https://doi.org/10.31925/farmacia.2025.1.15 **ORIGINAL ARTICLE**

OUTPATIENT UTILIZATION OF ANTIBACTERIAL DRUGS FOR SYSTEMIC USE IN MONTENEGRO IN 2000-2022: HOW FAR ARE WE FROM VALUES AND TARGETS OF THE EUROPEAN UNION?

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Abstract

This retrospective pharmacoepidemiologic study aimed to analyse outpatient utilisation of antibacterials for systemic use (ASU) in Montenegro in 2000 - 2022, comparing it with EU/EEA data to identify areas for improvement. Quantitative and qualitative indicators, such as defined daily dose per thousand inhabitants per day, drug utilisation 90%, distribution between broad- and narrow-spectrum ASU and AWaRe classification, were used. ASU were classified according to the ATC classification. Appropriate statistical tests were applied, using a significance level of $\alpha = 0.05$ and R software for analysis. The use of ASU in Montenegro increased by 71% in 2022 compared to 2000. A significant difference was found in the use of certain antibiotic sub-groups ($p < 0.05$). Cephalosporins were used significantly more in Montenegro compared to the EU/EEA ($p < 0.05$). A nearly 10-fold increase in the ratio of broad- to narrow-spectrum ASU utilisation (0.24 *vs*. 1.96) was found. The utilisation of the Access group decreased from 73% in 2000 to 50% in 2022 ($p < 0.05$); that was lower compared to the mean value in the EU/EEA. Although the increase in outpatient ASU consumption in Montenegro was in line with the unfavourable global trend, it was opposite to the majority of EU/EEA countries and requires additional analyses and interventions.

Rezumat

Lucrarea prezintă un studiu farmacoepidemiologic retrospectiv ce a analizat utilizarea în ambulatoriu a antibioticelor de uz sistemic (ASU) în Muntenegru în perioada 2000-2022, comparând-o cu datele UE/SEE pentru a identifica domeniile de îmbunătățire. Au fost utilizați indicatori cantitativi și calitativi, cum ar fi doza zilnică definită pe mia de locuitori pe zi, utilizarea medicamentelor în proporție de 90%, distribuția între ASU cu spectru larg și îngust și clasificarea AWaRe. ASU au fost clasificate în conformitate cu clasificarea ATC. Au fost aplicate teste statistice adecvate, utilizând un nivel de semnificație de $\alpha = 0,05$ și *software*-ul R pentru analiză. Utilizarea ASU în Muntenegru a crescut cu 71% în 2022 comparativ cu 2000. S-au constatat diferențe semnificative în utilizarea anumitor subgrupuri de antibiotice ($p < 0,05$). Cefalosporinele au fost utilizate semnificativ mai mult în Muntenegru comparativ cu UE/SEE ($p < 0,05$). S-a constatat o creștere de aproape 10 ori a raportului de utilizare a ASU cu spectru larg față de cele cu spectru îngust (0,24 *vs*. 1,96). Utilizarea grupului Acces a scăzut de la 73% în 2000 la 50% în 2022 ($p < 0,05$), ceea ce a fost mai scăzut în comparație cu valoarea medie din UE/SEE. Deși creșterea consumului de ASU în ambulatoriu în Muntenegru a fost în conformitate cu tendința globală nefavorabilă, aceasta a fost opusă majorității țărilor UE/SEE și necesită analize și intervenții suplimentare.

Keywords: antibacterial drugs, utilization, Montenegro, EU/EEA Recommendations

Introduction

In a few years, humanity will celebrate the centenary of the discovery of penicillin. It is unlikely that, back then, and especially during the golden decades of the antibiotic era that followed, anyone could have suspected that in the first quarter of the 21st century, antibiotic-resistant bacteria would cause more than 670,000 infections in the EU/EEA and that approx. 33,000 people would die annually as the consequence of these infections [35]. Globally, it was estimated that bacterial antimicrobial resistance (AMR) was directly responsible for 1.27 and contributed to 4.95 million deaths in 2019 [2]. The World Health Organisation (WHO) has recognised AMR as one of the top global public health and development threats, diminishing the efficacy of common antibiotics against widespread bacterial infections [30]. AMR increases the morbidity and mortality of hospitalised patients by affecting the frequency and duration of hospital treatment, as well as increasing the need for surgical revisions and the use of more effective and potentially toxic antibiotics [2, 17]. The World Bank estimated that AMR could cause additional healthcare costs of USD 1 trillion by 2050 and annual gross domestic product losses of USD 1 to 3.4 trillion by 2030 [13].

