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PHARMACOECONOMICS

Analysis of evidence supporting the Federation of Bosnia and Herzegovina reimbursement medicines lists: role of the WHO Essential Medicines List, Cochrane systematic reviews and technology assessment reports

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Abstract
Purpose We compared recently introduced Basic Medicines Lists of the Federation of Bosnia and Herzegovina (BH) (FBH Basic Lists (FBLs)) with the World Health Organization (WHO) Essential Medicines List (EML) and the evidence supporting the inclusion of additional medicines on FBLs.
Methods The sources of data included the 18th edition of the EML and the following FBLs: 2013 Hospital List, 2013 A List in Outpatient Setting, and 2012 List financed by the Federal Solidarity Fund. For medicines found on FBLs but not on EML, we searched the Cochrane Database of Systematic Reviews (CSR) and public health technology assessment (HTA) reports for evidence.
Results FBLs had 134 medicines and 17 combinations that were not on EML, as well as 9 medicines deleted and 4 rejected from EML. EML had 82 medicines and 10 combinations of medicines not included in FBLs. Out of 125 medicines on FBLs but not on EML, 52 (42 %) had good CSR evidence supporting their inclusion (n=38) or exclusion (n=14). For the rest (n=74), we found 24 favourable HTA reports. For the total of 89 medicines (27 %) listed on FBLs, we found no evidence (EML, CSR, HTA reports) good enough to justify their inclusion in FBLs.
Conclusions In circumstances of scarce financial resources, greater reliance on well-established, proven list is crucial. Independent, unbiased, high-quality evidence such as WHO EML, CSR and HTA reports (national or international with local adaptations) should be used when deciding on medicine reimbursement.

Keywords WHO · Essential medicines · Cochrane · Systematic reviews · HTA · Disinvestment

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Introduction

Pharmaceuticals are indispensable for the health system because they can reduce morbidity and mortality rates and improve the quality of life by complementing other types of health care services. As a key component of any health system, medicines are not only used to treat diseases but have important social, psychological and political functions [1]. Access to health care and essential medicines is increasingly being viewed as a fundamental human right [2]. Regardless of their size and wealth, health care systems around the world are under constant pressure to rationalize the use of medicines, as well as many other items, because there are no infinite resources to satisfy all health needs of their citizens [3]. The less money there is, the bigger the bids and harder the choices.

Most developed countries have a well-established transparent, multidisciplinary, evidence-based health technology assessment (HTA) process for supporting reimbursement decision [4]. In countries without official sustainable mandatory HTA process in place, reimbursement decisions are based mainly on the appraisal process of different committees in Health Insurance Funds or Ministries of Health.

In many low and middle-income countries, national medicines lists are set up based on the World Health Organization's

(WHO) Essential Medicines List (EML). When the first WHO EML was published in 1977, it was described as a peaceful revolution in international public health [5]. The WHO EML is based on the premise that some medicines are more useful than others and that any essential list should satisfy 85 % of the basic health needs of all residents in any country in the world [5]. Essential medicines are those that meet priority health care needs of the population [6] and are selected regarding their public health importance, efficacy and safety and comparative cost-effectiveness. Essential medicines are supposed to be available at all times in adequate amounts, in appropriate dosage forms, with assured quality and adequate accompanying information and sold at a price that both patients and health care providers can afford [7].

The current versions are the 18th WHO Essential Medicines List and the 4th WHO Essential Medicines List for Children, both updated in April 2013 and revised in October of the same year [6]. The WHO Expert Committee on Selection and Use of Essential Medicines holds meetings every two years to review the latest scientific evidence on the efficacy, safety and cost-effectiveness of medicines, aiming to revise and update the WHO Model List of Essential Medicines for both adults and children.

Since the usefulness of applying essential medicines' principles has already been demonstrated in different geographical and political settings, from the USA and Mexico to Libya and Croatia [8–11], the aim of our study was to compare recently introduced national Basic Medicines Lists of the Federation of Bosnia and Herzegovina (FBLs) with the WHO Essential Medicines List (EML) and the evidence supporting the inclusion of additional medicines on FBLs.

