

## Initiatives to reduce non-prescription sales and dispensing of antibiotics in the Republic of Srpska; findings and implications

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### Abstract

Objective: Irrational use of antimicrobials is a major driver of antimicrobial resistance, exacerbated by dispensing antibiotics without a prescription. Our previous study suggested this was a problem in the Republic of Srpska despite legislation. Since then, a number of activities have been initiated. Consequently, the study aimed to ascertain whether these multiple initiatives had reduced this. Methods: Patients visiting all community pharmacies in the Republic from October 2014 to July 2015 presenting with symptoms typical of an acute, viral and mostly uncomplicated upper respiratory tract infection, with results compared to the previous study. If an antibiotic was suggested, the maximum allowance was Euro 3/ pack. Findings: Self-medication with antibiotics significantly decreased from 58% to 18.5% of pharmacies. In both studies, most patients were offered over-the-counter medication. The most common reason for not dispensing an antibiotic was ‘antibiotics can be dispensed with a prescription only’. The penicillins were the most dispensed antibiotic. Fewer patients than the previous study were given instructions about antibiotic use and no discussion on their side-effects. Conclusion: Whilst encouraging that self-medication decreased significantly, 18.5% was disappointing given recent initiatives. Fewer instructions about antibiotics if an antibiotic was dispensed was also disappointing. This suggests the need for even stronger enforcement of the laws as well as further training of pharmacy personnel to ensure future appropriate use of medicines.

Key words: antibiotics; antibiotic resistance; pharmacies; non-prescription sales; Republic of Srpska

## Introduction

Irrational use (misuse) of antimicrobials is a major driver of antimicrobial resistance (AMR), increasing morbidity, mortality and costs [1]. This has resulted in a range of activities across countries and continents to raise its importance and reduce inappropriate antibiotic use [2]. The International Pharmaceutical Federation encourages pharmacists to improve their dispensing of antibiotics to reduce AMR rates in the future. Through a process of triage, pharmacists should evaluate what treatment approaches they should suggest for patients with upper respiratory tract infections (URTIs) [3], reflecting their unique position as one of the most accessible health professionals to promote health and well-being of patients [4]. This should not involve recommending an antibiotic as the vast majority of URTIs are viral in origin [1,5].

The misuse of antibiotics includes dispensing an antibiotic without a prescription, particularly important for URTIs [1,5]. This is illegal in most countries, referred to as self-medication with antibiotics; not to be confused with the legal selling over-the-counter (OTC) medicines [4]. Despite concerns, this practice is still seen worldwide [6]. Predisposing factors towards self-medication with antibiotics include their high perceived appropriateness, ease in obtaining them in some settings, patient attitudes favouring them for minor complaints, and the behaviour of some health care professionals [7].

The Republic of Srpska is one of two constituent entities in Bosnia and Herzegovina (B&H), with a population of 1.4 million. All pharmacists can dispense prescription only medicines (POMs) written by a physician or dentist. No pharmacist by law should dispense a POM without a prescription written by either a physician or dentist. Antibiotics are restricted to POMs in B & H [8], and medicines can only be dispensed without a prescription if designated as such, i.e. an OTC medicine. There are various fines if the laws are violated, including Euro500-1500 for pharmacy directors and Euro500-750 for pharmacy technicians. The Republic of Srpska Inspectorate is the responsible institution for supervising implementation of this legislation.

The role of community pharmacists in promoting pharmaceutical care is well recognized in the Republic of Srpska [9]. It implies professional communication with patients to deliver high-quality medicines and service. Consequently, pharmacists are expected to be health educators, with such behavior endorsed in their Code of Ethics [10]. It is expected that pharmacists will embrace the Code and be responsible for propagating the profession's core values to deliver high quality care.

However, despite these laws, endorsement of pharmacists' roles and possible fines, our 2010 study showed self-medication with antibiotics occurred in 58% of visits [11]. Since then, a number of activities have taken place to raise awareness of AMR and enhance the prudent use of antibiotics (Table 1).

