Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe

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Summary

Background There are no reliable data on antibiotic use in non-European Union (EU) southern and eastern European countries and newly independent states. We aimed to collect valid, representative, comparable data on systemic antimicrobial use in these non-EU countries of the WHO European region.

Methods Validated 2011 total national wholesale antibiotic-use data of six southern and eastern European countries and regions and seven newly independent states were analysed in accordance with the WHO anatomical therapeutic chemical (ATC)/defined daily doses (DDD) method and expressed in DDD/1000 inhabitants per day (DID).

Findings Total (outpatients and hospital care) antibiotic use ranged from 15·3 DID for Armenia to 42·3 DID for Turkey. Co-amoxiclav was mainly used in Georgia (42·9% of total antibiotic use) and Turkey (30·7%). Newly independent states used substantial quantities of ampicillin and amoxicillin (up to 55·9% of total antibiotic use in Azerbaijan). Montenegro and Serbia were the highest consumers of macrolides (15·8% and 19·5% of total antibiotic use, respectively), mainly azithromycin. Parenteral antibiotic treatment is common practice: 46·4% of total antibiotic use in Azerbaijan (mainly ampicillin; 5·3 DID) and 31·1% of total antibiotic use in Tajikistan (mainly ceftriaxone; 4·7 DID).

Interpretation This study provides publicly available total antibiotic-use data for 13 non-EU countries and areas of the WHO European region. These data will raise awareness of inappropriate antibiotic use and stimulate policy makers to develop action plans. The established surveillance system provides a method to develop quality indicators of antibiotic use and to assess the effect of policy and regulatory actions.

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Introduction

Increasing levels of antimicrobial resistance have been spawned by rampant antibiotic use as shown both at the population[1] and individual level.[2] The European Antibiotic Resistance Surveillance network reported a Europe-wide increase of antimicrobial resistance to Gram-negative pathogens, with alarming evidence of increasing resistance to third-generation cephalosporins, fluoroquinolones, and carbapenems in *Escherichia coli* and *Klebsiella pneumoniae* in 2011.[3] This threat is reinforced by globalisation and migration because it favours spread of the resistance problem. The World Economic Forum's *Global Risks 2013* report[4] concluded that "while viruses may capture more headlines, arguably the greatest risk of hubris to human health comes in the form of antibiotic-resistant bacteria". Sally Davies, England's chief medical officer, stressed the importance of international collaboration and the need for a global approach to contain antibiotic resistance.[5]

Standardised and feasible methods to survey antimicrobial use have been developed by the former European Surveillance of Antimicrobial Consumption (ESAC) project.[6,7] This project was transferred in June, 2011, to ESAC-Net of the European Centre for Disease Prevention and Control (ECDC).[8] For European Union (EU) member countries and two European Economic Area/European Free Trade Association countries (Norway and Iceland), ESAC-Net currently collects and analyses antimicrobial consumption data for both the community and the hospital sector.[9] For the remaining 11 southern and eastern European countries and 12 former countries of the Soviet Union (excluding the three Baltic states) of the WHO European region, valid antibiotic-use data are not available. To address this gap, the WHO Regional Office for Europe (WHO Europe) and the Laboratory of Medical Microbiology of the University of Antwerp, Belgium, established a surveillance network on antimicrobial consumption in non-EU countries of the WHO European region. The overall aim of the project was to set up a sustainable network of national antimicrobial surveillance systems to collect valid, representative, and comparable data on antimicrobial use in non-EU countries of the WHO European region.

Our aims were to report on the method of data collection employed and the encountered pitfalls; describe the

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For the **CIA World Factbook** see http://cia-world-fact-book.findthedata.org/d/d/2011

See **Online** for appendix

For more on the **Information Management System database** see http://www imshealth com/portal/site/ims/

characteristics of data sources, providers, and type of data available for the participating countries; assess data validity and representativeness at national level; do a cross-national comparison of 2011 antibiotic-use rates of 12 non-EU European countries and Kosovo; and provide region-specific quality targets to improve antibiotic use. All references, including in the reference list, to "Kosovo" mean "Kosovo (in accordance with UN Security Council resolution 1244 [1999])".

