionally, the challenge of giving patients access to antibiotics inappropriately is influenced by another group of providers: pharmacists. Pharmacists continue to be among the providers with the highest potential to influence antibiotic resistance, but in many cases their level of knowledge and attitudes leads to dispensing antibiotics to patients without a prescription, further contributing to the problem (WHO Regional Office for Europe, 2014). Several studies have shown that insufficient knowledge on the part of pharmacists was linked with dispensing of antibiotics without a prescription (Zapata-Cachafeiro et al., 2014; Ghiga & Stålsby Lundborg, 2016; Roque et al., 2013).

Health-professional education and training programmes

Few educational programmes on AMR for undergraduate medical students and health care professional educational programmes in Romania are designed to ensure health care providers are equipped with the right knowledge and attitudes to appropriately prescribe. The programmes lack the necessary components to improve knowledge and address AMR-related complications. While information about AMR, HAI and epidemiology is included in the curricula of microbiology, infectious diseases and epidemiology courses, no systematic or specific modules exist on antimicrobial prescribing and prudent use of antibiotics (ECDC, 2018c).

In terms of postgraduate courses on AMR-related issues available in Romania, a postgraduate course on family medicine (for the principal ambulatory antibiotic prescribers) exists, which is a month-long training module in infectious diseases, followed by several continuing professional development courses. The postgraduate AMR courses are only in the early inception phase. One continuing professional development course was introduced for the first time in 2016 and focuses on microbiology/epidemiology, prudent use of antibiotics and development of clinical guidelines and protocols.

Lack of awareness and education about AMR among patients and the general public

In addition to health care providers, neither patients nor the general population understand that their behaviour can contribute to AMR development (McCullough et al., 2016). Romanian citizens (and patients) have a limited level of knowledge and understanding about antimicrobials and AMR, which can have a number of negative consequences – including high levels of self-medication using antimicrobial drugs. The 2018 *Eurobarometer* survey about AMR found that 56% of Romanian respondents wrongly believe that antibiotics kill viruses and 7% do not know whether this affirmation is true or false. In addition, 25% of respondents don't know or don't agree that unnecessary use of antibiotics makes them ineffective, with Romania being in last places in terms of the proportion of EU respondents that are informed about the consequences of unnecessary antibiotic use (74%) (EC & Kantar Public, 2018).

An association exists between knowledge and beliefs about antibiotics and use of antibiotics without a prescription (EC, 2017b). In terms of the general public's behaviour in Romania, the 2018 *Eurobarometer* survey (EC & Kantar Public, 2018) revealed that more than a quarter (28%) of Romanian respondents said they had used oral antibiotics over the past 12 months, with 15% declaring they had not obtained the antibiotic from a doctor.

There is also a pattern of overuse of antibiotics, especially for respiratory infections, which are usually of viral aetiology. A quarter of Romanian respondents said that their last use of antibiotics was for a cold; 13% for bronchitis; 11% for influenza; and 11% for headaches.

Two cross-sectional studies describing awareness about AMR in Romania have also been carried out, showing a low level of awareness and a high level of self-medication with antimicrobial drugs. One of the studies aimed to describe the knowledge and perceptions about antibiotic use, and about antibiotic resistance in a group of self-medicating patients from eastern Romania, compared with a group of residents in a medical facility. The results of this study show that 40% of respondents considered (incorrectly) that antibiotics are efficient for the treatment of both bacterial and viral infections, and engaged in inappropriate practices in terms of antibiotic use (for example, 20% of respondents declared the intention to ask for antibiotic treatment for a common cold). Inadequate awareness about AMR was also reported in both groups included in the study (Topor et al., 2017). The other study investigated

the prevalence of self-medication with antimicrobial drugs among university students in a northeast region of Romania, and revealed that 44% of respondents using antibiotics in the last six months had used them without first seeking medical advice (Damian, Lupușoru & Ghiciuc, 2014).

Despite the fact that patients and the public do not have the knowledge and understanding required to enable them to behave in ways that could contribute to more appropriate antibiotic use (and thus a reduction in AMR), campaigns to promote caution in prescribing and using antibiotics to combat AMR have only been implemented or followed sporadically since they were introduced in Romania in 2015. In particular, those introduced under the initiative of European Antibiotic Awareness Day and World Antibiotic Awareness Week have only had limited impact, reaching only part of the population. Unfortunately, the limited influence of these campaigns means that only one in five Romanians remembered getting information about the unnecessary use of antibiotics in the past year (EC & Kantar Public, 2018). The main source of information remains health care professionals: 53% of Romanians report receiving information about not taking antibiotics unnecessarily from a doctor, and 28% from a pharmacist.

OPTIONS FOR ADDRESSING THE PROBLEM

The various causes of AMR in Romania call for interventions at different levels. According to the framing within this EBP, the problem of AMR and the related increase in HAIs is linked with the challenges involved in a number of existing health-system arrangements, including:

- » a lack of national oversight and strategic guidance to address AMR;
- » poor coordination and regulation related to the surveillance of AMR;
- » financial arrangements that make it difficult to develop and implement AMR-reduction efforts;
- » a lack of awareness and understanding of AMR among health care providers and patients.

To strengthen Romania's health system in order to tackle AMR, the authors propose three options, which collectively address these particular challenges.

1. Option 1: consolidate and coordinate the legal framework for AMR in Romania, focusing efforts at two levels:
 - » elaborating/enhancing the legal framework for AMR control at national level;
 - » developing a national ASP at operational level.
2. Option 2: align funding arrangements to facilitate AMR control, ASPs and IPC programmes.
3. Option 3: develop and implement programmes to provide information, improve education and strengthen communication (among health care providers and medical professionals, as well as the general public).

These options may be implemented together or individually, or some of their elements may be used to create new options. The options are presented to promote informed discussion, supported by notes from the authors regarding what is known from among the best available evidence relating to the benefits, harms, costs, need for local adaptations or stakeholders' views and experiences.

Policy option 1: consolidate and coordinate the legal framework for AMR

Several international organizations, including WHO, the EU and the ECDC have raised awareness and provided guidance about how health system policy-makers and stakeholders can support and promote the prudent use of antimicrobials within their own fields of influence (WHO, 2015a; Council of the EU, 2009, 2016; EC, 2017b). In the context of ongoing work against the rising threats from AMR at EU level, the ECDC has developed guidelines on the prudent use of antimicrobials in humans, based on current evidence and expert opinion (ECDC, 2017).

Antimicrobial stewardship (which aims for the development and implementation of a system-wide approach to promote and monitor the judicious use of antimicrobials in order to preserve their future effectiveness) (NICE, 2015) and ASPs (which are coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing) (Pollack et al., 2015) have been included in the ECDC guidelines, among the key elements to be introduced in any national strategy to combat AMR (ECDC, 2017). The 2019 WHO AWaRe classification of antibiotics was developed, to be used as a tool for countries to better support antibiotic monitoring and stewardship activities (WHO, 2019a).

According to a worldwide country situation analysis launched in April 2015, which focused on documenting country-level responses to AMR (WHO, 2015b), few countries have a comprehensive national plan based on a multisectoral approach, backed by sustainable financing. More countries reported having a national focal point for AMR and a national coordination mechanism; others had put in place certain relevant strategies and policies. Progress still needs to be made, even in countries with strong health care systems. Health systems with multiple challenges have even more problems to solve, particularly in terms of AMR policy regulation. Since the Romanian health care system faces multiple simultaneous critical issues, it is expected that mobilizing resources to tackle AMR will be challenging.

With this in mind, to achieve implementation of the option to consolidate and coordinate the legal framework for AMR. The aim would be to pursue two main courses of action:

1. elaborating/enhancing the legal framework for AMR control at national level (involving various types of regulation at different administrative levels);
2. developing a national ASP at operational level (involving inpatient and outpatient clinical settings and organizations that have oversight of antibiotic use).

ELABORATING/ENHANCING THE LEGAL FRAMEWORK FOR AMR CONTROL AT NATIONAL LEVEL

This approach involves the development of a national strategy and NAP, which establish strategic guidance and steps to elaborate a robust set of national guidelines for critical actions to help ensure AMR control. In January 2019 the WHO Library of national actions plans included NAPs from 24 countries of the WHO European Region, with some of them also reporting results (WHO, 2016).

The challenges of creating a national strategy and NAP are usually reported as: the novelty and rapid growth of the threat of AMR; lack of information and evidence at decision-making level; lack of evidence due to lack of surveillance (systems); reluctance to finance local actions without evidence of cost-effectiveness; and difficulty in establishing clear governance arrangements at all levels, to ensure leadership, engagement and accountability for actions to combat AMR (Dar et al., 2016; UN IACG, 2018).

According to WHO, AMR testing capacity should be increased by developing or strengthening reference laboratories capable of carrying out susceptibility testing in order to fulfil the core data requirements, using standardized tests to identify resistant microorganisms and operating in line with agreed quality standards (WHO, 2015a).

The appropriate strategic objectives for a Romanian national strategy and NAP overlap with the general objectives mentioned in the relevant literature, including in WHO's *Global action plan on antimicrobial resistance* (WHO, 2015a) and in the *Antimicrobial resistance manual for developing national action plans* (WHO, OIE & FAO, 2016). The objectives include:

1. improving awareness and understanding of AMR through effective communication, education and training;
2. strengthening the knowledge and evidence base through surveillance and research;
3. reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures;
4. optimizing the use of antimicrobial medicines in human and animal health;
5. developing the economic case for sustainable investment that takes account of the needs of all countries, and increasing investment in new medicines, diagnostic tools, vaccines and other interventions.