Methods

Study setting

Bosnia and Herzegovina is a country in Southeast Europe, which suffered terrible destruction in the war between 1992 and 1996 and is still deeply divided and politically unstable, struggling with post-communist socioeconomic transition. At the moment, there is no separate national medicines list or insurance coverage list, but there are 13 official public insurance funds which reimburse medicines in Bosnia and Herzegovina (BH): the Insurance Fund of Republika Srpska, Insurance Fund of Brčko District, Federal Solidarity Fund and 10 Cantonal Insurance Funds in the FBH. A detailed description of medicines reimbursement system is presented in the Supplementary document.

Data sources

We used the following data sources: the 18th edition of WHO Model List of Essential Medicines from 2013 and the List of Medicines Mandatory in Health Insurance System of FBH compiled in the same year, as well as The Decree on the List of Medicines publicly available at the website of the Federal Fund that finances and reimburses the so-called "*expensive medicines*" in the FBH. All three lists are publicly available online: on the official WHO sites [7], the official website of the FBH Ministry of Health [12] and the official website of the FBH Institute of Health Insurance [13]. The specialized terminology on all three lists follows the International Nonproprietary Names (INN, generic names) for medicines [14].

In the WHO Model List, medicines and medical products are divided in 29 therapeutic classes. Some medicines are marked with the square box symbol (□) as representative medicines for a clinically equivalent pharmacological class. For the purpose of this study, whenever a medicine was listed on the Essential Medicines List with a square box, the same pharmacological class was considered to be listed on the Essential Medicines List. We searched the core WHO EML, which is a list of minimum medicine needs for a basic health care system [6], as well as the complementary list, which presents essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, specialist medical care and/or specialist training are needed.

The Anatomical Therapeutic Chemical (ATC) Classification System [15] was used for the classification of medicines in both lists. The list of mandatory medicines in Health Insurance System of the FBH consists of two documents: the List of Medicines used in Outpatient Settings, with the A list (a mandatory list, 100 % reimbursed; n=147 medicines) and the B list (partially reimbursed medicines, for cantons with sufficient resources, n=86 medicines); and the List of Medicines in Hospital Settings (n=153 medicines), which consists only of parenteral formulations. The list of medicines mandatory in Health Insurance System of the FBH consists of generic names of the medicines [12]. For the purposes of this research, we analysed: the List A of Medicines in Outpatient Settings, the List of Medicines in Hospital Settings and the "expensive medicines list", collectively called the FBH Basic Lists (FBLs).

According to the report on expenditure in 2012 given by medicines and medical products of Bosnia and Herzegovina [16], nine ATC classes represented 95 % of the total medicines expenditure in BH: (1) C (cardiovascular) class, (2) A (gastrointestinal and metabolism), (3) N (nervous system), (4) L (cancer medicines) class, (5) B (blood), (6) J (systemic infections), (7) R (respiratory) class, (8) M (musculoskeletal) and (9) G (urogenital) class. Medicines from these nine ATC classes from the FBLs were compared to the WHO EML list. The medicines from ATC classes D (dermatologicals), H (systemic hormonal preparations), P (antiparasitic products), S (sensory organs) and V (various) were not analysed because they contribute only 5 % to the total medicine cost in the FBH. Medicines on the non-mandatory, B list and the special programme Solidarity Fund list were also excluded from the analysis.

Comparison between the WHO model list and FBLs

Medicines on FBLs were compared to the WHO EML to identify the following: (1) medicines shared by both lists (with or without differences in the dose, formulation and/or indication), (2) medicines listed only on the WHO EML and (3) medicines listed only on FBLs. Also, we searched Comparative Table of Medicines on the WHO EML from 1977 to 2011 [17], and whenever a medicine listed on current FBLs was identified as finally rejected of deleted in 2011, we searched the Technical Support Series (WHO report) [18], for the available reference to the EML medicine inclusion (deletion or rejection).