**Table 1.** Activities in the Republic of Srpska in recent years to try and enhance the prudent use of antibiotics

| Groups  | Summary of activities  |
|---|--|
| Nationally (including all key stakeholder groups) | <ul style="list-style-type: none"> <li>• In 2010, initiating activities in accordance with the Law on Protection of Population from Infectious Diseases [12], with the goal of implementing regional policies and action plans to enhance antibiotic use</li> <li>• Since 2013, Antibiotic Awareness Day every year in November</li> <li>• National campaigns raising awareness about the risks associated with AMR and inappropriate use of antibiotics among all stakeholder groups</li> <li>• Regular “Rational use of antibiotics today, more efficient health protection tomorrow” workshops for health professionals</li> <li>• Posters and flyers depicting concerns with self-medication with antibiotics</li> <li>• Public awareness about antibiotics and the increased risk of AMR through television programs and newspapers</li> <li>• National Committee for Resistance Control to Antimicrobial Medicines established at the Ministry (2015)</li> <li>• Rational use of medicines including antibiotics defined by National Medicines and Policy Medicines Program from 2013</li> <li>• In 2016, instigating a national Program to reduce AMR in the Republic lasting to 2020 [13]</li> </ul> |
| Pharmacists (specific)                            | <ul style="list-style-type: none"> <li>• In 2013 - the Pharmaceutical Association of the Republic of Srpska launched the ‘The Guideline for counselling patients in the pharmacy’ [14]. The aim is to help pharmacy personnel make decisions whether they can successfully treat the patient with non-pharmacological measures and/or with OTC medicines, or whether the patient needs to be referred to another health care professional</li> <li>• Special attention given to the importance of adequate communication and skills. Forty two of the most frequent diseases and conditions in pharmacist’s everyday practice were described including a diagnostic-therapeutic algorithm for the treatment of a common cold.</li> </ul>   |

Consequently, we wanted to study whether these multiple initiatives had resulted in reduced antibiotic self-medication since 2010 [11]. As a result, we sought to firstly determine whether, and to what extent, self-medication with antibiotics was still practiced; secondly, compare the results with 2010 [11], and lastly comment on the results and their implications for future initiatives.

## Methods

We employed the same methodology as before [11]. Consequently, this was an observational, cross-sectional study. In order to determine whether it was possible to obtain an antibiotic without a prescription for the treatment of a self-diagnosed URTI from community pharmacies, pseudo-patients were used. Using pseudo-patients is a well-recognized technique to reliably assess community pharmacy behaviour when presented with a need for treatment [15]. From now on, a patient is the pseudo-patient, i.e. person who pretended to be a patient. As part of the project, patients also assessed the level of professional services provided by pharmacy staff such as clear packet labelling and dosing instructions.

All community pharmacies across all regions (49 towns) were visited by patients from October 2014 to July 2015. Patients, who were not health professionals, were trained to

approach pharmacy staff, present with symptoms of a sore throat, runny nose, nasal congestion, mild cough and fatigue without elevated body temperature, and end with the question "... if an antibiotic could be given." These symptoms of an acute, viral and mostly uncomplicated URTI are not expected to be treated with an antibiotic [16]. Additional predefined information, provided only if asked, included the absence of other medical problems including penicillin allergy, the frequency of similar episodes ("not very often"), the duration of symptoms ("2-3 days") and previous experience with antibiotics ("yes but do not know which one"). Patients were advised neither to ask for a particular antibiotic nor to insist if an antibiotic was refused in order not to influence any pharmacist activity. If antibiotics were suggested, patients had up to three Euros per pack to spend, and to refuse symptomatic therapy if offered.

Clear and legible instructions written on the surface of the packages dispensed regarding oral dosing over 24 hours, and the dosage interval, e.g. three times daily, was rated as adequate. The lack of any of such data was considered as inadequate instructions. It was expected that no antibiotics would be dispensed, while appropriate counselling on potential treatment approaches would be provided. As seen in Table 1, the Guideline for counselling patients in the pharmacy gives a detailed guide on how pharmacy personnel can provide professional care for such patients [14].

