Acta Clin Croat 2023; 62:486-501
doi: 10.20471/acc.2023.62.03.11

Original Scientific Paper

PHARMACOVIGILANCE IN SERBIA: A TEN-YEAR PHARMACOEPIDEMIOLOGIC ANALYSIS

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SUMMARY – Pharmacovigilance as a science and group of activities related to detection, collection, analysis, understanding and prevention of adverse drug reactions (ADRs) is an essential activity in the regulatory system of drugs of any country. Defining increased patient safety as the main purpose of ADR reporting, a well-designed national pharmacovigilance system achieves its ultimate goal, i.e., protection of public health. In organizational and technical terms, the Republic of Serbia has a well-developed system of pharmacovigilance, created on the basis of a proven reliable system of the former SFR Yugoslavia, and carried out by the National Agency for Medicines and Medical Devices of Serbia (ALIMS), which conducts all organized activities aimed at strengthening the national system of ADR monitoring and reporting. Unlike the neighboring Croatia and Montenegro with similar pharmacovigilance systems, Serbia has only recently approached the WHO standard of 200 reports *per* million inhabitants despite a significant increase of 180 ADR reports *per* million inhabitants in 2019 (1251 in total). Considering this, our study aimed to provide a critical insight into the practice of pharmacovigilance in Serbia by pharmacoepidemiologic analysis of a ten-year period of ADR monitoring and reporting activities.

Key words: *Adverse drug reactions; Adverse drug reaction monitoring and reporting; Suspected drug; Adverse events following immunization*

Introduction

Ever since the well-known thalidomide tragedy in the middle of the last century caused the birth of a large number of newborns with severe congenital malformations around the world[1], detection, collection,

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Received September 30, 2021, accepted February 15, 2022

analysis, understanding and prevention of adverse drug reactions (ADRs) is one of the most important professional activities in all healthcare professions, and has great clinical, as well as public health significance globally. The activities of ADR monitoring and reporting, or pharmacovigilance, do not refer only to medicines but also to vaccines, blood and blood products, biological therapy, herbal medicines and supplements, as well as medical devices[2-4]. Nowadays, pharmacovigilance is an essential activity in the regulatory system of drugs of any country, which enables early detection of unexpected, delayed or severe adverse reactions to all preparations and agents used in preventive and clinical medicine. At the same time, defining increased patient safety as the main purpose of ADR reporting, a well-designed national pharmacovigilance system achieves its ultimate, i.e., protection of public health[2,5].

There is no drug that can be claimed to be completely safe[6]. The use of any drug correlates with the risk of more or less significant or severe side effects, i.e., all those effects that may occur during therapeutic use of some preparation but do not have a therapeutic purpose. It is important to note that this term refers only to those side effects that occur during the application of therapeutic doses in the usual and recommended way, regardless of the purpose of application, i.e., prevention, therapy, or diagnostics[7]. Adverse reactions may occur due to the impact of one or more related factors during drug administration. The most common reasons in the literature include non-selectivity of drug action and altered drug pharmacokinetics, ADRs of medicines used in the treatment of the same or related diseases (polypharmacy), individual physiological or pathophysiological specificity of the patient's body but also professional mistakes of the health staff and those related to patient self-medication[8-10]. ADRs are considered as one of the most common iatrogenic health disorders, whether they occur as a result of prescribing an inappropriate drug, administering an inappropriate dose (the most common mistake in practice), inappropriate way of administration, or irrational dispensing of drugs in pharmacies[11-13]. It should be noted that the prevalence of certain ADRs is very different; considering that, all these reactions can be classified into several groups as very common (in more than 10% of patients), frequent (1%-10% of patients), occasional (0.1%- 1% of patients), rare (0.01%-0.1% of patients) or very rare (less than 0.01% of patients treated with the drug)[6,7].