Evidence base for medicines present only on the FBLs

For those medicines included only in the FBLs, we first looked for an evidence base supporting their inclusion as effective interventions for specified indications. We used the Cochrane Database of Systematic Reviews as a source of the best quality guidelines for clinical practice [19]. We searched the Cochrane Summaries using the search strategy which included the generic name of the targeted medicine (INN) in title, abstract and keywords. From the offered list of articles, we analysed the full text of the most recent update of the retrieved systematic review.

Evidence base for medicines present on the FBLs but without supporting Cochrane systematic reviews

For medicines without a supporting CSR we searched the Centre for Reviews and Dissemination (CRD), University of York (National Health Service-NHS, National Institute for Health) website (http://www.crd.york.ac.uk/CRDWeb/) in order to find good evidence for including medicines in the national essential medicines list. We used INNs in "*any field*" and set methodological filters for "*published HTA reports*".

Results

Comparison between the WHO model list and FBLs

The medicines from 9 ATC classes on the FBLs (130 in A List of Medicines in Outpatient Setting, 130 in List of Medicines in Hospital Setting and 116 in the expensive medicines list) were compared. There was an overlap of 42 among 376 medicines on all three lists, so the total number of actually analysed medicines from the FBH lists was 334.

The 2013 WHO EML (core and complementary) contains 476 (414 unique) medicines. After excluding medicines without ATC code (n=28) and those from D, H, P, V and S ATC classes, the final study sample comprised 269 medicines. One third of these WHO EML medicines (n=89, 32 %) were not registered for the use in BH and underwent a special procedure of import, reducing the accessibility of a medicine. There were 124 medicines present in both lists (46 % of the WHO EML and 37 % of the FBLs). The FBLs contained 34 (27 %) medicines from the WHO EML with the same dose, formulation and indication; 54 (44 %) medicines had a different dose specified; 14 (11 %) differed in their formulation and only one (1 %) had a different indication (Table 1).

The WHO EML had 82 individual medicines and 10 combinations of those medicines (28 %) that were not on the FBLs (Table 1). These were mostly from the group of infectious disease medicines (predominantly antituberculosis and antiretroviral medicines; Table 1), with 35 medicines and 5 combinations that were listed only on the WHO EML (38 % of all medicines on the EML but not on the FBLs).

The FBLs had 134 medicines (and 17 medicine combinations) that were not on the WHO EML (Table 1), making 41 % of all the FBLs medicines. The most significant differences were for cancer medicines (n=39, 25 % of the medicines found only on the FBLs, predominantly non-classified cytostatics), cardiovascular (n=22, 15 %, mostly angiotensin-converting enzyme (ACE) inhibitors) and central nervous system (n=20, 13 %, mostly antipsychotics, opioid analgesics, antiepileptic medicines, antidepressants and anaesthetics).

While FBLs did not contain cheap and effective analgesic-antipyretic such as paracetamol, not even in child-friendly forms such as oral liquids or suppositories, present in the EML, it covered a number of combinations of antihypertensive medicines.

Additionally, we found nine medicines on the FBLs that had been already deleted from the WHO EML, mainly because of a lack of evidence for their efficacy and safety and also due to the fact that there are other safer and more effective medicines (Table 2). We also found four medicines on the FBLs that had been rejected from the WHO EML (Table 2), all four of them affecting the central nervous system.

Evidence base for medicines present only on the FBLs—comparisons with CSRs

We used CSRs in order to find a supportive evidence for reimbursement of medicines on FBLs but not on WHO EML (a total of 124 medicines, excluding combination of medicines, were deleted or rejected from the EML). We considered an evidence good enough to justify their inclusion in FBLs as same or more benefits as other medicines, same or more benefits as other medicines but substantial side effects and overview (both medicines with an overview had favourable reviews).

