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Evidence brief for policy

EVIPNet Europe

Number 5

Promoting appropriate use of antibiotics in hospitals to contain antibiotic resistance in North Macedonia

Evidence-informed Policy Network (EVIPNet) Europe

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ABSTRACT

The Ministry of Health of North Macedonia commissioned this evidence brief for policy, to be published under the aegis of the WHO European Evidence-informed Policy Network, to develop evidence-informed options for the country to consider in tackling the problem of empirical prescribing of antibiotics in inpatient facilities. Such treatment currently takes place without microbiological testing, largely contributing to spread of antimicrobial resistance. The work was carried out within the framework of the Biennial Collaborative Agreement between the Ministry of Health and WHO, involving high-level national policy institutions and national experts, and supported by technical experts of the WHO Regional Office for Europe. A working group comprising representatives from different clinical disciplines, pharmacology, public health and health care management worked on identifying, selecting, appraising and synthesizing relevant research evidence on the problem, three options for tackling it and considerations for implementing them. The three options are: revision, contextualization and implementation of guidelines for antibiotic therapy, including clinical pathways and feedback between primary and secondary care; establishment of antibiotic stewardship programmes in hospitals, accompanied by an antibiotic use reporting system; and strengthening curricula on prudent antibiotic use in undergraduate, postgraduate and continuous education for all health professions.

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PARTNERS IN THE REVIEW

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 in 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 scientific evidence available.

The Multisectoral Committee on Antimicrobial Resistance (AMR) was established under the Ministry of Health of North Macedonia to coordinate national efforts to combat AMR. The Ministry of Health is the highest health authority responsible for policy- and decision-making, as well as monitoring implementation of policies in health sector. It is also responsible for determining rules and preparing legislation related to health care provision at the national level. It regulates and partly carries out national public health tasks, and acts as a supervisory body to government agencies in the field of health care and public health.

Civil society is represented by the "Studiorum" Centre for Regional Policy Research and Cooperation, a nongovernmental think-tank working on economic and social aspects of European Union integration and globalization processes that are of essential importance for the countries in south-eastern Europe. Studiorum runs various policy-oriented programmes and research projects, which contribute to and complement the efforts of policy-makers in policy design and implementation.

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CONFLICT OF INTEREST

The authors or funder declare to have no professional or commercial interests related to any information, product or statement related to this evidence brief.

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PEER-REVIEW

This evidence brief for policy was reviewed by a small number of researchers and policy-makers to ensure its scientific rigour and relevance for the health system.

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ABBREVIATIONS

AMR	antimicrobial resistance
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ASP	antibiotic stewardship programme
ATC	Anatomical Therapeutic Chemical [classification system]
CAESAR	Central Asian and European Surveillance of Antimicrobial Resistance [Network]
CDC	Centers for Disease Control and Prevention [United States]
DDD	defined daily dose
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EU	European Union
EVIPNet (Europe)	Evidence-informed Policy Network (Europe)
HIF	Health Insurance Fund [North Macedonia]
MALMED	Macedonian Agency for Medicines and Medical Devices
NICE	National Institute for Health and Care Excellence [United Kingdom]
PPS	point prevalence survey

MAIN MESSAGES

The problem

Antimicrobial resistance (AMR), including antibiotic resistance, is recognized as a major threat to public health worldwide, accelerated by non-prudent antibiotic use. In North Macedonia, antibiotic consumption is very high. Accurate data on total consumption is estimated to be up to 35 defined daily doses (DDDs) per 1000 inhabitants per day – much higher than the European Union and European Economic Area mean consumption of 21.9 DDDs per 1000 inhabitants per day.

At the hospital level, evidence suggests non-prudent use of antibiotics due to lack of adherence to non-adapted clinical guidelines. This contributes to development of AMR, which increases the risk of uncontrolled spread of infections and hospital mortality.

Three viable options to address the problem

- Option 1. Revision, contextualization and implementation of guidelines for antibiotic therapy
  - A well established guideline programme is an important prerequisite for a national antibiotic stewardship programme (ASP) to be successful. Adherence to evidence-based guidelines at all levels of care minimizes the probability of adverse effects and associated mortality and contributes to reducing non-prudent antibiotic prescribing.
- Option 2. Establishment of ASPs in hospitals, accompanied by an antibiotic use reporting system
  - ASPs in hospitals contribute to reduced antibiotic consumption, length of hospital stay, morbidity, mortality and overall treatment costs. Surveillance of hospital antibiotic consumption and antibiotic resistance ensures significant reductions in inappropriate antibiotic use and costs. Among key elements of ASPs are leadership education and support to ensure dedicated time for professionals to organize ASPs.
- Option 3. Strengthening curricula on prudent antibiotic use
  - Proper clinical education on the prudent use of antibiotics, accompanied by skills for communication with patients, are preconditions for rational prescribing by both new graduates and experienced professionals across all health professions – including prescribers and pharmacists, but also nurses, microbiologists and other health professionals.

Implementation considerations to be borne in mind

» To reduce the levels of unnecessary antibiotic prescribing, policy options should be implemented as part of a wider national health policy. Each option proposed

contributes to more appropriate use of antibiotics in hospitals; while each can be implemented independently, combined implementation would be likely to have a greater impact.

» Development of effective locally adapted clinical guidelines largely relies on availability of facility-level antibiotic susceptibility and surveillance data. The current lack of antibiotic resistance reporting is largely due to lack of funds for diagnostics, which should be addressed in health financing policies.

» The ongoing stigma related to the reporting of antibiotic resistance requires ASPs to become an integral part of the system, in which resistance reporting would serve the purpose of better AMR management and constructive improvement of individual providers' practices.

EXECUTIVE SUMMARY

Non-prudent use of antibiotics is a globally recognized problem, leading to increasing antibiotic resistance and severely restricting therapeutic options: sometimes no effective drugs are available to treat life-threatening infections. Global evidence shows that antibiotic usage in hospitals is increasing, and that over a third of prescriptions are not compliant with evidence-based guidelines.

At the national level, antibiotic consumption is very high. Data on total antibiotic consumption (in particular self-medication and hospital consumption) are lacking but, based on experience, it is estimated that total consumption of antibiotics is up to 35 DDDs per 1000 inhabitants per day. This is much higher than the European Union and European Economic Area population-weighted mean consumption of 21.9 DDDs per 1000 inhabitants per day.

Non-prudent use of antibiotics in North Macedonia occurs at all levels of health care where prescribing and dispensing of medicines occur; it is influenced by many factors, including physicians' inappropriate prescribing practices, pressure from patients to prescribe, inadequate arrangements in the health care system and so forth.

At the hospital level, although both public and private hospitals have their own data, no formal figures on antibiotic use are available owing to the structure of the health care data collection and reporting systems, which are currently based on aggregated financial reporting of costs. A point prevalence survey conducted in 2015 in 12 university clinics in the capital city of Skopje identified excessive non-prudent antibiotic use. The total prevalence of patients receiving at least one antimicrobial agent was 64.2%, which was nearly double the mean global rate of 34.7%.

Further, existing clinical guidelines are not sufficiently followed by clinicians. One of the main reasons is that they are not adapted to the so-called positive list of drugs (drugs covered by the health insurance scheme) or to contextual factors within hospitals, such as opportunities for regular use of diagnostics to determine appropriate antibiotic therapy. As a result, non-prudent antibiotic use occurs in the form of excessive empirical prescribing, in terms of selection, dosage and/or duration of antibiotic therapy.

Non-prudent use of antimicrobials in North Macedonian hospitals results in increased AMR from invasive isolates. The development of AMR increases the risk of uncontrolled spread of infections with multidrug-resistant agents and has a potentially devastating effect on inpatient morbidity and mortality. It could also spread into the community, with potential for further increases of morbidity and mortality among outpatients.

The challenges to decreasing non-prudent and unnecessary prescribing in hospitals include:

- a lack of context-adapted clinical guidelines and a lack of communication of the setting-specific AMR surveillance data, leading to a lack of contextualization of the clinical guidelines to each hospital;
- a widespread practice of empirical prescribing, due to lack of funding for diagnostics;

- nonexistence of systematic data gathering on antibiotic use in hospitals.

Evidence is therefore needed on the contextual conditions to inform and implement effective interventions. Although a number of activities have been initiated, there is a common understanding that the country still has a long way to go to achieve prudent antibiotic use in every segment of its health system, including hospital settings.

Three options

Based on a review of the relevant scientific literature in English and Macedonian, and of guidance provided by major international organizations such as WHO and the European Centre for Disease Prevention and Control, the authors of this evidence brief for policy selected three viable options for reducing non-prudent and unnecessary antibiotic use in hospital settings in North Macedonia. The options were chosen because they address most aspects of the causes of the problem at the patient, prescriber and governance levels. Each option should be considered as part of a more comprehensive solution, and are not mutually exclusive. Given the specificities of the national context, the authors considered that the proposed options – chosen based on available global and national evidence – could produce the most significant improvement of antibiotic use when implemented in combination, as part of a comprehensive approach in conjunction with interventions in other segments of health care system. Implementation of only one or two of the proposed options would, however, also be of significant benefit to improve rational use of antibiotics in hospital settings.

Evidence to support option 1 – revision, contextualization and implementation of guidelines for antibiotic therapy, including clinical pathways and feedback between primary and secondary care – was found in 11 systematic reviews, one overview of systematic reviews, one narrative review and one primary qualitative study.

- Clinical guideline-adherent therapy minimizes the probability of adverse effects and is associated with a relative risk reduction in mortality.
- Context-adapted clinical guidelines and institution-specific treatment protocols for different infections contribute to better acceptance and follow-up by clinicians themselves, and are an integral part of this effort.
- Clinical guidelines are applicable to all levels of health care; they should thus specifically include descriptions of prescribing pathways between levels of care.

Evidence to support option 2 – establishment of ASPs in hospitals, accompanied by an antibiotic use reporting system – was found in five systematic reviews with meta-analysis, 12 systematic reviews and one review.

- ASPs in hospitals contribute to improving prescribing practices – in particular, reducing antibiotic consumption by almost one fifth, decreasing antibiotic costs, reducing length of hospital stay by 1.12 days and reducing the number of infections caused by certain multidrug-resistant organisms.
- Key elements essential to the success of implementing ASPs are education of leadership, gaining support from medical leaders, ensuring dedicated time for professionals to organize stewardship programmes and ensuring availability of local guidelines based on local data on resistance.

- Hospital ASPs, supported by information technology interventions, result in significant decreases in inappropriate antibiotic use and costs, especially in intensive care units. A variety of tools are available to assist with medical records, prescription and medication use evaluations that can be adapted to any specific setting.

Evidence to support option 3 – strengthening curricula on prudent antibiotic use in undergraduate, postgraduate and continuous education for all health professions – was found in three reviews of systematic reviews, seven systematic reviews, one review of studies and two primary studies.

- Continuing education of health care professionals and outreach visits by peer professionals can help to change prescribing behaviour.
- Although no systematic review was found of the effectiveness of undergraduate or postgraduate curricula on prescribing practices, educational interventions among established clinicians and for new prescribers as immediate postgraduate interventions in hospitals have proved effective in changing prescribing behaviour.
- Introducing antimicrobial stewardship in medical curricula for undergraduate, postgraduate and continuous medical education is considered very effective in addressing inappropriate and excessive antibiotic prescribing.

Opportunities for and barriers to implementation

To decrease the levels of unnecessary prescribing of antibiotics, policy options should be implemented as part of a wider national health policy. Thus, in the process of development of this evidence brief for policy, opportunities and barriers for implementation of the three options were considered.

