

# ASSESSING NON-PRESCRIPTION AND INAPPROPRIATE USE OF ANTIBIOTICS REPORT ON SURVEY



ASSESSING  
NON-PRESCRIPTION  
AND INAPPROPRIATE  
USE OF ANTIBIOTICS  
**REPORT ON SURVEY**

## Abstract

This survey was undertaken in the 18 countries and areas that are members of the WHO Regional Office for Europe Antimicrobial Medicines Consumption Network to assess the current status of regulatory and national/area-level activities in eastern European and central Asian countries and areas to support the appropriate use of antibiotics. All countries and areas reported an existing legislative framework governing the marketing authorization of antimicrobial agents, their distribution, assessment of the quality of products in circulation, their prescription and dispensing. Respondents reported a wide range of activities in support of appropriate use of antimicrobials that targeted the general public, doctors and pharmacists. Priority actions for improving the appropriate use of antibiotics identified by respondents were greater enforcement of existing regulations on prescribing and dispensing of antibiotics to ensure prescription-only access, educating health-care professionals about antimicrobial resistance and appropriate use of antibiotics, improving public awareness on rational use of antibiotics and establishing and implementing standard treatment guidelines for use in clinical practice.

## Keywords

ANTIMICROBIAL MEDICINES

ANTIBIOTICS

LEGISLATION AND REGULATION

PRESCRIPTION-ONLY ACCESS

APPROPRIATE USE OF ANTIBIOTICS

STANDARD TREATMENT GUIDELINES

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# Acronyms

AMC	WHO Regional Office for Europe Antimicrobial Medicines Consumption Network
AMR	antimicrobial resistance
ARNA	Antimicrobial Resistance and Causes of Non-prudent Use of Antibiotics in Human Medicine in the EU (project)
CI	confidence interval
CME	continuing medical education
EU	European Union
OTC	over-the-counter
SDG	(United Nations) Sustainable Development Goal

# Introduction

The human and financial costs of antimicrobial resistance (AMR) are well recognized, with estimates of 700 000 deaths globally due to drug-resistant infections (O'Neill, 2016), projected annual reduction in gross domestic product of 3.8% by 2050 (World Bank, 2016) and concerns about the risks AMR poses to achievement of the United Nations Sustainable Development Goals (SDGs) (United Nations Interagency Coordination Group on Antimicrobial Resistance, 2017). Progress to address AMR relies on coordinated responses across the human and animal health sectors, as well as the environment, trade, intellectual property and innovation (Wernli et al., 2017).

Momentum to address AMR continues to grow after the adoption of the WHO global action plan on AMR in 2015 (WHO, 2015), as reflected in the agendas of many high-level meetings such as the United Nations General Assembly in 2016, the G7 summit under the German Presidency in 2016, and the G20 summit in 2017, again under German leadership. The European Union (EU) has underscored the importance of the One Health approach, launching the One Health AMR action plan in 2017 (European Commission, 2017).

The WHO global action plan on AMR sets out five strategic objectives:

1. improve awareness and understanding of AMR
2. strengthen knowledge through surveillance and research
3. reduce the incidence of infection
4. optimize the use of antimicrobial agents in human and animal health
5. ensure sustainable investment in countering AMR.

Member States were asked to develop and implement comprehensive national action plans on AMR that are aligned to the objectives of the global action plan (WHO, 2016).

Specifically related to objective 4 of the global action plan (optimizing the use of antimicrobials) and its application to human health, Member States were asked to develop comprehensive action plans on AMR that incorporated the following elements:

- distribution, prescription, and dispensing of antimicrobials is carried out by accredited health professionals under statutory body supervision or other suitably trained person authorized in accordance with national legislation;
- marketing authorization is given only to antimicrobial agents that are quality assured, safe and efficacious;
- development and implementation of national and institutional essential medicine lists guided by the WHO Model Lists of Essential Medicines, reimbursement lists and standard treatment guidelines to guide purchasing and prescribing of antimicrobial medicines, and regulation and control of promotional practices by industry;
- laboratory capacity to identify pathogens and their antimicrobial susceptibility in order to guide optimal use of antimicrobial medicines in clinical practice;
- provision of stewardship programmes that monitor and promote optimization of antimicrobial use at national and local levels in accordance with international standards in order to ensure the correct choice of medicine at the right dose on the basis of evidence;

- identification and elimination of economic incentives in all sectors that encourage inappropriate use of antimicrobial agents, and introduction of incentives to optimize use; and
- effective and enforceable regulation and governance for licensing, distribution, use and quality assurance of antimicrobial medicines in human and animal health, including a regulatory framework for preservation of new antibiotics.

This survey was undertaken to assess:

- the current status of regulatory and national/area-level activities in eastern European and central Asian countries and areas to support the appropriate use of antibiotics; and
- the extent to which these activities map against key elements identified under objective 4 of the global action plan.

The work complements activities conducted in EU countries as part of the Antimicrobial Resistance and Causes of Non-prudent Use of Antibiotics in Human Medicine in the EU project (ARNA), specifically work package 2 – a questionnaire to ministries of health and relevant regulatory authorities (Paget et al., 2017).

# Methods

## Participating countries and areas

The 18 countries and areas that are members of the WHO Regional Office for Europe Antimicrobial Medicines Consumption Network (AMC) were invited to participate – Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Kazakhstan, Kyrgyzstan, Montenegro, North Macedonia, the Republic of Moldova, the Russian Federation, Serbia, Tajikistan, Turkey, Ukraine and Uzbekistan, as well as Kosovo.<sup>1</sup>

## Data collection

Invitations to participate in the survey were sent to ministries of health and public authorities. Countries and areas were asked to nominate one or more persons to complete the survey. Eligible participants were national and area AMC and AMR focal points, members of AMR committees, infectious diseases specialists, representatives of health insurance funds, institutes for rational use of medicines, public health institutes, professional associations of doctors and pharmacists, and representatives of the pharmaceutical industry, academic institutions and patient organizations. Where possible, more than one respondent was sought from each country/area; in some cases, there was a single consolidated response with several people contributing answers to the questions.

The survey was administered online, with participants able to respond in English or Russian. It was open between April and August 2018.