Regardless of differences in the ADR prevalence that occur as a result of heterogeneity of the global population (specificity related to the prevalence and manifestation of particular diseases, genetic characteristics, dietary habits, as well as differences in the practice of drug prescribing), all countries in the world are obliged to organize a system of monitoring the safety of drugs on the market[14,15]. Prior to placing a medicinal product on the market, information on its safety is limited exclusively to the results of preclinical and clinical studies conducted in conditions that do not necessarily reflect those in which a certain product will be used in clinical practice. Once approved, the drug becomes available to a heterogeneous patient population. Experience shows that delayed ADRs, those that occur rarely, as well as those related to its long-term use, can be observed only in the post-marketing phase of drug safety monitoring[16]. By ADR monitoring and reporting in the post-registration period, the quality of available information on dosage, way of administration, indications, contraindications, application of necessary precautions and side effects of a particular drug is improved, thus enabling additions and changes to the official instructions for use of drugs[17]. The pharmacovigilance system should enable detection of safety signals such as risk identification, characterization, analysis, minimization, communication and prevention in order to ensure the best possible benefit-risk balance of the drug in everyday practice, as well as the promotion of rational and safe pharmacotherapy[7,18]. After analyzing and confirming a new or insufficiently known safety risk of a drug, national pharmacovigilance institutions are obliged to take appropriate regulatory measures in order to warn health professionals and health care users of the newly identified risk. One of the main goals of post-marketing monitoring and reporting of ADRs is to more precisely define the relationship between the benefits and potential risks of using particular drug in practice, which leads to improvement of one of the important aspects of public health, i.e., safety in the medical treatment process[15,19]. The public health importance of ADR monitoring and reporting is evidenced by the results of numerous studies on the safety of drugs on the market, which indicate that these reactions are the immediate cause of about 5% of hospitalizations globally, one of the 10 most common causes of death, and a significant reason for additional economic costs of medical treatment[20,21]. Development of the national pharmacovigilance sys-

tems is also a strategically important element in the development of the national healthcare system, and can be reliably monitored based on the analysis of annual reports, which are publicly available in most European countries, including non-European Union (EU) countries. Considering this, our study aimed to provide critical insight into the practice of pharmacovigilance in Serbia, by pharmacoepidemiologic analysis of the ten-year period of ADR monitoring and reporting activities and comparison with data from annual ADR reports of Croatia and Montenegro, as well as information from relevant literature sources.

Materials and Methods

Using the publicly available data from annual reports of the Serbian Agency for Medicines and Medical Devices (ALIMS), we conducted a pharmacoepidemiologic analysis of the ADR monitoring and reporting activities in Serbia during the 2010-2019 period and compared them to data in annual reports of the Croatian Agency for Medicinal Products and Medical Devices (HALMED) and Agency for Medicines and Medical Devices of Montenegro (CALIMS). The results were discussed based on the information on pharmacovigilance activities in Croatia and Montenegro, ex-Yugoslav countries that have a similar pharmacovigilance regulatory system as Serbia, their global and local pharmacovigilance and public health significance, as well as the information from the relevant scientific literature that had been published in the last ten-year period. Literature sources included in discussion had to meet the following criteria: impact factor of the journal, number of citations, year of publication, and informative significance of the article in relation to pharmacovigilance in Serbia.

Analysis of the Pharmacovigilance Practice in Serbia during the 2010-2019 Period

The pharmacovigilance system in SFR Yugoslavia was well organized and reliable, which is supported by the fact that this country had actively participated in the World Health Organization (WHO) Program for International Drug Monitoring since 1974. This program started in 1968 with the aim to identify the earliest possible pharmacovigilance signals[22]. Even today, the four states that were parts of Yugoslavia (Serbia, Croatia, Montenegro, and Bosnia & Herzegovina) still have similar pharmacovigilance regulations. Annual reports on monitoring and reporting of ADRs in Serbia, Croatia and Montenegro are publicly available on the websites of national agencies for drugs and medical devices, whereas public access to reports from Bosnia and Herzegovina is still not possible[23]. In Serbia, post-registration supervision of ADRs is carried out by the ALIMS, which conducts all organized activities aimed at strengthening the pharmacovigilance system and regulatory system of medicines through the National Pharmacovigilance Center. ALIMS organizes and performs continuous supervision over the manner of collecting information on reactions to drugs on the

Table 1. Reported cases of adverse drug reactions in the Republic of Serbia during the 2010–2019 period

Year	Total number of reported cases of ADRs	Approximate number of reported cases of ADRs *per* million inhabitants*
2010	781	104
2011	962	128
2012	1179	164
2013	1173	163
2014	1016	141
2015	1170	162
2016	1105	154
2017	964	134
2018	1194	166
2019	1251	174

ADR = adverse drug reaction; *for the 2010-2011 period, the number of inhabitants in the Republic of Serbia of 7.5 million was used (according to the 2002 census), and for the 2012-2019 period, the number of 7.2 million inhabitants was used (according to the 2011 census).

market, processes the data obtained, and provides an expert assessment of reported ADRs[24].