Many health care facilities (more in the private sector) are reluctant to share resistance data because they are wary of damage to their reputation. Similarly, at national level, as a result of negative media attention, widespread information about resistance is still thought to be detrimental. Therefore, contributions in terms of data input into both national and international surveillance systems (reporting) should be mandatory and effective (Dar et al., 2016).

According to the available evidence, NAPs are coordinated at national (central) level using a multisectoral approach and are supported by various agencies and organizations. In some countries the data are transparently presented to the public to create accountability on implementing the plans. In countries with federal governance systems, some of the responsibilities from central level are assigned to regional governments. There are financial penalties for non-reporting and non-compliance with the requirements of the NAP (Birgand et al., 2018).

More examples of what can be considered good practice for AMR control based on national strategies and NAP initiatives across Europe are discussed in the following subsection (such as the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) (PHE, 2018), the Swedish strategic programme against antibiotic resistance (Strama) (Public Health Agency of Sweden, 2019) and the Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) (SARI Hospital Antimicrobial Stewardship Working Group, 2009); see Table 3).

DEVELOPING A NATIONAL ASP AT OPERATIONAL LEVEL

The option to develop an ASP at the operational level relates to situations in which the aforementioned problems exist at operational level (that is, in clinical settings with oversight of antibiotic use); namely, lack of relevant practices (or inappropriately implemented in some health care facilities) for ensuring appropriate antimicrobial prescribing; lack of availability of guidelines for appropriate use of antimicrobials; lack of data (or these data not shared/adapted to the local/national context). The review of the evidence for this EBP focused on the impact of endeavours at the hospital regulatory level in enabling the successful implementation and support for ASPs, based on local and national (or regional) data.

Box 7. Core elements of hospital ASPs

1. Leadership commitment is needed, with agreement to dedicate the necessary human, financial and information technology resources.
2. Accountability is achieved by appointing a single leader responsible for programme outcomes. (Previous experience with successful programmes can be used as a benchmark for physician leader effectiveness.)
3. Drug expertise is necessary: for this, a single pharmacist leader can be appointed, who is responsible for working to improve antibiotic use.
4. Quantifiable action is needed, such as carrying out a systemic evaluation of ongoing treatment need, after a set period of initial treatment (i.e. “antibiotic time-out” after 48 hours).
5. Tracking is facilitated by monitoring antibiotic prescribing and AMR patterns.
6. Information flow and reporting are essential, requiring regular dissemination of information on antibiotic use and AMR between doctors, nurses and relevant health system personnel.
7. Clinicians must be educated about AMR and optimal prescribing practices.

Source: CDC, 2014.

Given the complexity of medical decision-making on antibiotic use, the variability in size and competency among Romanian hospitals, and the fact that knowledge is lacking (or is not applied) on the specificity of AMR patterns, the hospital care setting in Romania should have the required flexibility to implement ASPs, which are found to be effective elsewhere. This is the conclusion of a high-quality systematic review published in 2018 to determine the effectiveness of national or subnational IPC programmes in high-income and upper-middle-income countries. However, the review also found that multimodal intervention and surveillance, monitoring and feedback are most strongly supported by high-quality evidence. The authors call for quality of evidence – particularly from low-income countries – to strengthen the uptake and international relevance of IPC interventions (Price et al., 2018).

ASPs are also found to be cost-effective at hospital level, as concluded by a high-quality systematic review conducted in 2017. However, owing to a lack of standardization in outcome measurements of the economic evaluations in the ASP setting, along with inconsistencies in the study design and depth of the ASP interventions, the review has highlighted the need for comprehensive cost–effectiveness data for ASPs and more prospective clinical and epidemiological studies, to enable robust economic analyses to be incorporated into clinical decisions. The review emphasized the need for research, as part of a more systematic approach, to evaluate the cost–effectiveness of individual ASP programmes, due to variability (Ibrahim et al., 2017).

Technology has been found to be useful. One systematic review shows information technologies being successfully used to facilitate the process of obtaining laboratory, clinical, and pharmacologic data for the surveillance of infectious diseases, including AMR infections. Using electronic surveillance systems may result in shorter delays in detecting targeted infectious

diseases, as well as improving data collection. The study also found one negative issue, related to the fact that most surveillance systems were developed and implemented in high-income countries; an effective, rapid surveillance system is most needed in resource-limited settings (Rattanaumpawan et al., 2017).

Implementing ASPs is also backed by both clinical and economical evidence. It was found that the implementation of ASPs in hospitals decreased several interrelated factors: total antimicrobial consumption, the use of restricted antimicrobial agents (including in ICUs), the use of broad-spectrum antibiotics, and hospital length of stay (Karanika et al., 2016). Hospital ASPs resulted in significant decreases in costs associated with antimicrobial consumption. The implementation of ASPs was found to be linked with a decrease in infections due to MRSA, imipenem-resistant *Pseudomonas aeruginosa* and extended-spectrum beta-lactamase *Klebsiella* spp. (Karanika et al., 2016). Box 7 outlines some of the core elements of hospital ASPs.

The elements are more detailed for different set-ups in health care in WHO's practical toolkit on ASPs in health care facilities in low- and middle-income countries (WHO, 2019c), with a key focus point being that multidisciplinary teams needed to be involved.

Specific stewardship actions – such as empirical therapy according to guidelines, de-escalation of antibiotic therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, and defining a list of restricted antibiotics – showed significant benefits for one or more of the four outcomes: clinical outcomes, adverse events, costs and bacterial resistance rates (Schuts et al., 2016). Guideline-adherent empirical therapy was associated with a relative risk reduction in terms of both mortality and antibiotic de-escalation (Schuts et al., 2016).

Other measures, such as audit and feedback, guideline implementation and support for decision-making substantially impacted patient outcomes, including mortality, length of stay, readmission or incidence of *C. difficile* infection (Wagner et al., 2014).

ASPs in outpatient settings are tremendously important, as the majority of antimicrobials are prescribed in outpatient settings, and inappropriate antibiotic use among outpatients is common. A systematic review aiming to evaluate the effect of outpatient ASPs on prescribing, patients, microbial outcomes and costs has identified medium-strength evidence that stewardship programmes incorporating communication skills training and laboratory testing are associated with reductions in antimicrobial use, as well as low-strength evidence that other stewardship interventions are associated with improved prescribing. Evidence of low-to-moderate strength suggests that ASPs in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes (Drekonja et al., 2015).

In terms of testing to tailor antibiotic use in outpatient settings, a review highlighted that point-of-care C-reactive protein testing was associated with a significant reduction in antibiotic prescribing at the index consultation, but was not associated with antibiotic prescribing at any time during the 28-day follow-up period (Huan et al., 2013). Another review – which aimed to synthesize the evidence of C-reactive protein-based algorithms on antibiotic treatment initiation and on antibiotic treatment duration in adults, children and neonates, as well as their safety profile – concluded that the use of C-reactive protein-based algorithms seems to reduce antibiotic treatment duration in neonates, as well as decreasing antibiotic treatment initiation in adult outpatients (Petel et al., 2018).

The ECDC, in its technical guidelines on the prudent use of antimicrobials in humans, makes the recommendation to ensure availability of national clinical guidance for prophylaxis and management of infections based on national AMR patterns for the community, long-term care

facilities, and hospitals (ECDC, 2017; PHE, 2015). Table 3 details some of the key findings from various important sources relevant to Option 1.

Table 3. Summary of key findings from systematic reviews and other important sources relevant to Option 1 (Consolidate and coordinate the legal framework for AMR)

Category of finding	Key findings
Benefits	<ul style="list-style-type: none"> » ASPs are generally associated with improvements in microbial outcomes, including institutional resistance patterns without significant adverse impact on patient outcomes (Wagner et al., 2014). » The implementation of ASPs in hospitals has decreased total antimicrobial consumption, the use of restricted antimicrobial agents (including in ICUs), the use of broad-spectrum antibiotics, and hospital lengths of stay (Karanika et al., 2016). » ASPs are associated with a decrease in infections due to MRSA, imipenem-resistant <i>P. aeruginosa</i> and extended-spectrum beta-lactamase <i>Klebsiella</i> spp. (Karanika et al., 2016). » The overall evidence showed significant benefits of empirical therapy according to guidelines, de-escalation of therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, defining a list of restricted antibiotics, and bedside consultation for one or more of the following four outcomes: clinical outcomes, adverse events, costs, and bacterial resistance rates (Schuts et al., 2016). Guideline-adherent empirical therapy is associated with a relative risk reduction in terms of both mortality and antibiotic de-escalation (Schuts et al., 2016). » Low- to moderate-strength evidence suggests that ASPs in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes (Drekonja et al., 2015).
Potential harms	<ul style="list-style-type: none"> » Many health care facilities (particularly in the private sector) are reluctant to share resistance data because they are wary of damage to their reputation. Similarly, at national level, as a result of negative media attention, widespread information about resistance is still thought to be detrimental (Dar et al., 2016).
Resource use, costs and/or cost-effectiveness	<ul style="list-style-type: none"> » National or subnational IPC programmes are cost-effective in high-income and upper-middle-income countries (Price et al., 2018). » Hospital ASPs result in significant decreases in antimicrobial consumption and cost, and the benefit is higher in the critical care setting (Karanika et al., 2016).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> » Future studies should focus on the sustainability of the outcomes and evaluate potential beneficial long-term effects of ASPs in mortality and infection rates (Karanika et al., 2016). » Comprehensive cost-effectiveness data for ASPs remain relatively scant, underlining the need for more prospective clinical and epidemiological studies to incorporate robust economic analyses into clinical decisions (Ibrahim et al., 2017).