Some of the survey items were adapted from the Member State questionnaire used in the ARNA project (Paget et al., 2017:Appendix A). The questions were a mix of fixed-response and open-ended questions that allowed respondents to provide additional information on some topics. Questions addressed the status of regulation and its enforcement in practice, development of action plans on AMR at country/area level, other activities in support of improved use of antibiotics, availability of over-the-counter (OTC) antibiotics without prescription, the use of clinical guidelines, possible perverse incentives to prescribe or dispense antibiotics, promotional activities by the pharmaceutical industry, and monitoring of antibiotic use and prescribing practices. Finally, respondents were asked, “If you were the Minister for Health/public health authorities or key advisor to the Minister for Health/public health authorities, what would be the three priority activities you would recommend to improve the appropriate use of antibiotics in your country/area?” The final version of the survey is available on request.

## Analysis of responses

The main unit of analysis is the country/area. Where there were multiple country/area respondents whose responses differed, a similar approach to that used in the ARNA study was adopted, in that

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<sup>1</sup> For the purposes of this publication, all references, including in the bibliography, to “Kosovo” should be understood/read as “Kosovo (in accordance with Security Council resolution 1244 (1999))”.

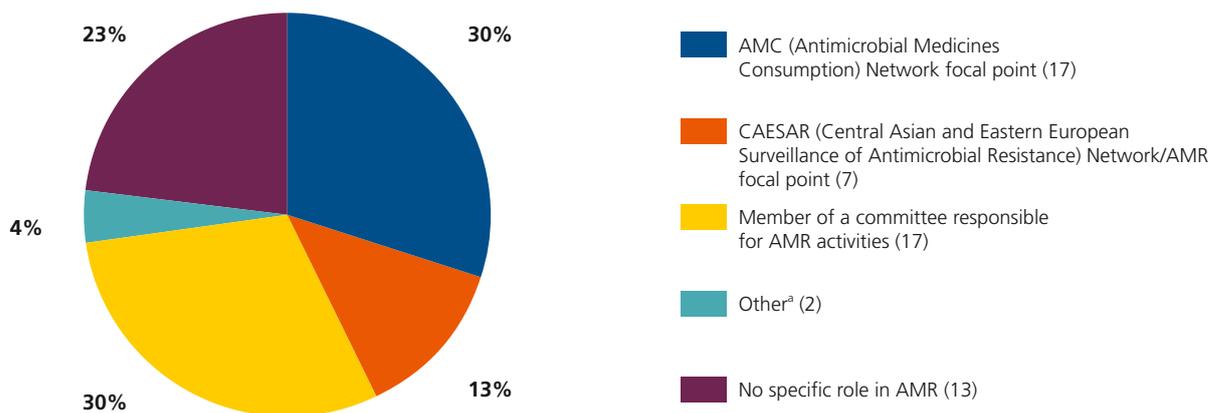
it was assumed that responses from ministries of health and public health authorities were most complete for the regulatory questions and that AMC and AMR focal points would be reliable sources for other activities in support of the AMR agenda. Where relevant, contradictory responses from some respondents have been included where these views expand the narrative of the country/area situation.

# Results

## Survey respondents

Responses were received from 45 participants from the 18 members of the AMC. In the cases of Tajikistan and Turkey, a single response represented the results of local consultation with several relevant experts. Respondents were predominantly from ministries of health, public health authorities, public health institutes and professional organizations (see Table 1). Almost a third of respondents (17/45; 30%) were AMC focal points, 13% (7/45) AMR focal points, and 30% (17/45) members of committees responsible for AMR activities (Fig. 1). A third (13/45; 23%) had no formal role in AMR activities at country/area level.

**Fig. 1** | Role of survey respondents in AMR activities at national/area level



<sup>a</sup> Other: WHO collaborating centre, member of the Expert Committee for the Revision of the List of Essential Medicines.

**Table 1** | Summary of respondents and their affiliate organizations

Country/area	Number of respondents	Respondents' organization
Albania	4	Institute of Public Health
		University of Medicine Tirana
		Institute of Public Health
		Not reported by respondent
Armenia	6	Ministry of Health
		Scientific Centre of Drug and Medical Technology Expertise
		Association for Pharmaceutical Development of the Republic of Armenia
		Arabkir Joint Medical Centre
		"Aware and Protected Consumer" nongovernmental organization
		Union of Manufacturers and Importers of Medicines of Armenia

Table 1 | contd

Country/area	Number of respondents	Respondents' organization
Azerbaijan	2	Ministry of Health Care
		Ministry of Health – Centre for Analytical Examination
Belarus	2	Ministry of Health
		Centre for Examinations and Tests in Health Service, Ministry of Health
Bosnia and Herzegovina	2	Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina
		Public Health Institute of the Republic of Srpska
Georgia	2	National Centre for Disease Control and Public Health
Kazakhstan	2	JSC "Astana Medical University"
		National Centre for Public Health
Kyrgyzstan	2	Department of Drug Provision and Medical Equipment under the Ministry of Health
		Ministry of Health
Montenegro	5	Nongovernmental organization representing parents
		Agency for Medicines and Medical Devices
		Pharmaceutical Chamber of Montenegro
		Medicor
		Ministry of Health
North Macedonia	3	Eurolek
		Private health practice – Vita Katerina
		Health Insurance Fund
Republic of Moldova	3	Medicines and Medical Devices Agency
		State University of Medicine and Pharmacy "Nicolae Testemitanu"
		Public Institution Coordination, Implementation and Monitoring Unit of the Health System Projects
Russian Federation	1	Smolensk State Medical University
Serbia	3	Medicines and Medical Devices of Serbia
		Institute of Microbiology, Faculty of Medicine, University of Belgrade
		Ministry of Health, Second Serbia Health Project
Tajikistan	1 <sup>a</sup>	State Health and Social Protection Surveillance Service, Ministry of Health and Social Protection of Population
Turkey	1 <sup>a</sup>	Turkish Medicine and Medical Devices Agency
Ukraine	2	Ministry of Health
Uzbekistan	2	Scientific Research Institute of Epidemiology, Microbiology and Infectious Diseases
		State Centre for Expertise and Standardization of Medicines, Medical Devices and Medical Equipment
Kosovo <sup>b</sup>	2	Institute of Public Health of Kosovo
		Kosovo Chamber of Pharmacists; Faculty of Pharmacy

<sup>a</sup> Participation as a country group.