From 2010 until 2019, a total of 10,795 ADR cases were registered in the Republic of Serbia[25-34] (Table 1). Annually, an average of approximately 1080 cases of ADRs are reported to the ALIMS, or just over 150 *per* million inhabitants. Since 2012, the total number of ADR cases reported in Serbia has not shown any major fluctuations on annual basis, except for 2017 when the number of reported cases was more similar to those at the beginning of the analyzed period. Analyzing the available annual reports of ALIMS, it is noticed that the largest number of reported ADR cases was registered in 2019, i.e., by 60.2% more than in 2010. Despite the ongoing efforts of ALIMS to improve pharmacovigilance activities in Serbia, with a significant increase of 174 ADR reports *per* million inhabitants in 2019 (1251 in total), Serbia has only recently approached the goal of 200 reports *per* million inhabitants, set by the WHO as a standard for a well-developed national pharmacovigilance system. In order to fully meet the set requirements, Serbia needs approximately 1500 ADR reports in one calendar year[34].

For comparison, in Croatia, which also 'inherited' the positive Yugoslav regulations in the field of pharmacovigilance activities, this standard was reached in the early 2000s, while in 2019 the total number of reported ADR cases by the HALMED from Croatia was 960 *per* million inhabitants[35-44]. At the same time, according to the official reports of the CALIMS from Montenegro[45-54], in 2019 this country forwarded to the WHO database more than 260 reports of ADRs *per* million inhabitants, which also met the previously mentioned WHO standard (Fig. 1).

Since 2011 (data on 2010 were not available), the majority of ADR reports to the ALIMS was sent by drug license holders, while the number of reports sent directly by healthcare professionals and patients was significantly smaller (Fig. 2). This higher number of ADR reports by drug license holders was certainly expected and represented a trend in EU member states and other countries with well-developed pharmacovigilance systems (USA, Canada, Australia)[34,55,56]. According to the State Ordinance on the manner of reporting, collecting and monitoring adverse drug reactions of the Republic of Serbia[57], the holder of a drug license is obliged to organize continuous monitoring of ADRs but also to establish, maintain and improve an appropriate pharmacovigilance system and supervision of one or more medicinal products for which it has a marketing license in the Republic of Serbia, as well as to implement appropriate measures if needed. Legal regulation of the obligations of drug

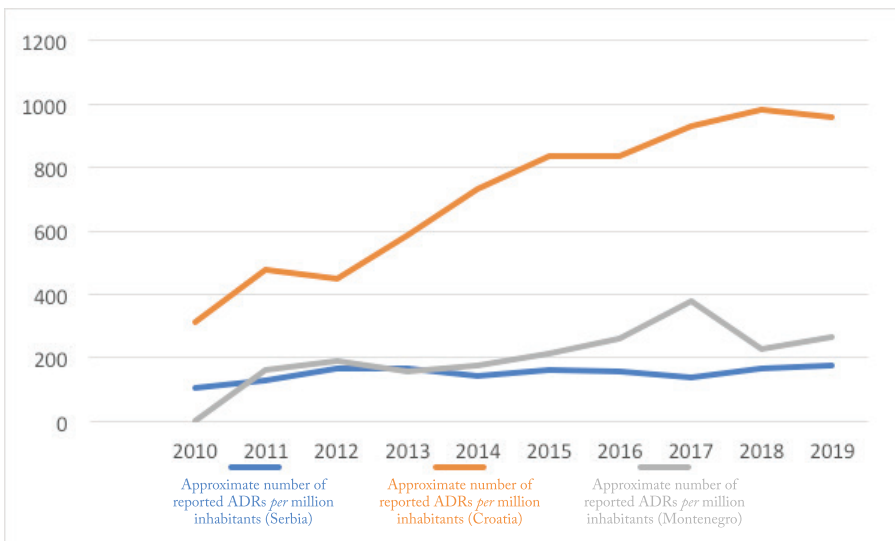

Fig. 1. Comparative overview of the approximate number of reported ADRs per million inhabitants in Serbia, Croatia and Montenegro during the 2010–2019 period.*

*Calculation based on the publicly available official population data of the national statistical institutes of Serbia, Croatia and Montenegro; ADRs = adverse drug reactions.

