Evidence brief for policy

EVIPNet Europe

Number 2

Promoting the appropriate use of antibiotics to contain antibiotic resistance in human medicine in Hungary

Evidence-informed Policy Network (EVIPNet) Europe

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ABSTRACT

The Ministry of Human Capacities of Hungary commissioned a policy brief, to be published under the aegis of the WHO Evidence-informed Policy Network (EVIPNet) Europe, to develop evidence-informed options for the country to consider in tackling the problem of antibiotic misuse. The task was implemented in frame of the Biennial Collaborative Agreement (BCA) between the Ministry of Human Capacities and WHO, involving high level national policy institutions and national experts, supported by the technical experts of WHO Regional Office for Europe. The National Healthcare Service Center of Hungary convened a working group comprising representatives from the clinical field, pharmacology, public health and health care management. The working group identified, selected, appraised, and synthesized relevant research evidence on the problem, three options for tackling it and considerations in implementing them. The three options are: developing a national antibiotic stewardship programme, complemented by evidence-informed clinical guidelines on the diagnosis and treatment of common infections; strengthening undergraduate and postgraduate medical, dental, and pharmacy education and training on the prudent use of antibiotics; and raising awareness of prudent antibiotic use through information campaigns, leaflets and interpersonal communication.

KEYWORDS

DRUG RESISTANCE, BACTERIAL
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ANTI-BACTERIAL AGENTS - THERAPEUTIC USE
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The Evidence-informed Policy Network (EVIPNet) Europe (www.evipnet.org) – a regional arm of the global Evidence-informed Policy Network (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 National Healthcare Service Center, Hungary (www.aeek.hu) manages state-owned hospitals in Hungary to provide good-quality, high-level, accessible and efficient health care services to the population and supports the health care system in continuously improving its performance. Methodological support includes human-resource and capacity management, quality assurance, continuous improvement of operational efficiency, centralized public procurement, health care and institutional performance appraisal.

The Ministry of Human Capacities, Hungary (www.kormany.hu) incorporates the State Secretariat for Healthcare, which is responsible for determining rules and preparing legislation related to health care provision on the national level. It also 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.

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ABBREVIATIONS

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
ASP	antibiotic stewardship programme
ATC	WHO Anatomical Therapeutic Chemical Classification System
B/N ratio	consumption ratio of broad- to narrow-spectrum agents
CDC	US Centers for Disease Control and Prevention
CDI	Clostridium difficile infection
CI	confidence interval
CRP	C-reactive protein
DDD	daily defined dose
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EU	European Union
EVIPNet Europe	Evidence-informed Policy Network Europe
ICACs	infection control and antibiotic committees
IMS Health	Intercontinental Marketing Services (IMS) Health
GPs	general practitioners
HAIs	health-care-associated infections
NICE	National Institute for Health and Care Excellence (United Kingdom)
RTIs	respiratory tract infections

MAIN MESSAGES

The problem

Antibiotic misuse is a significant threat to patient safety. It implies unnecessary or ineffective treatment, potentially leads to severe side effects, and drives the development of antibiotic-resistant bacteria, putting the general therapeutic benefit of antibiotics at risk. It also imposes an avoidable cost burden on the health care system. The misuse of antibiotics is prevalent worldwide in both hospital and ambulatory settings.

Evidence from systematic reviews and other sources on the proposed policy options

- Option 1. Developing a national antibiotic stewardship programme, complemented by evidence-informed clinical guidelines on the diagnosis and treatment of common infections
  - Antibiotic stewardship, defined as an organizational or health-care-system-wide approach to promoting and monitoring the appropriate use of antibiotics, is a key intervention that leads to improved efficiency and effectiveness of prescribing practices in both hospital and community settings.
  - Evidence-informed diagnostic and treatment guidelines should be prepared to set treatment standards and to support a national antibiotic stewardship programme, as well as audit at all levels of health care.
  - Government and care-provider support and resources are necessary to ensure a system-wide implementation of the programme.

- Option 2. Strengthening undergraduate and postgraduate medical, dental, and pharmacy education and giving training on the prudent use of antibiotics
  - Proper undergraduate education on the prudent use of antibiotics enables graduates to enter clinical practice with the right knowledge, skills and attitudes to become rational prescribers.
  - Postgraduate courses and the continuing education of clinicians and general practitioners should apply a combination of multiple educational methods to bring about change in prevailing prescribing practices.

- Option 3. Raising awareness of prudent antibiotic use through information campaigns, leaflets and interpersonal communication
  - Information campaigns targeting both the public and health care professionals may change misconceptions on antibiotic use and lead to a more rational selection of antibiotics by prescribers.
  - Information leaflets on common infections should be developed for use in adult and paediatric primary care to improve doctor–patient communication.

Implementation considerations

- Each of these individual policy options contributes to improved knowledge and practices leading to a more appropriate use of antibiotics. Given their different levels and target groups, however, combined implementation of all three would presumably have a greater impact.
- The existing legal framework in Hungary, as well as recently launched projects for health-system development, supports the implementation of the proposed policies.
- A shortage of key professionals, especially infectious disease specialists, clinical microbiologists and clinical pharmacists, and limited availability of certain essential antibiotics in Hungary may hinder both the planning and implementation of interventions.

EXECUTIVE SUMMARY

As WHO states clearly, misusing antibiotics puts everyone at risk (1).

Antibiotics are essential medicines in the treatment of bacterial infections and, in well defined cases, in their prevention. They have no effect on infections caused by viruses.

Misuse of antibiotics in human medicine means unnecessary or ineffective treatment. In the individual patient, this can lead to otherwise avoidable harm during treatment, while representing an unjustified excess resource need for the health care system. By driving the development of antibiotic-resistant bacteria, it also puts the general therapeutic benefit of antibiotics at risk. This is why antibiotics are increasingly losing their effectiveness, putting clinical treatment options at risk, worsening health outcomes and increasing medical costs.

Although the scientific community widely acknowledges antibiotic resistance as one of the most significant threats to patient safety in the world, the misuse of antibiotics remains common in both hospital and community settings.

Both international quality indicators of antibiotic use based on comprehensive surveillance data, and national studies indicate a widespread misuse of antibiotics in Hungary, even though the country is among the lower antibiotic users in the European Union (EU) in terms of quantity. Data suggest that patients are often treated unnecessarily with broad-spectrum antibiotics, which may result in more side effects, higher expenses and more rapid resistance development. Further, Hungary shows the largest seasonal variation in antibiotic use in community care among European countries. This reflects poor prescription practice, since it suggests a higher use of antibiotics for community-acquired infections of the upper respiratory tract during the autumn and winter months, which has no evidence base.

The misuse of antibiotics originates from physicians' inappropriate prescribing practices, but the population's attitudes and misconceptions, pressure from patients to prescribe, the unavailability of certain narrow-spectrum antibiotics, insufficient human resources, inadequate arrangements in the health care system and the marketing practices of pharmaceutical companies also play an important role. This evidence brief addresses these issues in detail to identify current gaps and key points among the factors underlying the problem of the misuse of antibiotics in Hungary.

Three options

Based on a review of the relevant scientific literature in English and in Hungarian and of guidance provided by major international organizations such as WHO and the European Centre for Disease Prevention and Control (ECDC), the authors of this publication selected three viable policy options for improving antibiotic use in human medicine in Hungary. These options were selected because they address most aspects of the causes of the problem at the patient, prescriber and governance levels. Presumably, they could produce the most significant improvement of antibiotic use when implemented in combination, as part of a comprehensive national strategy. Nevertheless, the implementation of only one or two options would also be of significant benefit. Option 1 has a key role, as it is the best supported by high-quality evidence, and may be considered a steppingstone for the other two.

As to option 1, **developing a national antibiotic stewardship programme complemented by evidence-informed guidelines on the diagnosis and treatment of common infections**, the following points were identified.

- Antibiotic stewardship, defined as a health-care-system-wide and organizational (hospital- or outpatient-provider-level) approach to promoting and monitoring the appropriate use of antibiotics, is a key policy whose systematic implementation leads to improved prescribing practices in both hospital and community settings.
- At the national level, the following interventions appear to be necessary to promote antibiotic stewardship: providing evidence-informed guidelines, ensuring access to narrow-spectrum antibiotics, supporting the employment of specialists in infectious diseases, streamlining the logistics of microbiological diagnostic testing, and testing and further developing the national system for monitoring resistant pathogens.
- In hospitals, systematic reviews provide strong evidence that the implementation of multifaceted antibiotic stewardship programmes (ASPs) improves prescribing practices and decreases overall antibiotic consumption, while reducing the average length of stay and overall hospital costs. There is also strong evidence on better outcomes in terms of infections caused by certain multidrug-resistant organisms and in-hospital mortality.
- The main stewardship interventions proven to be effective in hospitals are: therapeutic drug monitoring, preapproval strategies for antibiotic prescription, prospective audit and feedback, local guidelines, formulary restrictions and stewardship education.
- There is also strong evidence for ASPs reducing antibiotic consumption in community settings. The main stewardship interventions proven to be effective are: training in communication skills, increased laboratory testing and the use of point-of-care diagnostic tests as appropriate.
- In both hospital and community care, the audit of antibiotic prescription would be facilitated if data integrated with clinical diagnoses were available. This would enable targeted interventions to change the patterns of antibiotic use.

As to option 2, **strengthening undergraduate and postgraduate medical, dental, and pharmacy education and training on prudent antibiotic prescribing**, the following points were identified.

- Medium-quality evidence suggests that the continuing education of health care professionals and outreach visits by peers about prudent antibiotic use and antibiotic stewardship help to change prescribing behaviour.
- Although the authors found no study on the effectiveness of undergraduate or graduate educational programmes for appropriate antibiotic prescribing, multiple international organizations emphasize the need for educational programmes, and

several countries have already started such programmes to promote appropriate antibiotic use.

As to option 3, **raising awareness of prudent antibiotic use through information campaigns, leaflets and interpersonal communication**, the following points were identified.

- Numerous studies suggest that targeted national campaigns to increase both the public's and prescribers' knowledge on antibiotic resistance and appropriate antibiotic use can have a positive effect on prescribing practice.
- Country examples also show that the use of patient information leaflets on common infections during consultations with general practitioners (GPs) may effectively reduce antibiotic prescriptions and use, and patients' intention to reconsult.
- Leaflets, especially in combination with structured discussion, improve knowledge on antibiotics among adult patients and the parents of sick children.
- Evidence indicates that interventions to facilitate shared decision-making significantly reduce antibiotic prescribing for acute respiratory infections in primary care, without a decrease in patients' satisfaction with the consultation, or an increase in repeat consultations for the same illness.

Opportunities for and barriers to implementation

The authors also considered possible opportunities for and barriers to implementation. At present there is a window of opportunity to implement measures to address the need for improved antibiotic prescribing practices in hospital and ambulatory settings in Hungary. Government, clinical and academic stakeholders all acknowledge the importance of the prudent use of antibiotics, and the imminent threat posed by antibiotic resistance. Another high-level opportunity is the potential inclusion of the subject in the new public health strategy, commissioned by the Government, which is being prepared.

The current legal framework for tasks, responsibilities, human resources and infrastructure (with special emphasis on infection control and antibiotic therapy committees (ICACs) at the hospital, county and national levels) already allows and supports the implementation of many actions advocated under the three policy options. A number of national projects for patient safety in Hungary recently created an opportunity to invest in the development of professional guidelines and related training materials. Novel policy or regulatory actions at both the national and international levels may help to remedy the unavailability or shortage of certain narrow-spectrum antibiotics. Legislation supports quality improvement in medical practice in primary care; in particular, the newly introduced primary health care act establishes a new system of territorially elected, leading peer GPs at the district, county and national levels. The number of antibiotic prescriptions also figures among the national health insurer's quality indicators for adult and paediatric practices alike.

Nevertheless, some barriers to implementation have to be addressed. There is no institutional mechanism to prevent the withdrawal from the Hungarian drug market, for economic motives, of antibiotics that would be essential for the appropriate treatment of patients. The existing structure of microbiological diagnostic services and current reimbursement mechanisms also curtail easy access to those services, and there is a serious shortage of key professionals, especially infectious disease specialists, clinical microbiologists and clinical pharmacists, who are essential to effective planning and implementation. As to medical education, the schedule of training programmes is already fairly dense, and it is difficult to introduce new subjects or courses without exceeding the legal limits of training in terms of requirements for graduation and postgraduate core courses. As for changing attitudes through increased knowledge and awareness, the available media and information space is highly saturated, and transmitting messages on, for example, the importance and key principles of proper antibiotic use is challenging, especially if those messages are not coordinated with or even contradict the persuasive efforts of pharmaceutical companies.