<sup>b</sup> For the purposes of this publication, all references, including in the bibliography, to "Kosovo" should be understood/read as "Kosovo (in accordance with Security Council resolution 1244 (1999))".

## Action plan on AMR or antibiotic plan at country/area level

All 18 countries and areas reported the existence of an approved action plan on AMR or antibiotic plan (n = 9), or a plan in draft form or under development (n = 9). Survey responses were validated by follow up with AMC focal points and cross-referencing to the 2018 WHO global AMR survey (WHO, 2018).

Of the nine countries and areas reporting an approved plan,<sup>2</sup> eight were publicly available (that is, posted on the Ministry of Health website). Sixteen reported that an institution, body or coordinating committee was overseeing implementation or development of the plan. In 14 cases (88%), the plan included surveillance of AMR (such as reporting of resistant isolates). All plans included surveillance of antimicrobial medicines consumption.

## Regulatory provisions

### Marketing authorization

All 18 reported regulations governing the marketing authorization (licensing) of antimicrobials, stating that the regulations were enforced. Unregistered antimicrobial products, however, were reported to be available in the market place in five (28%), and respondents were unsure on this point in a further four (22%). Examples of unregistered products included illegal or unregulated imports from neighbouring countries and China, India, Pakistan and the Russian Federation. In some cases, anti-tuberculosis medicines were not registered in the country/area but were donated or supplied through agencies such as the Global Fund. Some reported importation of unregistered products to meet exceptional need, such as epidemics or when there was no licensed product in the marketplace. Reference was made to an unregulated private market in at least one participating country (Azerbaijan), with measures being taken to address this.

### Distribution

Regulations governing the distribution of antimicrobials to hospitals and pharmacies such as Good Distribution Practices were in place in 13 (72%) and were reportedly mostly enforced in 10 (77%).

### Quality of antimicrobials

All countries and areas except Albania reported regulations for monitoring the quality of antimicrobials in circulation; the regulations were said to be mostly enforced in all 17 through mechanisms such as import controls, inspections of wholesalers and pharmacies, and routine quality-control analyses of all medicines, including antimicrobials, in the marketplace. In some cases, batch-by-batch testing was followed by risk-mitigation strategies using selective and targeted testing of antimicrobials.

Despite the regulations and monitoring reported, five countries (28%; Armenia, Kazakhstan, North Macedonia, Tajikistan and Uzbekistan) reported concerns about the quality of antimicrobials in circulation at least "some of the time" and a further six suggested this occurred "rarely". Five countries (Albania, Belarus, Bosnia and Herzegovina, the Republic of Moldova and Serbia) reported that there

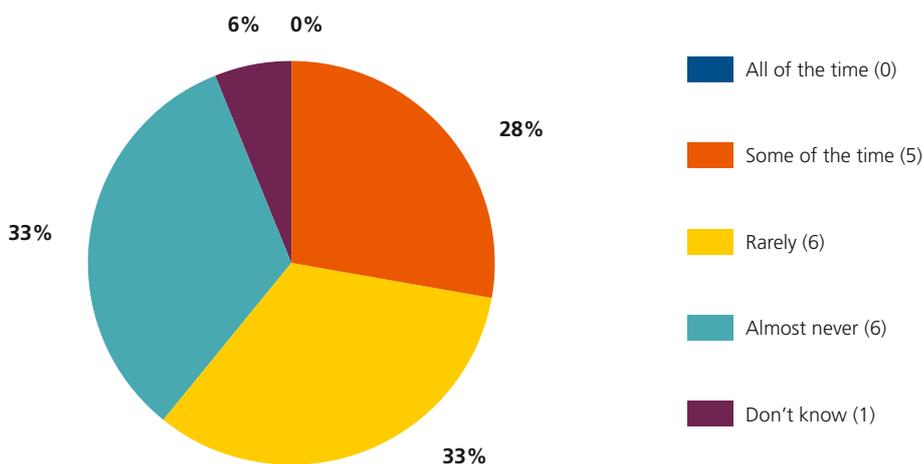
<sup>2</sup> Tajikistan launched its approved national action plan in November 2018, increasing the number with approved national plans to 10.

were “almost never” concerns about the quality of antimicrobials available (Fig. 2). Notably, respondents from Albania reported no regulations for monitoring the quality of antimicrobials in circulation.

Some of the 45 individual respondents expressing concerns about the quality of antimicrobials in circulation were from outside of the ministry of health, including several from academic institutions, a family doctor in private practice, a nongovernmental organization representing parents, and one respondent representing an association involved in pharmaceutical development.

Specific products for which concerns about quality had been expressed include ceftriaxone, ceftazidime and carbapenems. No further details on the results of analyses of suspect products were available. One respondent commented, “There are no specific examples, but the population using antibiotics produced by different countries talk about different effectiveness and quality”. Another commented, “We don’t have any concerns but there is a perception of bad quality in health-care professionals when it comes to generics. Mostly because of their price compared to the brand medicines.”

**Fig. 2** | Concerns about the quality of some antimicrobials available in your country/area (N = 18)



## Prescribing and dispensing of antibiotics

It was reported that a prescription is required to obtain antibiotics from a pharmacy in all countries and areas. Almost two thirds of respondents (11/17; 65%) suggested that these regulations are enforced, but respondents from six indicated that pharmacists “regularly” sell OTC antibiotics without prescription, and respondents from a further eight said this occurred “occasionally”. Respondents indicated these OTC sales included oral agents (14 countries and areas) and injection formulations (11), along with topical, eye and eardrop antibiotic formulations (14).

## Other methods of obtaining antibiotics

Eleven reported other ways that patients can obtain antibiotics apart from with a prescription from a doctor. These include from Internet pharmacies without a prescription (five), purchasing locally using a prescription written in another country (seven), and purchasing in another country with or

without a prescription (eight). Respondents from Albania, Armenia, Georgia, Montenegro, the Russian Federation, Serbia and Turkey reported that there were no other ways patients can obtain antibiotics apart from with a doctor's prescription.