The study was approved by the Ministry of Health in the Republic of Srpska. All project information has been kept by the main author's department (VM-P) within the Ministry of Health and Social Welfare. It was not passed to the Republic of Srpska Pharmacy Inspectorate as our objective was to ascertain whether self-medication with antibiotics still exists rather than potentially fine pharmacy personnel for any illegal behaviour. A report was completed by the patients after each pharmacy visit on a pre-designed form to facilitate reporting and data processing. The form had been validated as part of the previous study.

The analysis involved descriptive quantitative statistics, such as percentages. Pearson's chi-squared test with Yates' continuity correction using 2×2 contingency tables was used to compare the categorical variables from the present study with that of the study conducted in 2010. Where more than 20% of the expected cell frequencies were less than 5, we used Fisher's exact test. Cramér's *V* statistic was used for testing practical significance of these associations, with values of 0.1 regarded as a small effect, 0.3 as moderate effect and 0.5 as large effects. For statistical inference, a two-sided *p*-value less than 0.05 was accepted. Statistical analyses were performed using SAS software, version 9.4 (SAS, USA).

## Results

All 383 community pharmacies within the Republic of Srpska were visited. Antibiotics were dispensed without prescription at 71 pharmacies (18.5%) regardless of whether symptomatic therapy was offered (Table 2). This compares to 58.0% in 2010. Pearson's chi-square test used to examine the association between the prevalence of antibiotic dispensing and symptomatic therapy ( $\chi^2 = 72.58$ ,  $df=1$ ,  $p < 0.05$ ) was found to be statistically significant; with a moderate to large effect (Cramér's *V* = 0.38).

**Table 2.** Comparison of key characteristics in 2015 versus 2010

| Characteristic  | Study 1 (2010) | Study 2 (2015) |
|---|----------------|----------------|
| 1. Total number of pharmacies included, N               | 131            | 383            |
| 2. Antibiotic dispensed without a prescription          | 76 (58.0)      | 71 (18.5)      |
| 3. Symptomatic therapy:                                 |                |                |
| 3.1. Offered  | 88 (67.2)      | 277 (72.3)     |
| 3.1.1. offered and antibiotic dispensed                 | 43 (48.9)      | 38 (13.7)      |
| 3.2. Not offered  | 43 (32.8)      | 106 (27.7)     |
| 3.2.1. not offered and antibiotic dispensed             | 33 (76.7)      | 35 (33.0)      |
| 4. Neither antibiotic nor symptomatic therapy dispensed | 10 (7.6)       | 71 (18.5)      |
| 5. Antibiotic dispensed:                                |                |                |
| 5.1. Patient information given:                         |                |                |
| 5.1.1. Written  | 59 (77.6)      | 36 (49.3)      |
| 5.1.2. Oral   | 72 (94.7)      | 46 (63.0)      |
| 5.1.3. Both   | 57 (75)        | 31 (43.7)      |
| 5.1.4. None   | 2 (2.6)        | 21 (28.8)      |
| 5.2. Patient asked about penicillin allergy             | 59 (77.6)      | 45 (64.3)      |
| 5.3. Patient asked about taking other medicines         | 19 (25)        | 16 (22.5)      |
| 6. Type of antibiotic dispensed:                        |                |                |
| 6.1. Amoxicillin  | 65 (85.5%)     | 57 (80.3%)     |
| 6.2. Ampicillin   | 5 (6.6 %)      | 9 (12.7%)      |
| 6.3. Cefalexin  | 2 (2.6%)       | 3 (4.2%)       |
| 6.4. Azithromycin                                       | n/a            | 1 (1.4%)       |
| 6.5. Amoxicillin and enzyme inhibitor                   | n/a            | 1 (1.4%)       |
| 6.6. Doxycycline  | 4 (5.3%)       | n/a            |

Data are presented as Number (%). Study 1 = previous study performed by Marković-Peković et al [11]; Study 2 = present study results; n/a = not applicable.