Methods

Participating countries

The ministries of health of the participating countries nominated national representatives to participate in this WHO/Europe-ESAC project. Medicine agencies of health ministries from nine newly independent states (Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Moldova, Tajikistan, Ukraine, and Uzbekistan) and six south and eastern European countries (Albania, Bosnia and Herzegovina, Macedonia, Montenegro, Serbia, Turkey), plus Kosovo, agreed to participate. We added validated 2011 data for Croatia, a southeastern European country not reporting 2011 data to ESAC-Net.

Data collection

The participating country representatives constructed an exhaustive validated national antimicrobial drug register and use database, including detailed information (unit strength, pack size, galenic form, and route of administration) for all antimicrobial products available on the market. The database contained antibacterials for systemic use (anatomical therapeutic chemical [ATC] subgroup J01), antimycotics (J02), antifungals (D01BA) and antivirals for systemic use (J05), amantadine used as an anti-influenza drug (N04BB01), antibiotics for treatment of tuberculosis (J04AB and J04AM), oral and rectal nitroimidazole derivatives (P01AB), and antibiotics used as intestinal anti-infectives (A07AA). Antimicrobials for topical and vaginal use were excluded. Each medicinal product was classified in accordance with the WHO standardised and internationally recognised ATC coding system, classifying drugs according to their main therapeutic use. We further assigned to each product the WHO defined daily dose (DDD), a unit of measurement that is an international compromise of the assumed average maintenance dose per day for a drug used for its main indication in adults.[10] The implementation of the WHO ATC/DDD method enabled us to construct a database for measuring and comparing antimicrobial use. In close collaboration with the WHO Collaborating Centre for Drug Statistics Methodology of the Norwegian Institute of Public Health, we assigned provisional ATC codes and DDDs to products for which this value was not yet attributed.[10] These products mainly included combinations of drugs reported by the newly independent states—eg, ciprofloxacin and tinidazole, ornidazole, or metronidazole; and tetracycline and oleandomycin.

We calculated the defined daily dose per package (DPP=[unit strength×pack size]/DDD). The DPP at product level was then multiplied with the corresponding number of nationally reported packages of antimicrobial drugs brought and sold on the market in 1 year (number of DDD at product level). Denominator data used were the total number of inhabitants per year of a country (mid-year population) as provided by the respective national statistical offices or the United Nations Development Program.[11] For Serbia, we consulted the CIA World Factbook because it provided denominator data for Serbia only (omitting Kosovo; appendix). We subsequently calculated the outcome measurement unit, DDD/1000 inhabitants per day (DID), at product level.

Data aggregation

Data aggregation was done in accordance with the ATC classification.[10] For macrolides, we attributed a classification according to the mean plasma elimination half-life subdividing them into short-acting (half-life <4 h), intermediate-acting (half-life 4–24 h), and long-acting (half-life >24 h) macrolides.[12] The quinolone substances were classified according to three generations based on their chemical structure and antimicrobial activity.[13] Overall, 144 unique antibiotic substances were used in 2011, ranging from 41 substances in Kosovo to 72 in Turkey. Those substances were aggregated into ten pharmacological subgroups (ATC third level) and 35 chemical subgroups (ATC fourth level) for descriptive analyses.

Data validation

Data validation included thorough checking of every reported drug in the drug register database to ensure the WHO ATC/DDD classification method was correctly applied. We sought online supplementary information in case of poorly defined product labels (unit strength and pack size), for example, on Russian products. National representatives were supplied with a standard validation report providing longitudinal total and proportional antimicrobial volumes of use, expressed in DID. Results were then revised, corrected, or justified (gaps, drop or increase of use over time). Reference data from ESAC-Net were used to asses and interpret the data.[14]

We report on validated national antimicrobial wholesale data of ATC group J01 for 2011 collected from 12 non-EU European countries and Kosovo. The appendix summarises all data available by type of data, data suppliers and coverage, reported aggregation levels, and population data; information that was collected by means of a questionnaire. Eight countries delivered total care data, Kyrgyzstan and Montenegro supplied data separately for the community and hospital sector, and Turkey and Georgia provided ambulatory care data only. Turkey used the Information Management System database, which included complete, not extrapolated, data covering the whole ambulatory care sector. Armenia, Azerbaijan, Belarus, Turkey, and Kosovo

supplied quarterly data, allowing the investigation of seasonal variation. Data coverage was 100% for ten countries, greater than 98% for two countries, and, for political reasons, 70% for Georgia.