## Pharmacovigilance/medication safety monitoring

Almost all (16 of the 18) reported national, regional or local systems to report side-effects or adverse reactions to antibiotics (the exceptions were Georgia and Tajikistan). Most systems also allowed reporting of concerns about quality of antibiotic products, but the extent to which such reporting mechanisms are used varies enormously; in some, it seems systems exist but are not used to any meaningful extent.

## Activities in support of appropriate use of antimicrobials at country/area level

### General public

Respondents from 17 countries and areas reported measures to enhance the responsible use of antibiotics by the general public (the exception was Belarus). These included media campaigns, educational interventions, promoting access only with a prescription from a doctor, and campaigns on returning and/or safely disposing of unwanted antibiotics (Table 2).

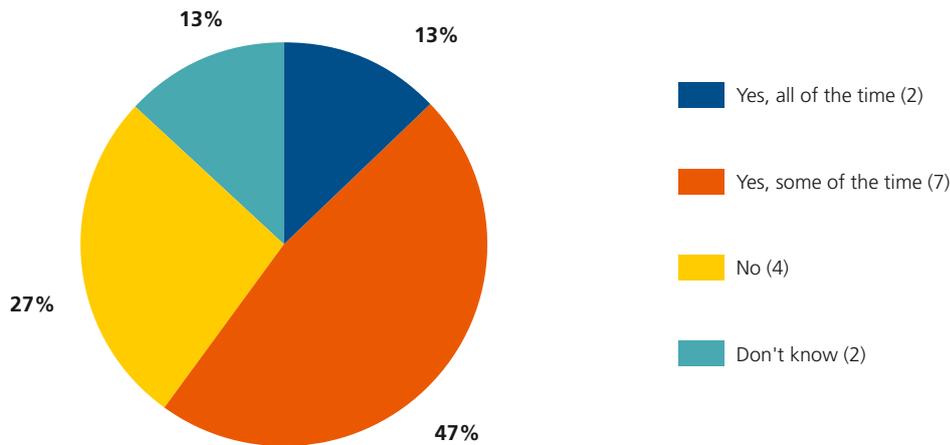
**Table 2** | Interventions directed at the general public

Interventions	Number of countries/areas responding "Yes" (n = 17)
Media campaigns to raise awareness of antimicrobial resistance	17
Educational interventions (such as in schools, social or sporting clubs)	13
Advice on only getting antibiotics with a prescription from a doctor	16
Campaigns to return unused antibiotics (to pharmacy, for instance)	5
Campaigns on how safely to dispose of unwanted antibiotics	6

### Doctors

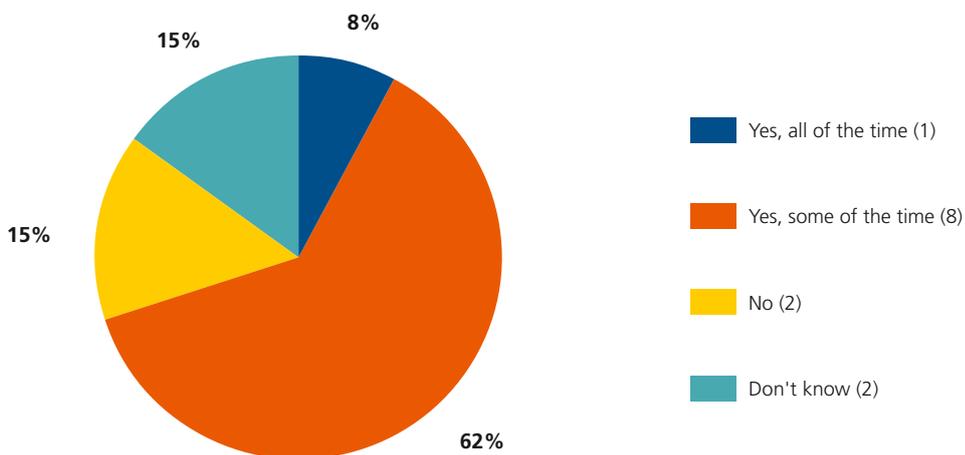
All countries and areas reported measures to enhance the responsible use of antibiotics by doctors. In each case, this included training on prescribing of antibiotics during undergraduate medical education. Compulsory continuing medical education (CME) for doctors that included the appropriate use of antibiotics was reported in 12.

Educational events (apart from CME) for doctors regarding appropriate use of antibiotics were reported in 15, with most of the events (60%) sponsored "all of the time" or "some of the time" by the pharmaceutical industry or wholesalers (Fig. 3).

**Fig. 3** | Sponsorship of educational events for doctors by the pharmaceutical industry or wholesalers (n = 15)

## Pharmacists

Thirteen countries and areas (72%) reported activities to enhance the responsible use of antibiotics by pharmacists. Training on prescribing of antibiotics occurred during undergraduate pharmacy education (12/13), as part of compulsory CME for pharmacists (8/13) and educational events (apart from CME) for pharmacists (11/13). Some 80% of the non-CME events were sponsored “all of the time” or “some of the time” by the pharmaceutical industry or wholesalers (Fig. 4).

**Fig. 4** | Sponsorship of educational events for pharmacists by the pharmaceutical industry or wholesalers

## Restrictions on prescribing of antibiotics in outpatient (ambulatory/primary) care

Thirteen countries and areas reported rules limiting the prescribing of some antibiotics in outpatient or primary care settings. Typically, restrictions applied to all parenteral products, selected products (including third-generation cephalosporins and amikacin) or those reserved for second-line treatment

only (such as macrolides and fluoroquinolones for community-acquired pneumonia). Medicines for tuberculosis cannot be prescribed in primary care in some countries and areas.

Seven reported limiting prescribing of some antibiotics for specific clinical conditions (such as benzathine benzylpenicillin for *Streptococcal* tonsillitis), typically in accordance with approved national/area clinical guidelines or treatment protocols. In some cases, the medicines reimbursed in health insurance programmes influenced prescribing choices – prescribing other medicines would mean the patient would pay the full cost out of pocket.

Only one country (Bosnia and Herzegovina) reported that doctors can offer a delayed prescription (a prescription a patient takes to the pharmacist at a later date if their symptoms do not improve or get worse).