INTRODUCTION

How the problem was raised

To increase patient safety, the Ministry of Human Capacities of Hungary commissioned an evidence brief for policy on containing antibiotic misuse and consequent resistance (Box 1). This brief focuses on the available evidence on antibiotic misuse and its impact in human medicine in Hungary, and proposes options for possible policy actions to be developed locally. This report was prepared to inform deliberations among policy-makers and stakeholders.

How this report was prepared

This report is the first evidence brief for policy produced in Hungary within the framework of the WHO Evidence-informed Policy Network (EVIPNet) Europe. Building on a national situation analysis on evidence-informed policy-making processes, a multidisciplinary group of experts prepared it, with the coordination of the National Healthcare Service Center of Hungary (Box 1). During the development process, the WHO Regional Office for Europe and Hungarian and international subject-matter experts continuously reviewed the brief. The authors reviewed global and local evidence to describe the problem of antibiotic misuse and policy options for addressing it, along with barriers to and opportunities for implementing the options (Box 2).

The search for evidence focused on systematic reviews of the effects of policy options and their implementation strategies. (Boxes 1 and 2 and Annexes 1–3). Other relevant study findings, key publications of major international organizations, government reports and unpublished literature were also used. The tacit knowledge of both experts (authors and reviewers) and stakeholders (elicited through Key informant interviews – Annex 4) forms an integral part of the brief.

Box 1. Background to the policy brief

This policy brief mobilizes both global and local research evidence about a problem, three options for addressing it, and key implementation considerations. Whenever possible, the policy brief summarizes research evidence drawn from systematic reviews. Single studies, grey literature (e.g. reports, guidelines), and relevant datasets were also considered. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and appraise research studies and to synthesize data from the included studies.

The evidence brief for policy does not contain recommendations. The three options discussed are only possible ways of policy development, supported by strong scientific evidence. They could be pursued simultaneously or elements could be drawn from each option to create a new one. The three options were selected because together they address a large spectrum of causes of the problem.

Box 1. (Contd)

Six steps were taken in preparing the evidence brief:

1. selecting a topic (the Ministry of Human Capacities);
2. convening a working group comprising representatives from the clinical field, pharmacology, public health and health care management (the National Healthcare Service Center);
3. developing and refining the terms of reference for the evidence brief, particularly the framing of the problem and the options for addressing it;
4. identifying, selecting, appraising, and synthesizing relevant research evidence on the problem, options, and implementation considerations;
5. interviewing key informants about local implementation considerations;
6. drafting the text to present, concisely and in accessible language, the global and local research evidence; and
7. finalizing the evidence brief for policy based on the input of several merit reviewers.

The policy brief was prepared to inform a policy dialogue in which research evidence is one of many considerations. Participants' views and experiences and their tacit knowledge of the issues at hand are also important inputs to the dialogue. One goal of the policy dialogue is to spark insights – insights that can only arise when all of those who will be involved in or affected by future decisions about the issue can work through it together. A second goal of the policy dialogue is to generate action by participants in the dialogue and those who review the dialogue summary. The policy dialogue took place on 11th December 2017.

Box 2. Mobilizing research evidence

The authors sought research evidence about the problem, policy options and implementation considerations from a range of published and grey literature sources. Published literature that provided a comparative dimension to an understanding of the problem was sought using the Medline/PubMed, Cochrane, Health Systems Evidence, Health Evidence and Google Scholar databases. Full text reviews were made of English- and Hungarian-language systematic reviews, meta-analyses, economic evaluations and single research studies published between 1 January 2010 and 30 September 2016. Some seminal documents published before and after these dates were also included.

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 and antibiotic consumption.

Grey literature was searched by reviewing the websites of leading international and national organizations, such as WHO, ECDC, the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the US Centers for Disease Control and Prevention (CDC).

The search strategy was stratified separately by three dimensions (problem, policy options, implementation considerations) using the following keywords: antibiotic, antibacterial, antimicrobial, misuse, overuse, "inappropriate use", stewardship, guideline, prescribing, education, training, financing, cost, benefit, "financial evaluation", reimbursement, implementation, strategy, feasibility.

Priority was given to research evidence that was published more recently and locally applicable (i.e. research conducted in the country). Certain key publications were included upon expert advice.

Box 2. (Contd)

The review authors' key findings were extracted from the identified reviews. Each review was also assessed in terms of its quality (Assessing Methodological Quality of Systematic Reviews (AMSTAR) rating of 0–11) and local applicability (proportion of studies conducted in the country). The quality of evidence was classified as follows:

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

Limitations of this report

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. Thus, this brief inevitably reflects the authors' and reviewers' decisions.

Although the One Health approach requires a common management of the relations of antibiotic misuse to human and animal health, most of the resistance problem in human beings has arisen from their antibiotic use (2). Therefore, the authors' review and synthesis of evidence concentrate on issues and possible interventions related to the human health care sector: i.e. the problem of antibiotic misuse in human medicine.

The information related to the costs and benefits of options is primarily drawn from the literature, which contains general information. Since each policy option offers multiple alternatives for implementation designs, the exact content of interventions would have to be decided before the direct and indirect costs, and benefits specific to the country situation could be calculated. This would be the task of further policy-development work.

THE PROBLEM OF ANTIBIOTIC MISUSE

Definition and framing

Antibiotic misuse is a major health policy problem, as it means unnecessary or ineffective treatment (Box 3), leads to potentially severe side effects and drives the development of antibiotic-resistant bacteria; these result in otherwise avoidable harm for patients and the health care system. The emergence of antibiotic-resistant bacteria is threatening the ability to treat common infectious diseases (3). These consequences mean higher costs to the Hungarian health care system and worse health outcomes in the population. International drug-specific quality indicators of antibiotic use, as well as national studies, suggest a widespread misuse of antibiotics in the country (4). Targeted health policy interventions are needed to move towards a safer and more cost-effective use of antibiotics.

Box 3. Forms of antibiotic misuse

Antibiotics are medicines used to treat infections caused by bacteria, or to prevent bacterial infections in certain cases (e.g. during surgery). They should only be used against bacterial infections, in accordance with the relevant professional guidelines, but their misuse is common in medical practice. Forms of antibiotic misuse include unjustified use (e.g. in case of viral infections), excessive prescribing (overuse) of certain products, inadequate selection, dosage or duration of the antibiotic therapy (e.g. using antibiotics in combination when a single antibiotic would be sufficient), or lack of treatment when it would be necessary (underuse).

The misuse of antibiotics stems principally from physicians' inappropriate prescribing practices, but the population's attitudes, arrangements for financing and the health care system, and pharmaceutical companies' marketing practices also play an important role, as highlighted by a systematic review by WHO (5). ECDC also emphasizes the need to address this problem at different levels, including those of international organizations, national governments, and health care providers and professionals (6).

Size of the problem

In Hungary, all systemic antibiotics are prescription-only medicines, and they are partially reimbursed by social insurance. Over-the-counter use is restricted to physicians and pharmacists, and is therefore marginal. More than 90% of all antibiotics are prescribed in ambulatory (community) care – with infections of the respiratory and urinary tracts being the most common indications. Hospital care accounts for about 10% of antibiotic use. (The

European Surveillance of Antimicrobial Consumption Network (ESAC-Net) offers a country overview for Hungary (4).)

This section describes the main patterns of systemic antibiotic use, with particular emphasis on antibiotic subgroups of the highest clinical relevance, and highlights drug-specific quality indicators of antibiotic use (7). The authors obtained the information presented from public statistics of the Hungarian National Health Insurance Fund (8), wholesaler distribution data from IMS Health (9) and data from ESAC-Net (4). Box 4 gives relevant definitions and common measures. Data on disease-specific quality indicators have not yet been systematically collected at the European level, so the results of local studies are presented where available.

Box 4. Definitions and common measures

A **systemic antibiotic** is taken by mouth or given by injection and affects the whole body (as distinct from an antibiotic applied externally).

A **narrow-spectrum antibiotic** is effective against specific families of bacteria and has lower propensity to cause resistance. No standard definition is available for all antibiotic subgroups.

A **broad-spectrum antibiotic** is effective against a wide range of bacteria and has higher propensity to cause resistance. No standard definition is available for all antibiotic subgroups.

A **first-choice (first-line) antibiotic** is recommended by professional guidelines for initial treatment of certain infections.

A **second-choice (second-line) antibiotic** should be used in case of failure of or intolerance to first-choice antibiotics, as per professional guidelines.

Empiric 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.

The **daily defined 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.

DDD per 1000 inhabitant-days (DID) (for outpatient data): Sales or prescription data presented in DDDs per 1000 inhabitants per day may provide an estimate of the proportion of the population treated daily with a particular drug. The figure 10 DDDs per 1000 inhabitant-days of antibiotics indicates that on average, 1% of the population on average receives an antibiotic daily.

DDD per 100 patient-days (for inpatient data), 30 DDDs per 100 patient-days of antibiotics provide an estimate of the therapeutic intensity and suggest that on average, 30% of the inpatients receive a DDD of an antibiotic every day

CONSUMPTION OF SYSTEMIC ANTIBIOTICS IN AMBULATORY (COMMUNITY) CARE IN HUNGARY

ESAC-Net defines four main consensus-based, drug-specific quality indicators of antibiotic consumption in ambulatory care: consumption, relative consumption, broad-to-narrow ratio and seasonal variation (Box 5). Table 1 shows the values of these indicators for Hungary against the distribution of reporting countries.

Consumption of antibiotics

In general terms, antibiotics are not consumed excessively in the community in Hungary relative to other European countries (Table 1, line J01_DID). Even at low overall consumption levels, however, antibiotics may be misused. Quinolone use in particular is at the highest end in Europe (Table 1, line J01M_DID). In general, this reflects poor prescribing practice, as quinolones (including fluoroquinolones) should only be used in case of known resistance to first- or second-choice antibiotics or reserved for hard-to-treat, complicated infections. There is general consensus on limiting fluoroquinolone use (7) due to their pronounced resistance-generating action (10-13) and serious adverse effects (14).

Relative consumption of different antibiotics

Narrow-spectrum penicillins, recommended by evidence-informed guidelines as the first-choice treatment for various infections, account for an unfavourably small part of total antibiotic consumption in Hungary (Table 1, J01C_E%). At the same time, the share of different combinations of penicillin, which should only be used as second-choice treatment in most cases, is among the highest in Europe (Table 1, J01CR_%, J01MA_%). Resistance to narrow-spectrum penicillins may only partially explain the low use of these drugs. The relative proportion of fluoroquinolone, an agent particularly associated with the development of antibiotic resistance in bacteria, was the highest in Hungary among European countries in 2015 (Table 1, J01MA_%).

Box 5. Drug-specific quality indicators in ESAC-Net

» **consumption:** total consumption of systemic antibiotics and its subgroups;

» **relative consumption:** consumption of narrow-spectrum beta-lactamase-sensitive penicillins, broad-spectrum combinations of penicillins including beta-lactamase inhibitors, third- and fourth-generation cephalosporins, and fluoroquinolones, as a percentage of total consumption;

» **broad-to-narrow ratio:** the ratio of the consumption of broad- to narrow-spectrum penicillins, cephalosporins and macrolides; and

» **seasonal variation:** overuse of systemic antibiotics and of quinolones in autumn-winter, compared to spring-summer.

Low values for all quality indicators except the relative consumption of narrow-spectrum penicillins suggest better quality (i.e. with the best quality being within the first quartile: between the minimum value and the twenty-fifth percentile). High values for the indicator of the relative consumption of narrow-spectrum penicillins suggest better quality (i.e. with the best quality being within the fourth quartile: between the seventy-fifth percentile and the maximum value).