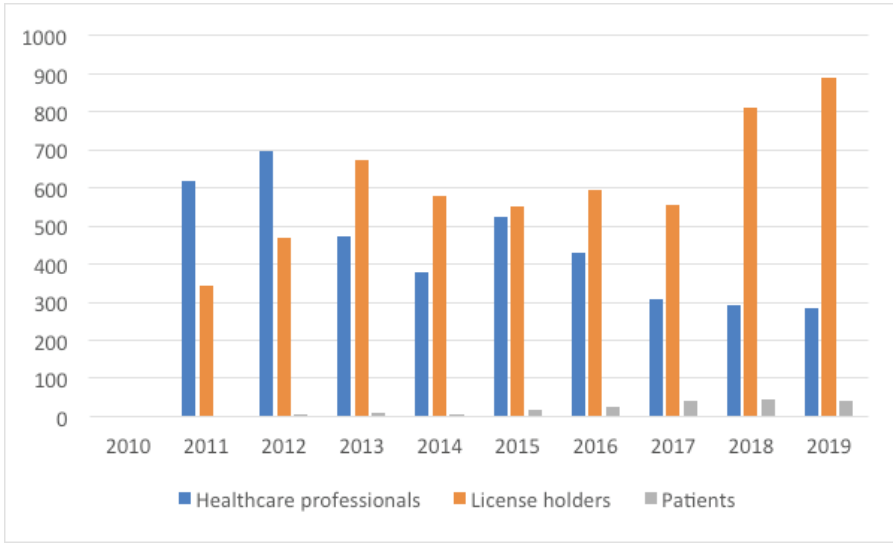

Fig. 2. Structure of adverse drug reactions reported in the Republic of Serbia during the 2011-2019 period (data on 2010 were not available).

license holders has resulted in a significant increase in the participation of pharmaceutical companies in pharmacovigilance activities in Serbia since 2012. In the period before the formulation and adoption of the mentioned State Ordinance from 2011, the participation of drug license holders in pharmacovigilance activities almost did not exist, or was insignificantly small. For example, in 2011, pharmaceutical companies in the Republic of Serbia reported only 13 ADR cases, whereas in 2010 a total of one ADR case was reported by drug licensees[25,26]. How significant this progress is for the pharmacovigilance system in Ser-

Table 2. Participation of pharmaceutical companies in pharmacovigilance activities in the Republic of Serbia during the 2012-2019 period*

Year	2012	2013	2014	2015	2016	2017	2018	2019
Company	Roche 74 (18.18%)	Roche 146 (22.50%)	Roche 161 (26.92%)	Bayer 113 (20.85%)	Merck 74 (12.96%)	Sandoz 123 (22.65%)	Boehringer Ingelheim 72 (11.92%)	Boehringer Ingelheim 123 (14.27%)
	Janssen 44 (10.81%)	Pfizer 139 (21.42%)	Bayer 90 (15.05%)	Roche 62 (11.44%)	Bayer 68 (11.91%)	Roche 63 (11.60%)	Sandoz 61 (10.10%)	Roche 112 (12.99%)
	Novartis 43 (10.57%)	Bayer 61 (9.40%)	Novartis 62 (10.37%)	GlaxoSmithKline 41 (7.56%)	Roche 66 (11.56%)	Bayer 57 (11.05%)	Novartis 59 (9.77%)	Pfizer 64 (7.42%)
	Bayer 40 (9.83%)	Merck 35 (5.39%)	Sandoz 37 (6.19%)	Richter Gedeon 38 (7.01%)	Pfizer 52 (9.11%)	Novartis 51 (9.39%)	Roche 53 (8.77%)	Merck 63 (7.31%)
	GlaxoSmithKline 36 (8.85%)	AstraZeneca 34 (5.24%)	Pfizer 35 (5.85%)	Pfizer 36 (6.64%)	Astellas 41 (7.18%)	Janssen 32 (5.89%)	Bayer 41 (6.79%)	Novartis 54 (6.26%)

*Excluding vaccines

bia can be understood by analyzing annual reports of the Montenegrin CALIMS, which in the 2019 report continued to warn of an unacceptably small number of reported ADRs by drug license holders despite the legally-based obligations[54]. Table 2 shows the pharmaceutical companies with largest participation in the total number of reported ADRs (excluding vaccines) in the Republic of Serbia in the 2012-2019 period.