Other measures targeting prescribing in primary health care settings included financial penalties for prescribing in excess of limits set for rational prescribing, review of appropriateness by health insurance companies, and feedback of prescribing data to physicians with provincial health authorities making doctor visits and interventions as needed. One respondent noted, “Unfortunately, there are no such events that would somehow be encouraged for the responsible use of antibiotics. We have a system of only ‘punishments’”.

## Restrictions on prescribing of antibiotics in hospital care

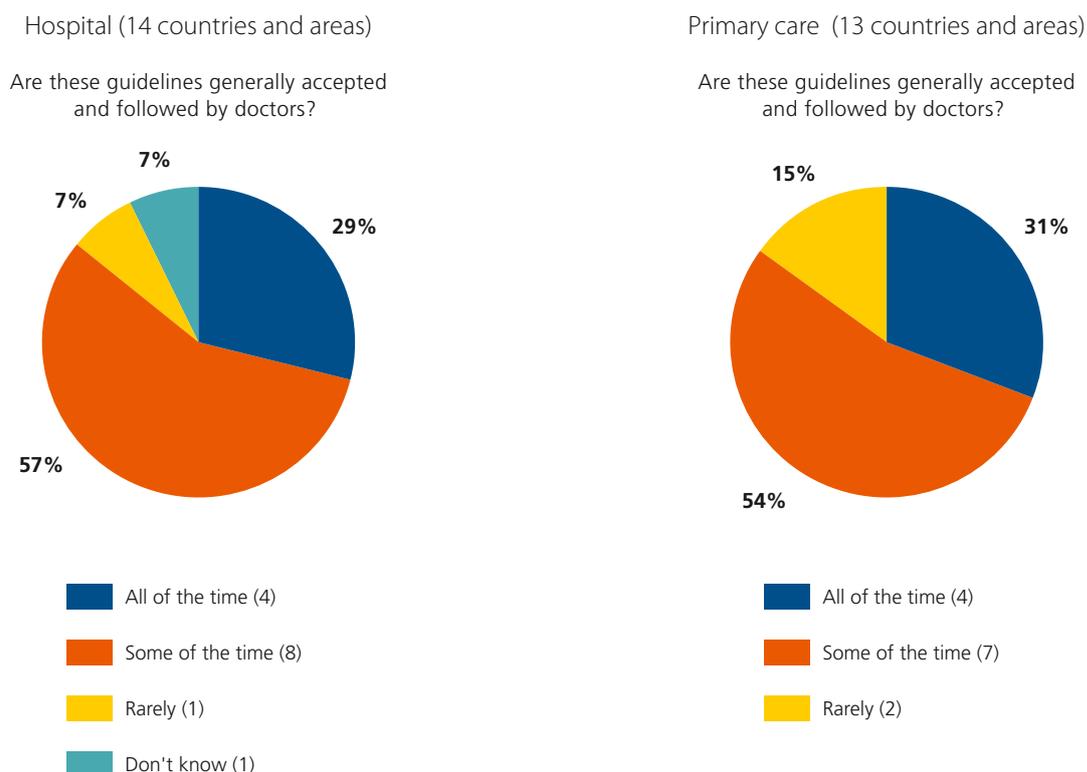
Ten countries and areas reported restrictions that limit prescribing of some antibiotics for specific clinical conditions only in hospital care. These were mostly parenteral medicines, but also included first-line treatments for tuberculosis in some settings. Some countries and areas specifically referred to restricted use of reserve antibiotics, including piperacillin + tazobactam, and 10 reported that certain antibiotics were restricted to particular specialties (prescribing of some antibiotic eyedrops was restricted to ophthalmologists, for instance); in other cases, authorization from an infectious diseases specialist was required before the antibiotic could be prescribed.

## Clinical guidelines and protocols

Most countries and areas (14/18) reported the existence of endorsed clinical guidelines or treatment protocols for some common infections in hospitals, and 13 reported guidelines for primary health care. Use of the guidelines in practice is less clear. Around 30% of respondents suggested that guidelines were generally accepted and followed by doctors “all of the time” in hospitals and in primary care (Fig. 5).

## Surveillance and auditing of prescribing practices

Four countries (Belarus, Kazakhstan, Serbia and Turkey) reported surveillance systems or audit procedures for doctors to review antibiotic prescribing practices in hospitals, with a further 10 reporting plans to introduce such surveillance. Surveillance variously took the form of participation in prescribing prevalence surveys, and regular review by clinical pharmacologists, pharmacists or infectious diseases specialists of volumes and indications for prescribing. Antibiotic prescribing was reported as an accreditation indicator in one country (Uzbekistan). All four countries with surveillance systems reported providing feedback to doctors on the audit results.

**Fig. 5** | Acceptance and use of guidelines in hospital and primary care

Surveillance of prescribing practices in primary health care was less common, with only two countries reporting such auditing (Bosnia and Herzegovina, and Turkey) and a further 12 countries and areas indicating they had plans to do so. Only Turkey reported providing feedback to doctors concerning their prescribing practice. This was facilitated by prescription information systems and e-prescriptions.

Auditing also gave rise to perverse practices in instances where the health insurance fund imposed fines for inappropriate prescribing. It was reported in one country that patient records and prescriptions are in accord with approved guidelines and protocols, but patients are discharged with different instructions and recommended treatments.

## Promotional activities by the pharmaceutical industry

Thirteen countries and areas reported measures to control the promotion of antibiotics by the pharmaceutical industry. Restrictions on pharmaceutical representatives visiting doctors, including only for scheduled meetings and group presentations rather than one-to-one meetings, were reported in six (Belarus, Montenegro, the Republic of Moldova, the Russian Federation, Turkey and Uzbekistan). One reported that while regulations stipulate that pharmaceutical representatives can visit hospitals only outside of working hours, pharmaceutical companies are given a platform for their presentations (and promotion of their products) at regular weekly medical meetings.