Table 1. ESAC-Net drug-specific quality indicators for antibiotic consumption in the community in Europe: values in Hungary against the distribution of reporting countries, expressed in DDD per 1000 inhabitants per day or as percentages, 2015

Quality indicator	Line	Hungary	Minimum value	Percentile			Maximum value
				25th	50th	75th	
Consumption	J01_DID	17.0	10.7	15.5	20.0	24.8	36.1
	J01C_DID	7.1	4.4	6.6	9.3	12.5	18.8
	J01D_DID	2.0	0.0	0.5	1.6	2.8	7.6
	J01F_DID	3.3	0.6	1.9	3.1	3.9	7.5
	J01M_DID	2.7	0.5	0.9	1.3	2.4	3.4
Relative consumption (%)	J01CE_%	0.7	< 0.1	0.5	1.7	5.8	26.4
	J01CR_%	33.6	< 0.1	13.9	23.1	32.3	43.7
	J01DD+DE_%	1.2	< 0.1	0.1	0.3	1.7	7.2
	J01MA_%	15.8*	2.3	5.1	7.5	9.5	15.8
Broad/ Narrow	J01_B/N	79.4	0.2	5.2	11.8	47.1	519.2
Seasonal variation	J01_SV	66.1*	11.9	20.9	32.9	35.9	66.1
	J01M_SV	62.9*	3.1	7.8	12.0	26.2	62.9

Notes. Terms used for the antibiotics covered in various lines in the table (J01 = systemic antibiotics; J01C = penicillins; J01CE = beta-lactamase sensitive penicillins; J01CR = combination of penicillins, including beta-lactamase-inhibitors; J01D = cephalosporins; J01DD = third-generation cephalosporins; J01DE = fourth-generation cephalosporins; J01F = macrolides, lincosamides and streptogramins; J01M = quinolones, J01MA = fluoroquinolones) are according to the WHO Anatomical Therapeutic Chemical Classification System (ATC). SV = seasonal variation. Colour coding: green indicates the most favourable quartile; orange, intermediate quartiles; red, the most unfavourable quartile.

* The highest value among reporting EU/The European Economic Area (EEA) countries.

Source. Antimicrobial consumption interactive database (ESAC-Net) (4).

These data suggest that acute infections are often not treated with first-, but with second-choice antibiotics in ambulatory care. National studies focusing on acute cystitis and community-acquired lower respiratory tract infections (pneumonia), which are among the most common indications for antibiotic treatment in the community, have also found inappropriate choices of antibiotics (15,16). Thus, patients unnecessarily consume second-choice, broad-spectrum agents, which result in more side effects, more rapid resistance development and higher costs.

The time trends of antibiotic use in the community over the past 20 years show some reasonable changes (e.g. a shift towards more up-to-date products: thus an increasing use of macrolides and decreasing use of tetracyclines) and some unwanted changes. The diminishing use of narrow-spectrum penicillins, the extreme dominance of a specific broad-spectrum combination of penicillin (amoxicillin and clavulanic acid) and the increasing use of other broad-spectrum agents, such as third-generation cephalosporins and fluoroquinolones, indicate the misuse of antibiotics. There is no level of resistance to first-choice antibiotics monitored at national level that would justify these trends overall (17).

Ratio of broad- to narrow-spectrum antibiotics

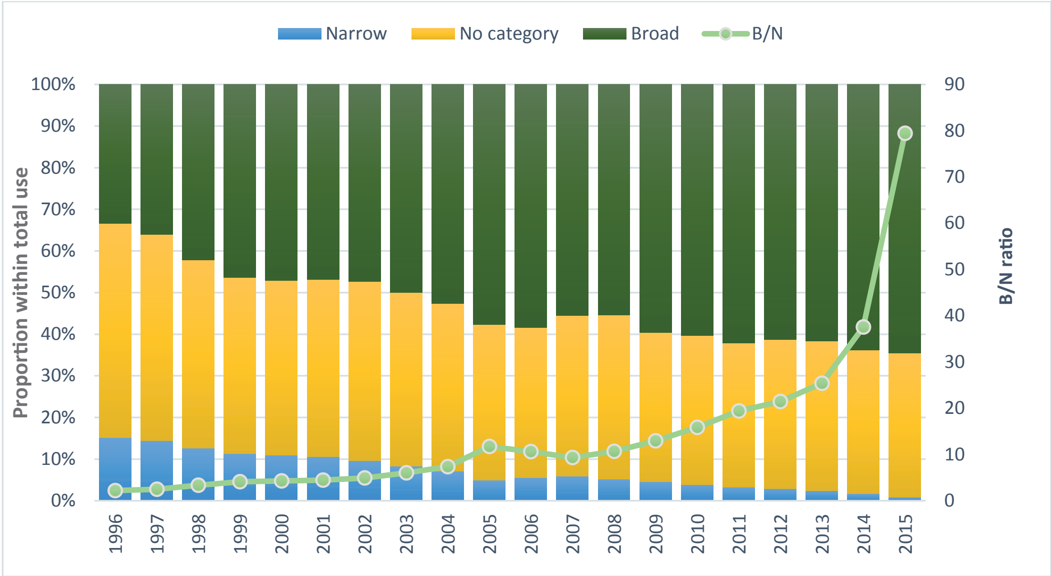
The consumption ratios of broad- to narrow-spectrum agents (i.e. B/N ratios) of selected antibiotic classes are helpful in assessing the overprescribing of powerful broad-spectrum products, which give rise to antibiotic resistance and have limited clinical indications. The ESAC-Net quality indicator targets the B/N ratio of penicillins, cephalosporins and macrolides, and Hungary is among the countries with the most unfavourable values in Europe (Table 1, J01_B/N).

The B/N ratio in Hungary has risen almost yearly until it reached the value of 80 by 2015 (Fig. 1). (Considering the sharp increase from 2014 to 2015, the reader should note that the steep increase of the ratio is not due to a significant change in the absolute values, but to the further decrease of an already very low level of narrow-spectrum antibiotic use.)

Seasonal variation

The overuse of systemic antibiotics, particularly of quinolones in autumn–winter, compared to spring–summer, reflects poor prescription practice among family doctors and other specialists in ambulatory care, since it suggests a higher use of antibiotics for upper respiratory tract infections in the community, which has no evidence base in systematic reviews (18,19). In 2015, Hungary had the highest seasonal variation in community antibiotic use, particularly of quinolones, in the EU (Table 1, J01_SV, J01M_SV).

Fig. 1. Use of broad- versus narrow-spectrum penicillins, cephalosporins and macrolides in ambulatory care in Hungary, 1996-2015



CONSUMPTION OF SYSTEMIC ANTIBIOTICS IN HOSPITAL CARE IN HUNGARY

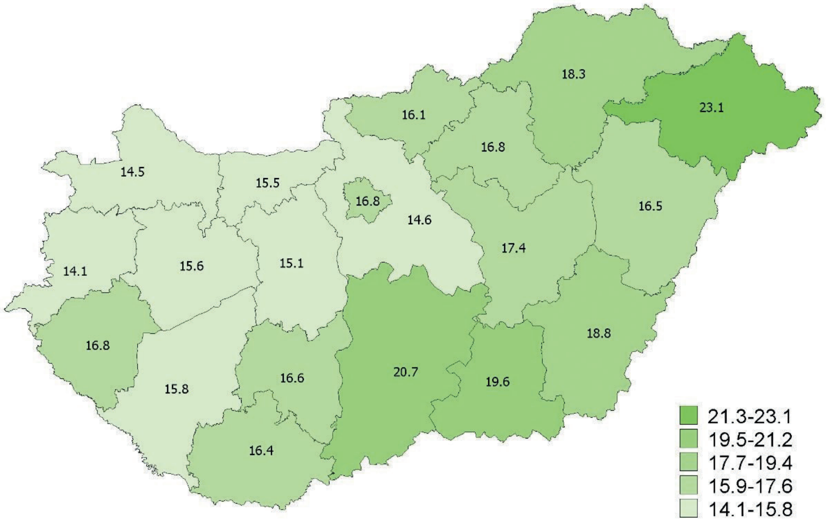
Antibiotic use in hospital care in Hungary is among the lowest in Europe (4,20). In the absence of sufficient data, however, it is difficult to tell whether this value results from good practice or indicates an underuse of antibiotics. Although antibiotic use has remained quantitatively stable (22.4 ± 1.5 DDD/100 patient-days) through the past 20 years, changes in the pattern of antibiotic use indicate unfavourable trends similar to those in ambulatory care.

The use of a broad-spectrum combination of penicillin (amoxicillin-clavulanic acid) has dominated antibiotic use in hospitals. This product accounts for 30% of all antibiotic use in hospital settings in Hungary, which cannot be justified by clinical indication or resistance data. From 1996 to 2015, the use of fluoroquinolones (2.3 vs 4.2 DDD per 100 patient-days) and of third-generation cephalosporins (1.0 vs 2.9 DDD per 100 patient-days) has substantially increased, indicating an unfavourable shift towards the use of broad-spectrum, second-choice agents. In addition, the use of narrow-spectrum penicillins fell to a minimal level: < 1% of penicillin usage in 2015.

Equity-related observations about the problem

Community consumption of antibiotics varies considerably across counties in Hungary (Fig. 2), the eastern part of the country generally showing higher values than Transdanubia. These geographical variations may in part reflect true differences in the health status of the population, but other factors may also play a role. For example, illicit trading to Ukraine and Serbia of antibiotics prescribed and dispensed in Hungary may bias consumption data for border areas. Nevertheless, an earlier national study found that higher antibiotic consumption in community care was associated with unfavourable socioeconomic status (21).

Fig. 2. Regional differences in antibiotic use in ambulatory care in Hungary (DDD per 1000 inhabitant-days), 2015



Source: IMS Health Kft (9).

While strongly linking antibiotic use to socioeconomic conditions in Hungary is difficult due to a dearth of data, research from other countries may provide important insights. A Swedish study, examining fluoroquinolone use in the treatment of urinary tract infections in women, found both regional variations in prescription rates and a significantly higher likelihood of getting a prescription for this broad-spectrum agent in women with at least secondary education than those with only primary education (22). Data from Germany and Italy suggest that area (regional income and occupational) deprivation and lower scores on the Human Development Index, respectively, may contribute to regional variations in antibiotic prescribing for children that are not justified by the prevalence of infectious diseases (23,24).

A systematic review and meta-analysis indicate significant gender and age differences in antibiotic prescribing in the community: women were 27% more likely than men to receive an antibiotic prescription during their lives (25). The highest gender discrepancy was found in the group aged 16–54 years. It was assumed that the higher prevalence of urinary tract infection among women cannot fully explain this (25). Further data suggest that medical visits for respiratory tract infections (RTIs) and inappropriate antibiotic prescribing for viral RTIs are significantly more common among women than men, even though RTIs are not more prevalent among women (26). A large cross-sectional study, however, did not confirm this finding (27). Concerning age, a population-based telephone survey conducted in a winter month among adults in the United States of America found that self-reported antibiotic use in the previous four weeks was highest among people in the groups aged 25–39 and 60 and above (28). A Dutch study assessing adherence to guidelines in paediatric primary care found that recommended narrow-spectrum penicillins were underused for fever, ear infections and RTIs in the youngest age group (children under 4 years) (29).

Consequences of the problem

The unjustified use of antibiotics (e.g. in case of viral infections) puts the patient at an otherwise avoidable risk of adverse effects related to antibiotic use, without any benefit. The general side effects of antibiotics include yeast infection, allergy and potentially severe diarrhoea. Several systematic reviews confirm that, in both community and hospital settings, Clostridium difficile infections (CDIs, previously known as Clostridium difficile associated diarrhoea) are often triggered by the use of broad-spectrum agents that eliminate the normal commensal microbial flora of the body, including the gut microbiome (30–33). Since the early 2000s, CDIs have risen in North America and Europe, primarily owing to an epidemic strain whose emergence could be linked to the excessive use of fluoroquinolones (34,35).

Antibiotic misuse is a key driver in accelerating the development of antibiotic-resistant bacteria (36–42). Systematic reviews show that the misuse of antibiotics may produce greater resistance not only in individual patients (43) but also in communities, regions and countries (42). Infections caused by antibiotic-resistant bacteria may only be treated with broad-spectrum or even last-resort agents, which would lead to further resistance issues. In cases in which last-resort drugs have also lost their effectiveness, physicians should consider out-of-date but still potentially effective antibiotics, which have higher toxicity and less efficacy (44). Morbidity and mortality increase after delayed or failed antibiotic treatment due to antibiotic resistance. High-quality systematic reviews indicate that inappropriate initial antibiotic therapy increases thirty-day and in-hospital mortality in patients with severe infections (45,46). In addition, patients infected with antibiotic-resistant bacteria have longer hospital stays and higher health care costs, at least partly owing to a higher need for surgical interventions to treat the infections (47). The availability of few new antibiotics, due to the lack of significant investments in antibiotic development, worsens the outlook (36). Further, antibiotic-resistant bacteria and infections caused by them are no longer restricted to hospitals but also present in the community (48), and in both adults and children (49).