We analysed country-specific total and proportional antibiotic use expressed in DID for the year 2011. The data were further compared with 2011 total care (ambulatory plus hospital care) ESAC-Net data of the ECDC. ESAC-Net data are publicly available at the ATC third and fourth level (ESAC-Net interactive database).[14] Supplementary data on the macrolides[12] and quinolones subgroups[13] were provided by the ECDC.

Antibiotic use in countries that could not yet deliver data (Albania, Macedonia, and Uzbekistan) or obtained poor data coverage (Ukraine) are not reported.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication, following agreement from all authors.

Results

Figure 1 depicts total antibiotic use (ATC group J01) expressed in DID in 12 non-EU European countries and Kosovo (year 2011). Antibiotic use among the participating countries differed significantly, ranging from 15·3 DID in Armenia to 42·3 DID in Turkey. We also compared antibiotic use to 29 ESAC-Net countries in 2011 (appendix).

Penicillins (ATC group J01C) were the most commonly used antibiotics in all countries. Highest proportional use of penicillins of total antibiotic use was noted for Georgia (67·6%; 14·2 DID), and then Azerbaijan (65·9%; 11·4 DID). Highest total penicillin use was reported for Tajikistan (18·2 DID; figure 2) and lowest for Armenia (6·1 DID). Narrow spectrum penicillin use, mainly phenoxymethylpenicillin, was low and varied from 0·02 DID in Belarus to 1·3 DID in Montenegro. Amoxicillin and ampicillin were very commonly used in Tajikistan (15·9 DID; 45·6% of total antibiotic use) and Azerbaijan (9·7 DID; 55·9%) and amoxicillin in Montenegro (9·1 DID; 23·6%). Highest use of combinations of penicillins (mainly co-amoxiclav) was noted for Turkey (13·0 DID; 30·7% for co-amoxiclav of total antibiotic use) and Georgia (9·0 DID; 42·9%), and lowest use was noted for Azerbaijan (0·5 DID) and Kyrgyzstan (0·6 DID). Penicillin (ATC group J01C) use was also compared with 29 ESAC-Net countries (appendix).

Highest total cephalosporin (ATC group J01D) use was noted for Turkey (14·1 DID; 33·4% of total antibiotic use) and lowest for Azerbaijan (0·8 DID; 4·3%; figure 3). Highest first-generation cephalosporin use was reported by Montenegro (2·9 DID), Serbia (2·3), Kosovo (2·1), and Kyrgyzstan (2·0), and lowest was reported by Georgia (0·02). Highest use of second-generation cephalosporins was

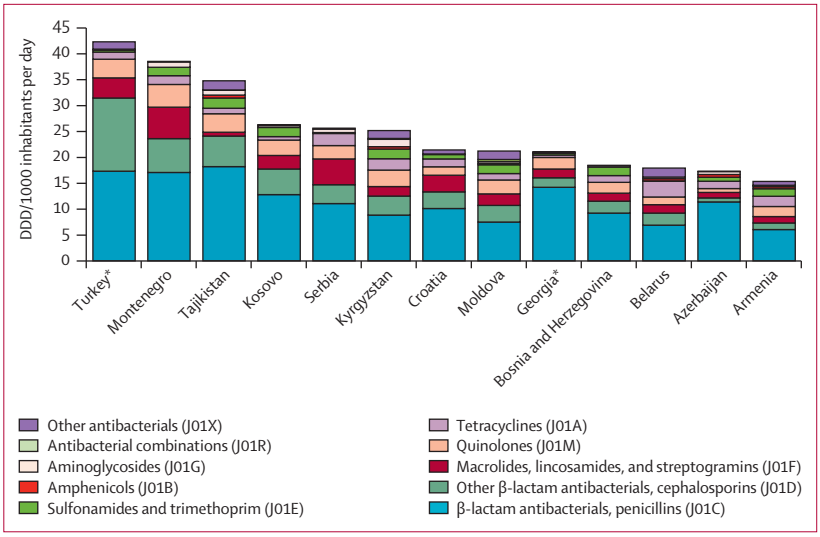

Figure 1: **Total antibiotic use in 12 European countries and Kosovo, 2011**
The category (WHO anatomical therapeutic chemical subgroup) "Other β-lactam antibacterials, cephalosporins" includes carbapenems and monobactams. "Other antibacterials" includes glycopeptide antibacterials, polymyxins, fusidic acid, imidazole derivates, nitrofuran derivates, and other antibacterials. DDD=defined daily doses. *Reported only outpatient antibiotic use.