For 38 (31 %) out of the 124 medicines, we identified an additional evidence which could justify their inclusion in the

Table 1 Comparison of the FBH basic list of medicines (FBLs) from the Federal A list of essential medicines in outpatient setting, federal list of essential medicines in hospital health care setting and "the expensive" medicine list with the WHO essential medicines list (EML)*

Finding	CV	CNS	GI	ONCOL	INF	BLOOD	RESP	MS	UG	Total
ATC code	C	N	A	L	J	B	R	M	G	
No difference	2	5	6	10	3 (1)	6	0	0	1	33 (1)
Different dose and/or indication and/or formulation	13	21	13	15	34 (6)	12	3	2	3	116 (6)
Only on EML (in combinations)*	6 (0)	8 (0)	15 (0)	4 (0)	35 (5)	3 (0)	6 (0)	1 (0)	4 (5)	82 (10)
Only on FBLs (in combinations)*	16 (4)	17 (3)	18 (0)	38 (1)	5 (1)	12 (4)	11 (3)	7 (0)	10 (1)	134 (17)
Total	37 (4)	51 (3)	52 (0)	67 (1)	77 (13)	33 (4)	20 (3)	10 (0)	18 (6)	365 (34)
FBLs, deleted from EML	2	0	2	1	1	1	2	0	1	9
FBLs, rejected from EML	0	4	0	0	0	0	0	0	0	4

*Disease groups: *CV* cardiovascular, *CNS* central nervous system, *GI* gastrointestinal, *ONCOL* oncological, *INF* systemic infection, *B* blood/hematopoietic, *RESP* respiratory, *MS* musculoskeletal, *UG* urogenital

FBLs (Table s1). The largest amount of favourable evidence was found for cancer medicines (18 out of 38, 47 %). For 24 medicines (19 %), we found enough high-quality evidence of their efficacy and safety (Table s1). Adequate CSRs were found to support the efficacy of 12 medicines (10 %), but with substantial safety issues, such as serious side effects.

For 86 medicines (69 %), we could not find a sufficient evidence supported by CSRs to recommend their use for various reasons. In some cases, there were no available CSRs on the medicine itself or relevant disease (n=37, 30 %) at all, or the retrieved systematic reviews were still in the protocol phase (n=5, 4 %). We identified completed CSRs on some of the considered medicines, but the findings were unfavourable regarding their inclusion in the reimbursement list, either due to a lack of substantial evidence for drawing a conclusion about a specific medicine (n=26, or 21 %), ineffectiveness or fewer benefits than other medicines (n=9, or 7 %), or less effective than its alternatives, with more side effects (n=4, or 3 %). For 4 medicines (3 %), CSRs emphasized suspected underreporting of side effects and likely bias because of pharmaceutical industry funding. One medicine (tamsulozin) had a CSR withdrawn until the update.

Overall, out of 124 medicines given on the FBLs but not on the EML, 51 medicines had acceptable CSR evidence either on their inclusion (n=38) or exclusion (n=13) from the reimbursement list.

Evidence base for medicines present only on the FBLs—comparison with published HTA reports

For the rest of 73 medicines for which there was no evidence, either on the WHO EML or on CSRs, that would be good enough to justify either their inclusion or exclusion from the FBLs, we extended our search to CRD (Table s2).

We found either full HTA reports or bibliographic records for 21 (29 %) medicines with an evidence that was good enough to justify their inclusion in a reimbursement list: 7 were made by the All Wales Medicines Strategy Group (AWMSG), 4 by the Canadian Agency for Medicines and Technologies in Health (CADTH), 4 by the National Institute for Health and Care Excellence (NICE), 2 by the Instituto de efectividad clinica e sanitaria (IECS), 2 by the Corvinus University Budapest, 1 by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG) and 1 the by Agency of Healthcare Research and Quality (AHRQ).

We could not interpret HTA reports for 41 (56 %) medicines, reasons varying from no available published HTA reports for 33 (45 %) medicines, language barrier (not even an abstract in English) which made conclusion making impossible for 2 (3 %) or only bibliographical record available for 6 medicines (8 %).

For the rest of 32 medicines, we found a favourable evidence for medicine inclusion in a reimbursement list for 11 (15 %) drugs. These were classified as "same" or "effective" in Table s2. There were n=13 (18 %) medicines which were labelled as an "option in specific clinical situations", "specialist only prescribing" or the ones with "restricted use". For 5 (7 %) medicines, HTA reports had conclusions on "not enough evidence", "limited" or "inconclusive evidence". A very unfavourable evidence regarding reimbursement, such as "not approved", "cannot be endorsed" and "not superior but expensive" was found for 3 (4 %) medicines.