Table 3. (Contd)

Category of finding	Key findings
Key elements of the policy option if it were tried elsewhere	<ul style="list-style-type: none"> » Strategies are in place to enhance the rational use of antibiotics in hospitals through availability of a multidisciplinary team of ASP experts (Germany) (de With et al., 2016); » The ESPAUR programme (2013 to 2018) suggested that stewardship activities have reduced levels of antibiotic prescribing, which in turn have reduced selective pressure contributing to the spread of resistant strains (PHE, 2018). One of the achievements of PHE (an executive agency of the now renamed Department of Health and Social Care) was to produce, develop and maintain key antimicrobial stewardship resources in primary care, available through the Treat Antibiotics Responsibly, Guidance, Education (TARGET) toolkit. » The Strama was formed in 1995 and has since been a driving force in the Swedish work against AMR. The Strama network has succeeded in substantially decreasing the level of antibiotic consumption in Sweden by initiating, adopting and coordinating long-term and structured measures characterized by extensive cooperation at both national and local levels. » SARI was launched in 2001 as an antimicrobial stewardship, IPC intervention programme, constituting a key component of the AMR prevention and control activities in the country. The Guidelines for antimicrobial stewardship in hospitals in Ireland makes recommendations for the acute (hospital) care setting, as well as for non-acute residential health care settings. » ASP programmes should use electronic surveillance systems that could facilitate the process of obtaining laboratory, clinical, and pharmacological data for the surveillance of infectious diseases, including AMR infections. Effective and rapid surveillance systems are most needed in resource-limited settings (Rattanaumpawan et al., 2017).
Stakeholders' views and experiences	<ul style="list-style-type: none"> » Implementation is difficult because the current level of knowledge is low and attitudes of professionals and the general population are not yet suitable. » More research and evidence are needed at local level.

Policy option 2: align funding arrangements to facilitate AMR control, ASPs and IPC programmes

Sustainable financial arrangements, dedicated to facilitating AMR, are part of the policy package recommended by WHO (Leung et al., 2011) as part of a list of critical actions. Such arrangements are specifically mentioned as being missing, in the 2017 Romanian evaluation that features in the Global Database for Antimicrobial Resistance Country Self-Assessment (WHO, OIE & FAO, 2017, 2018).

Proper budget allocation for AMR diagnostic and reporting activities – within financing mechanisms such as national framework contracts (which set up financing as part of the social insurance scheme) and the Ministry’ of Health’s national health programmes (which are financed for major public health problems) – should include budget for **monitoring and control** of AMR and HAIs.

International evidence shows that, from the payer perspective, there is a huge cost associated with treating antibiotic-resistant infections in patients. This does not include social perspective, or other hospital-related costs, so could be an underestimate of the true costs. The additional

cost of treating an antibiotic-resistant infection in the French health care system, for example, is estimated to be €1544 per case. Thus, the overall excess hospital cost of AMR was calculated at €287.1 million in 2015 (Touat et al., 2018). In the United States health care system, antibiotic resistance added US\$ 1383 to the cost of treating a patient with a bacterial infection in 2014. In the same year, the estimate amounted to a national cost of \$2.2 billion annually (Thorpe, Joski & Johnston, 2018).

The national or subnational IPC programmes in high-income and upper-middle-income countries are effective (Price et al., 2018). A 2016 systematic review (Arefian et al., 2016) analysing interventions for preventing HAIs showed that the median savings-to-cost ratio across all studies reporting both costs and savings values was US\$ 7.0 (interquartile range 4.2–30.9). This would mean that for every US\$ 1 spent on prevention, US\$ 7 are saved; however, the quality attributed to the study was low. Also, effective multimodal hand hygiene interventions are likely to be cost-effective in preventing MRSA bloodstream infections in ICU settings in middle-income countries, where baseline compliance is typically low (Luangasanatip et al., 2018). One measure used to reduce hospital-acquired MRSA infection is patient screening for antimicrobial-resistant pathogens, but targeted screening is more cost-beneficial than universal screening (Leonhardt et al., 2011).

Stewardship programmes are the most recommended and most used model of intervention and are mostly analysed from an economic perspective. The evidence found shows that hospital ASPs result in significant decreases in antimicrobial consumption and costs, and the benefit is higher in the critical care setting (Karanika et al., 2016). A structured review conducted in Organisation for Economic Co-operation and Development (OECD) countries to evaluate the cost-effectiveness of ASPs in hospital settings (limited to adult patient populations) found that in 35 of all 36 studies included, ASPs resulted in reduced pharmacy expenditure (Coulter et al., 2015).

Willingness to spend on health programmes is also influenced by public perceptions and willingness to pay, which results in adjusted evidence cost-benefit and cost-effectiveness ratios when viewed from the societal perspective. A study investigating how much value the public place on safety-related health care improvements (Singh et al., 2012) showed that health safety is 30% more valued than: genetic disorders, drug errors, interventions to prevent injury to health care staff, interventions related to lifestyle, and sports injuries.

The most recent and comprehensive analysis found in a November 2018 OECD publication – *Stemming the superbug tide: just a few dollars more* – shows a cost-effectiveness analysis and impact evaluation in terms of disability-adjusted life-years for different interventions (OECD, 2018b). The conclusion is that the following five interventions are considered so-called best buys in terms of their potential to significantly diminish the personal and economic costs of AMR.

1. The first intervention would be to improve health care facilities, including promotion of hand washing and better hospital hygiene.
2. The second would be stewardship programmes promoting more prudent use of antibiotics to end decades of overprescribing.
3. The third intervention would be to use rapid diagnostic testing to detect whether an infection is bacterial or viral.
4. The fourth solution would be implementing delayed prescription practices.
5. The fifth would be public awareness campaigns.

These interventions, combined into three packages – as detailed here, using average figures – can have a significant impact and cost-saving effect.

1. An approach targeting the hospital setting (with interventions including hand hygiene, ASPs and enhanced environmental hygiene practices) could result in:
 - reduction of the burden of disease from AMR by 85%;
 - cost savings of US\$ 4.1 (PPP) per capita per year.
2. Community actions (including delayed prescription practices, mass media campaigns and use of rapid testing) could result in:
 - a. reduction of the burden of disease from AMR by 23%;
 - b. cost savings of US\$ 0.9 USD (PPP) per capita per year.
3. A mixed intervention package (including ASPs, enhanced environmental hygiene in the health care setting, mass media campaigns, and use of rapid testing) could result in:
 - a. reduction of the burden of disease from AMR by 73%;
 - b. cost savings of US\$ 3 (PPP) per capita per year.

In conclusion, the mixed policy approach would cost about US\$ 2 (PPP) per capita per year, leading to an average net saving of around US\$ 3 (PPP) per capita per year (using average figures). According to the available evidence, in Romania the savings could be around US\$ 0.5 (PPP), with 1524 lives saved per year.

Table 4 details some of the key findings from various important sources relevant to Option 2.

Table 4. Summary of key findings from systematic reviews and other important sources relevant to Option 2 (Align funding arrangements to facilitate AMR control, ASPs and IPC programmes)

Category of finding	Key findings
Benefits	<ul style="list-style-type: none"> » The mixed policies for AMR control could save 1524 lives per year in Romania (OECD, 2018b). » Implementing ASPs in the hospital setting may be cost-effective (Ibrahim et al., 2017). » Prevention programmes for HAIs have very positive cost–benefit ratios (Arefian et al., 2016). » Infection control interventions to reduce spread of MRSA in acute care hospitals also showed a favourable cost–benefit ratio (Farbman et al., 2019). » There is also low quality of evidence to support the benefits of ASPs in acute care hospital settings (Morris et al., 2018). » Persuasive and structural antimicrobial stewardship interventions may provide health economic benefits in hospital settings (Naylor et al., 2017). » ASPs would also reduce pharmacy expenditure (Coulter et al., 2015).
Potential harms	<ul style="list-style-type: none"> » No potential harms were found.

Table 4. (Contd)

Category of finding	Key findings
Resource use, costs and/or cost-effectiveness	<ul style="list-style-type: none"> » The mixed-policy AMR approach would cost about US\$ 2 (PPP) per capita per year leading to average net savings of around US\$ 3 (PPP) per capita per year (OECD, 2018b). » Accurate contextualized business cases for ASPs are essential in order to obtain the necessary funding to render these programmes successful (Morris et al., 2018).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> » There is less uncertainty in 2019, since more studies and evidence are being produced. » There is some uncertainty from 2018, looking at the evidence available that year. No systematic reviews were identified. » Only one study (not a systematic review) explored the cost-effectiveness/cost-benefit of antimicrobial stewardship in a low-/middle-income country (Naylor et al., 2017). » No cost-effectiveness studies of ASPs in the community setting were available (Naylor et al., 2017). » No evidence was found on the health economic benefits of restrictive ASPs (Naylor et al., 2017). » Further research and full economic evaluations are needed in order to identify the most cost-effective ASPs in hospitals (Coulter et al., 2015).
Key elements of the policy option if it were tried elsewhere	<ul style="list-style-type: none"> » There is strong evidence of cost-efficiency for the mixed policy approach, identified in extensive studies (OECD, 2018b) » ASPs require evaluation and cost calculation for the following areas: implementation costs, material costs (antimicrobials), operational costs, length of stay costs, morbidity/mortality costs, other hospital costs, and societal costs (Dik et al., 2015).
Stakeholders' views and experiences	<ul style="list-style-type: none"> » There was no relevant data from the available systematic reviews.

Policy option 3: develop and implement programmes to provide information, improve education and strengthen communication

This option is related to the improvement of training and education in terms of AMR and prudent use of antibiotics at the level of health service providers and the general public.