Regarding opportunities, this is a very timely moment in North Macedonia, given that the Ministry of Health reappointed the Multisectoral Committee on AMR in November 2018, with a mandate to propose policy options to address non-prudent antibiotic use in the country, including in hospitals and inpatient settings. This represents an excellent window of opportunity not only to assess the current levels but also to establish a systematic mechanism for regular monitoring of antibiotic use in hospitals. The introduction of such a mechanism would add the missing piece to the puzzle of antibiotic use across all levels of care. This in turn would provide evidence to inform the policy process on choosing optimal approaches to addressing non-prudent antibiotic use in hospitals and in the health system in general.

The country expressed its commitment to address the issue by endorsing a strategy and action plan for the control of AMR 2012–16. An extension of the strategy to 2023 was adopted by the government in October 2019. Since 2013, the Ministry of Health's declaration of commitment to the fight against AMR has expedited the process for North Macedonia to join the Central Asian and European Surveillance of Antimicrobial Resistance Network and facilitated implementation of AMR surveillance and reporting mechanisms based on international standards for the majority of laboratories across the country. To standardize the work of microbiological laboratories, the European Committee on Antimicrobial Susceptibility Testing system was introduced in 2016–17. In addition, the country joined the WHO Evidence-informed Policy Network (EVIPNet) initiative in 2015, with the aim of establishing regular mechanisms for gathering evidence to inform health policies and decision-making processes.

Barriers to implementation have also been considered. One of the most significant is the anticipated difficulty of changing behaviour, which is influenced by an array of factors, explained in more detail below. Another important barrier is acceptance of new administrative tasks for physicians, related to the potential introduction of a reporting system on antibiotics prescribed and administered to patients. Finally, another major anticipated barrier is acceptance of change in the health system pertaining to accountability mechanisms for improving communication and exchange of information about prudent antibiotic use between authorities and health service providers.

INTRODUCTION

Background

Global evidence shows that antibiotic usage in hospitals is increasing, and that over a third of prescriptions are not compliant with evidence-based guidelines (1, 2). Despite such alarming evidence, North Macedonia does not have a consistent systematic mechanism to monitor use of antibiotics in hospitals, and at the moment only small-scale studies and ad hoc analyses at the facility level demonstrate alignment with the global trends in antibiotic use.

Non-prudent use of antibiotics in North Macedonia occurs at all levels of health care where prescribing and dispensing of medicines occur (3–5); it is influenced by many factors, including physicians' inappropriate prescribing practices, pressure from patients to prescribe, inadequate arrangements in the health care system and so forth (6).

To increase patient safety, the Ministry of Health, with the support of the WHO Regional Office for Europe, commissioned an evidence brief for policy to address inappropriate antibiotic use in hospitals and consequent antibiotic resistance (Box 1). Non-prudent antibiotic use occurs and requires action at every level of the health care system. While some measures are ongoing to address this issue at the primary health care level, use of antibiotics in secondary and tertiary care remains unaddressed, and no formal data on actual consumption are available. The focus of this evidence brief is therefore on hospital use of antibiotics, analysing the magnitude of the problem in the national context. It provides an overview of globally available evidence supporting the proposed options for policy action, which could be developed and tailored to the country's context, to inform deliberations among policy-makers and stakeholders.

Box 1. About the development of the evidence brief for policy

This evidence brief is intended to open a dialogue among stakeholders involved in policy- and decision-making, implementation and monitoring of implementation. It contains an evaluation of the issue as defined through an assessment of available data. It also points to data gaps in the monitoring of antibiotic use in the country, with particular focus on secondary and tertiary care.

Mobilizing both global and local research, the evidence brief puts forward three options to address the problem and key implementation considerations. Whenever possible, it summarizes evidence drawn from systematic reviews of the literature and occasionally from single research studies. The proposed policy options are framed to the particular context of the country.

This evidence brief is intended to serve as dynamic document for use in dialogue, through which the most suitable and feasible policy options could be considered and agreed upon, to inform the policy process for optimal design of antibiotic prescribing at all levels of care, with particular focus on hospitals. Its preparation involved the following steps.

Box 1. (Contd)

- A working group was established, comprising representatives from health authorities (Ministry of Health, Health Insurance Fund), research and academic institutions, professional associations and civil society.
- Terms of reference were developed and refined, particularly framing the problem and three viable options to address it, in consultation with the steering committee and a number of key informants from academia, policy and practice in the field.
- Relevant research evidence about the problem, options and implementation considerations were identified, selected, appraised and synthesized.
- A draft evidence brief was prepared to present concisely and in accessible language the global and local research evidence.
- A multi-stakeholder workshop was organized to enable practitioners from all levels of care, academia, policy-makers and patients to discuss the draft.
- The evidence brief for policy was finalized, based on the input of several reviewers.

The three options to address the problem are not designed to be mutually exclusive. They could be pursued simultaneously, or elements could be drawn from each to create a new alternative.

Development of the evidence brief for policy

This is the first evidence brief for policy produced in North Macedonia, within the framework of the WHO Evidence-informed Policy Network (EVIPNet) Europe. It was developed by a group of national experts coordinating discussions and contributions of the wider professional community in the field. During the development process, the WHO Regional Office for Europe and national and international experts in the subject area regularly reviewed the evidence brief. The authors analysed global and local evidence on the problem and policy options to address it, along with barriers to and opportunities for implementing the options (Box 2).

The main focus of the search for evidence was identifying systematic reviews of the effects of policy options and their implementation strategies (see Annex 1 for further details). Other relevant single research studies, economic evaluations, key publications of major international organizations, government reports and unpublished literature were also consulted. The tacit knowledge of both experts and stakeholders obtained from reviewers and elicited through key informant interviews and consultative workshops (see Annex 2) further forms an integral part of the evidence brief.

Box 2. Mobilizing evidence about options to address the problem

The available research evidence about options to address the problem was sought primarily using the Medline/PubMed, Cochrane, Health Systems Evidence, Health Evidence and Google Scholar databases. Full text reviews were made of English- and Macedonian-language systematic reviews, meta-analyses, economic evaluations and single research studies published between 1 January 2010 and 30 September 2017. Some important documents published before and after these dates identified through a search of references in the full text reviews analysed and from grey literature were also included.

Box 2. (Contd)

The initial publications were identified by searching the databases for papers containing topic-related keywords in the title and/or abstract. The keyword search included combinations of nouns: “antibiotics”, “prescribing”, “antibiotic stewardship”, “antimicrobial stewardship”, “intervention”, “guidelines”, “hospital”, “prudent use”, “appropriate use”, “rational use” and “irrational use”; and adjectives: “antimicrobial”, “inpatient” and “clinical”.

Data about the problem and its size were sought using national and international datasets, as well as surveillance reports on infectious diseases, health care-associated infections, antimicrobial resistance (AMR) and antibiotic consumption. Grey literature was searched by reviewing the websites of leading international and national organizations, such as WHO, the European Centre for Disease Prevention and Control (ECDC), the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the United States Centers for Disease Control and Prevention (CDC).

The reviews identified were used to extract their authors’ key findings. Each was also assessed in terms of its quality, using the Assessing the Methodological Quality of Systematic Reviews tool (AMSTAR), local applicability (proportion of studies conducted in the country) and equity considerations (proportion of studies that deal explicitly with prioritized groups). The overall evidence was then summarized based on the quality, local applicability, equity and issue applicability assessments.

Limitations

Summarizing evidence requires judgements about the scope and quality of evidence to be included or excluded, and choices on the way to interpret and report it. This evidence brief for policy thus inevitably reflects the authors’ and reviewers’ decisions.

AMR is directly related to antimicrobial use in humans and in animals, and antimicrobial misuse in particular accelerates this process (2). Many of the same pathogens (bacteria, viruses, fungi and parasites) affect both animals and humans via the environment they share, and 60% of all human diseases originate in animals. Thus, overuse of antimicrobials in animals increases chances of development and spread of AMR in humans. WHO, the Food and Agriculture Organization of the United Nations and the World Organisation for Animal Health have initiated a tripartite collaboration for coordinating global activities to address health risks at the animal–human–ecosystem interfaces (2, 7), further developed into the One Health approach to designing and implementing programmes, policies, legislation and research, in which multiple sectors communicate and work together to achieve better public health outcomes, including fighting AMR (8).

Although the One Health approach requires collective management of antimicrobial misuse in humans and animals, most antibiotic resistance in humans arises from human antibiotic use (9). The authors’ review and synthesis of evidence therefore concentrates on issues and possible interventions related to the human health care sector: the problem of antibiotic misuse in human medicine, and in the hospital sector in particular.

While global evidence suggests that antibiotic use in hospitals is rising, no systematically gathered and analysed data are available to support such a claim for North Macedonia. Nevertheless, the findings of small-scale studies undertaken at the facility level are aligned with the global trends, suggesting that this issue – once fully assessed – deserves urgent attention from policy- and decision-makers. The shortfall can therefore be considered an

opportunity not only to understand the current levels of antibiotic use but also to establish a regular mechanism for systematic monitoring of antibiotic use in hospitals, which is currently a missing piece of the puzzle.

The information related to costs and benefits is primarily drawn from the literature and is intended to serve as preliminary information for policy- and decision-makers to aid understanding of the advantages and disadvantages of each policy option. Since each option offers multiple alternatives for implementation design, the exact content of interventions would have to be decided in order to calculate country- and context-specific costs and benefits. This is a task of further policy development work.

THE PROBLEM OF NON-PRUDENT ANTIBIOTIC USE IN HOSPITALS

Definition and framing

The accidental yet revolutionary discovery of antimicrobial (and antibiotic) agents last century transformed medicine and approaches to treating communicable diseases and saving lives (10). Antibiotics soon became an important cure, increasing demand and mass production (11). In addition to treating community-acquired infections, antibiotics have facilitated and improved the safety and outcomes of health services at all levels, including general surgery, transplantations and cancer management (12). However, the world still faces infectious disease threats; trends in prevalence, incidence and global burden of disease indicate that communicable diseases are still high on the health agenda. It is estimated that over one third of the world's population may be infected by bacterial pathogens (13), with infectious diseases accounting for more than one quarter of deaths globally (14).

AMR (and specifically antibiotic resistance) is directly related to antibiotic use, and antibiotic misuse in particular accelerates this process (2). Forms of antibiotic misuse include unjustified use (as in the case of non-bacterial infections); excessive prescribing (overuse) of certain products; and inadequate selection, dosage or duration of antibiotic therapy (7).

Antibiotic resistance is a complex process by which bacteria change and develop properties that reduce the effectiveness of the drugs that were once potent against them (15–17). Research into antibiotics and antibiotic resistance has investigated a range of topics, from development of new antimicrobial agents (18–20) and rapid diagnostic techniques (21) to epidemiological causations (22), social norms of antibiotic use and misuse and the effects of health literacy on the issue (23–25). While research and development of new drugs and rapid diagnostic tests have stagnated through underinvestment, efforts have increasingly been put into prevention of antibiotic resistance through control of adherence to clinical guidelines in drug prescribing and use, strengthening control and prevention of infections and proper surveillance systems and monitoring of resistant bacteria. Policies have been developed in line with the recommendations for rational use of antibacterial agents and for compliance with infection prevention and control practices, and more health literacy and awareness-raising efforts are being organized, involving populations and individuals in rational decision-making about their treatment of choice (26).

Within the European Union and European Economic Area (EU/EEA), antibiotic resistance is more prevalent in the south than the north – lowest in Scandinavia and highest in the Mediterranean countries (27–29). In line with this, southern and eastern European countries tend to have higher consumption of antibiotics, defined through the standardized measure of defined daily doses (DDDs) per 1000 inhabitants per day, for varying reasons including differences in health systems and policies that allow antibiotics to be dispensed over the counter (12). In North Macedonia, over-the-counter sales of antibiotics and self-medication make a significant

contribution to overall antibiotic consumption; however, no figures are available on the share of this consumption, and this should be a subject for separate analysis.