Discussion

The results of this study demonstrated the usefulness of the WHO EML, CSRs and HTA reports in assessing an evidence for reimbursement of medicines given on the BH national basic medicines list. Out of 334 medicines listed on the FBLs, 151 were not included in the EML and 38 of these had a favourable CSR; 24 had a favourable HTA report to justify

Table 2 Medicines on FBLs that were deleted or rejected from the WHO essential medicines list (EML), according to WHO technical report series [18]

Medicine/disease group*	WHO technical report series (TRS), year	Explanation—reason for deletion/rejection
Deleted		
albumin/B	TRS895, 2000	The review by the Cochrane Collaboration suggests the likelihood of previously unrecognized hazards and a lack of evidence of better efficacy of albumin compared with alternatives.
aminophylline/RESP	TRS 933, 2005	The WHO Committee recommended that aminophylline and theophylline be deleted from the Model List because of the availability of safer and more effective alternatives on the Model List.
atenonol/CV	TRS 965, 2011	The WHO Committee noted that there is no high-quality evidence to support the use of atenolol for the treatment of heart failure. The Committee also took into consideration a meta-analysis (*298*) (5 studies, n=17,671, follow-up 4.6 years) that suggested older hypertensive patients treated with atenolol have a significantly higher mortality when compared to patients treated with other classes of cardiovascular medicines. Cardiovascular mortality was also higher in the atenolol-treated group than in the one with another antihypertensive treatment, and strokes were more frequent with atenolol treatment. The committee concluded that there was sufficient evidence of efficacy and safety compared to atenolol to support the request for bisoprolol to become the representative beta-blocker in sections 12.1 to 12.3 and also recommended, based on evidence of efficacy, safety and cost 1 to 12.3 and also recommended, should be added to the Model List for the treatment of heart failure.
atropine as spasmolytic for gastrointestinal diseases/GI	TRS933, 2005	The WHO Committee therefore recommended that atropine (as an antispasmodic) together with the whole section on antispasmodic medicines be deleted from the Model List because of a lack of evidence of efficacy and safety.
calcium carbonate/GI	TRS770, 1988	Calcium carbonate is deleted since it causes greater gastric secretion and acid rebound than other listed antacids (on FBLs recommended for hyperphosphatemia).
cisplatin/ONCOL	TRS958 2009	The WHO Committee therefore recommended that carboplatin replace cisplatin on the Complementary Model List (with a square box) for the treatment of advanced ovarian cancer.
doxazosin/CV	TRS895, 2000	Prazosin tablet, 500 f.1 g and 1 mg, replaces doxazosin in the complementary list as are presentative of the α-adrenoreceptor antagonist class of drugs since it is now less expensive than doxazosin (recommended on the FBLs for hypertension).
Immunoglobulin human normal (i.m. and i.v.)/INF	TRS 920, 2003	The WHO Committee noted that there is no need for this item in view of the availability of suitable vaccines that there are no WHO clinical guidelines recommending its use and that quality control of this blood product poses a problem. The committee thus recommended that immunoglobulin, human normal be deleted.
theophylline/RESP	TRS933, 2005	See aminophylline
Rejected		
escitalopram/CNS	TRS958, 2009	Overall the WHO Committee decided that the evidence provided in the application did not support the public health need or comparative effectiveness, safety and cost-effectiveness for the addition of escitalopram, paroxetine or sertraline to the Model List at this time.
lamotrigine/CNS	TRS958, 2009	The WHO Committee did not recommend the inclusion of lamotrigine on the Model List based on the lack of evidence of its superior efficacy and safety and cost-effectiveness with respect to comparators, and the availability of suitable alternative first-line antiepileptics which are already on the Model List. The Committee recommended a review of second-line antiepileptics for a future meeting, including a review of topiramate, lamotrigine and gabapentin as a second-line therapy for children and adults.
paroxetine/CNS	TRS958, 2009	The WHO Committee decided that the evidence provided was not sufficient to recommend the addition of paroxetine and sertraline or addition of a square box to fluoxetine.
sertraline/CNS	TRS958, 2009	See paroxetine