Decades of research and clinical experience have confirmed that the development and spread of AMR are associated with excessive and inappropriate use of antibiotics in healthcare, animal and plant production, as well as the increased mobility of people and goods [3, 24]. Although AMR affects the whole world, it seems to particularly burden countries with underdeveloped healthcare systems. Overcrowding, inadequate hygiene and sanitary conditions, healthcare that does not meet recommended standards, and the lack of control over human and antibiotic use in agriculture have been recognised as weaknesses of lower- and middle-income countries (LMICs), making them particularly vulnerable to AMR [2, 24, 34].

In order to support antimicrobial stewardship, WHO developed the AWaRe classification in 2017. According to this classification, antibiotics are classified into Access, Watch and Reserve groups, taking into account their different impact on the development of AMR [33]. The EU adopted five recommendations in mid-2023, the first two of which pertain to the outpatient use of ASU: to reduce the total use of antibiotics in humans by 20% during the period 2019 - 2030 and to ensure that at least 65% of the total consumption of antibiotics in human medicine by 2030 comes from the Access group [10].

Given that 80-90% of antibacterial prescriptions are issued in primary health care (PHC) [25, 2, 20, 11], investigating the outpatient use of these drugs should be the best starting point for planning and implementing various optimisation measures.

According to the first survey of the outpatient utilisation of antibacterial drugs for systemic use (ASU) in Montenegro (2000), which was done using the DDD/ATC methodology, beta-lactam antibiotics accounted for about 60% of all antibiotics used, which was considerably more compared to some Nordic countries. The outpatient utilisation of penicillins was higher compared to the total utilisation of those drugs in Finland but lower in comparison to Norway [8]. On the other hand, oral ampicillin had an outpatient consumption of 2.8 DDD/1000 inhabitants/ day (DTID), while in the Nordic countries this formulation was not used at all [8]. Four years later, after the implementation of some reform measures in this area, the outpatient prescription of ASU in Montenegro decreased by about 12%; oral ampicillin was quantitatively replaced by a fixed-dose combination of amoxicillin with clavulanic acid, but the prescribing of macrolides significantly increased by about 60% [7].

In the period from 2000 to 2022, a number of regulatory, legislative, organizational and educational measures were carried out at the national level to optimize the utilization of ASU: the list of reimbursed medicines (which included ASU) was updated at least once a year, the Information system for managing the distribution and use of medicines (2004) and electronic prescription (2008) were introduced, a national regulatory body specific to medicines and medical devices was established in 2009, national strategies for the control of AMR were adopted several times, National interdisciplinary commission for AMR control (2011) and the National commission for hospital infections (2011) were formed by the Ministry of Health, numerous educational activities and guidelines for prescribing of ASU were done, microbiological diagnostics was significantly improved, etc.

Based on the above, we hypothesised that applied measures significantly improved the outpatient use of ASU in our country. Additionally, we hypothesised that there was no significant difference in the consumption of ASU between Montenegro and the EU/EEA and that the defined EU/EEA targets are achievable. The objective of this investigation was to analyse the outpatient use of ASU in Montenegro in the period from 2000 to 2022 and to identify, by comparison with relevant data from the EU/EEA, possible weaknesses and deviations in order to support further efforts in reaching the EU/EEA values and targets in this area.

Materials and Methods

Study setting and design

Montenegro is a small European and Mediterranean country of the former Yugoslavia, which renewed its independence in 2006. This retrospective pharmaco-epidemiologic study of the outpatient use of ASU was conducted on a national sample of Montenegrin residents in 2000 (604,950 inhabitants) and 2022 (617,213 inhabitants) [23]. Within the frame of country's accession to the EU, a comparison of the obtained results with official data on the outpatient consumption of ASU in the EU/EEA in 2022 [9] was conducted to analyse the present situation more precisely and indicate possible ways of improvement.

Data collection procedures

In 2000 there was no national regulatory body specific to the field of medicines (CInMED) in Montenegro. Data on the ASU distributed to community pharmacies were obtained from all state and private wholesalers in the form of an annual report on the number of packages, afterwards converted into DTID [31, 32]. Data on the outpatient utilisation of ASU in 2022 were obtained from the CInMED electronic database. The'Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report 2022 by the European Centre for Disease Prevention and Control (ECDC) was used to compare the obtained results with official data from the EU/EEA [9].

Indicators of the outpatient utilization of ASU

For quantitative and qualitative assessment of the outpatient utilisation of ASU in Montenegro, the

following indicators were used: 1. Total number of DTID and the share of individual sub-groups (3rd level) and INNs (5th level of ATC classification) in outpatient use; 2. Drug Utilisation 90% (DU90%) and, within it, the share of narrow- and broad-spectrum ASU; 3. The ratio of the outpatient utilisation of broad- and narrow-spectrum ASU; 4. Belonging of ASU to the Access, Watch and Reserve groups; 5. The ratio of the outpatient utilisation of Access to Watch ASU.