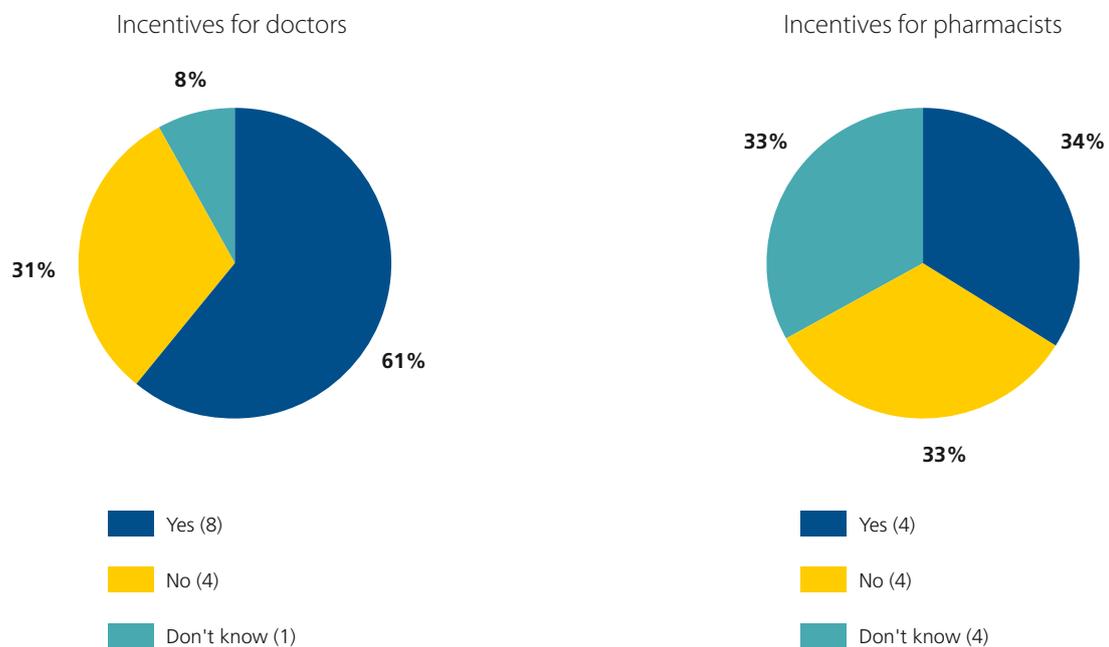
Only one country (Belarus) reported restrictions on pharmaceutical representatives visiting pharmacists.

Thirteen reported that pharmaceutical companies are not allowed to advertise antibiotics on the radio, television or in newspapers.

## Perverse incentives

Respondents were asked about their perceptions of the use of financial incentives by pharmaceutical companies or wholesalers to influence prescribing or dispensing of their products. Some 61% indicated that financial incentives were given to doctors and 34% suggested incentives were provided to pharmacists (Fig. 6).

**Fig. 6** | Perceived use of incentives to doctors and pharmacists



## Collaboration between health-care professionals

Only 4% of respondents suggested there was close collaboration between doctors and pharmacists in the country/area "all of the time", with some 30% reporting that such collaboration occurred "rarely" or "almost never".

When asked if pharmacists can influence doctors to change a prescription if they do not consider it appropriate, 75% of respondents replied "rarely" or "almost never". More than half (55%), however, suggested that pharmacists are in a good position in terms of skills and knowledge to provide advice on the use of antibiotics.

## Who can influence the situation with the use of antibiotics?

Respondents reported that policy-makers, prescribers and professional associations were most able to influence the situation with the use of antibiotics, with pharmacists and patients less able to do so (Table 3).

**Table 3** | Who do you feel is in a position to improve the situation with the use of antibiotics?

Groups	Number of respondents responding "Yes" (n = 45)
Policy-makers	35
Pharmacists	23
Prescribers	34
Patients/community	22
Professional associations, such as medical specialist groups, pharmacy groups	33

## Priority actions for improving the appropriate use of antibiotics

Given the large number of respondents, and the fact that some respondents identified more than three priority targets, the list of suggested priority actions was long. A number of themes nevertheless emerged, and these are summarized in Table 4.

**Table 4** | Priority actions for improving the appropriate use of antibiotics

Theme	Number of respondents
Enforcing and improving legislation on prescribing/dispensing of antibiotics	21
Educating health-care professionals	17
Improving public awareness on rational use of antibiotics	17
Establishing and implementing standard treatment guidelines	14
Strengthening surveillance and control of consumption/use of antibiotics	9
Strengthening surveillance of AMR	8
Implementing rapid diagnostic tests and increased laboratory confirmation	8
Multisectoral activities, including One Health approach	6
Implementing antimicrobial stewardship programme	5
Strengthening quality control of antibiotics	4
Strengthening prevention and control of infections	3
Strengthening collaboration between doctors, pharmacists and ministries of health and public health authorities	3
Introducing e-prescription	3
Restrictions on prescribing	3
Ensuring availability of older antibiotics	2
Ethics to govern industry promotional activities	1

Enforcing and improving legislation on prescribing and dispensing antibiotics was the most frequently mentioned strategy for improving the appropriate use of antibiotics, nominated by almost half of the respondents (21/45; 47%). Respondents nominated greater supervision and inspections of pharmacies, the use of penalties and fines for OTC sales and stricter controls on prescribers as specific activities to improve the situation.

Educating health-care professionals was nominated as a priority action by 17 respondents (38%). This included greater emphasis on training on rational prescribing of antibiotics for doctors in undergraduate and postgraduate education and in CME. Appropriate prescribing in paediatrics was mentioned specifically. Pharmacists' awareness and skills needed to be raised to ensure good dispensing practices. Increasing the awareness of the public on rational use of antibiotics was rated equally important to that of educating health-care professionals (17 respondents, 38%).

Fourteen respondents (31%) identified the importance of developing and implementing standard treatment guidelines for hospital and primary care settings. It was noted that guidelines should take account of local resistance patterns. One respondent referred to alignment of guidelines and treatment recommendations with WHO Access, Watch and Reserve classifications of antibiotics. Other respondents referred to the use of restrictions on which antibiotics could be prescribed in hospital and primary care settings.

Respondents noted the value of information on the consumption and use of antibiotics and the importance of strengthening surveillance systems. E-prescriptions were noted specifically by three respondents as a mechanism for improving appropriate use. Also important was strengthening of surveillance on AMR (eight each), use of rapid diagnostic tests, and laboratory confirmation to guide and inform antibiotic prescribing (eight respondents).