*Disease groups: *CV* cardiovascular, *CNS* central nervous system, *GI* gastrointestinal, *ONCOL* oncological, *INF* systemic infection, *B* blood/haematopoietic, *RESP* respiratory

their original inclusion in the FBLs. Finally, 89 medicines (27 %) listed on the FBLs had no evidence either in CSR or HTA-published reports that would be good enough to justify their presence on the FBLs. Out of these, 29 (9 %) had very unfavourable findings for being on a reimbursement list: 9 were deleted, 4 rejected from EML, 13 had very unfavourable CSRs and 3 had unfavourable HTA reports.

A remarkable discrepancy between the WHO EML and FBLs was also noticed in the number of the WHO EML medicines which were not included in the FBLs—approximately one third. Almost a half of the medicines given on the FBLs were not listed on the WHO EML. Also, more than one third of the medicines listed on the FBLs had no evidence supporting their inclusion in a reimbursement list. For 108 medicines on FBLs, we could not find an accompanying Cochrane systematic review that would justify their inclusion in a basic medicine list. With 9 medicines deleted and 4 rejected from the WHO EML, there were a total of 134 (40 %) medicines without an evidence supporting their inclusion in the FBLs. Out of these 134 medicines, for 40, we found a good enough evidence in CSRs to support their inclusion in the FBLs, and for 24 medicines, we found a reasonable and sound evidence in HTA-published reports for their inclusion in the FBLs.

Our study had several limitations due to the observational design of the study and lack of relevant information on the use of FBLs and actual costs and medicine consumption. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations, and the choice of medicines which ought to be regarded as essential still remains a national responsibility. WHO EML cannot serve as a strict model, and some differences between WHO and national lists are both expected and justifiable [5]. Local and regional morbidity patterns will result in certain medicines not appearing on the national list, or some medicine deemed as essential by WHO may not be licensed in a country. However, unlike the WHO EML, national essential medicines lists face many challenges—they must result in factual changes in the field, save costs, increase rationality in prescribing and improve patient outcomes. Another limitation is the fact that medicines included in our analysis may not have been a topic of either a systematic review or an HTA report. It is possible that there were newer medicines for which a systematic review was not conducted or could not be conducted because of the lack of relevant high-quality randomized controlled studies. Hence, our study aimed at analysis of the greater framework for evidence assessment instead of reasons for decision on individual medicines. Another study limitation could be the fact that in countries which used the full economic analysis as a part of HTA reports, some medicines could have proven clinical effectiveness but not cost-effectiveness, so the final decision on their reimbursement could be negative.

The observed discordance in anti-infective medicines could partly be explained by the fact that antituberculosis medicines in BH are all financed, supplied and distributed by the UNDP Programme "Reinforcement of DOTS strategy in improving the Programme of fight against tuberculosis, including control over emergence of multidrug-resistant tuberculosis and control over infection spread in Bosnia and Herzegovina"[20], mainly as combinations of tuberculostatic medicines, but four of these medicines (rifampicin, isoniazid + pyridoxine, pyrazinamide and ethambutol) are on the FBLs.

Medicines account for 20–60 % of health spending in low- and middle-income countries, compared to 18 % in the countries of the Organization for Economic Co-operation and Development (OECD) [21], while in transitional economies, pharmaceuticals account for 15 to 30 % of health spending [6]. Equitable access to quality pharmaceuticals is an essential component of any health system strengthening and primary health care reform, particularly in low- and lower middle-income countries. Sustainable and efficient financing of medicines and affordable prices are therefore essential to ensuring access to medicines and are two of several important building blocks in WHO access to medicines framework. A system that nominally offers more than it can afford may cause imbalance or even a collapse of otherwise sustainable and efficient financing, as well as create an open field for corruption and inequality.