Defined daily dose (DDD) is the assumed average daily maintenance dose of a drug used for its main indication for adults [31]. DTID provides a rough estimate of the proportion of a certain population treated with ASU during the day.

DU90% is a cheap, flexible and simple method to assess the quality of drug prescribing [4]. It was determined by calculating the outpatient use of each individual ASU in percentages and then ranking them from first to last. DU90% consisted of those ASUs whose sum of percentages was 90% of total utilisation.

The ratio of utilisation of broad- and narrow-spectrum antibiotics as a qualitative indicator of the outpatient use of ASU was defined by the ECDC, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) as the ratio of utilisation of broad-spectrum (ATC groups J01 (CR + DC + DD + (FA-FA01) + MA)) to narrow-spectrum (ATC groups J01 (CA + CE + CF + DB + FA01)) antibiotics in the community [9].

According to AWaRe classification, the Access antibacterials are recommended as empiric first- or second-line treatment options due to a lower resistance potential than other groups. Empiric use of the Watch group should be limited to severe infections and infections with pathogens resistant to antibacterials from the Access group. The Reserve group should be prescribed for the treatment of infections caused by multidrug-resistant bacteria when all alternatives have failed or are unsuitable [33, 36].

Statistics

Statistical analysis was done in the statistical software R. The results were interpreted at the level of statistical significance of $\alpha = 0.05$. To check the significance of the difference in the use of different INNs between 2000 and 2022, the Wilcoxon signed-rank test was used, considering the non-normal distribution of the data and dependent samples. The Friedman test was applied to check the significance of the difference in use of ASU according to the third level of ATC classification in 2000 - 2022. This test was used due to the analysis of several groups of related data (the same sub-groups were followed in different years), where the data were not normally distributed. In order to test the difference between Montenegro and the EU/EEA in 2022 for eight sub-groups of ASU, the Fisher's test was used. The same test was used to check the significance of the difference in INNs share in DU90%, as well as the share of narrow- and broad-spectrum ASU between 2000 and 2022. The difference in the share of Access and Watch groups was examined by the χ^2 (chi-square) test. This test enables the analysis of the connection between two categorical variables and the assessment of whether changes in the frequency distribution between the two variables are statistically significant.

Results and Discussion

The outpatient utilisation of ASU in Montenegro increased by 71% in 2022 compared to 2000, but without a statistically significant difference ($Z = 85$, $p = 0.304$; $p > 0.05$). A tenfold increase was found in the case of azithromycin, followed by cefixime (100%), amoxicillin with clavulanic acid and ciprofloxacin (both more than 100%). The SMX-TMP, all natural penicillins, and ampicillin had a downward trend in use (Table I).

According to the third level of ATC classification (Figure 1), all sub-groups were used significantly more in 2022 compared to 2000 (χ^2 (2) = 13.3, $p = 0.0013$; $p < 0.05$).

Table I

Outpatient utilisation of ASU in Montenegro in 2000 and 2022, in DTID and percentage

ATC code	INN	2000 DTID (%)	2022 DTID (%)	2000-2022 DTID (%)
J01AA02	Doxycycline	0.64 (3.7%)	1.71 (31.8%)	+ 1.07 (>100%)
J01CA01	Ampicillin	2.81 (16.1%)	0.16 (0.5%)	- 2.65 (-94%)
J01CA04	Amoxicillin	3.98 (22.9%)	5.79 (19.5%)	+ 1.81 (+45%)
J01CE02	Phenoxymethylpenicillin (PMP)	0.30 (1.7%)	/	- 0.30 (-100%)
J01CE10	Benzathine-PMP	0.22 (1.3%)	0.04 (0.1%)	- 0.18 (-82%)
J01CE30	Benzylpenicillin (BP), Procaine-BP	0.47 (2.7%)	0.05 (0.2%)	- 0.42 (-89%)
J01CR02	Amoxicillin, clavulanic acid	0.05 (0.3%)	3.42 (11.5%)	+ 3.37 (> 100%)
J01DB01	Cephalexin	2.49 (14.3%)	2.05 (6.9%)	- 0.44 (-18%)
J01DC04	Cefaclor	0.77 (4.4%)	/	- 0.77 (-100%)
J01DD04	Ceftriaxone	0.01 (0.1%)	0.80 (2.7%)	+ 0.79 (> 100%)
J01DD08	Cefixime	/	4.16 (14%)	+ 4.16 (+100%)
J01EE01	SMX-TMP	2.36 (13.6%)	0.94 (3.2%)	- 1.42 (-60%)