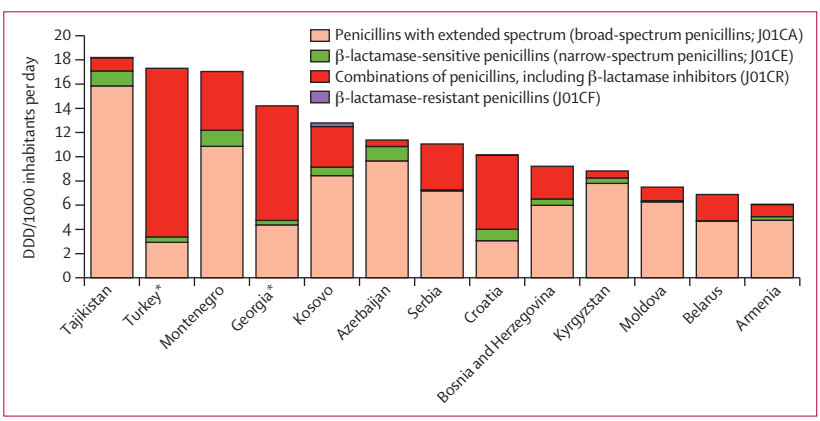

Figure 2: **Total penicillin (J01C) use subdivided into four main subgroups in 12 European countries and Kosovo, 2011**
DDD=defined daily doses. *Reported only outpatient antibiotic use.

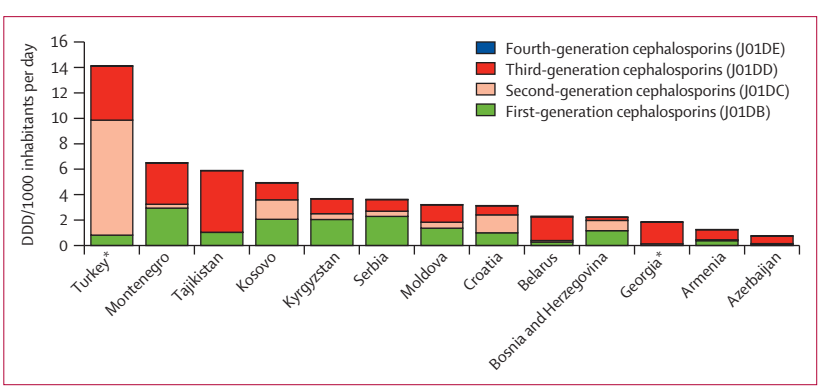

Figure 3: **Total cephalosporin use subdivided into four main subgroups in 12 European countries and Kosovo, 2011**
DDD=defined daily doses. *Reported only outpatient antibiotic use.

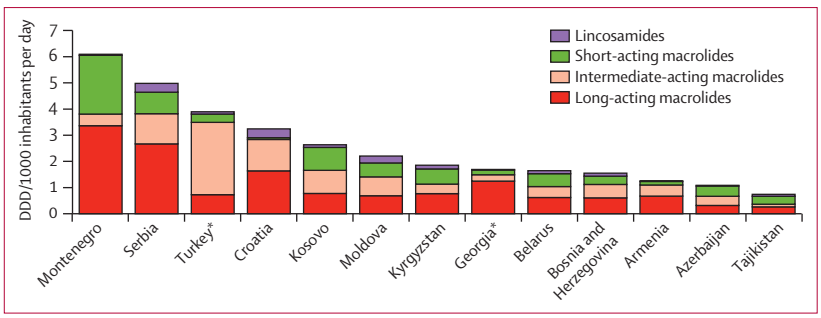

Figure 4: **Total macrolide (J01FA) and lincosamide (J01FF) use subdivided into four main subgroups in 12 European countries and Kosovo, 2011**
DDD=defined daily doses. *Reported only outpatient antibiotic use.