Box 3. Forms of antibiotic misuse and antibiotic resistance

Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic misuse in human medicine comprises many forms, including use beyond the scope of treating bacterial infections (e.g. against viruses); use outside the recommendations of a standard treatment protocol (e.g. longer preventive use before surgery); and use without consultation with a health professional (e.g. purchase and treatment without prescription, self-medication with leftovers).

Antibiotic resistance occurs when bacteria change in response to the use of these medicines. It is accelerated by the misuse and overuse of antibiotics and by poor infection prevention and control practices. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance, including by the public, policy-makers, health professionals, the health care industry and the agricultural sector (30).

Size of the problem

In North Macedonia, antibiotics can be prescribed at primary, secondary and tertiary level. All systemic antibiotics are prescription-only medicines, some of which are covered by health insurance, based on a predefined positive list of medicines. Data on total antibiotic consumption (in particular self-medication and hospital consumption) are lacking but, based on experience, it is estimated that the total consumption of antibiotics is up to 35 DDDs per 1000 inhabitants per day. This is much higher than the EU/EEA population-weighted mean consumption of 21.9 DDDs per 1000 inhabitants per day (31–35), and nearly three times higher than consumption in Austria and Slovenia (36). Alongside the regular prescribing pathways, as in other countries in southern Europe (such as Greece and Spain), it is also possible to obtain antibiotics without prescription directly from community pharmacies (33). Despite strict regulations regarding prescription-only dispensing, dispensing of antibiotics without prescription is a common practice; for some drugs the level is 50% higher than the quantities dispensed with a valid physician-issued prescription. Data obtained from the Health Insurance Fund (HIF) and Macedonian Agency for Medicines and Medical Devices (MALMED) for 2017 show that the ratio of the most commonly used antibiotics dispensed in community pharmacies with and without a prescription is 1.4:1 (with the highest ratio for amoxicillin + clavulanic acid at 1.5:1 and the lowest for azithromycin at 1.0:1).[1]

This section describes the main patterns of systemic antibiotic use at three levels of care, focusing on the main issues related to antibiotic prescribing and dispensing. Definitions of the main terms used are set out in Box 4.

1 Data from an internal report of the Multisectoral Committee on AMR, Ministry of Health, 2018.

Box 4. Definitions

Antimicrobial resistance (AMR) is resistance developed by microorganisms, such as bacteria, viruses, fungi and parasites to antimicrobial agents (30).

Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics, and its development is linked to how often antibiotics are used (30).

Empirical antibiotic therapy is treatment based on clinical experience, without the cause of the infection being known. It should be amended when the causative pathogen is identified.

Definitive antibiotic therapy is treatment given with knowledge of the aetiological pathogen and/or antibiotic susceptibility data.

Defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a statistical measure of drug consumption (37).

DDD per 100 bed-days is an indicator used to measure drug use by inpatients, for which a common definition of bed-day is a day during which a patient is confined to a bed and stays overnight in a hospital. Day cases (patients admitted for a medical procedure or surgery in the morning and released before the evening) are sometimes included as one bed-day and sometimes excluded (37).

Access antibiotics, according to the WHO model list of essential medicines, include antibiotics that should be widely available, affordable and quality-assured. This group includes, among others, broad- and narrow-spectrum penicillins, some third-generation cephalosporins and some macrolides and glycopeptides (38).

Watch group antibiotics, according to the WHO model list of essential medicines, include antibiotic classes that have higher resistance potential and so are recommended as first- or second-choice treatment only for a specific, limited number of indications. This group includes, among other, quinolones, fluoroquinolones, third-generation cephalosporins, macrolides, glycopeptides, carbapenems and penems (38).

Reserve group antibiotics, according to the WHO model list of essential medicines, include antibiotics that should be treated as "last resort" options; they should be accessible but their use should be tailored to highly specific patients and settings. This group includes, among others, fourth- and fifth-generation cephalosporins, polymyxins and aztreonam (38).

WELL MONITORED BUT HIGH ANTIBIOTIC USE AT THE PRIMARY CARE LEVEL

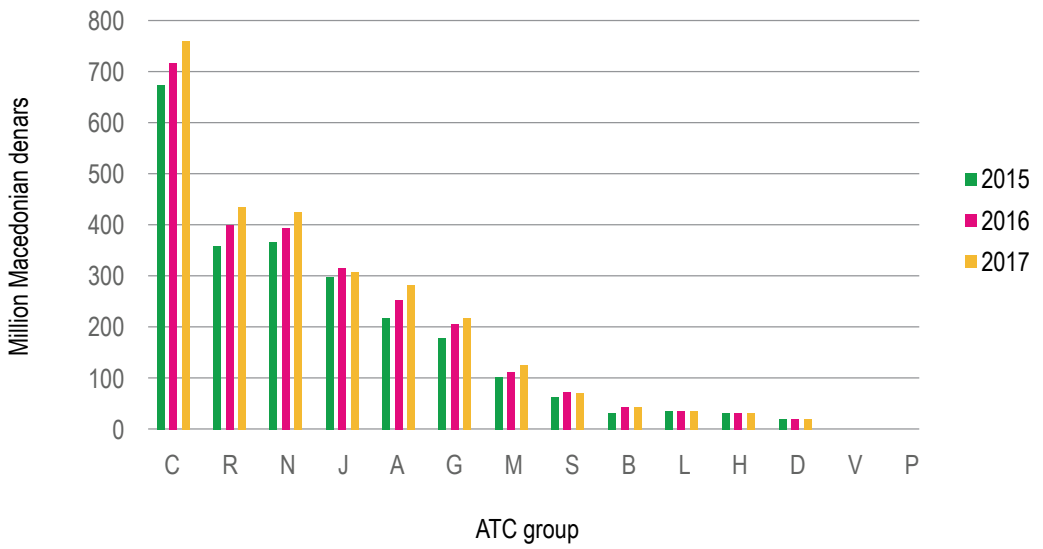
Since 2010, overall drug use at the primary care level in North Macedonia has increased in almost all Anatomical Therapeutic Chemical (ATC) groups. In absolute terms of number of prescriptions, however, prescribing of antibacterial drugs covered by the national compulsory health insurance in 2013 was 8.1% lower than in 2012 and 10.7% lower than in 2010, as a result of systemic measures and awareness-raising campaigns (39, 40).

In the following years, however, antibiotic prescribing and consumption rose again, influenced by various factors, the most important of which were reductions of antibiotic prices and lavish prescribing budget ceilings within the capitation. In 2017 antibiotic consumption covered by health insurance in primary care was 20.0 DDDs per 1000 insured inhabitants per day.

In monetary terms, the cost of antibiotics (ATC group J) covered by health insurance ranked fourth after cardiovascular (ATC group C), respiratory (ATC group R) and central nervous system (ATC group N) medicines (Fig. 1) (40). Insurance-covered antimicrobial prescribing levels in primary care alone in the past five years were 17–20 DDDs per 1000 insured inhabitants per day, which is close to the 2016 EU/EEA population-weighted mean consumption of 21.9 DDDs per

1000 inhabitants per day, but still much higher than the level in the Netherlands, which has the lowest level at 10.4 DDDs per 1000 inhabitants per day (34, 36).

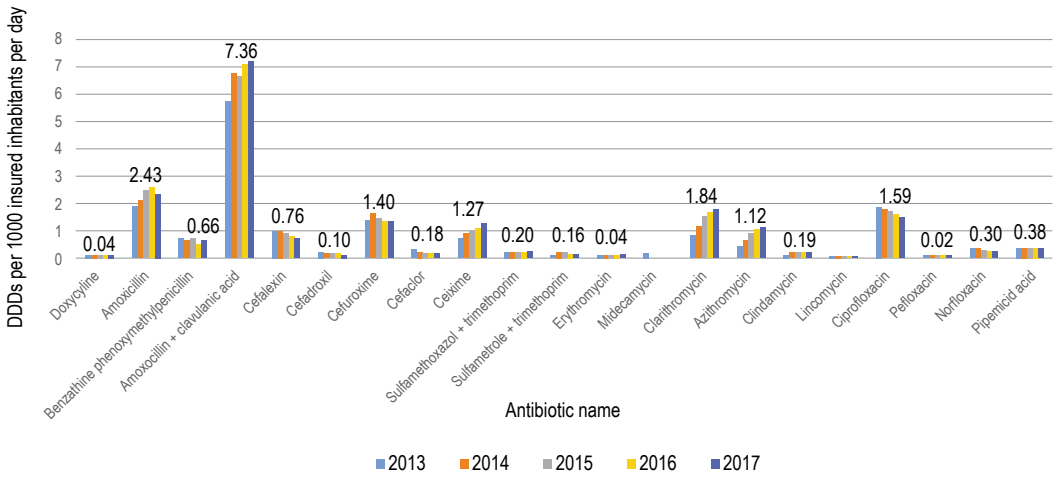
Fig. 1. Consumption of medicines covered by the HIF, by ATC group, 2015–17



Source: HIF, 2018 data.

In 2016 the total number of prescriptions for antimicrobial drugs in North Macedonia was 1.5% higher than in 2015. The main increase in prescribing was observed for the following medicines: amoxicillin + clavulanic acid, cefuroxime, sulfamethoxazole + trimethoprim and clindamycin (which belong to the access group of antibiotics, according to the WHO model list of essential medicines (38)), as well as azithromycin, cefixime and clarithromycin (which belong to the watch group of antibiotics). The most prescribed antibacterial medicine by number of dispensed prescriptions in 2017 was amoxicillin + clavulanic acid, which was also the most consumed, at 7.36 DDDs per 1000 insured inhabitants per day (Fig. 2) (41).

Fig. 2. Antibiotic consumption by ATC J01 level V, 2013–17



Source: HIF data.

According to HIF data, in 2017 beta-lactam antibacterials (ATC code J01C) were the most prescribed antibiotics, with amoxicillin + clavulanic acid accounting for one third of prescriptions (41).

SYSTEMATIC MONITORING OF ANTIBIOTIC USE IN HOSPITALS REQUIRED

No systematic data collection on antibiotic consumption in hospitals takes place in North Macedonia, mainly because hospitals procure their own antibiotics and no requirement to report on medicine procurement or use has been explicitly imposed. Reporting from hospitals to the HIF is in the form of aggregated invoices, comprising costs of interventions and medicines used (41). In mid-2019 the HIF initiated medicine consumption reporting from HIF-contracted hospitals; the effects of this system are yet to be assessed.

A nationwide assessment of antibiotic consumption at the hospital level undertaken in 2015 concluded that, owing to an absence of sufficient data and applicable clinical guidelines, it was not possible to assess the appropriateness of antibiotic prescribing in inpatient facilities. As a result, it was recommended that policy-makers should consider introducing a comprehensive reporting system on medicine use in hospitals.[2] In the absence of nationwide data, several smaller-scale studies were conducted.

A point prevalence survey (PPS) conducted in 2015 in 12 university clinics in the capital city of Skopje[3] identified excessive non-prudent antibiotic use. The total prevalence of patients

2 Data from an internal report of the Multisectoral Committee on AMR, Ministry of Health, 2015.

3 The survey was conducted in total of 44 wards in 12 clinics. Its dominant focus was on the following four clinics: University Clinic for Children Diseases (13 wards), University Clinic for Surgical Diseases "St. Naum Ohridski" (10 wards), University Clinic for Infectious Diseases and Febrile Conditions (6 wards) and University Clinic for Traumatology, Orthopaedic Diseases, Anaesthesia, Reanimation, Intensive Care (TOARILUC) (3 wards).

receiving at least one antimicrobial agent was 64.2%, which was nearly double the mean global rate of 34.7%. In the context of the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance project, the Skopje PPS demonstrated a very high prevalence rate compared not only to western European countries but also to neighbouring Kosovo[4] (47.4%) and Albania (39.3%). The only country found to have a higher prevalence rate was Nigeria, at 69.7%. The PPS showed that the most commonly prescribed antimicrobial was ceftriaxone (41.7%); the proportions for all other agents were less than 8% (ciprofloxacin, clindamycin, amikacin, metronidazole, cefotaxime, vancomycin, co-trimoxazole, gentamicin and so forth). By indication, ceftriaxone was the drug most commonly prescribed for surgical prophylaxis (66.5%) and community-acquired infections (38.3%); vancomycin for hospital-acquired infections (24.1%) and ciprofloxacin (19.1%) and co-trimoxazole (17.65%) for medical prophylaxis (42).