The increase in the medicines expenditure in the FBH is larger than the rise in total expenditure in health care, which has already caused frequent shortages of medicines [22, 23]. In 2012, the FBH total medicine expenditure was almost 395 million KM (€202.6 million; value added tax (VAT) included), or 337.6 million KM (€172.8 million) without VAT included (61 % of total medicine expenditure in BH) [16, 24]. Thus, the average medicine expenditure in the FBH in 2012 was 166.5 KM (€88.4) per person, and since the same year, the GDP per capita in the FBH was 7001 KM (€3590.3) [24], the medicine expenditure was 2.4 % of the GDP per capita with VAT included and 2.0 % without VAT included. In BH, there is a uniform VAT rate of 17 % on all goods. The total health expenditure in the FBH in 2012 was 1.5 billion KM (€792.8 million), and the medicine expenditure made up 26 % of the total health care expenditure. The mean value of reimbursed medicines for the whole Federation of BH was 87 KM (€44.6), and it was 3 % higher than in 2011 [25]. The medicine expenditure in 2012 was 551 million KM (€282 million) without VAT [16]. According to the preliminary results of the census conducted in October 2013, the total population in Bosnia and Herzegovina is 3,791,622, out of which 2,371, 603 people live in the Federation [26]. In 2012, the total medicine expenditure (VAT included) in the whole Bosnia and Herzegovina was 169.7 KM (€74) per person a year, with the gross domestic product by expenditure estimated at 27, 198 million KM the same year [27], which made medicine expenditure in Bosnia and Herzegovina to be 2.4 % of the

GDP (by expenditure). A neighbouring country, Croatia, spent 3392 million HRK (€443.1 million) in 2008, which is 766 HRK (€100) per capita, and their total pharmaceutical expenditure accounted for 13 % of the total health expenditure and 1.2 % of the GDP [28]. It should be kept in mind that Croatia had a zero percent VAT on reimbursed medicines until it joined the EU in 2013, when 5 % VAT was introduced, while in BH, there is a single VAT of 17 % on all goods, including medicines. The medicine expenditure in BH is almost twice as high as in the neighbouring Republic of Croatia: 2.4 % of the GDP (compared to 1.5 % in Croatia), with 25.5 % of the total health expenditure (compared to 13 % in Croatia), which means that BH spends more than it can afford and is definitely urged to spend the money from the public health care funds more wisely and to get as much of a value for the lower cost. This also emphasizes the importance of VAT exemption for medicines, since VAT on medicines in BH contributes with 0.36 % to the GDP. Also, according to WHO, countries should consider exempting essential medicines from taxation [21].

The results of this study, when compared to the results of a similar study conducted in neighbouring Croatia [11], are not surprising, especially if we bear in mind the fact that Croatia is classified as a high-income country by the World Bank [29]. BH is a middle-income country, and it was expected to get a smaller discrepancy between the EML and the number of medicines on the national reimbursement list in our results, as well as a shorter list of medicines which have no solid evidence for their inclusion in the reimbursement list. The Croatian national medicine reimbursement list had greater discordance with the EML, with 254 medicines and 33 combinations of medicines that were not on the WHO EML, compared to only 134 medicines and 17 combinations of medicines on the FBLs [11].

In the FBH, the level of transparency in the process of making reimbursement lists is very low. It is not clear who created the existing FBLs or which rules were followed. The overall criteria for medicine inclusion or deletion from cantonal lists are very general, concerning mostly technical characteristics of medicines. Pharmacoeconomic criteria are mentioned in official documents, but there are no specific instructions for accepting or rejecting/not including medicines. Budget impact analysis is not mentioned at all and would not be useful since there are not enough patient registries, and data on epidemiology of most diseases is very limited. By law, the Cantonal Medicine Committee members are obliged to ensure the secrecy in all the phases of the list creation [30].

There are some good examples of a successful procedure for generating a national expert consensus. For example, in the case of the Eritrean national list of medicines, the WHO model list served as a basis for the first draft, which was produced by 30 health professionals [5]. The comments for the second and third revised editions were reviewed at national workshops attended by more than 100 participants, including health professionals and officials of the Ministry of Health, professional associations, governmental and international organizations, as well as international consultants [5].