Considering the target audience of this option, evidence related to two specific components of this type of educational intervention are outlined:

1. the impact of educational AMR-related programmes for health care providers;
2. the impact of raising awareness and of implementing educational programmes at patient level and for the general population, targeting the general public.

Both components of this option – highlighting the impact of improving the education of professionals and that of raising general population awareness of AMR – are directly related to Option 1, in terms of the development of the legal framework for improving the AMR situation (aiming, as explored in the previous section, to introduce ASPs for the first time at national level, among other measures).

THE IMPACT OF EDUCATIONAL AMR-RELATED PROGRAMMES FOR HEALTH CARE PROVIDERS

This component refers to the introduction of specific training modules for medical professionals within the process of preparing human resources at undergraduate and postgraduate levels. A distinct part is dedicated to information, education and strengthening physician–patient communication. These proposals address the issue of lack (or scarcity) of a training process specifically dedicated to the prevention and control of AMR through ASPs, and deal with increasing awareness of the problems of AMR among health services providers.

Health service providers can play an important role in limiting AMR, provided they are up-to-date with the latest available information in the field and apply that information in day-to-day practice (WHO, 2015a).

One of the objectives proposed by WHO in the Global action plan on antimicrobial resistance is to improve the level of advice about and therefore understanding of AMR. Introducing education on AMR in the training programmes intended for human resources in health care settings is one of the proposed measures to achieve these objectives and to reduce the incidence of HAIs (WHO, 2015a).

Investing in a professional development plan to train future health care professionals – by updating the educational curricula of undergraduate medical schools, postgraduate medical specialties and colleges of pharmacy and nursing – is among the recommendations that have been made following the ECDC team country visit to Romania in March 2017. The aim should be that all professionals working in health care have an understanding of the AMR problem (ECDC, 2018c).

Although there is consensus among health professionals and other stakeholders that education is key to improving AMR, and these beliefs have led to the development of a wide range of interventions aiming to improve the education of both health professionals and the public, the transfer of the results of these practices into systematic reviews is still limited and in its early stages (Tonkin-Crine et al., 2017; Batura et al., 2018).

Undergraduate AMR education programmes

There is evidence that inclusion of appropriate antibiotic use in undergraduate and postgraduate curricula, accompanied by CME in the field of antibiotic therapy, have the potential to improve antibiotic prescription (Lee et al., 2015). Similarly, undergraduate training courses would be successful if the students were imparted with adequate knowledge, and trained in developing the right attitudes and behaviour.

One of the recommendations of a narrative review is to start education on prudent antimicrobial prescribing early in the undergraduate curriculum (preferably in the third year of undergraduate training in medicine) and at a corresponding level in the non-medical curricula of pharmacy, dentistry, midwifery, nursing and veterinary medicine, in order to reach all health professionals (Pulcini & Gyssens, 2013).

A cross-sectional survey, which aims to investigate the teaching of antimicrobial stewardship in undergraduate health care degree programmes in the United Kingdom, highlights that although antimicrobial stewardship principles are included in most undergraduate health care and veterinary degree programmes in the country, the education received is disparate

and could be strengthened through standardization and by presenting the less frequently discussed principles. For example, the most frequently taught principle was “adopting necessary IPC precautions”, followed by “timely collection of microbiological samples for microscopy, culture and sensitivity”, with the principle “use of intravenous administration only for patients who are severely ill, or unable to tolerate oral treatment” being taught less often (Castro-Sánchez et al., 2016).

A narrative review has been identified about undergraduate education on the transmission of infections in health care settings. Although the main source of MDR pathogens is thought to be the endogenous flora of patients, health care workers are also considered as an important source. The most common cause of spread of infection is transmission via the hands of health care workers; thus, information dissemination in educational curricula on the prevention of nosocomial transmission of resistant bacteria in hospitals should be improved (Lee et al., 2015).

A narrative review was also identified about undergraduate education on appropriate prescribing and use of antibiotics. Where professionals' AMR-related focus was mainly on HAIs in the past, it has been shown that antibiotic prescribing practices at community level, in primary care health settings (family medicine), have also had a strong impact on AMR (Garau et al., 2014). If medical prescribers do not have enough or have inappropriate knowledge in microbiology and antibiotics, they can choose a broad-spectrum antibiotic as treatment, for example. It is therefore important to increase efforts improve the education and prescribing knowledge and practices of current and future health practitioners. In order to tackle AMR problems related to prescribing behaviour, different countries are adopting different strategies to strengthen undergraduate medical, dental and pharmacy education and training on the prudent use of antibiotics.

Postgraduate AMR education programmes

Overprescribing of antibiotics by general practitioners (GPs) is seen as a major driver of antibiotic resistance (Oppong et al., 2018). Health service providers may adopt different behavioural approaches to antibiotic prescribing for acute respiratory infections, with some strategies resulting in a more judicious use of antibiotics at the patient level.

The German Society for Infectious Diseases published an article in 2016 on strategies to enhance rational use of antibiotics in hospitals, based on a structured literature research (de With et al., 2016). The article presented the requirements for successful implementation of ASPs, among which was the availability of a multidisciplinary team of ASP experts (with the necessary competences for interdisciplinary cooperation), which should be instructed by the hospital administration to draw up guidelines for the treatment of infectious diseases, derived by consensus with the users.

Regarding interventions to improve antibiotic prescribing at hospital level, several systematic reviews investigated the effectiveness and safety of interventions to help physicians prescribe antibiotics properly and what behavioural techniques could change health provider behaviour to influence the success of the interventions (Davey et al., 2013; Davey et al., 2017). In a systematic review conducted in 2013, pervasive interventions (such as dissemination of educational materials, reminders, audit and feedback, and educational outreach) were compared with restrictive interventions (interventions involving a change in the policy on antibiotic formulary, restricting the freedom of prescribers to select certain antibiotics). It was found that involving

health providers in the design of interventions and in measuring their effect is one of the most successful and sustainable persuasive interventions (Davey et al., 2013).

A high-quality systematic review evaluated the use of the strategy of postponing the use of antibiotics for the treatment of acute respiratory infections. There was no difference in the reduction of common cold and cold symptoms among the comparator groups (the antibiotic-receiving group, the antibiotic group receiving the recommendation to delay the use of the antibiotic in the hope of reducing the symptoms, and the group who did not receive antibiotics), but the decision to postpone the use of antibiotics led to a significant reduction in the use of antibiotics (Spurling et al., 2013).

The strategy of not prescribing antibiotics also led to a decrease in antibiotic use, but patient satisfaction was higher for patients who were treated with antibiotics, compared to those for whom treatment was postponed (odds ratio (OR) 0.52; 95% confidence interval (CI) 0.35–0.76). This study highlights that training health service providers on the outcomes of antibiotic use may be a way of lowering antibiotic consumption, with a corresponding decrease in AMR (Spurling et al., 2013). Furthermore, a cross-sectional study conducted among Canadian family physicians, to review knowledge levels on AMR and counselling practices on the prudent use of antibiotics in order to determine the potential changes brought about by a national awareness campaign, demonstrated an improvement since the campaign in patient counselling on the appropriate disposal of antibiotics (Smith et al., 2017).

A narrative review aiming to investigate the role of pharmacists in the appropriate use of antibiotics and to identify how the pharmacists' role could be enhanced to combat AMR in developing countries concluded that the establishment of properly qualified and trained pharmacy workforce has the potential to reduce overuse and inappropriate use of antibiotics. Another finding is that pharmacists can provide guidance to their health care colleagues on appropriate antibiotic prescribing (Sakeena, Bennett & McLachlan, 2018).

Information, education and strengthening physician–patient communication

One of the key issues influencing both prescribers and the public is the communication process between them. Several studies have revealed that educational programmes aiming to improve health care professionals' communication skills have been effective in reducing antibiotic prescription levels. Information on the role of an informed decision on antibiotic prescribing, the role of computerized communication training programmes on the prescription of antibiotics, and the role of health care providers in educating patients on AMR were also found in the evidence studied.

One of the systematic reviews studied aimed to assess the role of informed decisions on the prescription of antibiotics for acute respiratory infections in adults at the level of primary care services. According to the authors, making an informed decision means the decision-making process involves considering both the best scientific evidence and the values and preferences of the patient (Coxeter et al., 2015). The analysis showed that such interventions reduce the likelihood of using antibiotics in the short term (from 47% to 29%: risk ratio (RR) 0.61; 95% CI 0.55–0.68) without increasing the patient's demand for further medical consultation (RR 0.87; 95% CI 0.74–1.03) and without lowering patient satisfaction (OR 0.86; 95% CI 0.57–1.30) (with the last two results being statistically insignificant) (Coxeter et al., 2015).

An overview of systematic reviews of good quality also found that shared decision-making in the management of acute respiratory infections in general practice tended to reduce antibiotic prescribing while maintaining patient satisfaction and without increasing the likelihood of re-consultation (Tonkin-Crine et al., 2017).

An economic assessment in five European countries highlighted that computerized communication training programmes for GPs are cost-effective in reducing antibiotic prescribing for acute respiratory tract infections (Oppong et al., 2018).

A narrative review investigating the role of pharmacists in the appropriate use of antibiotics identified that a properly qualified and trained pharmacy workforce in developing countries has the potential to reduce overuse and misuse of antibiotics by providing education to patients that enables them to use antibiotics appropriately (Sakeena, Bennett & McLachlan, 2018).

Health care providers' attitudes have an important role in shaping public behaviour towards AMR. The results of a Eurobarometer study released in 2018 indicate that health service providers (either doctors or pharmacists) constitute the main source of information about antibiotics and AMR for more than three quarters of Romanian respondents (EC & Kantar Public, 2018). An international study in 2018 aiming to describe the educational programmes and resources on the topic of AMR and antimicrobial stewardship worldwide identified 94 educational initiatives, with most of these programmes targeting health care workers and a smaller number targeting pharmacists, nurses, midwives and students in the health care field (Rogers Van Katwyk, Jones & Hoffman, 2018).