CONSEQUENCES OF THE PROBLEM IN HUNGARY

Microbiological and epidemiological data on antibiotic resistance show an unfavourable and worsening situation in Hungary. Health-care-associated infections (HAIs) due to certain antibiotic-resistant bacteria and Clostridium difficile are notifiable in Hungary, using standard European case definitions. In 2014 and 2015, Hungarian acute and chronic care hospitals reported about 4000 HAIs due to antibiotic-resistant bacteria annually into the National Nosocomial Surveillance System (50). Between 2005 and 2015, the incidence of these infections increased significantly: from 5.4 to 24.8 per 100 000 patient-days (50,51). The increase in the most recent years is mainly due to infections caused by resistant types of a specific group of bacteria (so-called Gram negatives). This is of particular concern for several reasons:

1. these bacteria are a major cause of lower RTIs, bloodstream infections, and wound or surgical-site infections in health care settings, with significant mortality, and antibiotic resistance further increases the risk of death;
2. these bacteria have built-in abilities to find novel ways to become resistant and can pass genetic materials that allow other bacteria to become antibiotic resistant; and
3. current therapeutic options are limited to a very few antibiotics and resistance is emerging even among these (52).

The burden of health-care-associated CDIs is decreasing, yet still high: about 6600 reported cases in 2014 and 5800 in 2015, with a change in incidence from 37.5 to 32.8 cases per 100 000 patient-days (50).

Concerning resistance data, an important example is the antibiotic resistance of Escherichia coli isolated from outpatient urine samples, as this bacterium frequently causes community-acquired urinary tract infections. In 2015, data from the National Bacteriological Surveillance System (17) showed a high proportion of isolates resistant to second-choice antibiotics (20% in the case of amoxicillin/clavulanic acid), which indicates that, in general, these agents' relative ineffectiveness precludes their further routine use. Resistance to recommended first-choice antibiotics, however, was low (4% for nitrofurantoin), highlighting that these agents could still be used effectively. This further confirms that the misuse of broad-spectrum, second-choice antibiotics is common in community care in Hungary, which leads to increased resistance rates (17). The pathogens isolated from patients with invasive infections – most likely inpatients in hospital care – are reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net), allowing international comparison (17,53). In general, the proportion of antibiotic resistance of bacterial isolates from Hungary was higher than the European mean values in 2014 for most combinations of antimicrobial groups and bacteria, and the difference was statistically significant in almost all cases (17,53).

Factors underlying the problem

Inappropriate antibiotic use has various causes in general and in Hungary in particular. In 1999, WHO conducted and published a comprehensive literature review on factors contributing to the misuse of antibiotics, and listed numerous elements at different levels of the health system (5). The following section (organized into a problem tree in Annex 5) explores the possible causes of antibiotic misuse in Hungary according to the framework presented in the review. Given the primarily medical nature of antibiotic misuse, it addresses prescriber-level causes first. As the volume of scientific publications available on the topic was limited, local (national-level) evidence is in large part also based on reports, official documents, expert opinion and situation description and analysis.

PRESCRIBER LEVEL

In both adult and paediatric primary care, studies indicate that the misuse of antibiotics in Hungary is mainly related to the lack of consideration given to disease aetiology (e.g. bacterial vs viral infection), leading to a trial-and-error approach in antibiotic prescribing (54,55). Data from international studies suggest that inappropriate antibiotic prescription habits and attitudes, leading to antibiotic misuse, among physicians may also be related to the fear of patients possibly developing infectious complications, insufficiency of physicians' knowledge, response to patient pressures and acquiescence to pharmaceutical companies' pressure to prescribe certain antibiotics for financial gain (56–60). Notably, a systematic review found that physicians' perception of patients' desire for antibiotics was strongly associated with antibiotic prescribing for RTIs, in contrast to patients' desire for an antibiotic that was not or only modestly associated with a prescription (61). Prescribers may make seemingly convenient, but unjustified choices by prescribing antibiotics that they expect to be effective in almost all cases. Even if prescribers are concerned about antibiotic resistance or adverse effects, they do not commonly consider it when selecting therapy (60). All of these factors may contribute to the increasing prescription of second-choice, broad-spectrum agents over the past 20 years in Hungary by physicians in both community and hospital care.

Physicians' insufficient knowledge is likely related to the lack of sufficient attention paid to the prudent use of antibiotics, appropriate treatment of infections, and prevention and control of antibiotic resistance in undergraduate and postgraduate medical education in Hungary (62). The results of a representative European survey of final-year medical trainees (the PREPARE study – preparedness of undergraduate students to prescribe antibiotics) show that most Hungarian medical students do not feel that the knowledge they obtained in medical school prepared them to prescribe antibiotics properly. Six out of every seven respondents answered that they would need more education on antibiotics in general and/or their responsible use (63).

PATIENT LEVEL

The population's insufficient health literacy and health-related knowledge contribute to patients' inadequate attitudes, beliefs, perceptions and behaviour related to antibiotic use. A WHO world-wide survey of public awareness found, for example, that patients requested antibiotic prescriptions for viral infections because they did not know that antibiotics would be ineffective, did not follow the physician's instructions for prescribed antibiotic treatment or did not complete necessary treatment (64).

The 2016 Eurobarometer survey on antibiotic resistance found that the Hungarian public's knowledge on antibiotics had improved since the 2013 Eurobarometer survey (65). Nevertheless, Hungarians were still among the less knowledgeable: only 20% of respondents gave fully correct answers (EU range: 12–46%). The proportion of those taking antibiotics in the previous 12 months increased by 5% (65). The proportions of those in Hungary who used antibiotics to treat influenza, a cold or a sore throat were 20%, 16% and 25%, in contrast to averages for 28 EU countries of 11%, 16% and 14%, respectively (65). This was so despite the lack of evidence of any benefit from antibiotics for the common cold or persisting acute purulent rhinitis, and strong evidence that antibiotics can cause significant adverse effects in adults when given for the common cold and in all ages when given for acute purulent rhinitis, as demonstrated by a high-quality systematic review (66).

As to raising awareness in the public, only 19% of Hungarian respondents recalled receiving information about the unnecessary use of antibiotics in the previous 12 months: among the lowest figures in Europe. Compared to the EU average, Hungarians were more likely to get information on antibiotic use from doctors and pharmacists, and less likely to receive information through conventional media (television, radio, newspapers) (65). This suggests that, even though Hungary has adopted the goals and the communication tools and materials of the ECDC European Antibiotic Awareness Day since 2008, the public has not been widely reached (67).

GOVERNMENT AND HEALTH-SYSTEM LEVEL

One of the crucial factors is the lack of a comprehensive national strategy and action plan, which would include a national ASP on prudent antibiotic prescribing at all health-care levels, in hospitals, community care and long-term care (68). The country is preparing such a strategy and action plan (69).

Up-to-date diagnostic and treatment guidelines have also been unavailable for most community-associated infections and HAIs for several years. In their absence, market forces and manufacturers' marketing activity can largely influence prescribing practices. Earlier diagnostic and/or treatment guidelines (e.g. on sepsis, nosocomial and community-acquired pneumonia) have expired and not been updated (70).

The clinical relevance of statistical data on antibiotic use could be increased if prescriptions could be linked to the diagnoses identified by doctors, offering an accurate view on which diseases are the most urgent in terms of need for a change in antibiotic use. Currently, there is no such system available in Europe, which could serve as a methodological example.

Antibiotic misuse may also be linked to inadequate diagnosis due to an insufficient availability of timely microbiological results. The 2014 survey of the EU Laboratory Capability Monitoring System shows that utilization of diagnostic testing in Hungary is lower than the EU mean (71). In 2014, the blood culture test rate in Hungarian hospitals was the fourth lowest in Europe (53). Notably, sampling and diagnostic testing are not prerequisites for reimbursement. The reorganization and privatization of microbiology laboratories in Hungary in the past few years has resulted in considerably reduced local availability. Interviews of key informants showed that geographical and organizational distance hinders communication between physicians and microbiologists, vital for the timely delivery of results to guide treatment choices. In community care, low testing frequency results from the logistical and technical issues of sample transport to laboratories, as well as a long turnaround time for results. The use of point-of-care rapid diagnostic tests (e.g. the Strep test, C-reactive protein (CRP) test, influenza test) that may provide prompt information on the bacterial vs viral aetiology of RTIs is uncommon, as social insurance does not finance these tests.

Prescribers' misuse of antibiotics may also be connected to the low availability of infectious disease specialists, hospital pharmacists and clinical microbiologists in health care, to lead and support national and local activities to facilitate prudent prescribing. According to a national report, specialists in infectious diseases and medical microbiology were in short supply in Hungary in 2016 (72).

Another factor contributing to antibiotic misuse is the lack of restrictions on the use of powerful, broad-spectrum antibiotics in either hospital or community care. The limitations on antibiotic prescriptions are cost based: for example, when the most expensive drugs are prescribed, reimbursement is provided only for specific clinical conditions and only if written indication was given by an infectious-disease specialist. Further, owing to the low and continuously decreasing share of certain narrow-spectrum products (e.g. penicillins) among prescriptions, pharmacies are less likely to keep these otherwise recommended agents in stock. Certain narrow-spectrum agents (e.g. oxacillin, flucloxacillin) are not available on the Hungarian drug market and can be accessed only through individual import schemes. Importantly, antibiotics listed as "key access" agents on the 2017 WHO Essential Medicines List (benzathine benzylpenicillin, benzylpenicillin, cloxacillin) are not registered or currently available in Hungary (73). This issue should be viewed in the context of a recent market-availability survey, conducted in 39 developed countries, which highlighted that the availability of older but still clinically useful antibiotics is problematic in Europe, Australia, Canada and the United States as well (74). Importantly, even temporary shortages of narrow-spectrum antibiotics can trigger negative effects on prescribing patterns, leading to increased prescribing of broad-spectrum agents (75,76). As with most medicines in Hungary, antibiotic prescriptions are valid for three months: an unnecessarily long period, considering that these agents are typically prescribed for acute infections.

HOSPITAL LEVEL

Despite the existence of ICACs in hospitals as mandated by law (77), antibiotic stewardship and activities for infection prevention and control are often insufficient in Hungarian health care facilities, due to a widespread lack of specialized staff, dedicated funds, interdisciplinary ward rounds, close collaboration with the microbiology laboratory and the hospital pharmacy, and moral, technical and organizational support from hospital administration. Local antibiotic policies are also lacking; where they exist, they are not necessarily updated with surveillance data on antibiotic use, antibiotic-resistant bacteria and infections caused by them. Resources may vary significantly according to the level of care.

INDUSTRY LEVEL

In Hungary, the law bans consumer advertising of prescription drugs, including antibiotics. The promotion of drugs, including antibiotics to prescribers – pharmaceutical sales representatives' information and persuasive activities that target physicians to induce the prescription, supply, purchase and/or use of antibiotics – is a common practice, however, legal since the 1990s. Pharmaceutical companies wish to increase drug sales, and their activities may have an inappropriate impact on public health (78).

A study in the Netherlands found that GPs who reported having seen pharmaceutical sales representatives and were inclined to prescribe more new drugs also prescribed higher volumes of second-choice antibiotics for RTIs (79). Promotional activities by pharmaceutical sales representatives are assumed to have had an important impact on prescribing practices in Hungary, too.

In the absence of a comprehensive ASP and guidelines on appropriate prescribing practice, this may have been one of the major causes of the shift towards broad-spectrum antibiotics in the community shown by Fig. 1. In addition, misleading consumer advertising of certain over-the-counter products, especially throat lozenges for symptomatic relief of sore throat and inflammation that contain (unnecessary) local antibiotics, may help to promote the mistaken view in the population on the need to take antibiotics for acute tonsillopharyngitis or other upper RTIs.