A lack of adherence to clinical guidelines also contributes to unnecessary and non-prudent antibiotic use in hospitals. The Skopje PPS found that of 194 patients receiving surgical prophylaxis, none was given a single dose; only nine received one-day prophylaxis and the remaining 185 received prophylaxis for more than one day, contrary to clinical guidelines (42).

SPILL-OVER PRESCRIBING BETWEEN PRIMARY AND SECONDARY CARE

According to a retrospective (unpublished) observational study conducted in 2014 in primary care in North Macedonia, 58% of patients with acute respiratory infections were treated with an antibiotic. Most of the patients were children aged 0–10 years (44%) and working-age population of 20–50 years (20%). The most common acute respiratory infections were tonsillopharyngitis (88%) and bronchitis (68%), and the antibiotics most frequently prescribed were amoxicillin + clavulanic acid (34.8%), followed by cephalosporin (22.5%), amoxicillin (22%) and macrolides (11.6%). The majority of prescriptions were issued on a Monday, mostly for patients who had begun therapy prescribed by emergency services during weekends and night shifts. In most cases, the therapy was prescribed empirically and there is no evidence that clinical guidelines were used.

Discussions with clinical specialists, infectious disease specialists and microbiologists revealed that patients from primary care are often referred to secondary care having already started empirical therapy, which hinders proper diagnostics (e.g. microbiological testing and culturing). This further delays appropriate therapeutic decision-making, and imposes continuation of empirical prescribing. On the other hand, primary care physicians stated that they often have to prescribe to patients who have already started empirical therapy prescribed by night-shift or weekend attending services, which also hinders proper diagnostic procedures.[5] According to the literature, this kind of non-prudent antibiotic use is related to hierarchical positioning and vertical movement of patients across the system (43–45). It also results from so-called prescribing etiquette, referring to an unwritten social code of practice around antibiotic prescribing, which includes preserving clinical autonomy and reluctance to interfere with antibiotic prescribing of peers, at the same or different levels of care (46).

4 In accordance with United Nations Security Council Resolution 1244 (1999).

5 Unpublished discussions and conclusions of the 3rd Symposium on Antibiotics in Primary Care, organized by the Association of Family Medicine Doctors – Respiratory Group, November 2016, Skopje, North Macedonia.

Consequences of the problem

Inappropriate antibiotic therapy has a number of health and socioeconomic consequences, which have been described extensively in the literature (47–51). They can have negative effects at both the individual and the population level. This subsection provides an overview of some of the most important consequences of inappropriate prescribing of antibiotics in hospitals.

ANTIBIOTIC RESISTANCE AND ASSOCIATED COSTS

Antibiotic resistance is directly related to antibiotic misuse, and to inappropriate antibiotic prescribing in particular (2, 7, 52). Infections caused by multidrug-resistant bacteria are associated with prolonged hospital stays and higher mortality (51, 53) compared to infections caused by susceptible bacteria. Unfortunately, no official data are available at the country level on the extent to which resistant bacteria have influenced average length of hospital stay or patient outcomes, and even global evidence on this issue is very limited (53).

Antibiotic resistance recording and reporting began in North Macedonia in 2013 when the country joined the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) Network. Through this, the country reports AMR from all laboratories performing testing of blood and cerebrospinal fluid from hospitalized patients.

Country-level data for 2018 shows that Escherichia coli resistance ranged from 3% for ertapenem to 96% for aminopenicillins, with multidrug resistance in 40% of isolates. Multidrug resistance in Klebsiella pneumoniae was found in 79% of isolates. In Acinetobacter species resistance was 68% for amikacin and higher for all other agents, with multidrug resistance of 74%. Among Staphylococcus aureus isolates, 54% were methicillin-resistant (54).

The percentage of resistance in invasive strains isolated in the country is significantly higher than the average in the EU, but similar to those in southern and south-eastern European countries. According to the CAESAR Network's 2017 and 2019 annual reports, and in the opinion of the national professional community, this country-level data might be biased due to over-representation of more severely ill and pretreated patients receiving tertiary care (selective sampling) and an overall low number of isolates (low utilization of blood culture diagnostics) influencing the representativeness of the results (54, 55).

COSTS ARISING FROM NON-PRUDENT ANTIBIOTIC USE

Non-prudent antibiotic use is associated with increased direct and indirect costs at both the individual and system levels (49). Direct costs are those arising from excessive and unnecessary antibiotic prescribing at all levels of care, including in hospitals (56). A recent study in the United States showed that redundant and non-prudent antibiotic use occurs in hospital settings and was associated with almost 2% of the total expenses for all American hospitals in 2012 (57). The literature examined showed that physicians are rarely aware or concerned when it comes to costs of prescribing (58, 59), although some studies found that costs to the system (60–62) and costs to the patients were considered in decision-making (63). Other factors are usually viewed as more important than costs, including health condition, comorbidities and diagnostic uncertainty (59, 64–66).

Indirect costs are mainly associated with inappropriate antibiotic use and AMR (67, 68). Multidrug-resistant infections are associated with increased costs resulting from prolonged hospital stays (the principal contributor); the need to use more expensive antibiotics; and

expenses related to screening and surveillance, eradication regimens and consumables for protection of the staff such as gloves, gowns and aprons used to prevent cross-infection (68, 69).

In North Macedonia, no analysis was found on the costs of non-prudent antibiotic use or AMR. Although an AMR surveillance and reporting system is in place, the data so far have not been used to trace direct or indirect costs for the health system or individual patients. Based on the literature, it can be assumed that such costs are significant, and that understanding their type and magnitude might help to shape policies and allocate resources to prevent their occurrence.

Factors influencing antibiotic prescribing in hospitals

In 1999, WHO conducted a comprehensive literature review of factors influencing non-prudent use of antibiotics across the prescribing process and stakeholders, and divided them into system, provider, patient, health setting, industry and environmental factors (70). Based on this review and further literature searches, the most common underlying factors contributing to the problem of non-prudent and excessive empirical prescribing of antibiotics in hospitals include lack of appropriately applicable clinical guidelines and prescribing protocols; diagnostics and diagnostic uncertainty; physicians' knowledge and prescribing autonomy; and the influence of others. These are described in further detail in relation to North Macedonia in the following subsections.

EXISTENCE OF AND ADHERENCE TO CLINICAL GUIDELINES

As medicines represent a significant element of treatment pathways for many diseases, their common availability and the potential absence of professional supervision raise concerns regarding potential inappropriate use (71–73). This has been argued to result in potential misdiagnosis, masking of more serious conditions and harmful interactions with other medicines taken concurrently (73–75). Thus, providing professional support and expert knowledge for therapeutic decisions on medicines becomes an intrinsic part of the health care system.

Evidence-based clinical guidelines are established to standardize quality of care, including prescribing decisions of physicians at both primary (76) and other levels of care (64, 77). They are also a proven tool for addressing antibiotic resistance (78–80).

In North Macedonia, clinical guidelines for most medical specialties were translated and adopted during 2007 from Cochrane repositories of clinical guidelines, alongside a few from other sources. Some of these guidelines are reported to be unimplementable by practitioners because of lack of adaptation to national specifics of the health system and availability of resources (81). Because doctors' associations were not significantly involved in the development of guidelines there is a lack of feeling of ownership for them. This, together with the lack of contextual adaptation, represents a barrier to implementation. In addition, no system is in place to assess adherence to clinical guidelines routinely, and validation takes place only through a periodic accreditation process.

DIAGNOSTIC TOOLS AND RESOURCES

In addition to the lack of clinical guidelines to the national context, a lack of funding for diagnostics of infectious diseases at all levels of care is also reported; this was also identified

as a concern in the last two CAESAR Network reports (54, 55). This is particularly problematic in secondary and tertiary care facilities, where cases with higher complexity are admitted and treated (81). A literature review showed that, in inpatient settings, rates of administering antibiotics are still to a large extent based on clinical/empirical assessment, which accounts for over half of antibiotic use in hospitals (82–85). High levels of antibiotic use in hospital settings can be attributed to the lack of rapid diagnostic techniques, leading to major reliance on culture methods and biochemical assays as the most accurate and widespread identification of bacterial infections (86), which often take 36–48 hours to provide results. In addition, although early diagnosis usually implies lower costs thanks to a more effective approach to treatment, in public facilities in North Macedonia diagnostics and treatment are part of the same funding package, which frequently forces physicians to opt for empirical treatment, without carrying out expensive diagnostics (87). Thus, viral infections are often misdiagnosed as bacterial infections, leading to inappropriately prescribed antibiotics which, in conjunction with unnecessary use of broad-spectrum antibiotics for prophylaxis, continue to amplify the growth of resistance (86, 88). There is evidence of a misperception that infections are most effectively managed on the basis of clinical/empirical assessment (13), which further contributes to non-prudent antibiotic use and increased antibiotic resistance. A multi-stakeholder workshop on antibiotic stewardship held in the country in 2017 came to the conclusion that the frequency of empirical prescribing of antibiotics is greater than clinically acceptable, and that this is mainly due to the lack of diagnostics, resulting in defensive prescribing in cases of diagnostic uncertainty (81).

A relatively low number of blood cultures are taken in the country, hampering detection of resistant bacterial strains. The lower number of isolated strains in the country is not due to successful disease prevention but rather to the fact that blood cultures are taken and processed 10 times less often than in EU countries, and mainly after treatment failure (55). For example, North Macedonia has exceptionally low number of strains of Streptococcus pneumoniae compared to EU/EEA countries. In addition, 40% of the blood cultures taken are from children aged 0–4 years, which points to the fact that selective sampling takes place, not necessarily following a specific case definition. In a multi-stakeholder workshop on antibiotic stewardship conducted in the country in 2017, participants discussed that this finding could be related to low allocation in hospital budgets for diagnostic tests related to infectious diseases, defined through the diagnosis-related groups system for hospital financing (81). They also highlighted that the country has, in principle, sufficient microbiological laboratories with the capacity to perform species identification of bacterial pathogens and antimicrobial susceptibility testing.

PHYSICIANS' KNOWLEDGE AND EXPERIENCE

Inappropriate antibiotic prescribing can also stem from lack of familiarity with guidelines and local resistance data (89). Perceived risks of not treating, usually associated with diagnostic uncertainty, can also play a role in decision-making leading to defensive prescribing. One study found that physicians sometimes prescribed without medical indication to prevent complications, and felt comfortable with such decisions (90). Thus, physicians' knowledge and experience play a pivotal role in prescribing decisions, especially in hospital settings (87).

In one Scandinavian study (91), the authors concluded that doctors have an individual and constant pattern of prescribing antibiotics. Other studies show that guidelines might not always have sufficient impact to influence decision-making (92, 93), and that other factors can override the "written rules" when they differ from the physician's experience (94), from

other guidelines (92) or from the best interests of the patient (76). These other factors include professional experience (94–96), maintaining professional autonomy (97, 98) and the influence of others (87, 96).

This indicates that doctors' beliefs about prescribing and their behaviour are stable and consistent over time (99). Strategies to implement guidelines and change prescribing choice for the long term need to tackle these beliefs and habits (100). Physicians' knowledge is acquired through medical education, learning from peers and continuous professional development. A literature review showed evidence that targeted educational efforts at the practice level (93, 101) and monitoring of prescribing at the individual provider level (102) have significant influence in changing prescribing behaviour.