THE IMPACT OF RAISING AWARENESS AND IMPLEMENTING EDUCATIONAL PROGRAMMES FOR PATIENTS AND THE GENERAL POPULATION

This component tracks the impact of information campaigns, education and awareness-raising of the threat of AMR and emergency release requests for antibiotics, or misuse of them by the general population. The prescriber often felt the patient put pressure on them and demanded antibiotics, irrespective of their condition. This situation can be changed if the public is also well informed about what antibiotics can and cannot achieve (ECDC, 2018c).

Evidence was found about the positive impact of health literacy on the behaviour of patients and the general population, in terms of asking for a prescription of antibiotics or in using them. A systematic review of average quality indicates different levels of effectiveness achieved by educational interventions addressed to parents and children aiming to reduce the use of antibiotics (Paget et al., 2017; Andrews et al., 2012).

The result of a systematic review aiming to find the educational interventions that are effective and cost-effective in changing the public's behaviour – to ensure they only ask for antimicrobials when appropriate and use them correctly – show the impact of different forms of education (King et al., 2016). Weak evidence is available that “verbal education on antibiotic adherence from a pharmacist, or the combination of written and verbal education on antimicrobial use and AMR delivered by pharmacists, can improve patients' adherence to treatment and knowledge of antimicrobial use”. Interventions carried out in the general practice setting, targeting patients or paediatric patients through a combination of an educational video on antimicrobial use and AMR, and supplemented by an information leaflet delivered within the

primary care setting, can improve parents' knowledge of appropriate antimicrobial use but were not found to influence the level of AMR awareness (King et al., 2016).

There is weak evidence that an information leaflet distributed in the primary care setting to adult patients significantly decreases the patients' perceived need for antibiotics during post-test follow-up ($p < 0.001$ [pre- vs. post-testing for all participants]) and increased their knowledge about appropriate antibiotic use (King et al., 2016). In addition, the results of a review aiming to evaluate effectiveness of information leaflets used to inform patients about common infections during consultations in the general practice setting showed significant reductions in prescribing among the groups that received the leaflet, with a relative RR varying from 0.53 (0.40–0.69) to 0.96 (0.83–1.11) in three out of the four studies included (de Bont et al., 2015).

Regarding educational activities that target children, the evidence is inconsistent that school-based interventions have an impact on knowledge about appropriate use of antimicrobials; for example, using a computer game (e-Bug) for children aged 9–12 years did not increase the students' knowledge about appropriate use of antibiotics, but a two-day workshop for children aged 9–11 years and a one-week hands-on programme for secondary school students (aged 15–16 years) improved their knowledge about appropriate use of antibiotics. The programme for secondary schools has also improved the level of awareness of AMR (King et al., 2016).

The results of a *Eurobarometer* study from 2018 on public attitudes towards antibiotic use and AMR revealed that respondents who demonstrated a higher level of knowledge about the effect of antibiotics had consumed a lower proportion of antibiotics not prescribed by the doctor, and had consumed less antibiotics for illnesses or symptoms such as colds, flu, headache or cough (EC & Kantar Public, 2018).

A representative online panel survey conducted in 2015 among the general public in the United Kingdom showed that believing antibiotics were effective for influenza-like illnesses, along with low AMR awareness significantly predicted reported antibiotic use. In the same survey, a paradoxical effect of an information campaign was observed; namely 39% of respondents with low AMR awareness declared that the information they received as part of the campaign would drive them to ask a doctor for antibiotics more often. This led the authors to make the recommendation that public antibiotic stewardship campaigns should be tested on a small scale before wider adoption (Roope et al., 2018).

Educational campaigns to combat AMR by promoting caution in prescribing and using antibiotics have been under way in Romania since 2015. These campaigns are coordinated by the National Center for Health Status Evaluation and Health Promotion of the National Institute of Public Health and carried out under the initiative of the European Antibiotics Awareness Day. Improvement has been found in the general public's level of knowledge – e.g. an 8% decrease in the proportion of people who incorrectly believe that antibiotics kill viruses, and a 5% increase in the proportion of those surveyed who know that antibiotics are not effective for the treatment of viral infections/colds, – according to Eurobarometer surveys conducted in 2016 and 2018 (EC & Kantar Public, 2018). People who said they received information about unnecessary antibiotic use had a better level of knowledge than those who said they did not receive such information. The European Antibiotics Awareness Day is an annual European public health initiative that takes place on 18 November each year to raise awareness about the threat to public health of AMR and the importance of prudent antibiotic use (Paget et al., 2017).

Table 5 details some of the key findings from various important sources relevant to Option 3 (develop and implement programmes to provide information, improve education and strengthen communication).

Table 5. Summary of key findings from systematic reviews and other important sources relevant to Option 3 (Develop and implement programmes to provide information, improve education and strengthen communication)

Category of finding	Key findings
Benefits	<p>Education of health care providers</p> <ul style="list-style-type: none"> » One of the included reviews in an overview of high-quality, multifaceted interventions containing multiple components, including clinician and patient education, audit and feedback, and reminders. The conclusion of the investigation was that, since no review studied these interventions alone, the separate effects of each are unknown (Tonkin-Crine et al., 2017). » Multifaceted interventions (having more than one intervention component) were more effective than a single approach in the improvement of antibiotic use and prescribing practices (Paget et al., 2017). » The strategy of not prescribing antibiotics led to a decrease in antibiotic use, but patient satisfaction was higher for patients who were treated with antibiotics, compared to those for whom treatment was postponed (OR: 0.52; 95% CI 0.35–0.76) (Spurling et al., 2013). » Involving health care providers in designing interventions is a key element of intervention success and sustainability (Davey et al., 2013). » Interventions aiming to increase effective prescribing can improve clinical outcomes (Davey et al., 2013) » Online communication courses and C-reactive protein testing reduce the prescription of antibiotics for the treatment of acute respiratory infections in primary care (Oppong et al., 2018). » Inclusion of information on appropriate use of antibiotics in undergraduate and postgraduate curricula, accompanied by CME in the field of antibiotic therapy, has the potential to improve antibiotic prescribing practices (Lee et al., 2015). <p>Communication to/education of patients and/or the public</p> <ul style="list-style-type: none"> » Different levels of effectiveness in reducing the use of antibiotics are associated with various educational interventions targeting parents and children (Andrews et al., 2012; Paget et al., 2017). » Interventions aiming to involve the patient in decision-making on antibiotic use for the treatment of acute infectious respiratory diseases reduce antibiotic use (from 47% to 29%; RR 0.61; 95% CI 0.55–0.68 (Coxeter et al., 2015). » Shared decision-making in the management of acute respiratory infections in general practice tended to reduce antibiotic prescribing while maintaining patient satisfaction and without increasing the likelihood of re-consultation (Tonkin-Crine et al., 2017). » School-based interventions could have an impact on knowledge about appropriate use of antimicrobials, based on a two-day workshop for children aged 9–11 years and a one-week hands-on programme for secondary school students (aged 15–16 years). The programme for secondary schools has also improved the level of awareness of AMR (King et al., 2016). » There is evidence that an information leaflet distributed in the primary care setting to adult patients would significantly decreases the patients’ perceived need for antibiotics and increased their knowledge about appropriate antibiotic use (King et al., 2016). In addition, information leaflets used to inform patients during consultations about common infections showed significant reductions in prescribing among the groups that received the leaflet (de Bont et al., 2015).

Table 5. (Contd)

Category of finding	Key findings
Potential harms	<p>Education of health care providers</p> <ul style="list-style-type: none"> » The strategy of not prescribing antibiotics led to a decrease in antibiotic use, but patient satisfaction was higher (52%) for patients who were treated with antibiotics, compared to those for whom treatment was postponed (Spurling et al., 2013). <p>Education of patients and/or the public</p> <ul style="list-style-type: none"> » A paradoxical effect is reported in a representative online panel survey in the United Kingdom regarding the effect on asking for an antibiotic after receiving information about AMR. In this regard, public antibiotic stewardship campaigns should be tested on a small scale before wider adoption to avoid paradoxical unwanted outcomes (Roope et al., 2018).
Resource use, costs and/or cost-effectiveness	<p>Education of health care providers</p> <ul style="list-style-type: none"> » Computerized communication training/educational programmes in the field of reactive C-protein testing for GPs / family doctors were found to be cost-effective in reducing antibiotic prescribing for acute respiratory infections (Oppong et al., 2018). » Investment in a professional development plan to train future health care professionals requires agreement among stakeholders and appropriate funding. » Monitoring and evaluation of educational interventions can require additional financing.
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<p>Education of health care providers</p> <ul style="list-style-type: none"> » There is limited evidence from direct comparisons of the efficacy of different interventions, including simple versus multifaceted interventions (Davey et al., 2013). » Although evidence exists about introducing different aspects of the issue of AMR into undergraduate curricula, there are no systematic reviews focusing on the results of those interventions.