OPTIONS FOR ADDRESSING THE PROBLEM

The various causes of antibiotic misuse in human medicine in Hungary, as detailed above and in a problem tree (Annex 5), call for policy interventions at different levels. According to this brief's framing of the problem as one related first and foremost to medical practice, however, the authors propose three options principally addressing such causes for more detailed review:

1. developing a national ASP, complemented by evidence-informed guidelines for the diagnosis and treatment of common infections;
2. strengthening undergraduate and postgraduate medical, dental and pharmacy education and training on prudent antibiotic prescribing; and
3. raising awareness of prudent antibiotic prescribing and use through information campaigns, leaflets and interpersonal communication.

These options may be implemented together or individually, or some elements of them may be used to create new options. Option 1 needs special emphasis, however, because it is an integrative, multifaceted tool in itself, and is the best supported by scientific evidence.

The options are presented to promote discussion informed by the best available evidence. Stakeholders discussed the findings of the current brief at a policy dialogue on 11th December 2017.

Policy option 1. Developing a national ASP, complemented by evidence-informed guidelines on the diagnosis and treatment of common infections

OVERVIEW AND CONTEXT

Antibiotic stewardship is an organizational or health-care-system-wide approach to promoting and monitoring the judicious use of antibiotics, which is based on the principle that antibiotics should be prescribed and taken only when medically indicated and that, if antibiotic use is necessary, the optimal drug regimen, dose, duration of therapy and route of administration should be selected. ASPs are coordinated programmes that implement interventions to ensure appropriate antibiotic prescribing (80-82). Major public health bodies – including WHO, ECDC and CDC – as well as a number of national governments and professional organizations, have advocated the universal implementation of ASPs as a promising strategy to preserve the future effectiveness and therapeutic benefits of antibiotics (6,80,83-88).

According to EU guidelines (81), national governments are responsible for regulating access to and the use of antibiotics; ASPs at all levels of care; the timely surveillance of antibiotic consumption and resistance data; the development, implementation and monitoring of clinical guidance for infections; and the education of health care professionals on antibiotic stewardship. ASPs in hospital and community care should be based on national, evidence-informed guidelines on the general principles of prudent antibiotic use, as well as on the diagnosis and treatment of the most common infections, serving as standards for care and audit. Specific stewardship interventions may include guideline implementation, increased laboratory testing, preapproval strategies, delayed prescription, prospective audit and feedback, formulary restrictions, and communication-skills training (Box 6).

Owing to its comprehensive nature, this option addresses most government-, health-care-provider- and prescriber-level factors underlying the problem of antibiotic misuse. Meanwhile, as indicated above, the development of an ASP should be regarded in conjunction with the actual availability of human resources, timely microbiological diagnosis and recommended antibiotics, the need for which it may make apparent.

Box 6. The content of selected key stewardship interventions

Selected key stewardship interventions (89–93) comprise the following:

- **de-escalation:** a shift to a narrower-spectrum antibiotic, or to a lower dose.
- **preapproval strategies:** the use of certain antibiotics is subject to approval by an infectious disease specialist, clinical pharmacist or a clinical working group, which can specify the dose, mode of administration, length of treatment, etc.;
- **formulary restrictions:** restrictions to the list of antibiotics available in a health care provider institution – typically a hospital or long-term care facility – in line with the local guidelines of antibiotic use;
- **delayed prescription:** the physician (typically in primary care) prescribes a drug with instructions for the patient to take it only if symptoms persist or deteriorate;
- **prospective audit and feedback:** consultative review of clinicians' antibiotic prescriptions by an infectious disease specialist, microbiologist, clinical pharmacist, etc., who gives direct feedback on the appropriateness of antibiotic use, but leaves the final decision to the clinician; and
- **therapeutic drug monitoring:** measurement and assessment of drug concentration in samples from the patient, at certain times according to dosage.

EVIDENCE ON IMPACT

There is substantial evidence on the efficacy of ASPs from the perspective of a health care system. Four systematic reviews (84,94–96) and a NICE guideline (80) suggest that appropriate antibiotic use promoted by ASPs can effectively contribute to the containment of antibiotic misuse.

Hospital care

A medium-quality systematic review demonstrated that ASPs in hospitals result in improved prescribing practices, without any adverse patient outcomes, including mortality, length of stay, readmission and the incidence of CDIs. There is strong evidence that audit and feedback, formulary restriction and preauthorization, as well as guideline implementation, decrease antibiotic use or increase appropriate use (84). Further, a high-quality meta-analysis, a high-quality systematic review and a medium-quality systematic review (83,94,95) all found that, after the introduction of ASPs, the use of broad-spectrum antibiotics decreased significantly, and antibiotic costs dropped, as did the length of hospital stays and the number of infections caused by certain multidrug-resistant organisms. The benefit was found to be more marked in intensive care units. According to these reviews, guideline-adherent therapy and de-escalation (the recommended switch to a narrower-spectrum antibiotic or to a lower dose) were also associated with a significant reduction of relative risk for mortality.

A high-quality narrative review concluded that antibiotic stewardship interventions by infectious disease specialists were associated with a significant improvement in the appropriateness of antibiotic prescribing and with decreased antibiotic consumption (97), while a medium-quality systematic review concluded that involving hospital pharmacists in stewardship activities had positive effects (98). A qualitative review, including 31 studies on stewardship educational interventions in hospital settings, reported improvement in adherence to guidelines and a decrease in total antibiotics prescribed after the interventions in 41% of the reviewed studies (99). A medium-quality systematic review, in turn, established the link between better prescribing and less antibiotic resistance and fewer HAIs (89).

Community care

In community care, a medium-quality systematic review found medium-strength evidence that ASP activities, especially a more systematic laboratory-testing practice and communications-skills development for physicians, resulted in a reduction in antibiotic prescribing (100). As most antibiotics are prescribed for RTIs and urinary tract infections in ambulatory care, specific interventions targeting these conditions may result in greater reductions in prescribing than general approaches (101). A systematic review found that multiple, physician-targeted interventions to improve antibiotic use for RTIs in primary care were more frequently effective than interventions using just one element (102). Interventions to decrease overall antibiotic prescription were also more frequently effective than those to increase the selection of first-choice agents. Educational material for physicians was the most often effective element, and showed an independent association with a positive intervention outcome (102). As to the impact of educational interventions, a qualitative review including 47 studies on stewardship educational interventions in primary care settings reported improvement in adherence to guidelines and a decrease in antibiotics prescribed following the intervention in 46% of the reviewed studies (99).

Rapid point-of-care tests in primary care (e.g. CRP test, Strep test, influenza test) could help prescribers more systematically rule out bacterial infections and therefore reduce antibiotic use, but their implementation requires caution, as their utility may differ among patient groups (e.g. adult vs paediatric populations) and types of infection. For example, a high-quality meta-analysis found a significant reduction in antibiotic prescribing associated with the use of point-of-care CRP tests at the time of prescription in primary care practices (103). A recent review of systematic reviews also found medium-quality evidence in this respect, with no effect on reconsultation rates and patient satisfaction (104). Public Health England recommended the consideration of the use of these tests on the same grounds (105). A large Hungarian questionnaire survey (the unpublished data from which were presented at 24th Annual European Society for Paediatric Infectious Diseases Meeting in 2006) also concluded that using point-of-care CRP tests could decrease antibiotic consumption. There is no strong evidence, however, that point-of-care CRP tests produce reliable results in the diagnosis of sinusitis and lower RTIs in primary care (106,107).

Table 2. summarizes key findings from systematic reviews relevant to option 1: developing a national ASP complemented by guidelines on the diagnosis and treatment of common infections.

Table 2. Summary of key findings from systematic reviews relevant to option 1

Category of finding	Key findings
Benefits	» A high-quality meta-analysis shows a 19.1% decrease in antibiotic use after the implementation of hospital ASPs (95% confidence interval (CI) = -30.1 to -7.5) (95). » Two medium-quality systematic reviews present rather low-strength evidence of ASPs in hospitals resulting in better prescription and better outcomes (84,94). » According to a high-quality meta-analysis, guideline-adherent empirical therapy resulted in a relative risk reduction for mortality of 35% (relative risk, 0.65; 95% CI = 0.54 to 0.80) and de-escalation (recommended switch to a narrower-spectrum antibiotic or a lower dose) of 56% (relative risk, 0.44, CI = 0.30 to 0.66) (83). » A high-quality and a medium-quality systematic review demonstrate that ASPs result in better patient outcomes and reductions in mortality (83,94). » A medium-quality systematic review suggests that ASPs including microbiological testing and communications-skills development are also effective in reducing antibiotic use in the ambulatory setting (100).
Potential harm	» No systematic reviews dealing with patient outcomes reported any significant adverse effects from ASPs (84,94). » In ambulatory care, a high-quality systematic review showed that antibiotic treatment of the common cold presents a risk of adverse outcomes, so reducing antibiotic use may actually contribute to curbing adverse outcomes (66).
Resource use, costs and/or cost-effectiveness	» ASP development (guideline development and regular update) and implementation (monitoring and control activities, human resources, potentially increased testing frequency, etc.) require continuous funding at the levels of both the government and health care providers. » Hospital antibiotic stewardship policies result in significant decreases in antibiotic consumption and cost. The rates of infection due to specific antibiotic-resistant bacteria decreased and the overall length of hospital stay improved (100). » A high-quality meta-analysis showed a decrease in overall antimicrobial cost by -33.9% (CI = -42.0 to -25.9) and of length of stay by -8.9% (CI = -12.8 to -5) in a hospital setting (95).
Uncertainty about benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» The evidence on the efficacy of delayed prescriptions (prescriptions issued by health professionals for use by patients at a later date, if their symptoms do not improve) and systems for clinical decision support in reducing antibiotic consumption in ambulatory care is of low strength (100). » Certain point-of-care tests lack convincing evidence on reliability in sinusitis and lower RTIs (106,107). » The significance of positive effects of ASPs on patient outcomes is not established in all reviews (84).

Table 2. (Contd)

Category of finding	Key findings
Key elements of the policy option if it has been tried elsewhere	According to systematic reviews, the following interventions have been applied successfully (with at least medium-quality evidence supporting their efficacy): » therapeutic drug monitoring in hospital settings (reduced length of stay) (83); » preapproval strategies in hospital settings (reduced antibiotic consumption, length of stay and costs) (95); » prospective audit and feedback in hospital settings (reduced antibiotic consumption, length of stay and costs) (95); » stewardship education in hospital settings (reduced antibiotic consumption, length of stay and costs) (95); » guidelines in hospital settings (reduced antibiotic consumption, length of stay and costs) (95); » formulary restrictions in hospital settings (reduced antibiotic consumption, length of stay and costs) (95); » communication-skills training in outpatient settings (reduced antibiotic prescription) (100); » increased laboratory testing in outpatient settings (reduced antibiotic prescription) (100). ASPs of the United States CDC and of several other countries all underline the importance of commitment from management, the nomination of a dedicated leader, and complementary actions to put in place stewardship interventions (87). A systematic review found medium-quality evidence that restrictive interventions are more effective than persuasive ones in the short run (up to six months), but no significant difference in a longer timeframe. Structural interventions were also found to reduce antibiotic prescription (94). Restrictive interventions included: » compulsory order form; » expert approval for prescription; » removal of restricted antibiotics from the cupboard; » review of prescription and effective change. **Persuasive interventions included:** » distribution of educational materials; » educational meetings; » local consensus processes; » review of prescription and recommendation of change; » local opinion leaders; » verbal reminders provided on paper or computer; » audit and feedback. **Structural interventions included:** » changing from paper to computerized records; » rapid laboratory testing; » computerized decision support systems; » the introduction or organization of quality monitoring mechanisms
Stakeholders' views and experiences	» In Hungary, the interviews of key informants led to the conclusion that a wide range of stakeholders supports both national and local implementation of ASPs, but certain important barriers need to be tackled prior to establishing such a programme.

Policy option 2. Strengthening undergraduate and postgraduate medical, dental and pharmacy education on prudent antibiotic prescribing and training on prudent antibiotic prescribing

OVERVIEW AND CONTEXT

This option is about introducing a complex set of learning modules on antibiotics and antibiotic use and resistance into different undergraduate and postgraduate education programmes. It addresses an important part of the prescriber-level factors underlying the problem of antibiotic misuse. Option 2 is linked to option 1 by the need for sufficient education or training to accompany the introduction of any new stewardship intervention. Similar resource conditions for effectiveness also hold: it is important, for example, to ensure a high responsiveness of microbiological laboratories and comprehensive, reliable data systems on resistance patterns, linking diagnosis to pathogens if possible, to make genuine progress in appropriate prescribing.