INFLUENCE OF OTHERS

As noted above, physicians can be influenced by and can influence their colleagues by giving advice and by setting an example with their own prescribing practices (87). The influence of others' prescribing on a physician's decision-making has been assessed in the literature, and there is evidence that such influence is recognized and acknowledged in physicians' perceptions. Research into these attitudes shows that, further to their own experience, physicians greatly value the experience of colleagues and peers, especially among clinicians at the hospital level, who also have influence on decisions on prescribing in primary care (103, 104). Several other studies have concluded that primary care physicians feel reluctant to discontinue a prescription from a higher level of care, such as a specialist or hospital clinician (103, 105, 106).

Equity-related observations

Data on hospital and inpatient consumption of antibiotics in the country are very limited, and lack of data remains one of the major obstacles in assessing and addressing inappropriate use of antibiotics in hospitals. In addition, clinical guidelines, in terms of their applicability, do not relate to the health system settings and capacity in North Macedonia. This further hinders the ability to link data to diagnostic and treatment protocols, in order to assess efficiency and efficacy of antibiotic therapy in hospital patients. In addition, it prevents the development of local (health care setting-specific) guidelines, which are considered the norm in mitigation of antibiotic resistance. Although no systematic data gathering for antibiotic consumption in secondary and tertiary care takes place, however, the assessment of antibiotic use in hospitals undertaken in 2015 for the period 2011–14 showed no significant geographical difference between hospitals, which implies that the factors influencing inappropriate prescribing have to be addressed systematically, across all hospitals and inpatient facilities in the country.

As noted above, the survey of prescribing practices in primary care showed significant age differences in prescribing, with more abundant prescribing for children. A literature review revealed similar experiences in the Netherlands, where low adherence to guidelines in paediatric primary care was found in terms of use of narrow-spectrum penicillin for fever, ear infections and acute respiratory infections in children under 4 years of age (107). Assuming that this might also be the case for hospital prescribing patterns, further data gathering and analyses should be performed for both diagnosis- and age-disaggregated prescribing.

OPTIONS TO ADDRESS THE PROBLEM

The issue of unnecessary and excessive empirical prescribing of antibiotic therapy in hospitals is multifaceted and requires diverse approaches, involving multiple stakeholders. Many policy options can be considered to address the issue, including actions that are interlinked and can be undertaken in parallel or consecutively. This evidence brief for policy proposes three options for which sound evidence of positive outcomes exists; these should be discussed and reviewed in the light of the national context and other – societal, economic and cultural – circumstances, to determine the optimal and most feasible approach. The three options are elaborated in further detail in the following subsections.

Option 1. Revision, contextualization and implementation of guidelines for antibiotic therapy

OVERVIEW AND CONTEXT

Implementing clinical guidelines for treating infections has proved one of the most successful antimicrobial stewardship strategies (7, 108). North Macedonia currently has clinical guidelines for most conditions, including treatment of infections, but these are translations of guidelines developed by other institutions that are not fully adapted to the national context in general and to local resistance data in particular (81). Recommendations on antibiotic treatment of infections in hospitals developed by professional societies (81, 109, 110) have been applied widely in similar contexts – for example, in Slovenia (111). These could be used to review and adapt guidelines applicable to the specific context of North Macedonia. The review could also take into consideration the latest revision of the WHO model list of essential medicines, providing specific guidance on appropriateness of use of each antibiotic, based on the most recent antibiotic resistance data worldwide (38).

EVIDENCE ON THE IMPACT OF OPTION 1

Significant evidence exists about the efficacy of clinical guidelines in achieving rational antibiotic use and containment of AMR. The 2017 updated systematic review of Davey et al. suggests that appropriate antibiotic use, in conjunction with proper infection prevention and control activities as set out in guidelines, is likely to contain development of antibiotic resistance (7). Prudent antibiotic use benefits the patient, while at the same time minimizing the probability of adverse effects and development of antibiotic resistance. Importantly, guideline-adherent therapy is associated with a relative risk reduction for mortality (80, 108).

The global public health community, including WHO, the European Commission, ECDC and CDC, advocate adoption and use of clinical guidelines. The literature also shows, however, that adoption without adaptation to the national context may have adverse effects on practice (7).

A systematic review of antibiotic stewardship programmes (ASPs) in hospitals found that prescribing empirical antibiotic therapy according to guidelines was associated with reduced mortality in 31/37 studies (80). The relative risk reduction across all studies was 35% (relative risk ratio 0.65; 95% confidence interval 0.54–0.80, p<0.0001). Thus, empirical antibiotic therapy for the most common types of infection (such as respiratory and urinary), tailored to local resistance data, is recommended.

In many EU countries an estimated 60–70% of antibiotics are prescribed in primary care (36). While outside the scope of this evidence brief for policy, it is important to recognize that use of antibiotics in primary care greatly influences available choices of therapy in secondary and tertiary care. It is vital to be aware which antibiotics are prescribed to a patient in primary care if the same patient presents in a hospital to avoid physicians making incorrect choices. It is also essential that so-called reserve group antibiotics (such as colistin, vancomycin, moxifloxacin and so on) remain restricted to prescribing in hospitals, and particularly intensive care units. According to one systematic scoping review, an adequate hierarchy in prescribing is at the core of a successful strategy for prudent antibiotic use (112).

In many European countries (including the United Kingdom and the Netherlands) guidelines for antibacterial therapy are applicable across all levels of care (NICE (109); SWAB (110)). Both primary care physicians and medical specialists at other levels of care are part of a national committee that writes guidelines covering all possible patient settings (from primary to tertiary care, and sometimes even for long-term care facilities).

Table 1 sets out a summary of the key findings from the synthesized research evidence for this option. A further description of evidence is provided in Table A1 in Annex 1.

Table 1. Summary of key findings from systematic reviews relevant to option 1

Category	Key findings
Benefits	» At least three systematic reviews of medium quality found that through appropriate and prudent antibiotic use, in conjunction with proper infection prevention and control activities, antibiotic resistance can be contained (7, 78, 113). » An overview of 26 systematic reviews of high quality on educational techniques found that clinical guidelines were very effective in improving performance and patient health outcomes (114). » A systematic review of medium quality suggested that guidelines for diagnosis and management improve antibiotic prescribing (78). » According to a systematic review with meta-analysis of medium quality, adherence to guidelines for appropriate antibiotic use result in better patient outcomes and reduction of mortality. The relative risk reduction across all 37 studies was 35% (relative risk ratio 0.65; 95% confidence interval 0.54–0.80, p<0.0001) (80). » One review of medium quality found that the primary advantage of a prospective audit and feedback strategy is that doctors do not perceive a loss of prescribing autonomy in view of the fact that acceptance of recommendations is voluntary. It is therefore more acceptable to doctors and less open to active opposition. This strategy also provides opportunities for education through the feedback mechanism, and can be customized to the size of the institution depending on the resources available (115).

Table 1. (Contd)

Category	Key findings
Potential harms	» According to one systematic review of medium quality, evidence-based practice is thought to decrease therapeutic autonomy and thus reduce motivation to implement it (116). » At least one systematic review of medium quality found that when evidence-based practice is implemented, it does not always mean that high-quality evidence is being used; this may affect the quality of care provided (116). » At least one systematic review of medium quality found that lack of training in providing feedback and lack of trust in the formative nature of assessment had a negative effect on behavioural change in physician performance (117). » A systematic review of high quality suggested that poor adaptation of guidelines and relocation of resources can lead to inappropriate antibiotic use and increased costs (78).
Resource use, costs and/or cost-effectiveness	» According to one systematic review, a programme for development and implementation of evidence-based guidelines (for any clinical subject but certainly for appropriate antibiotic use) needs continuous funding at both governmental and facility levels (118). » One systematic review of high quality found that appropriate antibiotic use according to treatment guidelines (indication, choice, duration) contributes to improved drug utilization and better patient outcomes, and reduces unnecessary antibiotic use and expenses of potential complications. Therefore, the measure as a whole can be regarded as cost-effective (113). » One systematic review of high quality and at least one primary study found that implementing evidence-based practices reduces costs for health care organizations, and appropriate antibiotic use contributes to reducing treatment costs from eventual complications (113, 119). » According to an evidence-based guideline, prescribing pathways between primary, secondary and tertiary care is effectively improving patient outcomes, reducing antibiotic use and reducing costs (120).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» One qualitative study showed that clinical guideline adherence in hospitals is influenced by pretreatment in primary care (121). » According to at least one systematic review, prehospital antibiotic therapy and fluid resuscitation improve patient outcomes (122). » One systematic review of medium quality found that physicians recognize the potential value of guidelines but do not always trust the information contained in them and see the relevance to their patients (78). » At least two systematic reviews of medium quality found that even though evidence-based practice is embraced by health care workers and organizations, its implementation is still scarce (112, 116).

Table 1. (Contd)

Category	Key findings
Key elements of the policy option if tried elsewhere	According to international experiences described in the literature (123), the following elements have been key to successful application of guidelines: » necessary funding, infrastructure and regulatory support for implementation; » development of a set of quality indicators derived from accepted guidelines in order to measure and improve antibiotic prescribing (a well established guideline programme is an important prerequisite for a national ASP to be successful – evidence-based guidelines on the diagnosis and the treatment of common infections, and on the prophylaxis of infections in general, are essential to serve as a strong base for local guideline development in health care facilities); » regular monitoring of guideline compliance, generally instituted in national and local ASPs to fuel feedback to prescribers based on the results – this constitutes a core element of a functioning antimicrobial management team in a health care facility.
Stakeholders' views and experiences	» Health care professionals in the country confirm that current clinical guidelines are not adapted to the national circumstances and therefore not fully applicable. » Health care professionals consider that the preparation of guidelines should be part of the activity of professional associations: they need to be owners so that the guidelines can be accepted and applied. » Infection disease specialists and microbiologists insist that guidelines should be subject to regular revision, following national and local (hospital level) resistance data.

Option 2. Establishment of ASPs in hospitals, accompanied by an antibiotic use reporting system

OVERVIEW AND CONTEXT

Necessity for establishment of an ASP at the hospital level, as part of system-wide approach to promoting and monitoring appropriate use of antibiotics, is widely known (7, 124). The literature shows that many institutions establish ASPs to optimize antimicrobial therapy, reduce treatment-related costs, improve clinical outcomes and safety, and minimize or stabilize AMR (125, 126).

Antibiotic stewardship can be thought of as a menu of interventions that can be designed and adapted to fit the infrastructure of any hospital. ASPs encompass two intrinsically different sets of interventions describing either the "what" or the "how". The first set describes recommended antimicrobial care interventions – or antimicrobial prescribing practices that define "appropriate antimicrobial use" for hospital inpatients – regarding indication, choice of drug, dose, route or duration of treatment. Examples of such interventions are switching from intravenous to oral antimicrobial therapy, streamlining therapy in individual patients when appropriate (80) and using diagnostic tests to determine appropriate antimicrobial therapy (115).

The second set of interventions ensures that professionals actually apply these prescribing behaviours to daily practice. It includes many different behavioural change interventions –

such as provision of a formulary, prospective or retrospective audit and feedback, educational meetings, reminders, financial interventions or the revision of professional roles – that all can be implemented to improve appropriate antimicrobial use prescribing practices. Thus, the second set of interventions is applied among professionals to ensure that the first set is appropriately applied among patients. These behavioural change interventions either directly or indirectly (through interventions targeting the system/organization) target the professional and, overall, restrict or guide towards more effective professional use of antibiotics.

Implementation of hospital ASPs represents an important government-level intervention, and thus must be fully supported by the Ministry of Health. It is proposed that the intervention is firstly applied as a pilot in several hospitals, with full Ministry of Health support to ensure proper and uninterrupted implementation. The piloting phase can also largely benefit from the experiences of private hospitals in the country, which already have well established ASPs in place. Furthermore, the intervention can be extrapolated to the national level through the hospital accreditation mechanism, as stewardship programmes are an important aspect of patient safety (127).