CSRs offer very valuable information on relative efficacy and safety of medicines, but their production is time-consuming, and decision makers can decide not to reimburse a medicine if it is above incremental cost-effectiveness ration threshold, even though the referencing CSR finds it is safe and effective. Sixty-seventh World Health Assembly, held in May 2014, urged its member states to consider establishing national systems of health intervention and technology assessment, encouraging the systematic utilization of independent health intervention and technology assessment in support of universal health coverage to inform policy decisions, including priority-setting, selection, procurement supply system management and use of health interventions and/or technologies, as well as exchanging information and sharing experience with other member states [31]. Countries with less developed HTA systems, such as those in the central and eastern Europe could greatly benefit from joining international HTA networks, like in EUnetHTA, since the potential efficiency/quality gains for the European countries with less developed HTA systems are the highest [32]. In countries without established HTA process, independent, high-quality evidence sources such as the WHO EML, CSRs, as well as HTA reports, with local (national or regional) adaptations ought to be used when deciding on reimbursement, together with a more public and evidence-based approach. The whole process of decision-making itself should be as transparent—publicly discussed and available and effectively disseminated to all stakeholders. An independent public HTA department or official national HTA agency would be a good solution for BH. It could establish sustainable international collaboration, facilitate decisions on medicines reimbursement and other health technologies through adaptation of existing HTA reports to the local circumstances and produce its own reports. Until such HTA institution is possible in BH, pharmacoeconomic principles, as a part of HTA, should be widely promoted, together with evidence-based medicine principles. Establishing a Cochrane team in BH, in order to promote dissemination of EBM, would be useful, as was demonstrated in Croatia [33].

Regarding the medicines that had unfavourable findings for inclusion on the reimbursement list, one has to bear in mind that once placed on a reimbursement list, these are very difficult to be "delisted". Delisting could be referred as disinvestment of medicines, which is defined as "complete or partial withdrawal of resources from health care practices, procedures, technologies and medicines that are deemed to deliver little or no health gain for their cost, and thus are not efficient health resource allocations" [34]. There are several barriers to the implementation of such a different way of thinking: time required for such exercise, pre-assumption that sophisticated outcome measures, such as quality-adjusted life years are necessarily required for

such a process, greater stakeholder involvement required for the process of decision-making [35] and the need for all the stakeholders to understand the levels of evidence, be willing to act in the best interest of the society and make their decisions free of emotional burden. As disinvestment is an emerging field, there is also the need for more evidence to inform prioritization, development and implementation of strategies in different contexts [36]. Questions are rarely asked in the public about how the money for reimbursement of medicines is used and are often considered politically dangerous [11, 35, 37]. As demonstrated by Hodgetts et al. [38], evidence-informed disinvestment decision-making is feasible and potentially less controversial than often presumed.

In conclusion, in the circumstances of very limited financial resources that are being reduced even further and when there are frequent shortages of medicines due to rising instability in financial sustainability of public health insurance funds, it is crucial to rely on a well-established, proven evidence (such as WHO EML, CSRs and HTA reports) on medicine reimbursement. The evidence we presented in our study comes in all shades of strengths, so it could be used in order to invest the scarce resources in the most useful way for the whole society, at the same time, respecting relevant social and cultural circumstances. The results of our study may provide support to decision makers for useful methodology improvements on classification of evidence for future reimbursement lists, providing them with a scaled evidence for priorities both in reimbursement and in disinvestment process. It would be appropriate to decrease the number of decision makers in BH and ensure that unique decisions on reimbursement are made on a national level. With such a decentralized political arrangement and divided budgets, this may not be possible. Finally, establishment of an independent, government-financed body, which could help in providing scientific criteria for a transparent decision-making system in reimbursement, is inevitable.

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Contribution of authors AM conceived and designed the study. MMK collected the data. MMK and AM analysed the data. MMK and AM contributed reagents/materials/analysis tools. MMK wrote the paper. Am provided the critical revision of the manuscript.

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