EVIDENCE ON IMPACT

A medium-quality review suggests that the development of teaching curricula by inclusion 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 (108).

STRENGTHENING UNDERGRADUATE EDUCATION

To avoid later difficulties in changing the established prescribing behaviour of trained physicians, significant attention should be given upfront to shaping prescribing behaviour: improving the education of medical, dental and pharmacy students (108). The PREPARE study, conducted among final-year medical students in Europe, found that the higher the self-reported preparedness to deal with general antibiotics and the prudent use of antibiotics among medical students in a country, the lower the country's scores on antibiotic resistance in EARS-Net (63). This correlation may be explained by, among other elements, medical professionals' favourable general attitude to the prudent use of antibiotics, reflected in curricula as well as in prescription habits. While no study is available to measure the effectiveness of an undergraduate educational programme on prudent antibiotic prescribing for medical students (105), several WHO publications, recommendations and policy options targeting the threat of antibiotic resistance emphasize the intuitive importance of early training to promote appropriate antibiotic prescribing (109,111,112). The aim is to ensure that graduates enter clinical practice with the right skills and attitudes to be both effective practitioners and committed stewards of antibiotic resistance containment (111).

STRENGTHENING POSTGRADUATE AND CONTINUING EDUCATION

Educating resident doctors and specialty trainees on antibiotic use is similarly important. According to studies carried out in different European countries, however, junior doctors commonly consider their training on antibiotic use to be insufficient. Studies conducted in France, Scotland and Spain show that they would welcome more local antibiotic guidelines, specific teaching sessions, specific antibiotic management teams or readily accessible advice from a group or an infectious-disease specialist, to improve antibiotic prescribing (113,114).

Guidance from WHO and ECDC also emphasizes that new developments in the field of antibiotic therapy should be regularly presented within the framework of continuing education (6,109,111).

Evidence from the above-mentioned medium-quality review suggests that interventions focusing on clinician education programmes can achieve reductions in antibiotic prescribing (108). Examples of these include interactive seminars, mail campaigns, small-group education focusing on evidence-informed medicine and communication skills, educational outreach visits, guidelines and leaflets, and a combination of these educational strategies.

Two further medium-quality reviews underline that passive forms of education appear unsuccessful in prompting clinicians to modify their prescribing practice (101,115). Education or educational materials need to be supplemented with another type of intervention targeting physicians (e.g. computer reminders, audit and feedback, communication skills training), preferably as part of an ASP.

Table 3 summarizes key findings from systematic reviews relevant to option 2: strengthening undergraduate and postgraduate medical, dental, and pharmacy education on the prudent use of antibiotics

Table 3. Summary of key findings from systematic reviews relevant to option 2

Category of finding	Key findings
Benefits	» A medium-quality review found that antibiotic prescription was reduced by 34% on average (range: 9–52%) in intervention groups of medical professionals receiving continuing education measures compared to control groups. The number of inappropriate antibiotic prescriptions was also reduced by an average of 41% compared to control groups (108). » A medium-quality review showed that outreach visits, where professionals are visited in their own practices, and computer reminders seem effective in changing prescribing behaviour (115).
Potential harm	» Key informant interviews revealed that the length of medical training in Hungary is fixed and curricula are already quite dense, so introducing a new subject might entail reduced attention to others.
Resource use, costs and/or cost-effectiveness	» Curriculum development, increased training and education require additional funding.
Uncertainty about benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» No study is available that would specifically measure the effectiveness of educational programmes for medical students on appropriate antibiotic prescribing. The need for such programmes is quite intuitive, and multiple organizations recommend them, but the actual results have to be monitored.

Table 3. (Contd)

Category of finding	Key findings
Key elements of the policy option if it has been tried elsewhere	» In certain developed and developing countries, such as the United Kingdom and Zambia, respectively, 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 (108,111,116). » 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 (117,118).
Stakeholders' views and experiences	» During key informant interviews, stakeholders expressed support for the development of medical curricula and postgraduate education dealing with antibiotic stewardship and prudent prescribing.

Policy option 3. Raising awareness of prudent antibiotic use through information campaigns, leaflets and interpersonal communication

OVERVIEW AND CONTEXT

This option is about raising general awareness of prudent antibiotic use and the threat of antibiotic resistance due to misuse, principally through information campaigns, information leaflets and interpersonal communication. While it addresses patient-level factors underlying the problem of antibiotic misuse that relate to lack of knowledge or awareness or misperceptions, it also concerns prescribers and prescribing behaviour, which comprise an important channel for transmitting information and attitudes to patients. As with option 2, these interventions should fit closely with the ASP proposed in option 1.

EVIDENCE ON IMPACT

Evidence on the effectiveness of this type of intervention relies more on individual country experience than systematic evaluation. Published results are mixed, and it is important to consider the great heterogeneity in the actual objectives, methods, target populations and evaluation. While improved awareness and knowledge do not always translate into appropriate behaviour, they can be considered necessary starting points.

NATIONAL OR REGIONAL INFORMATION CAMPAIGNS

A review of information campaigns to improve the use of antibiotics in outpatients in high-income countries identified 22 national or regional campaigns in 1997–2007 (119). Health authorities were involved in organizing almost all these campaigns, which typically targeted both the public and prescribers. All campaigns focused on RTIs, since these are responsible for most antibiotic prescriptions but often do not require antibiotic treatment. The campaigns promoted similar key messages and consisted of a mixture of messages framed both negatively (e.g. "antibiotics won't help your defences against a cold") and positively (e.g. "get smart about antibiotics").

In Australia, Belgium, France, Greece and Italy, carefully planned, executed and documented campaigns led to improvements in prudent antibiotic use (120–125). A French national programme, called "Keep Antibiotics Working", targeted both the general public and health care professionals to encourage the surveillance of antibiotic use and resistance, and to promote better targeted antibiotic use. This was followed by a public campaign entitled "Antibiotics are not automatic" each winter, with the primary goal of decreasing prescriptions, particularly during the RTI epidemic season and among children, for whom more than 40% of prescriptions are written. As a result of the campaigns, a 27% reduction in prescriptions was seen over five years (120). In Belgium, complex campaigns making use of booklets, handouts, posters, prime-time television spots and websites resulted in reductions of antibiotic consumption by 3.4–6.5% each year, after controlling for the severity of influenza epidemics (122). In Italy, a "low cost" local campaign – comprising posters, brochures, advertisements in local media products and a newsletter on local antibiotic resistance targeting doctors and pharmacists – resulted in a 4.3% drop in antibiotic prescribing. The drop was more marked in beta-lactamase-resistant penicillins, in line with a message to prescribers to avoid them (123). Although a multifaceted campaign was not successful in reducing the total level of prescriptions in Greece, it did result in substantially more appropriate antibiotic use (124). In Australia, coordinated community campaigns using newsletters and brochures, mass-media activity (billboards, television, radio and magazines) and small grants to promote local community education resulted in a substantial reduction in antibiotic prescriptions, particularly for upper RTIs: 10.8 fewer original antibiotic prescriptions per GP per year (125).

Public Health England's online initiative invites health care professionals or leaders, members of the public, students and educators to become "antibiotic guardians", making a simple pledge to make better use of antibiotics. Evaluation showed that it has increased self-reported knowledge and changed self-reported behaviour, particularly among people with prior awareness of the issue of antibiotic resistance (126).

Nevertheless, many campaigns are not robustly evaluated; even when an evaluation took place, there is a dearth of data on cost–effectiveness. In fact, the uniqueness of each intervention makes comparing campaigns and identifying their effective components rather difficult.

PATIENT INFORMATION LEAFLETS

A medium-quality systematic review found information leaflets given to patients during GPs' consultations for common infections to be promising tools to reduce antibiotic prescriptions. The results on reconsultation rates for similar symptoms vary, with a tendency toward fewer reconsultations when patients receive the leaflets (127). Another medium-quality systematic review and meta-analysis found that, in paediatric primary care, materials on RTIs designed to engage children in addition to parents were effective in modifying the parents' knowledge and behaviour, resulting in reductions in consulting rates (128). An assessment by NICE found that leaflets alone led to improvements in knowledge among adults, but not among parents of young children. There was evidence, however, that leaflets in combination with structured discussion, held either face to face or via a video presentation, improved antibiotic knowledge and behaviour in both groups (129).

In England and Wales, a cluster randomized controlled trial evaluated the effect of using a booklet on the management of infections in children during GP consultation. The booklet was designed for GPs to use as an aid during the consultation before being passed on to parents to take home and refer to in the future. Assessing the impact on 558 children in 61 practices, the trials found that booklet use was associated with a reduction in antibiotic prescribing of 40% (at that consultation). Participating GPs were specially trained in using the booklet via an online platform prior to the study (130).

INTERPERSONAL COMMUNICATION

It is assumed that educational messages on antibiotic resistance and its implications could be most effective if people feel personally addressed by them (80). A communication may emphasize that losing antibiotics as effective treatment options could directly affect the health of recipients or their loved ones. Reports in the literature suggest that campaigns using written materials and the mass media could be more effective if physicians facilitated the transmission of information to the public, including patients (108).

A high-quality systematic review concluded that, for adult patients, shared decision-making significantly reduces antibiotic prescribing for acute RTIs in primary care, without a decrease in patients' satisfaction with the consultation or an increase in repeated consultations for the same illness (131). Shared decision-making includes: explaining the medical problem to the patient; discussing treatment options and communicating the benefits and risks of each. (For a detailed definition, see Elwyn, Laitner, Coulter, Walker, Watson & Thomson (132).) In paediatric primary care, interventions aimed at parents and/or clinicians can reduce rates of antibiotic prescribing for children with RTIs, as indicated by another high-quality systematic review. The most effective interventions involved: targeting both parents and clinicians during a consultation, providing automatic computer prompts for evidence-informed prescribing, and promoting clinician leadership or participation in the design of treatment guidelines and/or peer education (133). Table 4 summarizes key findings from systematic reviews relevant to option 3: raising awareness of prudent antibiotic use through information campaigns, leaflets and interpersonal communication.

Table 4. Summary of key findings from systematic reviews relevant to option 3

Category of finding	Key findings
Benefits	» Several country examples suggest that national campaigns to increase public knowledge and awareness of antibiotic resistance may have an indirect positive effect on prescribing practice (see below). » The use of patient information leaflets on common infections during GP consultations may effectively reduce antibiotic prescriptions, antibiotic use and patients' intention to reconsult (112,113). » Interventions intended to facilitate shared decision-making significantly reduce antibiotic prescribing for acute RTIs in primary care, without a decrease in patients' satisfaction with the consultation, or an increase in repeat consultations for the same illness (131).
Potential harm	» None of the systematic reviews provided information about the potential harms of programmes to raise awareness.

Table 4. (Contd)

Category of finding	Key findings
Resource use, costs and/or cost-effectiveness	» Public communication campaigns and leaflets need substantial funding. They can be cost effective by decreasing unnecessary antibiotic prescriptions, but their cost–effectiveness is yet to be proven.
Uncertainty about benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	» The results of these interventions are mixed, and rely more on individual country experience than systematic evaluation. New interventions should be closely monitored for reach, impact and cost–effectiveness.
Key elements of the policy option if it has been tried elsewhere	» In France, a national programme targeted both the general public and health care professionals, to encourage surveillance of antibiotic use and resistance and to promote better-targeted antibiotic use. 27% reduction in prescriptions was seen over five years (120,121). » In Belgium, a national campaign conveyed simple messages through booklets, handouts, posters, television spots and websites. Television advertisements were reported to be the most memorable (122). » In Italy, a local public campaign to lower antibiotic consumption used posters and local broadcast media. Information was also provided directly to doctors and pharmacists. The antibiotic use reduced by 4.3% (123). » In Australia, an annual social-marketing campaign (including information distributed via newsletters and brochures, billboards, television, radio and magazines and small grants to promote local community education) over four consecutive years had positive outcomes: improved consumer awareness, beliefs, attitudes and behaviour; and a decline in antibiotic prescriptions dispensed in the community (125). » In England and Wales, a campaign focusing on primary care used a booklet on the management of infections in children during GP consultations. The booklet was designed to be used as an aid for GPs during the consultation before being passed on to parents to take home and refer to in the future. Antibiotic prescribing at the consultation was reduced by 40% (130).
Stakeholders' views and experiences	» Experience in Hungary with large media campaigns in this field is limited. Owing to their relatively high costs, the campaigns' effectiveness would have to be proved before they would be launched. Smaller, more targeted interventions (e.g. using leaflets) would probably be easier to implement.