EVIDENCE ON THE IMPACT OF OPTION 2

Evidence from at least five systematic reviews shows that ASPs in hospitals contribute to improved prescribing practices (7, 80, 124, 128, 129). Overall antibiotic use among inpatients was reduced by almost one fifth, and antibiotic costs, average length of hospital stay and the number of infections caused by certain multidrug-resistant organisms also decreased (7, 124, 130). Hospital ASPs, possibly supported by information technology interventions (131), result in significant decreases (20–50%) in inappropriate antibiotic use and costs; this is even more evident in intensive care units (130). Davey et al. (7) and Teerawattanapong et al. (132) also reported improved situations with infections caused by specific antibiotic-resistant pathogens and reductions of overall average hospital length of stay by 1.12 days.

Davey et al. (7) showed that persuasive interventions (such as education, reminders and feedback) are slightly less effective than restrictive interventions (such as prior authorization of prescription for a selected group of antibiotics, a restricted hospital antibiotic drug list, automated stop orders and similar). The downside of restrictive interventions may be that they may lead to a breakdown of communication and trust between controlling (infectious disease specialist, microbiologist and pharmacist) and prescribing teams. There is some evidence that restrictive interventions are more effective in outbreak settings, where a rapid response is required.

Table 2 sets out a summary of the key findings from the synthesized research evidence for this option. A further description of evidence is provided in Table A2 in Annex 1.

Table 2. Summary of key findings from systematic reviews relevant to option 2

Category	Key findings
Benefits	» One systematic review with meta-analysis of high quality found that ASPs reduce economic burdens for hospitals through reduced antibiotic use and reduced antibiotic resistance (133). » At least two systematic reviews with meta-analysis of medium quality found that presence of targeted ASPs in hospitals decreases total antibiotic usage, improves the quality of prescribing and reduces adverse patient outcomes, specifically for Clostridium difficile infections (128, 129). » One systematic review of high quality found that audit and feedback can improve quality of care by 10% (134). » At least four systematic reviews of high and medium quality encouraged implementation of evidence-based practices for higher quality of care, since they significantly improve skills, knowledge and attitudes of providers (112, 116, 135, 136).
Potential harms	» No systematic reviews provided information about the potential harm of introducing ASPs, but not all reviews analysed established the significance of positive effects of ASPs on patient outcomes.
Resource use, costs and/or cost-effectiveness	» At least one systematic review of high quality found that ASP development and implementation need continuous funding at both governmental and facility level (124). » According to one systematic review of medium quality, hospital ASPs result in significant reductions in antibiotic consumption and costs. Rates of infection caused by specific antibiotic-resistant bacteria decreased and the overall length of hospital stay improved (78). » A high-quality systematic review with meta-analysis showed a decrease in overall antimicrobial cost by −33.9% (confidence interval −42.0 to −25.9) and of length of stay by −8.9% (confidence interval −12.8 to −5.0) in a hospital setting as a result of antimicrobial stewardship interventions (133).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» The significance of positive effects of ASPs on patient outcomes was not established in all reviews. » One systematic review of high quality suggested that the effectiveness of an intervention on antibiotic prescribing depends on the physician's prescribing behaviour or preference and the barriers to change (124). » Two systematic reviews of high quality suggested that most interventions are multifaceted, making specific recommendations about key components difficult (78, 137).

Table 2. (Contd)

Category	Key findings
Key elements of the policy option if tried elsewhere	» One systematic review with meta-analysis of high quality found that the basis of a national ASP is related clinical guidelines that address primary care, hospital care and long-term care facilities (131). » One overview reviewed key elements essential to the success of implementing ASPs and found that these are education of ASP leadership, gaining support from medical leadership, ensuring dedicated time for professionals to organize the programme and ensuring availability of local data on resistance (123). » Two systematic reviews of high quality and a meta-analysis of medium quality specified that feedback is most effective when baseline adherence to recommended practice is low, and when it is provided by a supervisor or a colleague, delivered intensively and more than once (preferably in written form), individualized and including specific goals and action plans (134, 138, 139). » One systematic review of high quality found that general implementation principles suggest that performing a thorough analysis of barriers and facilitators will ease implementation of ASPs in local practice (7). » According to evidence-based guidelines, in inpatient settings, antibiotic use should be monitored via antibiotic administration, instead of purchasing/costing data (140).
Stakeholders' views and experiences	» Health professionals understand and consider antimicrobial stewardship to be a necessary part of prudent antibiotic use. » According to health professionals, further support from the system is needed to have a comprehensive and coordinated approach to prudent antibiotic use. » According to health professionals and facility managers, the process of introducing prudent antibiotic use should commence within each department and at facility level, in a form of internal review, consultation and ASP education where necessary.

Option 3. Strengthening curricula on prudent antibiotic use in undergraduate, postgraduate and continuous education for all health professions

OVERVIEW AND CONTEXT

Education and knowledge – contextualized knowledge in particular – play an important part in diagnosis and prescribing decisions. Undergraduate and postgraduate education set the foundation of the medical profession, and continuous education for health professionals plays an important role in staying up to date with medical advancements and increasing knowledge on new health technologies and therapies. In particular, this is important with regard to antibiotic prescribing, given the continuously changing landscape of antibiotic resistance. Two studies reported that introducing a set of learning modules on antibiotic use and resistance into different undergraduate and postgraduate education programmes better prepares future health professionals (141), and continuous medical education helps them to keep up to date with appropriate prescribing and correct use of antibiotics, based on laboratory diagnostics when necessary, and assists with behaviour change (142, 143). In addition, a review of systematic reviews found that continuous education contributes to better adherence to clinical guidelines and better patient outcomes (114, 144).

Option 3 is linked to options 1 and 2 since sufficient education or training needs to accompany both better adherence to revised clinical guidelines and the introduction of a stewardship intervention at the hospital level. Prescriber education is more effective as a supplementary strategy to other interventions for both inpatient and outpatient facilities (115).

EVIDENCE ON THE IMPACT OF OPTION 3

Literature is extant on educational interventions for influencing behaviour, including on the effects of education on physicians' prescribing behaviour. The evidence presented for this option is derived from two overviews of systematic reviews, two reviews with meta-analysis and seven systematic reviews. In all of these, most of the studies about continuous medical education on antibiotic prescribing and AMR were performed either in hospitals or at the primary care level.

Two systematic reviews and one survey suggest that the development of teaching curricula to include the topic of appropriate antibiotic use at both the undergraduate and postgraduate levels, along with continuing education on new developments in the field of antibiotic therapy, would contribute to improvements in antibiotic prescription (7, 145, 146). Another review found that physician's education plays an important role in optimizing antibiotic use (147).

Continuing medical education improves both physician performance and patient health outcomes (148), especially when using interactive methods – such as audit/feedback and peer-to-peer consultation (114). In addition, educational interventions supported by guidelines for diagnosis and/or management improve antibiotic prescribing (147).

Table 3 sets out a summary of the key findings from the synthesized research evidence for this option. A further description of evidence is provided in Table A3 in Annex 1.

Table 3. Summary of key findings from systematic reviews relevant to option 3

Category	Key findings
Benefits	» An overview of 39 systematic reviews of high quality found that continuing medical education improves both physician performance and patient health outcomes, with more reliably positive effects on the former than the latter. Continuous professional development activities that are more interactive, use more methods and are focused on outcomes considered important by physicians lead to more positive outcomes (148). » An overview of 26 systematic reviews of high quality on educational techniques found that interactive methods – such as audit/feedback and peer-to-peer consultations – were the most effective at improving performance and patient health outcomes (114). » A systematic review of medium quality found that antibiotic prescription was reduced by 34% on average in intervention groups of medical professionals receiving continuing education compared to control groups. The number of inappropriate antibiotic prescriptions was also reduced by an average of 41% compared to control groups. Also, found that guidelines for diagnosis and management improve antibiotic prescribing (147). » A systematic review found that physician education is important in optimizing antibiotic use (113). In addition, a systematic review and a narrative synthesis found that training of teams can meaningfully improve participant knowledge or attitudes, teamwork, clinical care and even patient outcomes, including those concerning adverse events, mortality and morbidity across a range of clinical contexts (146, 149).
Potential harms	» No systematic review provided information about the potential harm of introducing antibiotic stewardship in the medical education curriculum.
Resource use, costs and/or cost-effectiveness	» One systematic review, one evidence-based guideline and one expert committee report suggested that curriculum development, increased training and education require additional funding (7, 140, 144).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» One study suggested that students take on the practice of their older colleagues, which might not always be aligned with adherence to clinical guidelines (145).

Table 3. (Contd)

Category	Key findings
Key elements of the policy option if tried elsewhere	» One systematic review suggested that interventions should focus on changing physicians' behaviour rather than simply providing information and also found that multimedia and multicultural approaches provide optimal results (78). » Several systematic reviews concluded that no single intervention can be recommended for all behaviours in any setting for any outcome, and that interventions need to be adapted to the specific setting and antibiotic resistance data (78, 137, 146, 148). This is supported by a critical analysis suggesting that education strategies pertaining to active involvement of clinicians have greater effectiveness than the passive ones (150). » One systematic review found that the use of specific education interventions for clinicians and electronic decision-supporting tools improves antibiotic prescribing for acute respiratory infections (151). » According to one systematic review, education of physicians is of pivotal importance to prevent non-prudent and inappropriate antibiotic use – mostly in distinguishing between bacterial and viral infections – and to ensure appropriateness of use of narrow-spectrum instead of broad-spectrum antibiotics, where applicable (137). » At least one study and one expert committee report found that in some countries (including the United Kingdom and Zambia) the undergraduate curriculum now includes education on prudent antibiotic use. This covers education on microbiology, infectious diseases and clinical pharmacology, with an emphasis on prudent antibiotic prescribing (144, 147). » At least one study reported that in the United Kingdom a competency framework has been developed for prescribers, requiring skills in preventing and controlling infections, prescribing appropriate antibiotics for prophylaxis and treatment, understanding antibiotic stewardship in day-to-day practice and continuing professional development (152).
Stakeholders' views and experiences	» During key informant interviews, stakeholders expressed support for the development of medical curricula in undergraduate and postgraduate education, as well as for the development of targeted antibiotic stewardship courses in continuous professional development.

CONSIDERATIONS FOR IMPLEMENTING THE THREE OPTIONS

Potential barriers

OPTION 1. REVISION, CONTEXTUALIZATION AND IMPLEMENTATION OF GUIDELINES FOR ANTIBIOTIC THERAPY

Despite goodwill towards guidelines among practitioners, there is a growing consistent trend of reported difficulty in their implementation (100). One major barrier, as highlighted above, might be the lack of adjustment of guidelines to the specifics of the context, at both national and facility levels. In addition, revisions of guidelines need to bring practitioners on board, as lack of involvement could also pose a threat to effective adherence and implementation. In addition, a lack of sufficient antibiotic resistance data might limit the credibility of locally adapted guidelines. Therefore, the process of writing or adapting guidelines should be a joint activity between prescribing physicians at all levels of care, microbiologists and pharmacists, and patients where applicable; this would enable suitable adjustments to correspond to detected antibiotic resistance.

Communication between primary care physicians and medical specialists in hospitals in North Macedonia is generally regarded as poor and insufficient, and information exchange about prescribing practices is poor. The role of primary care physicians is limited in comparison to specialists in terms of use of diagnostic tests and prescription of antibiotics for specific clinical diagnoses. On the other hand, specialists do not have detailed insight into the health status of the patient – such as information on chronic diseases, other comorbidities or immunological status – when prescribing therapy, especially on an outpatient basis. According to the participants in the multi-stakeholder consultative workshop held in 2017, this greatly influences effective treatment of patients; similar results are described in the literature (47, 121, 153).