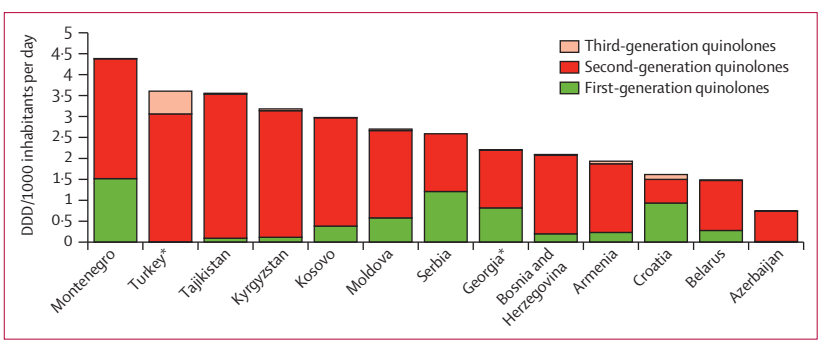

Figure 5: **Total quinolone (J01M) use subdivided into three main subgroups in 12 European countries and Kosovo, 2011**
DDD=defined daily doses. *Reported only outpatient antibiotic use.

reported by Turkey (mainly cefuroxime; 9·0 DID) and then Kosovo (1·5) and lowest by Tajikistan (0·02). Highest third-generation cephalosporin use was reported by Tajikistan (4·9 DID), Turkey (4·2), and Montenegro (3·2) and lowest by Bosnia and Herzegovina (0·2). Most newly independent states consumed in total and proportionally more third-generation cephalosporins than the other countries (mainly ceftriaxone; up to 91% of total cephalosporin use in Georgia and 80% in Tajikistan, Azerbaijan, and Belarus). Montenegro mainly consumed cefixime for oral use (2·1 DID). Southern and eastern European countries consumed mainly first-generation cephalosporins (cephalexin). Turkey was the only country that reported third-generation cephalosporins cefdinir and cefditoren for oral use (1·6 DID, 11·3% of total cephalosporin use). Cephalosporin (ATC group J01D) use was also compared with 29 ESAC-Net countries (appendix).

Highest macrolide (ATC group J01FA) and lincosamide (J01FF) use was noted for Montenegro (6·1 DID; 15·8% of total antibiotic use) and Serbia (5·0 DID; 19·5%), and lowest for Tajikistan (0·7 DID; 2·1%; figure 4). Montenegro reported the highest use of short-acting macrolides (2·2 DID, mainly erythromycin), with Kosovo and Serbia the next highest (0·9 and 0·8 DID, respectively). Highest use of intermediate-acting macrolides was reported by Turkey and Serbia (2·8 and 1·2 DID, respectively, mainly clarithromycin), whereas use in the other countries was less than 1 DID. Highest use of long-acting macrolides (azithromycin) was noted for Montenegro (3·4 DID), Serbia (2·7), and Georgia (1·2). Macrolide (ATC group J01FA) and lincosamide (J01FF) use was also compared with 29 ESAC-Net countries (appendix). Streptogramin (J01FG) use was not reported.

Highest quinolone (ATC group J01M) use was noted for Montenegro (4·4 DID; 11·4% of total antibiotic use) and lowest for Azerbaijan (0·7 DID; 4·3%; figure 5). Montenegro and Serbia reported highest use of first-generation quinolones (1·5 and 1·2 DID, mainly pipemidic acid) and then Georgia (0·8 DID, mainly norfloxacin). Highest use of second-generation quinolones was reported by Tajikistan, Turkey, Kyrgyzstan, Montenegro, and Kosovo (3·4–2·6 DID, mainly ciprofloxacin). Highest use of third-generation quinolones was noted for Turkey (0·5 DID, mainly gemifloxacin) and then Croatia (0.1 DID, mainly moxifloxacin); minor use was reported for all other countries—no use was reported for Serbia. Quinolone (ATC group J01M) use was also compared with 29 ESAC-Net countries (appendix). Seasonal variation of quinolone use showed an increased use of levofloxacin during the winter season in Turkey, Armenia, and Azerbaijan. Higher volumes of moxifloxacin use were reported during the winter season in Turkey; no increase during winter season was not for the other quinolones (appendix).