ATC code	INN	2000 DTID (%)	2022 DTID (%)	2000-2022 DTID (%)
J01FA01	Erythromycin	0.46 (2.6%)	0.85 (2.9%)	+ 0.39 (+85%)
J01FA09	Clarithromycin	/	1.05 (3.5%)	+ 1.05 (+100%)
J01FA10	Azithromycin	0.54 (3.1%)	5.02 (16.9%)	+ 4.48 (>1 00%)
J01FF01	Clindamycin	0.01 (0.1%)	0.20 (0.7%)	+ 0.19 (> 100%)
J01MA02	Ciprofloxacin	0.14 (0.8%)	2.39 (8%)	+ 2.25 (> 100%)
J01MA06	Norfloxacin	0.25 (1.4%)	/	- 0.25 (-100%)
J01MA12	Levofloxacin	/	0.24 (0.8%)	+ 0.24 (+100%)
J01MB04	Pipemidic acid	1.00 (5.8%)	/	- 1.00 (-100%)
J01XE01	Nitrofurantoin	/	0.15 (0.5%)	+ 0.15 (+100%)
J01B, J01G, J01R	Other antibacterials	0.73 (4.2%)	0.68 (2.3%)	-0.20 (-51%)
J01	**Total**	**17.40 (100%)**	**29.70 (100%)**	**+12.30 (+71%)**

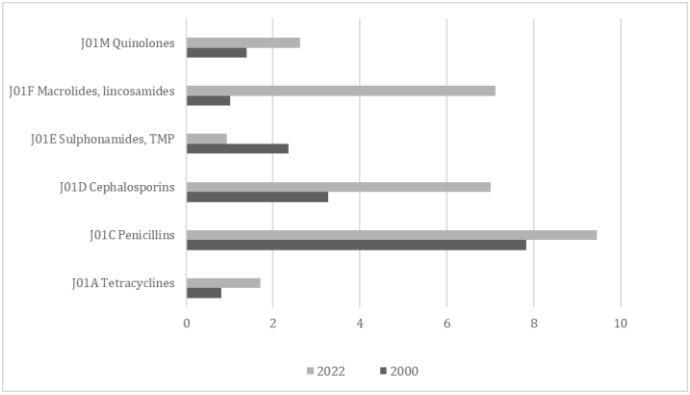

Figure 1.
Outpatient utilisation of ASU in Montenegro according to the third level of ATC classification in 2000 and 2022, in DTID

In comparison to the EU/EEA [9], the outpatient use of almost all ATC sub-groups of ASU was higher in Montenegro, achieving a statistically significant difference in the case of cephalosporins ($p = 0.042$, $p < 0.05$). Only the ATC sub-group J01X (Other antibiotics) had seven times higher utilization in EU/EEA compared to Montenegro (1.00 *vs*. 0.15 DDD) (Figure 2).

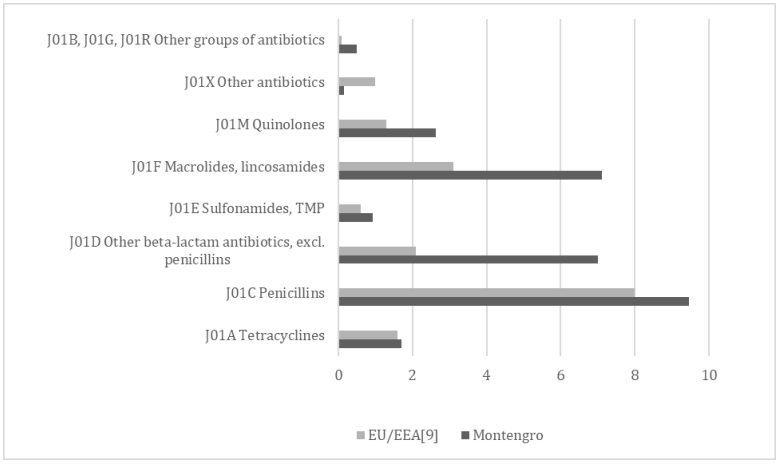

Figure 2.
Outpatient utilisation of ASU in Montenegro and the EU/EEA [9] according to the third level of ATC classification in 2022, in DTID

Ten ASU entered the DU90% in 2000 in comparison to nine in 2022 (Table II). Their order was changed, but without a statistically significant difference in ranks ($p > 0.05$). The outpatient utilisation of these nine drugs (in DTID) in 2022 was 70% higher compared to DU90% in 2000, but also without a statistically significant difference. A statistically significant difference was found between the share

of narrow-spectrum (59 *vs.* 31%) and broad-spectrum ASU (26 *vs.* 64%) in DU90% between 2000 and 2022 ($p < 0.05$). The ratio of the outpatient utilisation of broad- to narrow-spectrum ASU in Montenegro in 2022 was almost 10 times higher than in 2020 (1.96 *vs.* 0.24), but compared to the mean value in the EU/EEA [9], it was two times lower (Figure 3).