Table 5. (Contd)

Category of finding	Key findings
<p>Key elements of the policy option if it were tried elsewhere</p>	<p>Education of health care providers</p> <ul style="list-style-type: none"> » Education on prudent antibiotic prescribing is a component of the undergraduate curriculum in the United Kingdom and Scotland (Lee et al., 2013). » The University of Rotterdam (The Netherlands) has included a one-week module on several concepts of AMR, hygiene and prudent antibiotic prescribing as part of the core curriculum of the second year of medical school. » The University of Nijmegen offers an additional elective, problem-based module on antibiotic policy for third-year students, dealing with the history of infectious diseases, hygiene and infection control, antibiotic guidelines, principles of prophylaxis and laboratory techniques, among others (Pulcini & Gyssens, 2013). » In Scotland, an extensive range of e-learning resources have been developed to train both undergraduate and postgraduate health care professionals on prudent antibiotic prescribing (Pulcini & Gyssens, 2013). » In the UK, the Prudent Antibiotic User (PAUSE) initiative was a learning resource comprising shared standardized teaching materials for prudent antimicrobial prescribing, for use in the undergraduate medical curriculum (Pulcini & Gyssens, 2013). » At European level, the ECDC chose hospital prescribers as the target audience for their European Antibiotic Awareness Day campaign in 2010. » An open access curriculum has been developed in the context of the EU-funded research project “Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe” (GRACE) (Pulcini & Gyssens, 2013).
<p>Stakeholders' views and experiences</p>	<p>Education of health care providers</p> <ul style="list-style-type: none"> » Changing professionals' behaviour regarding AMR requires long-term effort. » Appropriate curricula on antimicrobial stewardship are the joint responsibility of academia (in terms of research) and the ministries of health and education (Pulcini & Gyssens, 2013). » Education about prudent antibiotic prescribing in educational curricula requires commitment from medical schools at national level and to agree that antimicrobial stewardship is among the necessary interventions required to improve practices (Lee et al., 2015). <p>Education of patients and/or the public</p> <ul style="list-style-type: none"> » Changing population behaviour regarding AMR requires long-term effort.

CONSIDERATIONS IN IMPLEMENTING THE THREE OPTIONS

The three options presented are the extracted results of the extensive search of global evidence on both the problem and solutions to the problem. While these results are backed by science and input from experts in the field, they would need to be implemented in care facilities at health system level, with all categories of stakeholder involved, within the available budget, and taking into account day-to-day care constraints.

Recognizing these challenges, potential barriers to and opportunities in implementation of each of the options identified by the EBP authors are set out in the subsections that follow. It is worth noting that the authors' field of view – in terms of barriers and opportunities relating to implementation of the various options – included health care recipients, health care providers and stakeholders, along with a wider view of the health system itself.

Potential barriers

OPTION 1. CONSOLIDATE AND COORDINATE THE LEGAL FRAMEWORK FOR AMR

Care recipients

The care recipients know little about AMR and its consequences. HAIs have received more coverage by the mass media. Patients are currently used to having access to inpatient care without constraints (no family physician as gatekeeper, and so on) and receiving antibiotics whenever they think they need them.

Care providers

Care providers will face difficulties when new or tougher regulations are introduced to combat AMR and HAIs. These barriers relate to the lack of: trained personnel; financial resources to implement new training and ASPs; and financial allocation for materials for various care-related tasks (screening, testing, etc.).

Despite the fact that AMR strategies to combat HAIs are being advocated by infectious disease specialists (such as microbiologists and epidemiologists) and discussed by national and international policy-makers, another barrier may be limited coverage of antimicrobial stewardship for AMR across different clinical specialties.

Stakeholders

Understanding the problem and its causes in depth is critical in order to arrive at appropriate solutions. Decision-makers, politicians and other stakeholders cannot be fully informed about the problem while health care workers themselves are not fully aware knowledgeable on the matter.

Health system constrains

Globally, countries are using situation analyses to examine aspects of their health systems. WHO's *Worldwide country situation analysis: response to antimicrobial resistance*, carried out in April 2015 (WHO, 2015a) revealed that progress needs to be made even in countries with strong health care systems. Health systems in which multiple challenges remain, such as health reforms and financing restructuring, have even more problems to solve in order to achieve effective AMR policy regulation (as is the case in Romania). A first step was made with a recently issued Government Decision (Government of Romania, 2018) to set up a national multisectoral committee working towards limiting AMR; however, there are still potential barriers to overcome.

OPTION 2. ALIGN FUNDING ARRANGEMENTS TO FACILITATE AMR CONTROL, ASPS AND IPC PROGRAMMES

Care recipients

This option does not imply direct payments from care recipients. Therefore, there is no barrier to implementation to be recognized here.

Care providers

Care providers have to be able to manage national financing programme for AMR. Since national programmes are already used to tackle other public health problems, some health care providers are already familiar with such a system. However, those for whom national financing programmes are new will need to learn how to administer them.

Stakeholders

To implement an effective national financing programme, the decision-makers need to involve the technical health commission or other appropriate actor within the Ministry of Health, for scientific advice and evidence, as well as to establish the financial background for budget calculations and allocation. Since data on AMR and HAIs are underreported, building the case for financing and budget allocation will be difficult.

Health system constraints

Financing is a critical problem for the health system in Romania. Financing for a national AMR programme will compete with other health system requirements, especially financing of drugs and materials for acute care.

OPTION 3. DEVELOP AND IMPLEMENT PROGRAMMES TO PROVIDE INFORMATION, IMPROVE EDUCATION AND STRENGTHEN COMMUNICATION

Care recipients

One systematic review of high quality identified that the public have an incomplete understanding of antibiotic resistance, along with misconceptions about it and its causes. They attributed its development to the actions of others, while also believing that strategies to minimize resistance should be addressed to doctors (McCullough et al., 2016).

In particular, patients in Romania are faced with limited access to credible sources of information, and barriers to access to health services. In addition, their attitudes may be dominated by mistrust to State-backed information activities, and the available time for patient education is limited during medical visits to family physicians.

Care providers

Educational training and curricula vary across different hospital specialties and at different stages of training for young physicians (residents). In addition, the rapid turnover of junior staff and the difficulties faced in maintaining a local continuous educational programme limit the success of in-hospital education and training.

Another barrier to the adoption of a good prescribing practices may be the knowledge and behaviour of prescribing physicians, who focus on the patient's individual outcome, at the exclusion of the risk of antibiotic resistance.

It has been pointed out that medical curricula are already dense, so if new subjects are to be introduced, another subject need to be removed or reduced.

Stakeholders

In order to design and implement educational programmes for undergraduate students (especially education on appropriate antibiotic prescription and ASPs), good communication, collaboration, commitment and agreement are needed between all academic institutions, the Ministry of Health and the Ministry of Education. Efforts are required at national level to improve current educational programmes, as well as to develop appropriate educational programmes specifically targeting each group of professionals implicated in the health system.

There is also insufficient national expertise and specialized human resources for training; a specific human resources strategy is needed to address the AMR problem.

Health system constraints

The Romanian health system does not yet have the extended expertise and financial resources to develop and implement an integrated programme and national education campaign on AMR. Close collaboration is required between health care providers and academic researchers, as well as between hospitals and medical schools, to establish the necessary link between undergraduate and postgraduate educational programmes, in particular to strengthen internship training.

Potential opportunities

OPTION 1. CONSOLIDATE AND COORDINATE THE LEGAL FRAMEWORK FOR AMR

Care recipients

Mass media coverage of certain recent cases (such as the Hexifarma fake biocides scandal, cases of HAIs in maternity and burn units) have drawn attention to the subject of hospital hygiene and increased general concerns and pressures relating to quality of care services within the Romanian health system. A regulatory framework to help tackle these aspects of the problem would therefore be well received.

Care providers

As discussed in the earlier sections outlining the problem, health care providers are under pressure, both legally and morally, to tackle increasing mortality and morbidity levels resulting from AMR. Implementing a new set of rules is a particularly useful solution, provided the legislation, programmes and protocols are practical and feasible for the care providers to apply.

Stakeholders

A Government Decision approved in November 2018 established the National Committee for Limiting AMR (*Comitetul Național pentru Limitarea Rezistenței la Antimicrobiene*). The Committee is an administrative and technical structure, without legal personality, coordinated by the Ministry of Health. The Committee is responsible for issuing recommendations to relevant institutions on the training of human health care and veterinary staff on the judicious use of antibiotics, testing antibiotic resistance, reporting resistance to antibiotics, and communication in the field of AMR. It also has the role of recommending and taking measures to inform the general public about the judicious use of antibiotics and the risks associated with their inappropriate use (Government of Romania, 2018).

The preparation of this EBP can be seen as an important step forward to initiate and strengthen a national programme to control AMR. It can be used as a resource to further develop and implement the necessary mechanisms at national and local levels.

Health system

It is generally accepted that the Romanian health system needs to be reformed in order to be aligned with current standards and practices, and in particular several key documents and strategies that have been approved over the course of a decade. Against the background of the current changes that the system is undergoing, making adjustments to introduce measures to tackle AMR is easier than it might have otherwise been.

OPTION 2. ALIGN FUNDING ARRANGEMENTS TO FACILITATE AMR CONTROL, ASPS AND IPC PROGRAMMES

Care recipients

There are extensive lists of medicines and medical tests funded by the social system, for both outpatient and inpatient care and at different levels of coverage. The mechanisms for sustaining health care delivery therefore exist, and with these being used, patients should face no financial challenges in terms of the actions required to control AMR.

Care providers

Extensive evidence is available of the cost-effectiveness of ASPs in both hospital and outpatient settings. There is also a natural competition between health providers, in terms of eagerness to provide the best quality of care. Implementing the right mechanisms (as listed in the subsection detailing Option 2), based on a regulatory framework (as detailed in Option 1) and with the knowledge and acceptance of the population (as outlined in Option 3), health care providers have a great opportunity to not only increase quality, but also to benefit from cost savings in their implementation of AMR-reduction measures.

Stakeholders

A common challenge for the health care sector is serving more people, with less money. Implementing the actions to combat AMR presented in the description of Option 2 can help achieve this aim.