Highest tetracycline (ATC group J01A) use was reported for Belarus (3·0 DID; 16·9% of total antibiotic use), and then Serbia (2·3; 9·0%) and Armenia (2·0; 13·0%), and lowest for Georgia (0·5 DID; 2·3%; appendix, also includes 29 ESAC-Net countries).

Highest sulphonamide and trimethoprim (ATC group J01E) use, mainly sulfamethoxazole and trimethoprim, was noted for Tajikistan (2·0 DID; 5·6% of total antibiotic use) and Kyrgyzstan (1·9; 7·5%), and lowest for Belarus (0·1; 0·4%).

Substantial use of amphenicols (ATC group J01B) was reported for Azerbaijan, Armenia, Kyrgyzstan, Belarus, and Tajikistan (0·4–0·6 DID). Combination products that were not yet listed in the ATC/DDD classification system added overall 0·013 DID in Georgia to 0·44 DID in Moldova.

Highest total parenteral antibiotic use was noted for Tajikistan (11·5 DID; 31·1% of total antibiotic use), and ceftriaxone alone accounted for 4·7 DID (12·7% of total antibiotic use; appendix). However, highest proportional parenteral use was noted in Azerbaijan (8·0 DID; 46·4% of total antibiotic use), and ampicillin alone accounted for 5·3 DID or 31% of total antibiotic use. Lowest total parenteral use was noted for Turkey (0·9 DID; 2·1%).

Discussion

To our knowledge, this study for the first time presents reliable total antibiotic-use data for 13 southern and eastern European countries, Kosovo, and newly independent states, expressed in DID (panel). We were able to compare their antibiotic-use patterns with those of 29 ESAC-Net countries because we used the same methods as developed

in the former ESAC project[1] and the validation process was based on standard reports developed by ESAC. Our main findings are that total antibiotic use ranged from 15·3 DID for Armenia to 42·3 DID for Turkey; co-amoxiclav was commonly used in Georgia and Turkey; newly independent states used substantial quantities of ampicillin and amoxicillin; Montenegro and Serbia were the highest consumers of macrolides, mainly azithromycin; and parenteral treatment with antibiotics is common practice in the newly independent states.

Compared with ESAC-Net countries, Turkey had the highest antibiotic use in Europe, and on the basis of this finding, the Turkish government already published a *Rational Drug Use National Action plan 2013–2017*, with quantitative targets to reduce antibiotic use (by 2 DID annually between 2014 and 2017). Armenia had very low antibiotic use, similar to northern EU countries. However, this low antibiotic use might relate to underuse because of limited access to drugs for a substantial proportion of the population, particularly in rural regions and among poor people, as shown in a recent survey on health inequalities in Armenia.[15] Belarus is also a European country in which antibiotic use was low, but here health services have remained affordable for virtually everyone after the collapse of the Soviet model of health care, which sought to achieve universal, free access to basic health services.[16] This low antibiotic use might illustrate the effect of better coverage or more rational use of medicines and state budget.

Because of poor information systems in most surveyed countries and lack of universal coverage in these countries, data collectors had to go through several sources of information, such as wholesalers' data (available from the ministry of health in most countries; appendix). However, the advantage of collecting sales data over reimbursement data is the inclusion of antibiotics procured over the counter without a prescription.[17] For countries with centralised procurement of hospital medicines (such as Kyrgyzstan), ambulatory care data have been complemented with hospital reimbursement data. Data on humanitarian assistance and local manufacturers were also considered for countries with big volumes of donations (such as Armenia and Tajikistan) and big manufacturers (such as Serbia, Turkey, and Ukraine). For most countries, reliable denominator data were available; however, estimates were used for Bosnia and Herzegovina, and Kosovo.