Table II

DU90% of ASU in Montenegro (2000 vs. 2022) in DTID and percentages

Ord. No	INN (DTID, %) 2000	INN (DTID, %) 2022
1.	Amoxicillin* (3.98, 23%)	Amoxicillin* (5.79, 20%)
2.	Ampicillin* (2.81, 16%)	Azithromycin** (5.02, 17%)
3.	Cephalexin* (2.49, 14%)	Cefixime** (4.16, 14%)
4.	SMX, TMP** (2.36, 14%)	Amoxicillin, clavulanic acid** (3.42, 12%)
5.	Pipemidic acid** (1.00, 6%)	Ciprofloxacin** (2.39, 8%)
6.	Cefaclor** (0.77, 4%)	Cephalexin* (2.05, 7%)
7.	Doxycycline** (0.64, 4%)	Doxycycline** (1.71, 6%)
8.	Azithromycin** (0.54, 3%)	Clarithromycin** (1.05, 3%)
9.	BP, PBP* (0.47, 3%)	SMX, TMP** (0.94, 3%)
10.	Erythromycin* (0.46, 3%)	/
Total	**15.53 (90%)**	**26.53 (90%)**

Legend:* Narrow-spectrum antibiotic, ** Broad-spectrum antibiotic

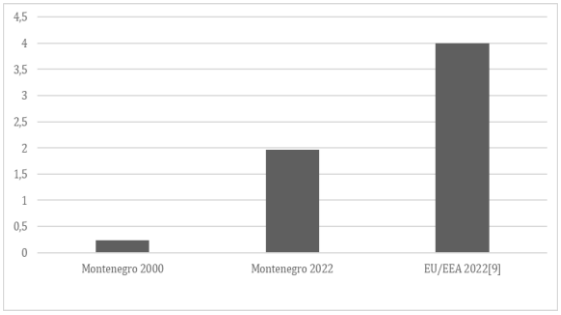

Figure 3.
The ratio of the outpatient utilisation of broad-spectrum to narrow-spectrum ASU in Montenegro (2000 *vs.* 2022) in comparison with EU/EEA [9] in 2022

In 2000, three-quarters of the outpatient ASU used in Montenegro (73%) belonged to the Access group, which was significantly more in comparison to 2022 (50%) (Pearson statistic = 9.6898, $p = 0.0018$; $p < 0.05$). Compared to the EU/EEA average in 2022 (both outpatient and inpatient use) [9], the obtained value was lower (50% *vs.* 60%), but without a significant difference (Pearson statistic = 1.3926; $p > 0.05$) (Figure 4).
The ratio of the outpatient utilisation of Access to Watch ASU in Montenegro decreased for 62% (2.69 *vs.* 1.02) in 2000 - 2022. In comparison to EU/EEA in 2022 [9], it was lower for 31.5%. (Figure 5)

The outpatient use of ASU in Montenegro increased by 71% during a twenty three-year period. In 2022, it was 75% higher compared to the EU/EEA [9], that took us away from the recommended target of reducing the use of these drugs by 20% in the period 2019-2030 [10]. The highest increase was found in macrolides, cephalosporins and quinolones, which were also the groups where the biggest differences (in the case of cephalosporins showing statistically significant difference) between Montenegro and the EU/EEA were observed [9].

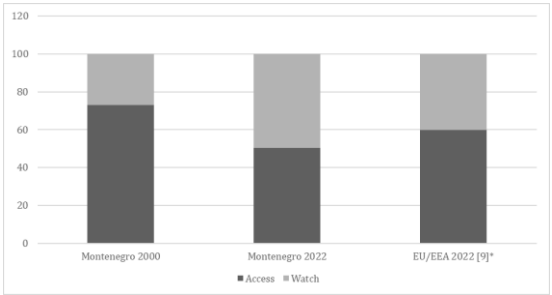

Figure 4.
The share of Access and Watch groups in outpatient utilisation of ASU in Montenegro (2000 *vs.* 2022) in comparison with EU/EEA (2022) [9], in percentages.
* both outpatient and inpatient utilization are included