Other possible barriers to implementation of option 1 relate to wider health system organization. These include insufficient collaboration and communication between primary and secondary care, limitations on laboratory analyses for primary care (financial limitations and limited authorization), possible access to antibiotics in pharmacies without prescription or medical indication and lack of mechanisms for enforcement of guidelines across health system.

OPTION 2. ESTABLISHMENT OF ASPS IN HOSPITALS, ACCOMPANIED BY AN ANTIBIOTIC USE REPORTING SYSTEM

The reviewed literature suggests that antibiotic stewardship depends on many factors, local settings and context-based circumstances. In North Macedonia, some of the most concerning barriers to implementation of ASPs in hospitals relate to the current organization of the health

system at the facility level. This includes a lack of funding for undertaking diagnostics, as well as a lack of access to antibiotic resistance data and antibiotic use levels in each hospital, which could serve as guidance for local guideline development. In addition, the system lacks a dedicated multidisciplinary antimicrobial stewardship team consisting of clinicians, nurses, a microbiologist and a pharmacist, due to a lack of health professionals in general. This also results in a lack of staff time to dedicate to an antibiotic stewardship team. While these issues could be addressed at the facility level, barriers of wider concern include a lack of involvement of pharmacists in antibiotic prescribing – often pharmacies in hospitals serve as inventory of medicines and have no advisory role. In addition, many hospitals have no clinical pharmacist, and medicines are dispensed by the pharmaceutical technician or chief nurse. There is also a lack of microbiologists in most university clinics and hospitals, and this gap is filled via appointment of an external microbiologist to the committees for intra-hospital infections, which is a legal obligation of each hospital.

Further, as noted above, the current reporting system of medicine consumption at the facility level is not sufficient to understand or analyse antibiotic consumption, which is crucial in monitoring the rational use of antibiotics. In mid-2019 the HIF initiated a separate medicine consumption reporting system for hospitals; this is expected to contribute to better understanding of antibiotic consumption in inpatient facilities.

Finally, the ongoing stigma attached to reporting of antibiotic resistance (with fear of penalties and public disgrace) requires that antibiotic stewardship becomes an institutionalized part of the system, and not solely linked with prescribing or treatment by particular specialists.

OPTION 3. STRENGTHENING EDUCATION CURRICULA ON PRUDENT ANTIBIOTIC USE

The view that it is sufficient to convince physicians of the right thing to do as a way to improve prescribing is a very simplistic one; it ignores all the complexities that come with a consultation and the difficulties of actually changing practice, from both the individual and the health system perspective (7, 81, 124, 125, 130, 154).

Among the identified barriers to implementation of this option is a reluctance to change curricula for students in undergraduate and postgraduate levels. The main reason for this is that the curricula content is already fully established, and adding a new subject, course or additional modules within existing subjects might pose additional burden to students. On the other hand, new modules might be added to replace some existing ones, which could cause conflict with competing stakeholders. One key informant also emphasized that the medical curricula for undergraduate studies were changed recently, and that re-launching the process might require additional time and effort.

With regard to continuous medical education, some key informants pointed out that there are a number of modules in diverse disciplines already, and that adding a mandatory one for antibiotic prescribing might not be welcomed by practising physicians.

Equity considerations

OPTION 1. REVISION, CONTEXTUALIZATION AND IMPLEMENTATION OF GUIDELINES FOR ANTIBIOTIC THERAPY

As noted above, the survey of practices in primary care showed significant age differences in prescribing, favouring antibiotics for acute respiratory infections in children aged 0–10 years, mostly for conditions for which clinical guidelines do not suggest antibacterial treatment (such as tonsillopharyngitis and bronchitis). This suggests that specific attention might be needed to address the prescribing practices of hospital paediatricians by initiating a revision and contextualization of the clinical guidelines for professionals working with children and younger patients.

In addition, and as evident from the spill-over effect of antibiotic prescribing from primary to secondary care described above, specific focus on the revision and contextualization of the clinical guidelines should cover defining clinical pathways of feedforward and feedback with regards to antibiotic prescribing between primary care physicians and specialists.

OPTION 2. ESTABLISHMENT OF ASPS IN HOSPITALS, ACCOMPANIED BY AN ANTIBIOTIC USE REPORTING SYSTEM

The assessment of antibiotic use in hospitals undertaken in 2015 for the period 2011–14 showed no significant geographical difference between hospitals, which implies that the factors influencing inappropriate prescribing need to be addressed systematically across all hospitals and inpatient facilities in the country. Furthermore, and in line with the higher prescribing in younger patients identified, tailor-made antibiotic stewardship interventions need to be considered for particular specialties, pertaining but not limited to paediatricians, pulmonologists, infectious disease specialists, intensive care specialists and so forth. In addition, to achieve effective antibiotic stewardship interventions, clinical pathways for timely diagnosis and effective communication with laboratories should be considered and set in place to address potential time lags, which contribute to increased empirical prescribing.

OPTION 3. STRENGTHENING EDUCATION CURRICULA ON PRUDENT ANTIBIOTIC USE

The undergraduate medical education curricula and training programmes are already fairly well established, and while review of all curricula might be a possibility for the future, at the moment it is difficult to introduce new subjects or courses without exceeding the curricular limits of training. In this respect, although it is important to include prudent antibiotic use in the education of every future doctor, an initial approach might be to introduce antibiotic stewardship as part of an elective course scheme, which could be a basis for defining profiles of specializations beginning from undergraduate level in the future.

Regarding continuous education, antibiotic stewardship should be a required course for all doctors at all levels of care, irrespective of specialization. Nevertheless, greater focus should be put on prescribing physicians, and as noted above, on paediatricians, pulmonologists, infectious disease specialists and intensive care specialists at secondary and tertiary care levels, based on current prescribing practices.

Table 4 below sets out a summary of the potential barriers for all options.

Table 4. Potential barriers to implementing the proposed options

Level	Option 1	Option 2	Option 3
Recipients of care			
Knowledge and skills	Knowledge regarding treatment of infections and AMR is lacking (100).	Time and resources for health information provision to patients are lacking (87).	Health literacy and knowledge about effects of non-prudent antibiotic use are lacking (87).
Attitudes regarding programme acceptability, appropriateness and credibility	Although not very likely, there could be reluctance to accept new approaches to treatment, considering it might reduce patient participation in decision-making about their health (87).	Lack of involvement of patients in development of ASPs could lead to lack of compliance (87).	No significant influence is expected from patients, although in general the same barriers are to be expected as for other options, if this is to be implemented jointly with option 1 or 2 (multi-stakeholder consultative workshop discussions).
Motivation to change or adopt new behaviour	Potential exists for lack of collaboration from patients (multi-stakeholder consultative workshop discussions).	Potential exists for lack of collaboration from patients (multi-stakeholder consultative workshop discussions).	No significant influence is expected from patients (multi-stakeholder consultative workshop discussions).
Providers of care			
Knowledge and skills	Lack of training in providing feedback and lack of trust in the formative nature of assessment could have a negative effect on behavioural change in physician performance (117). Conflicting guidelines exist, alongside a lack of locally adapted guidelines (155).	Information on the levels of use of antibiotics in each hospital is lacking (155). There is a lack of involvement of physicians, pharmacists and microbiologists in antibiotic prescribing (155, 156).	Adding new modules as replacements for existing ones could cause conflict with competing stakeholders (multi-stakeholder consultative workshop discussions).

Table 4. (Contd)

Level	Option 1	Option 2	Option 3
Attitudes regarding programme acceptability, appropriateness and credibility	Evidence-based practice is thought to decrease therapeutic autonomy and thus could contribute to reduced motivation to implement it (79, 98). There is a lack of agreement with the guidelines, including their applicability to patients; a lack of involvement in the development of guidelines, leading to a lack of ownership; no positive expectations regarding outcomes; and the inertia of existing practices and routines (116).	Staff lack time to dedicate to work in an antibiotic stewardship team (78). A high level of stigma for reporting antibiotic resistance is evident, combined with fear of penalties and public disgrace (multi-stakeholder consultative workshop discussions).	Practice is usually passed on to young doctors by older colleagues, which might not always be aligned with adherence to clinical guidelines (145). There is reluctance to change curricula for students at undergraduate and postgraduate levels, as the content is already well established (multi-stakeholder consultative workshop discussions).
Motivation to change or adopt new behaviour	When evidence-based practice is implemented, it does not always mean that high-quality evidence is being used, which may affect the quality of care provided (116).	There may be a lack of willingness for compliance (87) and reluctance to change practice (117).	There may be a lack of willingness for compliance (87) and perceived threat from reduced professional autonomy (116).
Other stakeholders (including other health care providers, community health committees, community leaders, programme managers, donors, policy-makers and opinion leaders)			
Knowledge and skills	Systematic knowledge about the current application of existing guidelines is lacking (155).	Knowledge about the benefits of antibiotic stewardship is lacking (155). Skills to construct appropriate antibiotic stewardship systems and teams are lacking (7).	Awareness of the impact of integrated and multifaceted educational interventions on overall knowledge and skills of current and future professionals is lacking (155).

Table 4. (Contd)

Level	Option 1	Option 2	Option 3
Attitudes regarding programme acceptability, appropriateness and credibility	Current guidelines are not applicable since they are not adapted to the context (155). Context-adapted clinical guidelines are unlikely to be accepted if developed without the professional community and practitioners (multi-stakeholder consultative workshop conclusion).	Antibiotic stewardship at the facility level is still not recognized as important (78).	The medical curriculum for undergraduate studies was changed recently, and opening the process again could require additional time and efforts (key informant interview).
Motivation to change or adopt new behaviour	Introduction of strict implementation of clinical guidelines could be considered a step to reduce clinical autonomy (78).	Effectiveness of an intervention on antibiotic prescribing depends on the physician's prescribing behaviour or preference and the barriers to change (124).	A number of modules are available in diverse disciplines; adding a mandatory one for antibiotic prescribing might not be welcomed by practising physicians (key informant interviews).
Health system constraints			
Financial resources, human resources, education system, system's capacity to develop, implement and monitor norms and standards	Mechanisms and policies to enforce guidelines are lacking (116). Resources to implement and monitor them are also lacking (78, 140). Poor adaptation of guidelines and allocation of resources leads to inappropriate antibiotic use and increased costs (78).	Human resources are lacking at every level (laboratory, clinical, administration) (78). Mechanisms to enforce ASPs are lacking (101, 123). There is potential for cost increases and prolonged consultation times (78, 140). No specialized infection control units or personnel monitor the work of physicians and follow up on their adherence to guidelines/clinical pathways (78). Funding for diagnostics and lack of access to reports on antibiotic resistance in hospitals, which could serve as guidance for adjustment of local protocols, are lacking (157).	Funding for curriculum development, training and education is lacking (155). Difficult to implement setting-specific interventions if antibiotic resistance data is not available at facility level (146, 148).

Table 4. (Contd)

Level	Option 1	Option 2	Option 3
Social and political constraints			
Political stability and technical capacities	Frequent changes of policy- and decision-makers (in the Ministry of Health and hospital management) affect sustainability (multi-stakeholder consultative workshop discussions).	Frequent changes of policy- and decision-makers (in the Ministry of Health and hospital management) affect sustainability (multi-stakeholder consultative workshop discussions).	Mechanisms for coordinated curricula development that would reflect the evidence from the practice are lacking (multi-stakeholder consultative workshop discussions).

Potential opportunities

To overcome the barriers listed above, this evidence brief for policy also considers potential opportunities, adapted to the specificities of the national context.