In both studies, OTC therapy to alleviate symptoms were offered in 67.2% of pharmacies in 2015 compared with 72.3% in 2010 ( $\chi^2 = 1.02$ ,  $df=1$ ,  $p=0.262$ ; Cramér's  $V=0.05$ ). This included throat and nasal sprays, decongestants, oral expectorants, antihistamines and analgesics. In the present study, among pharmacies were OTC medicines were offered, significantly fewer dispensed an antibiotic without a prescription ( $n = 36$ , 13.0%) compared to 43 (48.9%) in 2010 ( $\chi^2 = 48.57$ ,  $df=1$ ,  $p < 0.05$ ; Cramér's  $V=0.37$ ). A total of 106 pharmacies in the present study (27.7%) that did not offer symptomatic therapy in the form of OTC medication compared with 32.8% in 2010. Amongst these, an antibiotic was dispensed without a prescription in 33.0% of pharmacies compared to 76.7% in 2010 ( $\chi^2 = 21.85$ ,  $df=1$ ,  $p < 0.05$ ; Cramér's  $V=0.40$ ) (Table 2).

At pharmacies that refused to dispense an antibiotic without a prescription, the most common explanation given was that “an antibiotic can be dispensed with a prescription only” or “an antibiotic cannot be dispensed without a prescription”, followed by an explanation that the presented symptoms were of a minor disease or a viral origin requiring no treatment with an antibiotic (Table 3). Patients were also advised they should consult their doctor, explaining that an antibiotic cannot be dispensed without a consultation.

**Table 3.** Explanations by pharmacy staff when refusing to dispense an antibiotic

| Explanations of the pharmacy staff   | Study 1 (2010) | Study 2 (2015) |
|--|----------------|----------------|
| Antibiotics cannot be dispensed without a patient's consultation with a doctor | 24 (43.6%)     | 5 (1.6%)       |
| Antibiotics can be dispensed with a prescription only                          | 23 (41.8%)     | 282 (91.0%)    |
| Antibiotics cannot be dispensed without a prescription                         | 8 (14.6%)      | 19 (6.1%)      |
| Antibiotics unnecessary as presented symptoms of a minor disease               | n/a            | 3 (1.0%)       |
| Antibiotics unnecessary as presented symptoms of a viral origin                | n/a            | 1 (0.3%)       |
| Total (N)  | 55             | 310            |

NB: Data are presented as Number (%). NB: Study 1 = previous study performed by Marković-Peković et al [11]; Study 2 = present study results; n/a = not applicable.

Amoxicillin (80.3%), ampicillin (12.7%) and cefalexin (4.2%) were the antibiotics mostly sold in the present study when an antibiotic was dispensed (n=71) (Table 2), with prices ranging from €1.3 to €2.5 per pack. The average cost per pack in 2015 was €1.79 +/- 1.18 versus €1.51 +/- 0.39 in 2010, which differed significantly ( $p < 0.05$ ). However, the effect size (Cohen's d) was only 0.2; consequently, in practice no difference. Both azithromycin (€8) and co-amoxiclav (€8.50) were offered once. In 2010, amoxicillin was most often dispensed (85.5%), followed by ampicillin (6.6%) and doxycycline (5.3%) (Table 2). There was no association between the type of antibiotic dispensed and the study period ( $p = 0.1732$  Cramér's  $V = 0.23$ ). In both years, the best-selling amoxicillin was made by the local manufacturer Hemofarm (part of Stada Group), priced at €1.30 per pack.