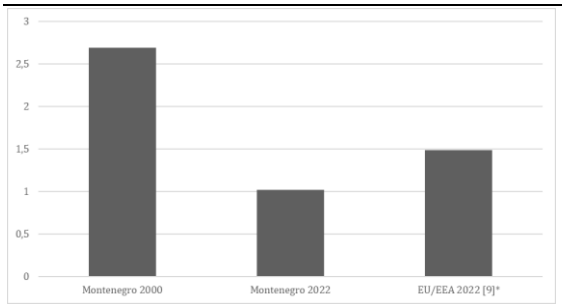

Figure 5.
The ratio of the outpatient utilisation of Access to Watch ASU in Montenegro (2000 *vs*. 2022) in comparison with EU/EEA in 2022 [9]
* both outpatient and inpatient utilization are included

The share of broad-spectrum ASU significantly increased, which was not a favourable trend, but compared to the EU/EEA [9], the ratio of broad- to narrow-spectrum ASU was two times lower in 2022. The participation of Access group significantly decreased in Montenegro from 2000 to 2022, which was lower compared to the EU/EEA average in 2022, where both outpatient and hospital consumption were included [9]. Achieving the EU target of at least 65% Access group share in the next six-year period could be possible, if appropriate measures are implemented on time.

Although it was difficult to find more studies that followed such a long period, the available data from developed countries indicate that during the last ten years a downward trend in the community ASU consumption was found [1, 9, 26], in some cases statistically significant [9]. In contrast to some EU countries, where the outpatient use of ASU also decreased in the period 1997 - 2022 (36.5 *vs*. 22.6 DTID in France, 32.4 to 21.7 DTID in Spain, 28.8 *vs*. 17.1 DTID in Portugal, etc.) [5], in Montenegro it increased by 71% in 2000 - 2022. In Canada, during the nineteen-year period (2000 - 2018), outpatient prescribing of antibiotics decreased by 23% [22]. Our results confirmed an unfavourable trend that ranks Montenegro among the European countries with the highest consumption of ASU and the highest risk of developing AMR at the same time. Of the EU/EEA countries, only Greece had a slightly higher outpatient use of ASU in 2022 than Montenegro [9]. There are several possible reasons for the differences in the outpatient use of ASU between Montenegro and EU/EEA countries. Although there are national guidelines for the treatment of infections in PHC, which don't differ significantly compared to EU/EEA countries, it is questionable to what extent prescribers follow them. Whether due to the possible high incidence of AMR in everyday clinical practice or due to the pressure of patients to prescribe a specific antibiotic, doctors frequently decide to prescribe a broad-spectrum ASU. In Montenegro, family doctors also prescribe ASUs that are previously ordained by specialists from the secondary or tertiary levels of health care (surgeons, urologists, pulmonologists, etc.) as a continuation of hospital treatment or after ambulatory examination. This contributes to more frequent prescribing of ASU in PHC, but also to an increase in the share of broad-spectrum antibiotics. Additionally, the general impression is that in recent decades, information from social networks and similar ways of communication has overcome the trust of a large number of patients in doctors, so the purchase of ASU on a patient's own initiative without a doctor's prescription can't be ruled out, although it is officially prohibited. Similar to the findings from Romania [19], there is also the low level of knowledge of the population regarding the clinical benefits of antibiotics and potential risks of their irrational use. Unfortunately, doctors in PHC are burdened with a large number of patients on a daily basis and with a lot of administrative tasks, so they don't have enough time to devote to patient education on this topic. According to Klein EY *et al*. global consumption of antibiotics in the period 2000-2015 increased by 65%, but in LMICs it reached as much as 114% [15]. A recent study by Ventura-Gabarro *et al*. found a temporary reduction in the outpatient use of ASU in 2020 compared to 2019 in the EU/EEA, but in 2022 there was an increase of 8.4% compared to 2019 in approximately 50% of member states [29]. According to CInMED, the outpatient use of ASU in 2021 increased by 15% compared to 2019 (29.25 *vs*. 25.39 DTID) and remained at approximately the same level a year later [12]. Most likely, COVID-19 increased the already high outpatient utilisation of ASU in our country and additionally moved it away from the EU/EEA target, which implies a reduction in the use of antibiotics in humans by 20% in the period 2019 - 2030 [10].