One of the main problems in the countries included in this study is the widespread practice of selling antibiotics over the counter. Outdated (2001) data are available for eight newly independent states, showing that on average 21·8% of the adult population purchased medicines without a prescription.[16] However, according to a survey done in 2012 among the WHO/Europe-ESAC project group members, more than 50% of antibiotics are sold over the counter in most of their countries. There are several reasons for the unauthorised over-the-counter sales of antibiotics, including lack of sustainable health-care systems, poor enforcement of regulation, and lack of a comprehensive medicines reimbursement system leaving medicines as out-of-pocket payments. The reliance on direct out-of-pocket payments is serious a problem in many of the countries included in this study, undermining the principle of equity with respect to both financing and access to health care. High rates of self-medication with antibiotics might go along with the underuse of health services[18] or might lead to diagnostic and health-care system seeking delays.[19] Therefore, restriction of over-the-counter use of antibiotics is urgently needed, and could be partly achieved by implementing national regulatory instruments,[20] public awareness campaigns,[21] or enhancing efforts in educating health-care providers towards appropriate prescribing.[19] Aggressive promotion by industry and lack of trust towards doctors' skills is another reason for self-medication in some of these countries, and regaining this trust should also lead to improve patient

For the **Turkish rational drug use plan** see http://www.akilciilac.gov.tr/

***Panel:* Research in context**

Systematic review

We searched Pubmed with keywords related to antibiotics, subgroups of antibiotics, surveys, and countries involved in our study. We did not identify any specific published works providing an overview of common patterns of antibiotic use. Increasing levels of antimicrobial resistance correlate with inappropriate antibiotic use as shown at the population[1] and individual level.[2] Monitoring of antimicrobial use is a crucial component to identify targets for improving antimicrobial use and to further correlate with antimicrobial resistance surveillance programmes.[1] The internationally recognised WHO anatomical therapeutic chemical (ATC)/defined daily doses (DDD) method allows the measurement and comparison of drug use in populations.[10] This standardised method has been employed to survey antimicrobial use within Europe by the European Surveillance of Antimicrobial Consumption (ESAC) project,[6,7] and currently by ESAC-Net of the European Centre for Disease Prevention and Control.[14] For other southern and eastern European countries and the former Soviet Union countries of the WHO European region, valid antimicrobial use data were not available.

Interpretation

For the first time, validated data on antibiotic use in seven newly independent states (Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Moldova, Tajikistan), five southern and eastern European countries (Bosnia and Herzegovina, Croatia, Montenegro, Serbia, Turkey), and Kosovo, have been collected and analysed in accordance with the WHO ATC/DDD method. Findings were benchmarked to ESAC-Net data.

We identified substantial differences in the quantity and quality of antibiotic use, with Turkey using most antibiotics (42·3 DDD/1000 inhabitants per day) and Armenia the least (15·3 DDD/1000 inhabitants per day). In general, broad-spectrum penicillins (amoxicillin and ampicillin) were most commonly used, but co-amoxiclav was most used in Georgia and Turkey. Montenegro and Serbia particularly used the long-acting macrolide azithromycin. Remarkably high parenteral antibiotic use was noted for all newly independent states, with Tajikistan showing the highest total parenteral use (mainly ceftriaxone) and Azerbaijan showing the highest proportional parenteral use (mainly ampicillin). This high use of injectable antibiotics relates to the inappropriate use of antibiotics in outpatients.

These data for the first time allow the auditing of antimicrobial use, help identify targets for quality improvement, and aid the development of national action plans to enhance judicious antibiotic use. This study provides the foundation for a sustainable long-term surveillance network on antimicrobial use in this part of the WHO European region. Consequently, long-term antimicrobial use data will aid the assessment and improvement of future action plans.

satisfaction and prescription-based antibiotic use.[15] However, it is clear that only strengthening (both widening and deepening) of health coverage can become the basis for rational use of any prescription medicines, including antibiotics. In the future, reimbursement data should also be collected in these countries because the difference with sales data might provide a rough estimate of non-reimbursed (principally over-the-counter) sales.[17]

Amoxicillin was widely used in all newly independent states (except Georgia), southern and eastern European countries, and Kosovo. Although the recommended antibiotic treatment for community-acquired lower-respiratory-tract infections in Europe is amoxicillin or a tetracycline,[22] strikingly high use of this antibiotic might still relate to unnecessary use. Indeed, antibiotics virtually never benefit patients with acute cough, which is one of the most common reasons for consulting in primary care and prescribing antibiotics.[23,24] The combination of amoxicillin and a β-lactamase inhibitor, which overcomes some types of resistance, is not a first-line agent for empirical treatment for most commonly encountered infections in primary care. Yet, in Turkey and Georgia this drug is used extensively, which raises concern regarding its appropriate use.