Health system

Under the 2014–2021 EEA financial mechanism between Iceland, the Principality of Liechtenstein, the Kingdom of Norway (donor states), and the Government of Romania, opportunities exist to finance specific areas of interest, including public health challenges experienced at European level, aiming to prevent and control contagious diseases, and taking into account the challenges related to AMR (Ministry of European Funds of Romania, 2016).

From the third-party payer perspective, the actions proposed to combat AMR are cost-effective, with a favourable cost-benefit ratios.

OPTION 3. DEVELOP AND IMPLEMENT PROGRAMMES TO PROVIDE INFORMATION, IMPROVE EDUCATION AND STRENGTHEN COMMUNICATION

Care recipients

There is increasing being paid in the mass media to the issue of medical problems, and this trend could be taken advantage of in order to promote appropriate AMR-related information to the general public.

Care providers

Developing personnel communication skills is a constant preoccupation at health provider level. Providing care teams with relevant and reliable education and information will increase not only their trust in the services they provide but also their communication with the patients.

Risk of infection is one of the most preoccupying aspects for patients in hospital. However, effective implementation of these activities to tackle the AMR problem can help to overcome this fear, improving not only patient satisfaction but also general perception of health providers.

Stakeholders

There is a constant focus on preventive medicine and measures to assure quality of care. The topic is broad and complex, addressing many issues, including the package of actions needed to fight AMR. The actions outlined can have an immediate impact on a large scale, showing that there are concerns regarding quality and that people's lives are taken seriously.

Health system

AMR is a global problem and efforts are needed across the whole health care system to combat it; without action, it will surely worsen. Communicating with the general population on this topic will increase health literacy at national level, and improve awareness and education, therefore also contributing to the continuous development of the health care system and in turn improving health.

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ANNEXES

ANNEX 1.

Summary of systematic reviews AND OTHER STUDIES relevant to Option 1

Systematic review	Option element	Focus of systematic review
Wagner et al. (2014). Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. <i>Infect Control Hosp Epidemiol.</i> 35(10):1209–1228.	Developing an operational-level national antimicrobial stewardship programme (ASP) for inpatient hospital settings	ASPs in inpatient hospital settings
Karanika et al. (2016). Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. <i>Antimicrob Agents Chemother.</i> 60(8):4840–4852.	Developing a national operational-level ASP with clinical and economic outcomes of implementing hospital-based ASPs	Clinical and economic outcomes of implementing hospital-based ASPs
Schuts et al. (2016). Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. <i>Lancet Infect Dis.</i> 16(7):847–856.	Developing a national ASP at operational level with current evidence on hospital antimicrobial stewardship objectives	Antimicrobial stewardship
Drekonja et al. (2015). Antimicrobial stewardship in outpatient settings: a systematic review. <i>Infect Control Hosp Epidemiol.</i> 36(2):142–152.	Developing a national ASP for operational-level antimicrobial stewardship in outpatient settings	Antimicrobial stewardship in outpatient settings

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
Research to date has established that ASPs (including audit and feedback, guideline implementation and decision support) improve prescribing and microbial outcomes without significant adverse impact on patient outcomes. The current knowledge situation is sufficient to make stewardship implementation a priority in all hospitals, especially given the emerging AMR threat.	2013	7/11	0/37
Hospital ASPs result in a significant decrease in antimicrobial consumption and cost, and the benefit is higher in critical care. Infections due to specific antimicrobial-resistant pathogens and the overall hospital length of stay are improved as well.	2015	9/11	0/26
<p>Overall, the quality of evidence was in general low and heterogeneity between studies was mostly moderate to high. For several objectives (empirical therapy according to guidelines, de-escalation of therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics and bedside consultation) the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a relative risk reduction of 35% for mortality and 56% for de-escalation. Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having local antibiotic guidance.</p> <p>The findings of beneficial effects on outcomes with nine antimicrobial stewardship objectives suggest that these can guide stewardship teams in their efforts to improve the quality of antibiotic use in hospitals.</p>	2014	10/11	0/149
Low- to moderate-strength evidence suggests that ASPs in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes. Effectiveness depends on the type of programme. Most studies were not designed to measure patient or resistance outcomes. Data regarding sustainability and scalability of interventions are limited.	2013	7/10	0/50

ANNEX 1. (Contd)

Systematic review	Option element	Focus of systematic review
<p>Price et al. (2018). Effectiveness of national and subnational infection prevention and control interventions in high-income and upper-middle-income countries: a systematic review. <i>Lancet Infect Dis.</i> 18(5):PE159–171.</p>	<p>Developing a national ASP at the operational level</p>	<p>Investigating evidence on the effectiveness of IPC interventions implemented at national or subnational levels to inform the development of WHO guidelines on the core components of national IPC programmes</p>
<p>Ibrahim et al. (2017). Economic evaluations on antimicrobial stewardship programme: a systematic review. <i>J Pharm Pharm Sci.</i> 20(1):397–406.</p>	<p>Developing a national ASP at operational level with economic evaluation of ASPs</p>	<p>Cost-effectiveness evaluation of implementing an ASP in the hospital setting.</p>
<p>Rattanaumpawan et al., 2017. Systematic review of electronic surveillance of infectious diseases with emphasis on antimicrobial resistance surveillance in resource-limited settings. <i>Am J Infect Control.</i> 46(2):139–146.</p>	<p>Developing a national ASP at operational level</p>	<p>Electronic surveillance of infectious diseases with emphasis on AMR surveillance in resource-limited settings</p>

Note. – = not applicable.

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
<p>Evidence of effectiveness was found in all categories but the highest quality evidence was on multi-modal interventions and surveillance, monitoring, and feedback.</p> <p>The authors call for improvements in study design, reporting on research, and quality of evidence, particularly from low-income countries.</p>	2017	8/10	0/30
<p>Implementing an ASP in the hospital setting may be cost-effective. However, comprehensive cost-effectiveness data on ASPs remain relatively scant, underlining the need for more prospective clinical and epidemiological studies to incorporate robust economic analyses into clinical decisions.</p>	2017	9/10	0/5
<p>Information technologies can be used to facilitate the process of obtaining (in less time) laboratory, clinical, and pharmacologic data for the surveillance of infectious diseases, including AMR infections. These systems require greater resources.</p>	2016	4/11	0/110

ANNEX 2.

Summary of systematic reviews and other studies relevant to Option 2

Systematic review	Option element	Focus of systematic review
Naylor et al. (2017). Is antimicrobial stewardship cost-effective? A narrative review of the evidence. Clin Microbiol Infect. 23(11):806–811.	Cost-effectiveness, cost-utility and cost-benefit of ASPs	Providing evidence on the cost-effectiveness, cost-utility and cost-benefit of ASPs, and providing recommendations for future research (appropriate health economic methodological choices)
Dik JH et al. (2015) Financial evaluations of antibiotic stewardship programs-a systematic review. Front. Microbiol. 6:317.	Financial evaluation of ASPs	Evaluation of the current financial situation pertaining to ASPs and of the quality of the studies examined
Ibrahim et al. (2017). Economic evaluations on antimicrobial stewardship programme: a systematic review. J Pharm Pharm Sci. 20(1):397–406.	Economic evaluation of ASPs.	Cost-effectiveness evaluation of implementing ASPs in the hospital setting
Morris et al. (2018). Rationale and development of a business case for antimicrobial stewardship programs in acute care hospital settings. Antimicrob Resist Infect Control 7:104.	ASPs in acute care hospital settings	Assessing existing regulatory requirements and human resources recommendations for ASPs and creating a spreadsheet-based business case model for ASPs in acute care hospital settings

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
<p>Overall, even if cost-effectiveness evidence for antimicrobial stewardship is increasing, it remains limited, especially in the community setting.</p> <p>In the hospital setting, the reviewed studies suggest that persuasive and structural antimicrobial stewardship interventions may provide health economic benefits, with no evidence being found on the health economic benefit of restrictive ASPs.</p> <p>Only one study explored the cost-effectiveness/cost-benefit of antimicrobial stewardship in a low- to middle-income country.</p> <p>Robust health economics research needs to be completed to enhance the generalizability and usability of cost-effectiveness results.</p>	2017	–	0/6
<p>This review gives an extensive overview of the current financial evaluation of ASPs and the quality of these economic studies, showing that there still is major potential to improve financial evaluations of ASPs. The studies evaluated do not use similar or consistent methods or outcome measures, making it impossible draw sound conclusions and compare them. The following areas of expenditure are identified as needing to be evaluated and better predicted: costs of implementation and operation, antimicrobials, length of stay, morbidity/mortality, other hospital costs, and societal costs.</p>	2014	2/10 (not a systematic review)	0/99
<p>Implementing ASPs in the hospital setting may be cost-effective. However, comprehensive cost-effectiveness data for ASPs remain relatively scant, underlining the need for more prospective clinical and epidemiological studies to incorporate robust economic analyses into clinical decisions.</p>	2017	6/11	0/5
<p>There is evidence to support the benefits of ASPs. Worldwide evidence for legislative and/or regulatory requirements and human resources recommendations for ASPs is scarce.</p> <p>A spreadsheet-based business case model for ASPs was created but, as regulatory requirements for ASPs increase, it will be necessary to create accurate business cases for ASPs in order to obtain the necessary funding to ensure the success of these programmes.</p>	2016	–	0/3

ANNEX 2. (Contd)

Systematic review	Option element	Focus of systematic review
<p>Coulter et al. (2015). The need for cost-effectiveness analyses of antimicrobial stewardship programmes: a structured review. <i>Int J Antimicrob Agents</i> 46(2):140–149.</p>	<p>Cost-effectiveness of ASPs</p>	<p>Cost-effectiveness of ASPs in hospital settings and among adult patient populations</p>
<p>Arefian et al. (2016). Economic evaluation of interventions for prevention of hospital acquired infections: a systematic review. <i>PLoS One</i> 11(1):e0146381.</p>	<p>Economic evaluation of interventions for prevention of hospital acquired infections (HAIs)</p>	<p>Assessing the cost and benefit of interventions to prevent HAIs</p>
<p>Farbman et al. (2013). Cost-benefit of infection control interventions targeting methicillin-resistant <i>Staphylococcus aureus</i> in hospitals: systematic review. <i>Clin Microbiol Infect.</i> 19(12):E582-93.</p>	<p>Cost-effectiveness and cost-benefit of infection control interventions against methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)</p>	<p>Cost-effectiveness and cost-benefit of infection control interventions against MRSA</p>

Note. – = not applicable.