When it comes to certain INNs, amoxicillin was the most frequently consumed ASU in Montenegro in both 2000 and 2022. This can be considered as expected because it is still the first-choice antibiotic for most infections in PHC [38]. In the UK, amoxicillin was the most commonly prescribed antibiotic in PHC in 2022, but its consumption was markedly less compared to our result (2.69 *vs*. 5.79 DTID) [28]. With approximately 50 million prescriptions, amoxicillin was also the most prescribed oral antibiotic in the USA in 2022 [6]. Broad-spectrum azithromycin moved from eighth place in 2000 to second place in 2022 in Montenegro, while its outpatient use increased tenfold. The explanation of this result could be a favourable pharmacokinetics of this drug, which implies a three-day oral application with one daily

dose that ensures a good adherence, a broad antibacterial spectrum, a lower potential for interactions compared to older erythromycin and clarithromycin, etc. Studies reported an increase in azithromycin use during COVID-19 in some countries [16, 27], which was most likely the situation in Montenegro as well. In the USA, azithromycin was also in second place among all prescribed oral antibiotics in 2022 with a share of 22% [6]. An increase in the outpatient use of this drug decisively influenced the consumption of macrolides in the EU/EEA in 2022 compared to the pre-pandemic period [29]. Significantly higher utilisation of cephalosporins in Montenegro compared to the EU/EEA in 2022 was driven by cefixime, a broad-spectrum oral cephalosporin of the third generation, with a share of 14% in the total outpatient use of ASU. Obtained results require further analysis because this drug is not the recommended first choice in the treatment of PHC infections [38]. Additional attention also deserves the finding that nitrofurantoin was used in a negligible amount in 2022 and SMX/TMP had a downward trend of use because these drugs are considered the first-choice treatment of urinary tract infections in PHC [38]. Most likely, they were replaced by broad-spectrum ASU (such as cefixime, azithromycin and fluoroquinolones), increasing the risk of AMR and other negative consequences. According to the recent results of Rusu A et al. [21], the most common cause of uncomplicated urinary tract infections in women, *E. coli*, is still significantly sensitive to nitrofurantoin in Romania. Although there are no precise data, this is probably the case in Montenegro. For this reason, educational activities should be strengthened to reduce the prescription of broad-spectrum ASU and to promote nitrofurantoin as the first-choice treatment of uncomplicated urinary tract infections.

The share of narrow-spectrum antibiotics in DU90% significantly decreased in Montenegro from 2000 to 2022, mostly due to the increased use of broad-spectrum ones. Amoxicillin retained the first place in DU90 in 2022, with an approximately equal share of about 20% as in 2000. Ampicillin for oral use "lost" its second place in DU90 about twenty years ago [7] because it was removed from the list of reimbursed medicines due to its less favourable pharmacokinetic profile compared to amoxicillin. However, it is worrying that two broad-spectrum ASU, such as azithromycin and cefixime, were in third and fourth positions in 2022 and together made up approximately a third (31%) of DU90. Ciprofloxacin is in fifth position with a share of 8%, which is also very high considering an outpatient setting. This increase in the prescription of broad-spectrum ASU that aren't the first choice in the treatment of infections in PHC is very worrying, primarily due to the risk of accelerated development of AMR. We can only assume what the reasons are. The first one could be the high prevalence of AMR in the first-line ASU recommended by official national recommendations. Also, the favourable pharmacokinetics of both azithromycin and cefixime allow for their once-daily administration, which ensures better adherence compared to antibiotics taken three or four times a day. In addition, once-daily use could be a key factor in patient self-medication, which unfortunately can't be ruled out. Prescribing broad-spectrum ASU can also be a "buying peace of mind" for overburdened prescribers who are more confident that the drug will be effective and that the patient will not come back. A part of these broad-spectrum ASU was ordained on the secondary or tertiary level of healthcare, but the "real prescribing" is done by doctors in PHC. It is interesting that the EU/EEA population-weighted mean ratio of the outpatient utilisation of broad- and narrow-spectrum ASU in 2022 was 4.0 [9], two times more compared to our result. According to the same report, there were significant variations of this ratio among EU/EEA countries (from 0.1 in Norway to 24.7 in Hungary) [9]. With 1.96, Montenegro would be approximately at the level of Belgium, Latvia, Slovenia and Spain [9], but this result shouldn't lead us to the wrong conclusion about the acceptable value of this indicator because the outpatient use of both broad- and narrow-spectrum ASU was much higher in our country. The restrictive-prescribing stewardship implemented in Chinese PHC in 2014 significantly reduced total antibiotic consumption (by 32.58%) but led to an immediate and significant increase in the ratio between broad- and narrow-spectrum antibiotic use, though both had a significant downward trend [37]. The last example indicates that antibiotic stewardship programmes should be carefully designed and implemented, with continuous monitoring of their effectiveness.