Several respondents referred to inclusion of the clinical pharmacist as part of antimicrobial stewardship teams in hospitals, suggesting an enhanced role for pharmacists as part of the health-care team in at least some countries/areas. The importance of increased collaboration between doctors and pharmacists was noted.

Six respondents nominated the value of the One Health approach and the importance of intra- and intersectoral activities, recognizing the impact of the use of antibiotics in animal medicine and food production on the development of AMR and the potential environmental impacts of disposing of expired antibiotics.

# Discussion

The results of this survey suggest that a legislative framework governing the marketing authorization of antimicrobial agents, their distribution, assessment of the quality of products in circulation, their prescription and dispensing already exists in all 18 participating countries and areas. Respondents have suggested that legislation and regulations are mostly enforced.

Almost all countries and areas reported a pharmacovigilance programme for reporting adverse events and adverse drug reactions to antimicrobials, although the descriptive accounts provided suggest that the extent of use of these reporting systems varies widely.

Respondents reported a wide range of activities in support of appropriate use of antimicrobials that targeted the general public, doctors and pharmacists. Many, but not all, of the countries and areas confirmed that endorsed clinical guidelines or treatment protocols for some common infections were in place in hospitals and for primary health settings, but acceptance and use of the guidelines in practice is less clear.

The survey has a number of limitations. The responses reflect the opinions of the participants, but responses cannot entirely be separated from the views of the organizations participants represent. Respondents were predominantly from ministries of health, public health authorities, public health institutes and professional organizations. Only one third had no formal role in AMR activities at country/area level. This report has tried to capture multiple perspectives on the topics, and to capture differences in responses from those outside formal roles in AMR in the results.

While a pilot test of the survey was conducted (both English and Russian versions) using questions from the ARNA survey, there is always the risk of lack of clarity in questions and misunderstanding of the question being asked. Attempts were made to mitigate some issues by allowing respondents to answer in English or Russian. Some questions in the survey were conditional on earlier responses that allowed "skip" questions to minimize the reporting burden and the risk of survey fatigue, where respondents lose interest in a long survey. There were many responses to the final question on priority actions for improving the appropriate use of antibiotics, which suggests that survey fatigue was not a major issue in this study, but there appear to be some significant differences between survey responses and other evidence (objective and subjective) on some issues.

Respondents from only six country and areas indicated that pharmacists "regularly" sell antibiotics OTC without prescription, and respondents from a further eight said this occurred "occasionally". It was not possible to define exactly what "regularly", "some of the time" and "occasionally" meant, so these categories may have meant different things to different respondents. The decision was made not to ask for quantitative estimates of the extent of OTC supply of antibiotics, as it was felt that most respondents would not be able to accurately answer such a question. The responses nevertheless seem at odds with other evidence that suggests widespread availability of OTC antibiotics in a number of the countries and areas. In addition, almost half of the respondents identified enforcement and improvement legislation on prescribing and dispensing of antibiotics as a priority action for improving the use of antibiotics.

Richardson et al. (2014) noted that in theory, there is a strict delineation between those pharmaceuticals that are available OTC and those that are available only on prescription in former Soviet Union countries. In practice, however, this distinction has been strictly enforced only for narcotics, psychotropic medicines

and their precursors. It is difficult to accurately estimate the extent of OTC availability of antibiotics. Versporten et al. (2014) refer to the results of a 2012 survey conducted by WHO European Region/European Surveillance of Antimicrobial Consumption project members that suggested more than 50% of antibiotics in eastern Europe and central Asia are sold OTC.

A systematic review and meta-analysis across 38 studies from 24 countries (Auta et al., 2018) found that the pooled proportion of non-prescription supply of antibiotics was 62% (95% confidence interval (CI): 53–72). The pooled proportion of supply following a patient request was 78% (95% CI: 59–97) and, based on community pharmacy staff recommendation, was 58% (95% CI: 48–68). Most of the studies were conducted in Asia, mostly using simulated patients with concealed identities. Few were conducted in eastern Europe, but Hoxha et al. (2015) concluded 80% (95% CI: 76–84) availability without prescription in Albania. Marković-Peković et al. (2012, 2017) conducted two studies in Bosnia and Herzegovina (Republic of Srpska), concluding 58% (95% CI: 50–66) availability without prescription in 2010 and 18.5% (95% CI: 15–22) availability in 2015, after concerted efforts to reduce non-prescription sales and dispensing of antibiotics.

These results suggest significant availability of antibiotics OTC despite legislation prohibiting such supply. In addition, Marković-Peković et al. noted that fewer “patients” in the 2015 study received advice about possible side-effects or instructions on how to take the antibiotic than in the 2010 study. The authors concluded that stronger enforcement of laws was needed, alongside more training for pharmacy personnel.

Almost all countries and areas reported legislation for monitoring the quality of antimicrobials in circulation, with the regulations largely being enforced. Only five countries (Armenia, Kazakhstan, North Macedonia, Tajikistan and Uzbekistan) reported concerns about the quality of antimicrobials in circulation at least “some of the time” and a further six suggested this occurred “rarely”. Five (Albania, Belarus, Bosnia and Herzegovina, the Republic of Moldova and Serbia) claimed there were “almost never” concerns about the quality of antimicrobials available. Notably, all four respondents from Albania reported no regulations for monitoring the quality of antimicrobials in circulation.

The relatively low levels of concern about the quality of antimicrobials in circulation are in contrast with reports in the published literature. Richardson et al. (2014) suggest that fake or poor-quality products are a concern for patients across former Soviet Union countries, and claim that while there are nominal policies for ensuring the quality of pharmaceuticals, “few studies have been undertaken to ascertain the proportion of substandard pharmaceuticals on the market, largely on account of the prohibitive cost of such research”. Perhaps the challenges lie in separating the facts about quality of medicines available and perceptions of consumers and health-care professionals. A respondent noted, “There are no specific examples, but the population using antibiotics produced by different countries talk about different effectiveness and quality”.

A review of generic medicines policies conducted by Health Action International (Kaplan et al., 2016) suggested that perceptions of generics in the countries of the former Soviet Union are predominantly negative. The report noted a number of contributing factors, including poor enforcement of the medicine control system, restrictions on medicine prescribing from the point of view of doctors, and pharmaceutical company promotion directed at doctors and consumers. It suggested that use of brand names of medicines in undergraduate and postgraduate medical education in some settings sets the pattern for subsequent prescribing in clinical practice.