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
<p>The main antimicrobial stewardship strategy implemented was prospective auditing with intervention and feedback, followed by the use of rapid testing technology for the treatment of bloodstream infections. All but one of the 36 studies reported that ASPs resulted in a reduction in pharmacy expenditure. The two studies that performed a full economic evaluation found the ASPs to be cost-effective.</p> <p>Further research and full economic evaluations are needed in order to identify the most cost-effective ASPs in hospitals.</p>	2014		0/36
<p>Prevention programmes for HAIs have very positive cost-benefit ratios. Improved reporting quality in health economics publications is required.</p>	2014	9/10	0/27
<p>Infection control interventions to reduce spread of MRSA in acute-care hospitals showed a favourable cost-benefit ratio. Higher savings/cost ratios were observed in the intermediate- to high-endemicity setting compared with the low-endemicity setting, in hospitals with <500-beds and in interventions of >6 months.</p>	2011	7/11	0/36

ANNEX 3.

Summary of systematic reviews AND OTHER STUDIES relevant to Option 3

Systematic review	Option element	Focus of systematic review
Coxeter et al. (2015). Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. <i>Cochrane Database Syst Rev.</i> 12(11):CD010907.	Information, education and strengthening physician–patient communication	Assessing interventions that aim to facilitate shared decision-making to increase or reduce antibiotic prescribing for acute respiratory infections (ARIs) in primary care
Oppong et al. (2018). Cost-effectiveness of internet-based training for primary care clinicians on antibiotic prescribing for acute respiratory tract infections in Europe. <i>J Antimicrob Chemother.</i> 73(11):3189–3198.	Postgraduate AMR education programme	Assessing the cost-effectiveness (compared with standard care) of: (i) training general practitioners (GPs) in the use of C-reactive protein testing; (ii) training GPs in communication skills; and (iii) training GPs in both C-reactive protein testing and communication skills
Andrews et al. (2012). Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. <i>PLoS One</i> 7(1):e30334.	The impact of raising awareness and implementing educational programmes for patients and the general population	Assessing the effectiveness of interventions directed towards parents or caregivers, which were designed to influence consulting and antibiotic use for respiratory tract infections in children in primary care settings
Lee et al. (2015). Educational effectiveness, target, and content for prudent antibiotic use. <i>Biomed Res Int.</i> 15:214021c.	Undergraduate and postgraduate AMR education programmes	Assessing the effectiveness of educational strategies and educational programmes for clinicians

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
<p>There is evidence of moderate quality that interventions aiming to facilitate shared decision-making reduce antibiotic use for ARIs in primary care.</p> <p>Interventions that aim to facilitate shared decision-making reduce antibiotic prescribing in primary care settings in the short term. Effects on longer-term rates of prescribing are uncertain and more evidence is needed to determine how any sustained reduction in antibiotic prescribing affects rates of hospital admission, pneumonia and mortality.</p>	2014	10/10	0/11
<p>Internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care, if the cost of antibiotic resistance is accounted for in the equation.</p>	2018	–	0/5
<p>Materials designed to engage children in addition to parents were effective in modifying parental knowledge and behaviour, resulting in reductions in consulting rates. Providing parents with delayed prescriptions significantly decreased reported antibiotic use (and in addition, a delayed or no prescribing approach did not diminish parental satisfaction).</p>	2011	7/11	0/23
<p>Inclusion of appropriate antibiotic use in undergraduate and postgraduate curricula, accompanied by continuing medical education (CME) in the field of antibiotic therapy have the potential to improve antibiotic prescription.</p>	2014	–	–

ANNEX 3. (Contd)

Systematic review	Option element	Focus of systematic review
<p>Batura et al. (2018). How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low-income and middle-income countries? A protocol for a systematic review. <i>BMJ Open</i> 8(5):e021517.</p>	<p>Effectiveness and cost-effectiveness of behaviour change interventions</p>	<p>Defining a protocol for a systematic review on the effectiveness of behaviour change interventions in improving the prescription and use of antibiotics in low- income and middle-income countries</p>
<p>King et al. (2016). Antimicrobial stewardship: the effectiveness of educational interventions to change risk-related behaviours in the general population: a systematic review. <i>Rand Health Q.</i> 5(3):2.</p>	<p>The impact of raising awareness and implementing educational programmes for patients and the general population</p>	<p>Reviewing the evidence of effectiveness and cost-effectiveness on changing the public's risk-related behaviour pertaining to antimicrobial use</p>
<p>Davey et al. (2013). Interventions to improve antibiotic prescribing practices for hospital inpatients. <i>Cochrane Database Syst Rev.</i> 4:CD003543.</p>	<p>The impact of educational AMR-related programmes on health care providers</p>	<p>Estimating the effectiveness of professional interventions that are effective in antibiotic stewardship for hospital inpatients, in terms of evaluating the impact of these interventions on reducing the incidence of antimicrobial-resistant pathogens or <i>Clostridium difficile</i> infection and their impact on clinical outcomes.</p>
<p>Davey et al. (2017). Interventions to improve antibiotic prescribing practices for hospital inpatients. <i>Cochrane Database Syst Rev.</i> 2:CD003543.</p>	<p>The impact of educational AMR-related programmes on health care providers</p>	<p>Estimating the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and investigating the effect of two intervention functions: restriction and enablement</p>

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
<p>Low- and middle-income countries are especially vulnerable to antibiotic resistance, owing to high infectious disease burden and limited resources for treatment. High prevalence of antibiotic prescription and use resulting from a lack of health care provider knowledge, prescribing habits and perceived patient needs further exacerbate the situation. The different determinants of antibiotic resistance, including inappropriate prescribing and use of antibiotics in low- and middle-income countries must be addressed through sustainable and scalable interventions.</p>	-	<p>- (Protocol)</p>	-
<p>Antimicrobial stewardship interventions can safely reduce unnecessary antibiotic use in hospitals, despite the fact that the majority of interventions did not use the most effective behaviour change techniques.</p>	2014	9/11	0/29
<p>This review shows that evidence exists demonstrating persuasive methods of improving antibiotic prescribing practices in hospitals, resulting in a decrease in the number of HAIs.</p>	2009	7/11	0/19
<p>This review shows that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce AMR or HAIs, and interventions to increase effective prescribing can improve clinical outcomes.</p>	2015	11/11	0/89

ANNEX 3. (Contd)

Systematic review	Option element	Focus of systematic review
de Bont et al. (2015). Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice: a systematic review. <i>BMJ Open</i> 5(6):e007612.	The impact of raising awareness and implementing educational programmes for patients and the general population	Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice
Tonkin-Crine et al. (2017). Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. <i>Cochrane Database Syst Rev</i> . 9:CD012252.	Develop and implement programmes to provide information, improve education and strengthen communication	Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care
Spurling et al. (2013). Delayed antibiotics for respiratory infections. <i>Cochrane Database Syst Rev</i> . 4:1–64.	Education of health care providers	Delayed prescription of antibiotics for respiratory infections

Note. – = not applicable.

Key findings	Year of last search	AMSTAR or SURE checklist (quality) rating	Proportion of studies that were conducted in Romania
The use of patient information leaflets on common infections during GP consultations may effectively reduce antibiotic prescribing and use, as well as patients' intention to reconsult. GPs are therefore encouraged actively to use patient information leaflets during consultations for common infections.	2014	7/10	0/8
C-reactive protein testing, shared decision-making, and procalcitonin-guided management reduce antibiotic prescribing for patients with acute respiratory infections in primary care. These interventions may therefore reduce overall antibiotic consumption and consequently antibiotic resistance. There do not appear to be negative effects as a result of these interventions on the outcomes of patient satisfaction and re-consultation, although there was limited measurement of these outcomes in the trials. Most of this research was undertaken in high-income countries, and it may not be possible to generalize for other settings. The quality of evidence for the interventions regarding educational materials and tools for patients and clinicians was either low or very low, which prevented any conclusions being drawn.	2017	9/10	0/44 trials
For most symptoms, such as fever, pain and malaise, there was no difference between immediate, delayed and no prescription of antibiotics. The only differences recorded were minor, and these favoured immediate antibiotics for relieving pain and fever for sore throat, and pain and malaise for infections of the middle ear. There was little difference in adverse effects of antibiotics for the three prescribing strategies and no significant difference in complication rates. Patient satisfaction was slightly reduced in the group receiving antibiotics after a delay (87% satisfied) compared to those receiving them immediately (92% satisfied). Satisfaction rates were similar between those that were delayed and those who received no antibiotics (83% satisfied).	2013	9/11	0

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World Health Organization
Regional Office for Europe
UN City, Marmorvej 51
DK-2100 Copenhagen Ø,
Denmark

Tel: +45 45 33 70 00
Fax: +45 45 33 70 01
E-mail: euwhocontact@who.int
Web: www.euro.who.int

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