OPTION 1. REVISION, CONTEXTUALIZATION AND IMPLEMENTATION OF GUIDELINES FOR ANTIBIOTIC THERAPY

- Existing clinical guidelines could be used as a basis for revision and adaptation to the national context.
- Health professionals working at all three (primary, secondary and tertiary) levels of care are willing to sit at the same table to discuss problems and possible solutions.
- Professional associations exist that could be used as vehicles for discussing updated and proposed clinical guidelines and, once endorsed, for ensuring that doctors are educated to implement the guidelines and for promoting adherence (7, 140, 144).
- The Ministry of Health understands the problem of non-applicability of clinical guidelines and has recently initiated a process of revision – practitioners through their professional associations should insist on participating in this process.

OPTION 2. ESTABLISHMENT OF ASPS IN HOSPITALS, ACCOMPANIED BY AN ANTIBIOTIC USE REPORTING SYSTEM

- Managers in some hospitals have raised awareness about prudent antibiotic use. Piloting of antibiotic stewardship in these hospitals could be used as a primer for other hospital settings.
- Activities to improve infection prevention and control practices in hospitals, including law-regulated committees to monitor intra-hospital infections, are ongoing.
- The established system for antibiotic consumption in primary care could serve as a template/model for monitoring antibiotic consumption in hospitals.
- Committees for intra-hospital infections are in place that can undertake the role of monitoring antibiotic use in hospitals (antibiotic stewardship teams) and provide

advice in particular cases of overprescribing doctors. The rulebook regulating these committees enlists this function (monitoring of antibiotic consumption). The advantage of these committees is their multidisciplinary structure, involving clinicians, microbiologists, epidemiologists, infection control nurses and similar.

» The antibiotic stewardship team present in one private hospital (including a pharmacist, microbiologist and internist with distinct roles in monitoring antibiotic use within the entire process) could serve as model for public hospitals to establish similar teams.

OPTION 3. STRENGTHENING EDUCATION CURRICULA ON PRUDENT ANTIBIOTIC USE

» A system is established for relicensing medical doctors, dentists and pharmacists and for continuous professional education, as well as training and awareness-raising at all levels of care, including some modules for prudent use of antibiotics – improved clinical practice and rapid diagnostics. This could be used as a vehicle for education and awareness-raising of the importance of antibiotic resistance reporting and development of local susceptibility data reports by regions/hospital wards, where specific antimicrobial stewardship courses could be made mandatory for all health care professionals within their continued professional education programmes.

» Appropriate monitoring and reporting of antibiotic use (in terms of quantity) exists at the primary level. This system could be complemented with additional features to follow antibiotic use by patients across all levels of care.

» Awareness of the existence of the problem could be further raised using the ongoing dialogue between primary and secondary care physicians at expert level through symposia and meetings organized by professional associations.

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ANNEXES

ANNEX 1.
Summary of evidence relevant to the three options

All the information provided in Tables A1–A3 was considered by the authors in compiling Tables 1–3 in the main text of this evidence brief for policy.

Table A1. Summary of evidence relevant to option 1

Systematic review	Focus
Wagner B, Filice GA, Drekonja D, Greer N, MacDonald R, Rutks I et al. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Infect Control Hosp Epidemiol. 2014;35:1209–28.	Impact of ASPs in hospital settings
Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.	Interventions to improve antibiotic prescribing practices for hospital inpatients
Baysari MT, Lehnbom EC, Li L, Hargreaves A, Day RO, Westbrook JI. The effectiveness of information technology to improve antimicrobial prescribing in hospitals: a systematic review and meta-analysis. Int J Med Inform. 2016;92:15–34.	
Andrews T, Thompson M, Buckley DI, Heneghan C, Deyo R, Redmond N et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PLoS One. 2012;7:e30334.	Effectiveness of different education and communication interventions between clinicians and patients to reduce antibiotic use
Drekonja DM, Filice GA, Greer N, Olson A, MacDonald R, Rutks I et al. Antimicrobial stewardship in outpatient settings: a systematic review. Infect Control Hosp Epidemiol. 2015;36:142–52.	Antimicrobial stewardship in outpatient settings

6 AMSTAR I is the Assessing Methodological Quality of Systematic Reviews quality rating.

	Key findings	AMSTAR[6] checklist rating	Proportion of studies conducted in North Macedonia
	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 state of knowledge is sufficient to make stewardship implementation a priority in all hospitals, especially given the emerging threat of resistance.	7/11	0/37
	The results show that interventions to reduce excessive antibiotic prescribing in hospital inpatients can reduce antibiotic resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcomes. This update provided more evidence on unintended clinical consequences of interventions and the effect of interventions to reduce exposure of patients to antibiotics.	7/11	0/ 89
	While the review stated that there was little evidence of an effect of information technology interventions to improve antibiotic prescribing on patient mortality or length of stay, it concluded that they can improve the appropriateness of antibiotic prescribing.	7/11	0/47
	The review concluded that, in practice, change is needed by both doctors and patients to reduce antibiotic use and control resistance. The finding was that framing education around specific presenting symptoms may be more meaningful to patients than less focused approaches of general health education interventions directed toward patients.	8/11	0/20
	The review found medium-strength evidence that stewardship programmes incorporating communication skills training and laboratory testing are associated with reductions in antibiotic use, and low-strength evidence that other stewardship interventions are associated with improved prescribing. Medication costs were generally lower with stewardship interventions, but overall programme costs were rarely reported. No studies reported microbial outcomes, and data regarding outpatient settings other than primary care clinics are limited.	7/11	0/50

Table A2. Summary of evidence reviews relevant to option 2

Systematic review	Focus
Wagner B, Filice GA, Drekonja D, Greer N, MacDonald R, Rutks I et al. Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Infect Control Hosp Epidemiol. 2014;35:1209–28.	Impact of ASPs in hospital settings
Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.	Interventions to improve antibiotic prescribing practices for hospital inpatients
Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847–56.	Assessment of evidence on hospital antimicrobial stewardship objectives using qualitative indicators
Drekonja DM, Filice GA, Greer N, Olson A, MacDonald R, Rutks I et al. Antimicrobial stewardship in outpatient settings: a systematic review. Infect Control Hosp Epidemiol. 2015;36:142–52.	Antimicrobial stewardship in outpatient settings

	Key findings	AMSTAR checklist rating	Proportion of studies conducted in North Macedonia
	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 state of knowledge is sufficient to make stewardship implementation a priority in all hospitals, especially given the emerging threat of resistance.	7/11	0/37
	The results show that interventions to reduce excessive antibiotic prescribing in hospital inpatients can reduce antibiotic resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcomes. This update provides more evidence about unintended clinical consequences of interventions and about the effect of interventions to reduce exposure of patients to antibiotics.	7/11	0/ 89
	The review compared studies using 11 quality indicators and found that empirical therapy according to guidelines, de-escalation of therapy, a switch from intravenous to oral therapy, therapeutic drug monitoring, use of a list of restricted antibiotics and bedside consultation (especially for Staphylococcus aureus bacteraemia) can lead to significant benefits for clinical outcomes, adverse events and costs.	11/11	0/146
	The review found medium-strength evidence that stewardship programmes incorporating communication skills training and laboratory testing are associated with reductions in antibiotic use, and low-strength evidence that other stewardship interventions are associated with improved prescribing. Medication costs were generally lower with stewardship interventions, but overall programme costs were rarely reported. No studies reported microbial outcomes, and data regarding outpatient settings other than primary care clinics are limited.	7/11	0/50

Table A3. Summary of evidence relevant to option 3

Systematic review	Focus
Andrews T, Thompson M, Buckley DI, Heneghan C, Deyo R, Redmond N et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. PLoS One. 2012;7:e30334.	Effectiveness of different education and communication interventions between clinicians and patients to reduce antibiotic use
Silverberg SL, Zannella VE, Countryman D, Ayala AP, Lenton E, Friesen F et al. A review of antimicrobial stewardship training in medical education. Int J Med Educ. 2017;8:353.	Antimicrobial stewardship training in medical education
Brennan N, Mattick K. A systematic review of educational interventions to change behaviour of prescribers in hospital settings, with a particular emphasis on new prescribers. Br J Clin Pharmacol. 2013;75:359–72.	Educational interventions to change behaviour in hospital settings
Lee CR, Cho IH, Jeong BC, Lee SH. Strategies to minimize antibiotic resistance. Int J Environ Res Public Health. 2013;10:4274–305.	Educational effectiveness, target and content for prudent antibiotic use
van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. Br J Gen Pract. 2012;62:e801–7.	Physician-targeted interventions to improve antibiotic prescribing
Lee CR, Lee JH, Kang LW, Jeong BC, Lee SH. Educational effectiveness, target, and content for prudent antibiotic use. Biomed Res Int. 2015;2015:214021.	Effects of different clinician education interventions on improving antibiotic prescribing

	Key findings	AMSTAR checklist rating	Proportion of studies conducted in North Macedonia
	The review found that framing education around specific presenting symptoms may be more meaningful than less focused approaches of general health education interventions.	7/11	0/20
	This study enhanced understanding of the extent of antimicrobial stewardship in the context of medical education, and demonstrated that medical schools are implementing antimicrobial stewardship interventions. However, rigorous evaluation of programmes to determine whether such efforts are effective is lacking.	6/11	0/48
	72% of the interventions analysed across 64 articles were considered effective in changing behaviour.	7/11	0/64
	The study found that efforts on a national level to improve current educational programmes are required and it is necessary to develop appropriate educational programmes targeted specifically to each group. In addition, appropriate curricula to teach medical and nonmedical undergraduate students should be developed as soon as possible. Because the undergraduate training track is the time when knowledge, attitudes and behaviours of medical professionals are shaped, educating them about prudent antibiotic prescribing will be significantly effective in minimizing antibiotic resistance.	4/11	0/28
	The review concluded that physician education is effective in decreasing antibiotic use. However, it also showed that just delivering guidelines is not enough to restrict antibiotic prescribing; there is a need to intensify and contextualize educational efforts and create ASPs adapted to the local situation.	3/11	0/58
	Most studies showed that a reduction in antibiotic prescribing was achieved through interventions focused on clinician education programmes, such as interactive seminars, mailing campaigns, small-group education focusing on evidence-based medicine and communication skills, educational outreach visits, guidelines and leaflets, and a combination of these strategies. On average, antibiotic prescription of the intervention group was reduced by 34.1% (between 9% to 52%) compared with the control group. The number of inappropriate antibiotic prescriptions was also reduced by 41% more on average than the control group. These results indicate that clinician education can significantly improve antibiotic prescribing.	4/11	0/28

ANNEX 2.
Tacit knowledge sources for the evidence brief for policy

Topic	Expertise and position of participants	
	Key informant interviews	Consultative workshops
Antibiotic use in practice	Leading infectious disease specialists and medical directors in hospitals Leaders and experts in public health	Infectious disease specialists and medical directors in hospitals Leaders and experts in the field
Microbiology laboratories	Practitioner microbiologists, infectious disease specialists from both public and private providers	Practitioner microbiologists, infectious disease specialists from both public and private providers Academic staff at medical and pharmaceutical faculties
Regulation and information systems for antibiotic use	Policy-makers from health authorities (Ministry of Health, HIF, MALMED)	Policy-makers from health authorities (Ministry of Health, HIF)
Roles, responsibilities and regulation of public bodies regarding antibiotic use	Policy-makers from health authorities (Ministry of Health, HIF, MALMED)	Policy-makers from health authorities (Ministry of Health, HIF)
Potential issues in implementation of policies on antibiotic use	Policy-makers from health authorities (Ministry of Health, HIF, MALMED)	Policy-makers from health authorities (Ministry of Health, HIF)
General practice	Representatives of professional associations of general practitioners and family medicine specialists	Leading general practitioners, family medicine specialists
Undergraduate and postgraduate education	Academic staff of medical, dental and pharmaceutical faculties Professional chambers of health professionals (medical, pharmaceutical)	Academic staff at medical and pharmaceutical faculties Professional chambers of health professionals (medical, pharmaceutical)
International best practice	A staff member who deals with antibiotic resistance within an international organization	Staff members and technical officers of an international organization who deals with antibiotic resistance

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