These issues of perception of poor or lower-quality generics should be addressed, as they may skew prescribing choices and medicine purchases towards higher priced innovator products that are believed

to be better quality. The reliance on higher priced innovator brands over cheaper generic products is particularly important when most medicine costs are borne out of pocket by patients (Balabanova et al., 2012). It is also relevant for health systems that are purchasing medicines for hospitals or subsidizing them through health insurance programmes. Misleading promotion by the pharmaceutical industry may also be contributing to the lack of confidence in generic medicines (de Joncheere & Paal, 2003). In addition, survey respondents believed that incentives are used to influence prescribing choices by doctors and dispensing and sales of antibiotics by pharmacists.

Policy responses to promote the acceptance and use of generic medicines (Robertson & Pedersen, 2018) include the following advice:

- where the quality of generic medicines is assured, focus messages to health-care professionals and patients on equivalence between the originator brand and generic products;
- where quality cannot be assured, focus activities on regulatory authority strengthening and capacity building to ensure the quality of products in circulation and build confidence and trust in the effectiveness and safety of generic medicines;
- link reimbursement to the lowest priced generic product to help create financial incentives for consumers to choose generic medicines; and
- remove or eliminate inappropriate incentives to doctors and pharmacists to prescribe and dispense more expensive originator brand products.

The pharmaceutical industry may be influencing clinical practice in a number of ways – through direct promotion to doctors and consumers and payment of incentives to doctors and pharmacists, but also as major providers of postgraduate education to doctors and pharmacists in settings where there are often few sources of objective and independent drug information (de Joncheere & Baal, 2003). In this survey, most respondents suggested that non-CME events for doctors and pharmacists were sponsored by the pharmaceutical industry or wholesalers either “all of the time” or “some of the time”. Greater regulation and control of the activities of pharmaceutical companies and medicine wholesalers should be considered, and independent sources of information on medicines made more readily available. An ethical framework for governing industry promotional activities could be a useful step.

While greater surveillance and monitoring of the prescribing and supply of antibiotics are highly desirable and important aspects of improving the appropriate use of antibiotics, it is important to consider perverse behaviours that may occur when penalties are applied for so-called poor performance. One respondent noted that, “Patient records and prescriptions are in accord with approved guidelines and protocols; however the patient is discharged with different instructions and recommended treatments.” A greater emphasis on positive rewards for good performance may assist.

According to survey responses, surveillance of prescribing practice in primary health care was less common than in hospitals, with only two countries (Bosnia and Herzegovina, and Turkey) reporting such auditing and a further 12 countries and areas indicating plans to do so. Only Turkey reported providing feedback to doctors concerning their prescribing practice, facilitated by prescription information systems and e-prescriptions. Several respondents identified e-prescribing as a tool to improve the appropriate use of antibiotics. There is a great deal of work required in most of the surveyed countries and areas to institute such tools to take full advantage of their capacity for accounting purposes (to track medicine expenditure) and as a quality improvement tool (to assess alignment of practice with evidence-based guidelines).

Enforcing and improving legislation on prescribing and dispensing antibiotics was the top-ranked priority action for improving their appropriate use. Anecdotally, legislative impediments to inspections

of pharmacies exist in some settings: for example, inspectors are unable to visit newly established pharmacies during the first three years of operation or only after notification 10 days in advance of an official visit. These rules suggest an emphasis on a business model of health care, rather than quality of care.

One third of respondents identified establishing and implementing standard treatment guidelines as a priority action for improving use of antibiotics. The survey did not canvass how guidelines are developed, how effectively they are disseminated and implemented, or schedules for revision of guidelines that might exist in countries and areas. Many endorsed clinical guidelines may be available on ministry of health or public health authorities' websites, but assuring their use in routine practice requires their dissemination and access in easy-to-use formats to guide decision-making at the point of care.

The survey suggests there are important opportunities to enhance the role of pharmacists to support responsible use of medicines. Respondents acknowledged that pharmacists are well-placed to advise patients on the appropriate use of antibiotics, but this needs to be underpinned by training and updating of knowledge to ensure that recommendations and advice are evidence-based.

The results highlight limited collaboration between pharmacists and doctors in most of the participating countries and areas. Only 4% of respondents suggested there was close collaboration between doctors and pharmacists "all of the time", with around 30% reporting that such collaboration occurred "rarely" or "almost never". From a professional perspective, it is disheartening to find that 75% of respondents reported that pharmacists "rarely" or "almost never" influenced a doctor to change a prescription that they considered inappropriate. This suggests enormous opportunities exist to develop the role of the pharmacist as a recognized member of the health-care team.

A report from the WHO Regional Office for Europe (2014) explored the role of the pharmacist in combating AMR and identified a number of issues that need to be addressed, including:

- dispensing antimicrobials without a prescription
- enforcing rules relevant to unauthorized dispensing
- developing appropriate regulations, where necessary
- using repeat prescriptions for antimicrobials
- adjusting quantity dispensed versus quantity prescribed
- managing waste (used antibiotics)
- using pharmacies in campaigns to promote awareness on the use of antimicrobials
- providing information (pharmacist to patient) on antimicrobials, AMR and AMR-related issues
- training pharmacy students and pharmacists in AMR and AMR-related issues
- cooperating with prescribing physicians
- providing antibiotic stewardship in primary care settings.

Repositioning the pharmacist as an active contributor to the health-care team will require changes to undergraduate and postgraduate training and continuing education to ensure that pharmacists have the necessary knowledge and skills to take on these tasks (Guinovart et al., 2018).

Finally, two respondents nominated ensuring the availability of older antibiotics as an important initiative to improve antibiotic use. Further work is required at area, national and international levels to ensure that older, effective, narrow-spectrum agents remain available to patients who need them (Guimaraes, 2017).

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**World Health Organization Regional Office for Europe**  
UN City, Marmorvej 51, DK-2100 Copenhagen Ø, Denmark  
Tel.: +45 45 33 70 00 Fax: +45 45 33 70 01  
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