CONSIDERATIONS IN IMPLEMENTING THE THREE OPTIONS

Potential barriers

OPTION 1: ASP

National level

As to access to and the availability of recommended antibiotics, the National Institute of Pharmacy and Nutrition lacks the authority to prevent the withdrawal of products from the Hungarian drug market for economic motives or to require pharmaceutical companies to manufacture certain products. The application of individual import schemes is time consuming, and thus inconvenient for securing the availability of essential antibiotics for the treatment of acute infections.

Also, developing and periodically updating national guidelines to support prudent antibiotic prescribing is labour intensive, so it requires institutional and budgetary support. The development of clinical guidelines in Hungary has slowed down in recent years, owing to the onerous methodology required by law (129), and to a lack of corresponding human and financial resources. For the monitoring of compliance with guidelines and stewardship interventions, the powers of the control bodies (including that of positive or negative financial sanctions) as defined by law (135), and the resources at their disposal would both need to be increased.

Provider level

The experts interviewed confirmed the official data indicating a shortage of key professionals – infectious disease specialists, clinical microbiologists and clinical pharmacists – who could contribute to and advance ASPs in Hungary. The Decree of the Ministry of Health No. 20/2009 (VI.18.) on prevention of HAIs, minimum professional requirements and supervision of these activities (77) requires every hospital to employ a full- or part-time infectious-disease specialist, and to set up and operate an ICAC, but the shortage of specialists prevents a number of health care facilities from meeting this requirement. Stewardship activities may be more easily introduced and managed in large, acute hospitals than in smaller facilities that may have less access to the medical expertise supporting stewardship (136).

Human resources also appear to be a recurrent problem in primary care. GPs' mean age is high (almost 57 years in 2015 in adult practices (137)), and their workload in some districts is overwhelming. In part, GPs may not necessarily follow and apply the latest professional guidance owing to time constraints.

Prescriber level

Although many physicians recognize the emergence of antibiotic-resistant bacteria as an important issue, they are often primarily concerned with their individual patients' direct clinical outcomes, and the risk of antibiotic resistance is a factor likely to influence their antibiotic choices only marginally. A medium-quality systematic review identified physicians' knowledge, attitudes and behaviour as barriers to their adoption of evidence-informed diagnostic and treatment guidelines (138). According to NICE, potential barriers to compliance with antibiotic-stewardship measures also include prescribers' fear of leaving patients untreated, lack of information on the impact of their prescribing on antibiotic resistance and lack of critical evaluation and reflection on their prescribing practice (80).

OPTION 2: EDUCATION DEVELOPMENT

As learned from key informants, improvements in prescribing practice deriving from changes in education take time to appear, and this may dissuade stakeholders who would seek promptly evident results. One key informant also emphasized that the schedule of training programmes for medical and dental students and graduates is already fairly dense, and it is difficult to introduce new subjects or courses without exceeding the legally set limits on training in terms of the requirements for graduation and postgraduate core courses. The introduction of a new subject or course may therefore necessitate a revision of and reductions in the training time dedicated to other disciplines, possibly leading to conflicts of interest among the stakeholders concerned.

OPTION 3: AWARENESS RAISING

At present, media and information space is highly saturated, so transmitting messages such as those on the importance and key principles of proper antibiotic use is challenging. Large media campaigns are costly, and financial considerations may not allow the planning of a campaign that would be sufficiently extensive and effective in a given setting. Further, drug companies may have a different agenda and better resources to communicate their own messages.

Key informants also mentioned that the pressures to prescribe from patients and pharmaceutical companies reinforce each other. A GP who prescribes an antibiotic at the patient's request often chooses an expensive broad-spectrum product of an influential pharmaceutical company. Further, shortage of time during patient–doctor visits impedes detailed discussions and the communication of key messages.

Potential opportunities

OPTION 1: ASP

National level

The present legal framework is favourable to the implementation of an ASP in hospitals, as the ministerial decree No. 20/2009. (VI.18.) on prevention of HAIs and professional minimum standards requires ICACs at the provider, county and national levels (77). In primary care, the number of antibiotic prescriptions figures among the national health insurer's quality indicators for adult practices (139). Although these indicators currently only trigger marginal financial reward, their importance could be increased.

The assessment of prescribing practices should not only be based on quantitative, but also on qualitative measures. For this to be achieved, data collection and database systems should be developed. Linking antibiotic prescription to clinical diagnoses could an important step ahead in this sense.

Closely linked to the prudent use of antibiotics, the containment of antibiotic resistance is advocated by the government health strategy for 2014–2020 (140), bringing in yet more political support. With a new national public health strategy in preparation, there is room for further high-level action in this area (141). The recent launch of a number of national projects on patient safety has created the opportunity to invest in the development of professional guidelines and related training materials. Novel policy or regulatory actions at both the national and international levels, such as launching joint EU-level procurement, may help to remedy the unavailability or shortage of antibiotics (74,142).

Provider level

As experts highlighted in interviews, strengthened hospital ICACs could be powerful supporters of hospital managers in locally implementing ASPs. ICACs could meet quarterly or biannually to discuss hospital issues, challenges and aims, and later to monitor progress towards local targets. Besides, meetings among clinical staff and department heads for clinical-practice improvement can be used to gather information on cases of particular interest for antibiotic stewardship, as well as systemic problems to be fed into the agenda of ICAC or managerial meetings. Tailoring local ASPs in this way would ensure hospital-wide support and acceptance.

In hospitals, incorporating antibiotic stewardship into the mandatory induction training for new medical staff and regular in-house training of clinical personnel would be easy ways to ensure that each and every staff member is aware of the requirements for prudent antibiotic prescribing. A number of the experts interviewed emphasized that a number of hospitals already have smart policies and best practices intended to rationalize antibiotic use.

Prescriber level

Legislation supports quality improvement in medical practice, especially in primary care. The recent primary health care act (143) establishes a new system of territorially elected, leading peer GPs at the district, county and national levels. The future tasks of leading peer GPs at the district level could include advocacy of ASP directives and guidelines, and monitoring compliance among GPs.

OPTION 2: EDUCATION DEVELOPMENT

The momentum generated by the widespread recognition in medical education circles of the significance of the problem of antibiotic misuse and consequent antibiotic resistance is a major enabler of option 2. The subject of infectious diseases is already mandatory at the faculties of general medicine at the University of Debrecen, the University Pécs and the University Szeged; this previously optional subject will become mandatory at Semmelweis University, in Budapest, in the 2018–2019 academic year. Advances at Semmelweis University, described by key informants, include the integration of the principles of antibiotic stewardship into pharmacology education at the Faculty of Dentistry, and plans for this in the faculties of General Medicine and Pharmacy. Key informants also noted that the structure of some successful training programmes organized by professional associations (such as the two-day course on life support for advanced sepsis in emergency medicine) may be used as a model in developing the agenda for short practical courses on antibiotic stewardship and the prudent use of antibiotics.

While respecting university autonomy, the Ministry of Human Capacities (which incorporates the state secretariats for Healthcare and Education) defines the subject matter of mandatory postgraduate core courses within the current legal framework. Legislative modifications could ensure in a straightforward way that no resident doctor could enter clinical practice without a sound understanding of the importance and principles of the appropriate use of antibiotics.

The training of hospital directors and health-care managers, who have a key role in stewardship implementation, includes elements of patient safety. Infection control and antibiotic stewardship could be included among these, e.g. as a project work of organisational development.

OPTION 3: AWARENESS RAISING

Key informants emphasized that experience with campaigns to promote seasonal influenza vaccine confirms GPs' positive role as mediators, and that training GPs in targeted topics can be straightforward and effective. The primary health care act, which entered into force in August 2015, emphasizes the expansion of preventive services and definitive health care within primary care, which would further support opportunities for communication of campaign messages between health care professionals and people visiting GPs' offices as patients or family members.

Cost–effectiveness considerations

Any policy measure requires resources in time, equipment and/or expenditure. Every intervention also has an opportunity cost by using resources (e.g. specialist time) that could also be used to fulfil other important tasks in the health system. As a WHO global report underlines, currently available data do not allow precise estimates of the overarching societal effects and economic costs of antibiotic misuse or resistance (144). Economic evaluations of interventions to curb misuse could start after the exact definition of those interventions. ASPs in particular may contain a wide variety of different elements, which is one of the reasons why their costs are difficult to evaluate in general terms. According to the literature, the introduction and appropriate implementation of ASPs have the potential to lead to substantial savings, although these are seldom quantifiable. While no evidence could be identified on the volume of financial benefits, either on a global scale or in individual countries, high-quality evidence exists for estimated savings in particular dimensions.

A NICE study examining the possible consequences of implementing an ASP points to the following potential benefits: reductions in antibiotic prescription, the costs of treatment (due to fewer infections caused by antibiotic-resistant bacteria) and the number of infections requiring hospital admission. The study presents the case of a 1% drop in admission rates to illustrate the potential related savings (129).

High-quality evidence from a systematic review shows that hospital ASPs result in a significant reduction of antibiotic use and related costs, particularly in intensive care units. The costs of inpatient care diminished by a third. Further, indirect savings (e.g. fewer side effects from drugs, shorter average length of stay) follow the direct shrinking of costs (95).

Medium-quality evidence from a systematic review of the Cochrane Collaboration, updated in 2017, demonstrates the reduction of the average length of antibiotic treatment (by 1.9 days: from 11.0 days to 9.1) and of the average length of hospital stay (by 1.1 days: from 12.9 days to 11.8) resulting from hospital ASPs (94).

In ambulatory care, particularly in primary care, where the great majority of antibiotic prescription takes place, the literature presents medium-strength evidence about the reductive effect on antibiotic use of communication-skills training and increased microbiological testing. In a medium-quality systematic review, the few studies that contained information on costs showed decreases by about 20–30% in intervention groups compared to control groups (100).

Individual studies also suggest a cost-effective utilization of rapid CRP tests in primary care, with the benefits of reduced antibiotic use and increased quality-adjusted life-years exceeding the cost of tests (89,146–147). The studies providing evidence on cost–effectiveness are also included in a high-quality systematic review of the area (103).

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ANNEX 1.
Summary of systematic reviews relevant to option 1

Systematic review	Option element	Focus of systematic review
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(10):1209–28.	Antimicrobial stewardship programmes (ASPs) in inpatient-hospital settings	ASPs in inpatient-hospital settings
Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013;(4):CD003543.]	Interventions to improve antibiotic prescribing practices for hospital inpatients	Interventions to improve antibiotic prescribing practices for hospital inpatients
Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother. 2016;60(8):4840–52.	Clinical and economic outcomes of implementing f hospital-based ASPs	Clinical and economic outcomes of implementing f hospital-based ASPs
Schuts EC, Hulscher ME, Mouton JW, Verduin CM, Stuart JW, Overdiek HW et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):847–56.	Current evidence on hospital antimicrobial stewardship objectives	Antimicrobial stewardship

Key findings	Date of last search	AMSTAR[a] checklist (quality) rating	Proportion of studies conducted in Hungary
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.	November 2013	7/11	0/37
The results show that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce antimicrobial resistance or hospital-acquired infections, and interventions to increase effective prescribing can improve clinical outcome. This update provides more evidence about unintended clinical consequences of interventions and about the effect of interventions to reduce exposure of patients to antibiotics. The meta-analysis supports the use of restrictive interventions when the need is urgent, but suggests that persuasive and restrictive interventions are equally effective after six months	December 2006 (Effective Practice and Organisation of Care (EPOC) Specialized Register February 2009)	7/11	0/89
Hospital ASPs result in a significant decrease in antimicrobial consumption and cost, and the benefit is higher in critical care. Infections due to specific antimicrobial-resistant pathogens and the overall hospital length of stay are improved as well.	8 July 2015	9/11	0/26
Overall, the quality of evidence was in general low and heterogeneity between studies was mostly moderate to high. For several objectives (empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics and bedside consultation) the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a relative risk reduction of 35% for mortality and 56% for de-escalation. Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. The findings of beneficial effects on outcomes with nine antimicrobial-stewardship objectives suggest they can guide stewardship teams in their efforts to improve the quality of antibiotic use in hospitals.	11 April 2014	10/11	0/149