According to the EU/EEA recommendations, at least 65% of the total consumption of antibiotics in human medicine by 2030 should be from the Access group [9]. In 2000, nearly three-quarters of the outpatient ASU used in Montenegro belonged to the Access group. This result indicates that almost a quarter of a century ago, we met the current EU/EEA target, but unfortunately, this is not the case now. Klien EY et al. found an upward global trend in the use of Watch antibiotics by 90.9% in 2000 - 2015, compared to an increase of 26.2% in the Access group [14]. The increased consumption of Watch antibiotics was greater in LMICs than in high-income countries. The ratio of the outpatient utilisation of Access to Watch ASU in Montenegro decreased by 62% from 2000 to 2022; that was higher compared to global data for 2000 - 2015 (an average decrease of 38.5%) [14] and

could be explained to some extent by the longer follow-up period. However, based on the results obtained, the reasons for such a significant decrease in the share of the Access group in Montenegro can't be precisely identified, but some of them can be assumed. A careful look at the most frequently prescribed ASU in the period 2000 - 2022 shows that broad-spectrum azithromycin, cefixime and ciprofloxacin were crucial to increasing the share of the Watch group. At the same time, the decrease in the prescription of penicillins, SMX/TMP, cephalexin and pipemidic acid was key in the reduction of the Access group in the total outpatient use of ASU. Possible high incidence of AMR to penicillins, which are still the first choice for the treatment of most infections in PHC, could be a key medical factor for obtained results. It should also be noted here that the high level of AMR, if it exists, is just the consequence of the irrational use of ASU, and in this case, we have a vicious circle from which it will be difficult to escape. The more convenient use of azithromycin and cefixime in one daily dose and ciprofloxacin in two, a broader antibacterial spectrum that, in the case of azithromycin and ciprofloxacin, includes mycoplasma and chlamydia (which increases the likelihood of the effectiveness of empirical therapy), and the impact of COVID-19 on increased prescribing of azithromycin, etc., would be some of the key non-medical factors that influenced the obtained result. It shouldn't be forgotten that patients who practise self-medication also prefer a quick and safe solution that is easier to reach by using broad-spectrum ASU, particularly azithromycin. Achieving the EU target of at least a 65% share of the Access group in the next six years seems quite ambitious now, but it would be acceptable for our country to reach the current EU value by 2030 if appropriate measures are implemented on time. In order to increase the share of the Access group to 65% by 2030, a comprehensive and systematic approach to this issue both at the national and local level is needed. It should include an objective and detailed expert analysis of the current situation, followed by the creation and implementation of appropriate educational, regulatory and organisational measures and activities in order to achieve the set goal. This study has several limitations. A long follow-up period prevented us from finding official, publicly available national statistics on the consumption of ASU in DTID, so we mainly used available literature data. In addition, the applied methodology did not allow for a more detailed qualitative analysis of the utilisation of ASU, including diagnoses, prescribing habits, prevalence of AMR, patient characteristics, etc. By comparing the values of DDD for ASU used in the observed years, we found that only the DDD value for amoxicillin was changed (both as a monocomponent drug and as a fixed combination with clavulanic acid). In 2000, the DDD for both drugs (in the second one calculated on amoxicillin) was 1g, and in 2022 it was 1.5g, which influenced the obtained result related not only to the outpatient use of amoxicillin, but also to the overall outpatient use of ASU, given that amoxicillin was the most commonly used drug in both observed periods. Additionally, the AWaRe classification is not sufficient to assess the quality of ASU and can only be used for a rough, initial assessment at the national level and comparison with other countries, as shown in this study. For a more detailed qualitative assessment of ASU use, it would be necessary to take into account data on the frequency of AMR to individual drugs, ASU prescribing for specific diagnoses and compliance with national guidelines, to analyse separately prescribing by family doctors from prescribing by specialists from secondary and tertiary levels of health care, etc. This study didn’t examine the possible influence of non-medical factors on the use of ASU, such as shortages, registration and reimbursement status, etc.

Conclusions

Based on the obtained results, we can reject the hypothesis that measures applied improved the outpatient use of ASU in Montenegro in the period from 2000 to 2022. Although the increase of ASU consumption was in line with the unfavourable global trend, it was opposite to the majority of EU/EEA countries and requires additional analyses and interventions. When it comes to the outpatient use of ASU, by the end of the first quarter of 21st century, Montenegro had moved away to a considerable extent from the values and targets of the EU/EEA, whose membership it aspires to. Current EU/EEA goals were achieved in 2000, but we abandoned them in the meantime. However, based on the experience of other, primarily developed countries, it can be assumed that EU/EEA targets could be achievable within the next six-year period. The first step should be an objective identification and analysis of existing weaknesses and deviations, that should be followed by the creation and implementation of a comprehensive intervention at different levels to improve the current situation in this area. The results of this study can serve these purposes to a certain extent.

Conflict of interest

The authors declare no conflict of interest.

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