The results showed significantly fewer patients were given oral instructions regarding their antibiotics in 2015 compared to 2010 (64.8% vs. 94.7%, respectively) ( $\chi^2 = 18.94$  df=1,  $p < 0.05$ ; Cramér's  $V = 0.38$  (Table 2). This was also apparent for written instructions, where significantly fewer patients in 2015 were given such instructions compared to 2010 (50.7 vs. 77.6%, respectively) ( $\chi^2 = 10.49$  df=1,  $p < 0.05$ ; Cramér's  $V = 0.28$ . Of the written instructions, 65.7% were rated as adequate, 11.4% adequate but illegible and 22.9% inadequate (data not shown). In 2010, written instructions varied from illegible and accurate to clear and accurate. In addition, significantly fewer patients were given both oral and written instructions for use in the present study compared to 2010 (45.1 vs. 75%, respectively) ( $\chi^2 = 13.77$ , df=1,  $p < 0.05$ ; Cramér's  $V = 0.31$ ) whereas significantly more patients (29.6) received no instructions for use compared with 2010 (2.6%) (Table 2) ( $\chi^2 = 18.20$  df=1,  $p < 0.05$ ; Cramér's  $V = 0.37$ ).

When patients were dispensed an antibiotic without a prescription, they were only asked about taking medicines for other conditions on 22.5% of occasions, down from 25% in 2010 ( $\chi^2 = 0.03$ , df=1,  $p = 0.726$ , Cramér's  $V = 0.03$ ). A history of allergy to penicillin was asked on 64.3% of occasions, although down though from 77.6% in 2010 ( $\chi^2 = 2.55$ , df=1,  $p = 0.075$ , Cramér's  $V = 0.15$ ).

## Discussion

Antibiotics could still be purchased without a prescription; however, significantly down from 2010 at 19.1% of pharmacies versus 58% (Table 2). This was expected to be lower given the multiple initiatives and potential fines. Encouragingly, in more than two thirds of pharmacies, symptomatic therapy with appropriate advice was offered, an increase compared to 2010 (Table 2). Consequently, we believe that professional standards are mostly adhered to [9, 14]. However, we would expect symptomatic therapy to be offered in every case, building on the pharmacists' professional knowledge and skills, with additional support of the nationwide Guideline for counselling patients (Table 1).

Most pharmacists or technicians who dispensed an antibiotic, offered a broad-spectrum antibiotic but not an expensive one, contrary to other studies [17]. However, patients were faced with having to refuse an antibiotic on the grounds of cost when azithomycin and co-amoxiclav were offered. It is possible that such an approach was chosen as pharmacy personnel are aware of the financial capabilities of their patients who they were unwilling to lose. This is evidenced by the limited number of patients who refused to buy an expensive antibiotic when offered. However, further research on this issue is needed. Narrow-spectrum penicillins were not offered at all, although they are available, which again may be due to cost issues.

Disappointingly, significantly fewer patients were given oral instructions (63% vs. 94.7%); significantly fewer given written instructions (49.3% vs. 77.6%); and significantly fewer both oral and written instructions in 2015 vs 2010 (Table 2). Significantly more patients in 2015 also received no instructions regarding the antibiotics sold versus 2.6% in 2010, which is disappointing. Such behavior may be due to a desire by pharmacy personnel to leave no trace to avoid potential fines. Alternatively, negligence, lack of interest in the patient and/or the assumption that patient already knows how to use the medicine. Whatever the reason, each represents unacceptable behavior, which should be investigated further.

A comprehensive instruction should also include information about possible side-effects of any dispensed medicine. However, none of the patients reported such information being discussed. Encouragingly in most of cases of an antibiotic being sold, patients were asked about a history of penicillin allergy. Disappointingly, information about other medicines was only asked in a quarter of cases of a sold antibiotic, similar to 2010 (Table 2). These areas of concern need to be improved alongside greater enforcement of fines to improve future antibiotic use and reduce AMR.

In conclusion, non-prescription dispensing of antibiotics still occurs in the Republic of Srpska; however, at a significantly lower rate than before. Consequently, we believe intensified multiple activities included multiple activities among pharmacists have improved antibiotic use. This is similar to other studies which showed multifaceted programmes reduce inappropriate prescribing and dispensing of antibiotics [5,18], and should be continued.

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## Conflicts of Interest

We accept that the main author is employed by the Ministry of Health. However we have sought to reduce potential conflicts of interest to ascertain the current situation in the Republic of Srpska. The other authors declare they have no conflicts of interest to declare. There was no financial support for this study.

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