Systematic review	Option element	Focus of systematic review
Pulcini C, Botelho-Nevers E, Dyar OJ, Harbarth S. The impact of infectious disease specialists on antibiotic prescribing in hospitals. Clin Microbiol Infect. 2014;20(10):963–72.	Impact of infectious disease specialists on antibiotic prescribing in hospitals	Impact of infectious disease specialists on antibiotic prescribing in hospitals
Tonna AP, Stewart D, West B, Gould I, McCaig D. Antimicrobial optimisation in secondary care: the pharmacist as part of a multidisciplinary antimicrobial programme – a literature review. Int J Antimicrob Agents. 2008;31(6):511–7.	Antimicrobial optimization in secondary care: the pharmacist as part of a multidisciplinary antimicrobial programme	Pharmacist as part of a multidisciplinary antimicrobial programme
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.	Effectiveness of information technology to improve antimicrobial prescribing in hospitals	Effectiveness of information technology to improve antimicrobial prescribing in hospitals

Key findings	Date of last search	AMSTAR[a] checklist (quality) rating	Proportion of studies conducted in Hungary
The review strongly argues for the added value of infectious disease specialists for (antibiotic stewardship) AMS in hospitals. Their impact is likely to be greater when a multidisciplinary AMS team is actively involved.	30 September 2012	8/11	1/31
The hospital pharmacist emerged as a key member of the (antimicrobial multidisciplinary team) AMDT. The dispensary pharmacist was mainly involved in the screening processes and was crucial in implementing restriction policies. The general ward-based clinical pharmacist was involved in guideline development, formulary management, intravenous-to-oral conversions and evaluations of programme outcomes through monitoring of drug usage, and facilitated the identification of patients with specific needs who could be referred to the specialist pharmacist. A role emerged for the specialist pharmacist who was an integral part of the AMDT and was involved in activities including reviewing more complex patients, attending ward rounds and streamlining of initial empirical antimicrobial treatment. Outcomes of interventions reported in primary research have been classified into: drug outcomes, where most trials measured and reported an increase in adherence to guidelines; microbiological outcomes, only considered in a few trials; clinical outcomes, with different parameters measured and a maintenance or improvement reported; and financial outcomes. The latter were reported in all trials with numerous cost savings, although not all were statistically significant. Moreover, the cost of the intervention was not always considered.	2006	4/9	0/28
Information-technology interventions can improve the appropriateness of antimicrobial prescribing. High-quality, systematic multisite comparative studies are critically needed, however, to assist organizations in making informed decisions about the most effective such interventions.	March 2015	7/9	0/45

Systematic review	Option element	Focus of systematic review
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(2):142–52.	Antimicrobial stewardship in outpatient settings	Antimicrobial stewardship in outpatient settings
van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, 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(605):e801–7.	Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections (RTIs)	Effectiveness of physician-targeted interventions to improve antibiotic use for RTIs
Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. Br J Gen Pract. 2013;63(616):787–94.	Point-of-care diagnostic testing in outpatient settings	Effect of the use of point-of-care diagnostic tests on antibiotic prescribing

[a] AMSTAR = Assessing Methodological Quality of Systematic Reviews

Key findings	Date of last search	AMSTAR[a] checklist (quality) rating	Proportion of studies conducted in Hungary
Low- to moderate-strength evidence suggests that ASPs in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes. Effectiveness depends on programme type. Most studies were not designed to measure patient or resistance outcomes. Data regarding sustainability and scalability of interventions are limited.	November 2013	7/10	0/50
This review emphasizes the importance of physician education in optimizing antibiotic use. Further research should focus on how to provide physicians with the relevant knowledge and tools, and when to supplement education with additional intervention elements. Feasibility should be included in this process.	2009	2/10	0/58
Point-of-care C-reactive protein testing significantly reduced antibiotic prescribing at the index consultation for patients with RTIs. Further studies are needed to analyse the confounders that lead to the heterogeneity.	June 2013	9/11	0/13

ANNEX 2.
Systematic reviews relevant to option 2

Systematic review	Option element	Focus of systematic review
Ranji SR, Steinman MA, Shojania KG, Sundaram V, Lewis R, Arnold S et al. Closing the quality gap: a critical analysis of quality improvement strategies. Volume 4 – Antibiotic prescribing behavior. Rockville: Agency for Healthcare Research and Quality (AHRQ); 2006 (Technical Review 9).	Antibiotic prescribing behaviour	Antibiotic prescribing behaviour
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(605):e801–7.	Effectiveness of physician-targeted interventions to improve antibiotic use for RTIs	Effectiveness of physician-targeted interventions to improve antibiotic use for RTIs
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.	Educational effectiveness, target, and content for prudent antibiotic use	Educational effectiveness, target, and content for prudent antibiotic use

Key findings	Date of last search	AMSTAR checklist (quality) rating	Proportion of studies conducted in Hungary
Quality-improvement efforts appear generally effective at reducing both inappropriate treatment with antibiotics and inappropriate selection of antibiotics. While no single quality-improvement strategy was more effective than others, active clinician education may be more effective than passive education, particularly for addressing the antibiotic treatment decision. Greater reductions in overall prescribing may be achieved through targeting prescribing for all acute RTIs, rather than single conditions. The available evidence is of only fair quality, and further research is needed on the cost–effectiveness and potential harms of these interventions.	2004	6/11	0/114
This review emphasizes the importance of physician education in optimizing antibiotic use. Further research should focus on how to provide physicians with the relevant knowledge and tools, and when to supplement education with additional intervention elements. Feasibility should be included in this process.	2008	2/10	0/58
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 being shaped, educating them about prudent antibiotic prescribing will be significantly effective in minimizing antibiotic resistance.	2014	4/11	1/28

ANNEX 3.
Summary of systematic reviews relevant to option 3

Systematic review	Option element	Focus of systematic review
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.	Educational effectiveness, target, and content for prudent antibiotic use	Educational effectiveness, target, and content for prudent antibiotic use
de Bont EG, Alink M, Falkenberg FC, Dinant GJ, Cals JW. Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice: a systematic review. BMJ Open. 2015;5(6):e007612.	Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice	Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice
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(1):e30334.	Interventions to influence consulting and antibiotic use for acute RTIs in children	Interventions to influence consulting and antibiotic use for acute RTIs in children
Coxeter P, Del Mar CB, McGregor L, Beller EM, Hoffmann TC. Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. Cochrane Database Syst Rev. 2015;(11):CD010907.	Shared decision-making on antibiotic use	Shared decision-making on antibiotic use

Key findings	Date of last search	AMSTAR checklist (quality) rating	Proportion of studies conducted in Hungary
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 being shaped, educating them about prudent antibiotic prescribing will be significantly effective in minimizing antibiotic resistance.	2014	4/11	1/28
Overall, this review provides evidence that the use of patient information leaflets on common infections during general practitioner (GP) consultation may effectively reduce antibiotic prescriptions and antibiotic use and patients' intention to reconsult. GPs are therefore encouraged actively to use patient information leaflets during consultations for common infections.	April 2014	7/10	0/8
The key finding for clinicians is that interventions (such as written materials with focused information for parents) can reduce the number of consultations for RTIs by 10–40%, and that delayed prescribing can reduce the use of antibiotics by up to half. Importantly, reductions in antibiotic use do not seem to occur at the expense of parent satisfaction. Given the high frequency of paediatric consultations in primary care, a change in parental consulting behaviour for RTIs could potentially create a "virtuous cycle" of reductions in workload and antibiotic use. The review found moderate evidence that interventions are more effective when delivered to parents and children. The review's findings provide policy-makers with evidence they need to implement or commission effective interventions in community settings to reduce consultations and antibiotic use.	–	7/11	0/23
Interventions to facilitate shared decision-making reduce antibiotic prescribing in primary care in the short term. Effects on longer-term rates of prescribing are uncertain and more evidence is needed to determine how any sustained reduction in antibiotic prescribing affects hospital admission, pneumonia and death.	December 2014	10/10	0/10

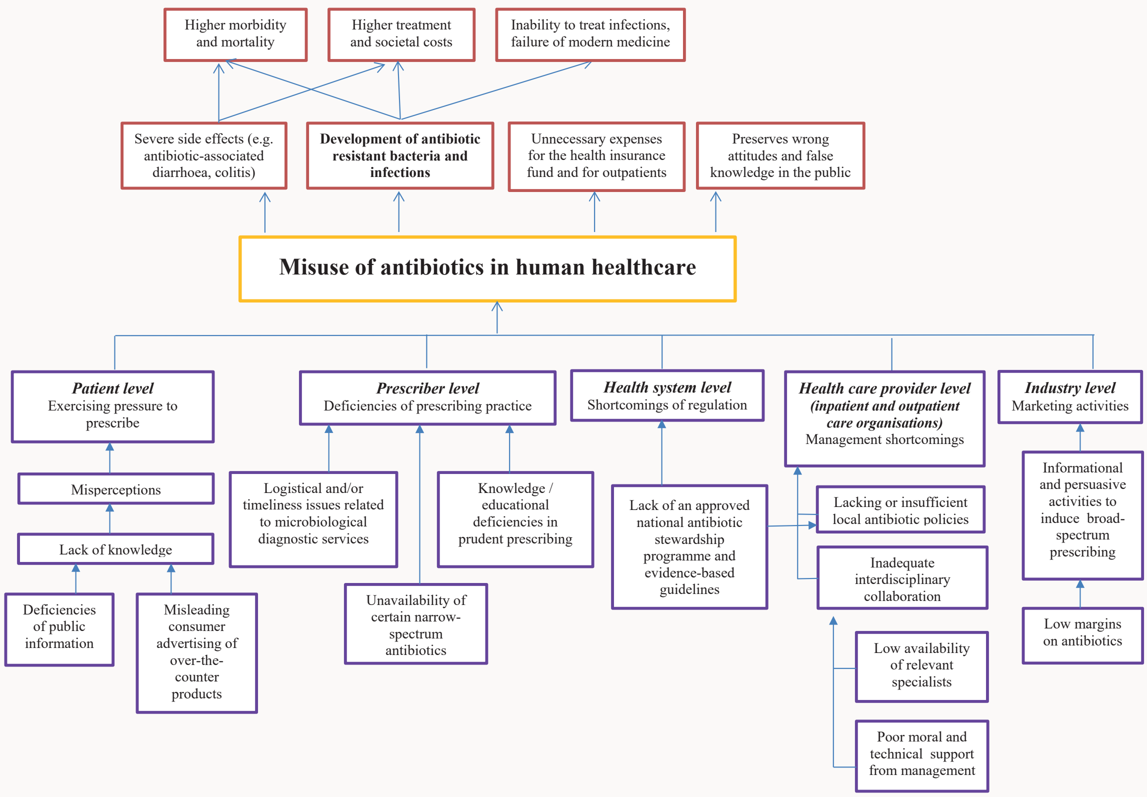
Systematic review	Option element	Focus of systematic review
Vodicka TA, Thompson M, Lucas P, Heneghan C, Blair PS, Buckley DI et al. Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review. Br J Gen Pract. 2013;63(612):e445–54.	Antibiotic prescribing	Reducing antibiotic prescribing for children with RTIs in primary care

	Key findings	Date of last search	AMSTAR checklist (quality) rating	Proportion of studies conducted in Hungary
	Conflicting evidence from the included studies found that interventions directed towards parents and/or clinicians can reduce rates of antibiotic prescribing. The most effective interventions target both parents and clinicians during consultations, provide automatic prescribing prompts and promote clinician leadership in the intervention design.	June 2012	8/11	0/17

ANNEX 4.
Key informant interviews conducted for the brief

Topic	Informant(s)
Antibiotic use in practice	A leading infectious-disease specialist in a hospital in the capital city The medical director and leading infectious-disease specialist in a municipal hospital Leaders and experts in public health
Microbiology laboratories	Leading microbiologists, infectious disease specialists and a laboratory-medicine specialist
Regulation and information systems for antibiotic use	High-level decision-makers in public administration for health
Roles, responsibilities and regulation of public bodies regarding antibiotic use	A high-level decision-maker in public administration for health
Potential issues in implementation of policies on antibiotic use	A high-level decision-maker in public administration for health A high-level decision-maker in the ministry responsible for health care
General practice	A leading general practitioner
Undergraduate and postgraduate education	A leading officer of a medical school
International best practice	A staff member of an international organization who deals with antimicrobial resistance

The following problem tree explores the causes of antibiotic misuse in Hungary



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