The southern and eastern European countries, Kosovo, Kyrgyzstan, and Moldova consumed high volumes of first-generation cephalosporins, similar to the use in northern EU countries.[25] The newly independent states and Montenegro had much higher third-generation cephalosporin (mainly ceftriaxone) use compared with the rest of Europe. Because of its long half-life and once-daily dosing requirement, ceftriaxone is an attractive option for outpatient parenteral therapy.[26] However, third-generation cephalosporins might select for bacteria that produce extended-spectrum β-lactamases, so antibiotic resistance should be monitored in these countries.[27]

The long-acting macrolides (mainly azithromycin) are responsible for high total macrolide use (mainly in Montenegro and Serbia), but also proportionally within this group of antibiotics (in most countries included in this study). Our findings suggest that this subgroup of antibiotics is still prescribed inappropriately in this part of Europe. Use of so-called respiratory quinolones (levofloxacin and moxifloxacin) increased during the winter season in those countries where quarterly data were provided. Because quinolones are not recommended as first-line therapy for the treatment of many infectious diseases, their high use noted in some of the countries included in this study raises concern, especially for prevention and control of multiply and extensively drug-resistant *Mycobacterium tuberculosis*.

An interesting finding of this study is untypically high use of amphenicols (chloramphenicol in particular) in some of the newly independent states. This finding could partly be explained by the fact that chloramphenicol had been widely used in these countries for treatment of diarrhoea.

Finally, a remarkable finding of our study is the high parenteral use. In the former ESAC project, it was reported that only 2% of outpatient antibiotics in 20 European countries participating in ESAC were used for parenteral treatment.[28] Although our study includes data from both hospital and community care, injectable antibiotics given in hospitals solely cannot account for the recorded high parenteral use. Indeed, most antibiotics are used in outpatients and for countries participating in the former ESAC project that reported combined hospital and outpatient use, the proportions of hospital use were below 10% for most countries.[29] Therefore, we think that the remarkably high parenteral use is explained by the high outpatient use of injectable antibiotics (mainly ampicillin and ceftriaxone), certainly in the newly independent states. In Italy, outpatient parenteral treatment, mainly ceftriaxone, was popular because physicians and patients thought parenteral administration of antibiotics to be more effective than oral administration of these drugs, even for treatment of benign infections in primary care.[30] More in-depth studies are needed to explore indications of parenteral use and to explain the success of these antibiotics among patients and physicians.

The purpose of collecting indicators of antibiotic use is to identify inappropriate prescribing and to provide a means to measure the effect of interventions. Benchmarking, by comparison of antibiotic use between countries, is an important stimulus to quality improvement.[31,32] Our study identifies opportunities for quality improvement (eg, reduce total use of antibiotics, reduce use of co-amoxiclav and azithromycin in southern and eastern European countries and Kosovo, and reduce parenteral use in newly independent states).[31,32] Policy makers and medical professionals should use these data to trigger actions and to develop, implement, and assess national guidelines.

In conclusion, our study shows striking differences of antibiotic prescribing in non-EU countries and Kosovo in the WHO European region and should be considered as a first step to improve antibiotic use in these countries and areas. Our effort should be continued and expanded to other countries of the region; we should also survey antibiotic resistance, because surveillance provides an essential component for policy development and containment of antibiotic resistance.

Contributors

NS and HG initially proposed the idea for this study. AV was responsible for data collation, validation, and analysis, and contributed in writing the article. HG was responsible for the analysis and interpretation of data and writing of the article. GB was responsible for running the network and was involved in data validation and interpretation. All authors contributed to the interpretation of the data and the write up. All authors and members of the WHO/Europe-ESAC Project Group critically reviewed the report.

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Declaration of interests

We declare that we have no competing interests.

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