The previously mentioned higher participation of drug license holders in the activities of ADR monitoring and reporting positively influenced the efficiency of the Serbian national pharmacovigilance system and can be partly explained by tightening of legal regulations that require a high degree of their involvement in post-marketing monitoring of drug safety. However, insufficient involvement of Serbian healthcare professionals in pharmacovigilance activities is evident and worrying, considering that numerous studies have shown that the effectiveness of the national program of post-registration monitoring of drug safety largely depends on the active participation of healthcare professionals in early ADR identification and reporting[58]. Due to their professional position, they are generally able to spot, identify and report ADRs in a timely manner but in everyday clinical practice this important professional activity is often neglected. According to the literature sources, the potential reasons for this phenomenon include preoccupation with daily professional activities, the burden of various administrative procedures, focusing only on ADRs registered during hospitalization, fear of legal liability due to reporting ADRs that could potentially have been prevented, feeling ashamed and/or guilt due to professional mistake, poor training, inadequate interpersonal communication between physicians and other healthcare professionals, as well as the lack of motivation for this kind of professional activity[59-63]. Investigating the hepatotoxicity of drugs based on reported ADRs, Petronijević *et al.* in a study from 2011 also identified the need of enhancing reporting of ADRs and strengthening risk communication in the national pharmacovigilance system of Serbia, as well as the possible reasons for ADR underreporting in this country, i.e., the lack of reporting knowledge, well-known ADRs, and insecurity about causality relationship[64]. In addition, annual ALIMS reports show an unequal representation of healthcare professionals who report ADRs; the most common are medical doctors (about 70%) and pharmacists (slightly less than 30%), whereas data on reporting ADRs by nurses are still not available in reports, although this profile of healthcare providers is directly involved in the drug administration process, and represents an important source of information on ADRs in healthcare systems all over the world[65]. Finally, the importance of the so-called spontaneous ADR reporting (voluntary reporting of adverse reactions not only by health professionals but also by patients themselves) is increasingly prominent in recent years, which can also be noticeable in the WHO health promotion programs and public health campaigns worldwide. Active participation of patients in ADR reporting is an extremely important source of data on ADRs, which bolsters the national pharmacovigilance system[66]. Despite certain problems, spontaneous ADR reporting

Table 3. Sex-related distribution of reported adverse drug reactions in Serbia during the 2010-2019 period

Sex	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Female (%)	55.17	62.42	59.59	66.00	58.39	57.90	53.10	57.25	53.65	54.78
Male (%)	43.31	35.71	37.76	34.00	33.37	37.83	40.91	40.86	44.68	43.33
Unknown (%)	1.52	1.87	2.65	-	8.24	4.27	5.99	1.89	1.67	1.89

Table 4. Age groups with highest incidence of adverse drug reactions in Serbia during the 2010-2019 period

Age group (yrs)	Year									
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	18-59	16-69	16-69	61-70	61-70	51-60 61-70 ≤10	41-64 18-40 65-74	41-64 18-40 65-74	41-64 65-74 18-40	41-64 65-74 18-40

enables detection of new ADRs and a more objective view of the prevalence and severity of known ADRs, which significantly contributes to the safe use of drugs and medical devices[67,68]. Considering the reports from Serbia, a more significant participation of patients in ADR reporting in Serbia has been noticeable since 2015 (Table 3), but only in the national context. In comparison, in the last annual report, HALMED stated as many as 495 reports of ADRs by patients in Croatia, i.e., 12.7% of the total number of received reports.

Analyzing direct ADR reporting to ALIMS by healthcare professionals in Serbia during the analyzed ten-year period, information was mostly delivered by mail, although there is a clear tendency in the neighboring and EU countries to report ADRs electronically, primarily due to greater simplicity, efficiency and reliability of this way of sending information, as well as easier data processing at the global level. In 2019, a total of 41.3% of ADR reports were submitted by mail, 33.9% by e-mail, while only 14% of healthcare professionals used the online application to submit detected ADRs, despite the fact that this application is available on the ALIMS website and is easy to use. At the same time, the Croatian HALMED registered an increase in electronically ADR reporting in 2019 (*via* online application and mobile application), by 14.9% more than in 2018, while the number of reports submitted by mail decreased in 2019 by 19.9% compared to 2018[43,44]. The advantages of electronic reporting of ADRs include direct data entry into the national database, which reduces the possibility of human error caused by manual data entry, while the time required to process applications is obviously shorter. Another positive example from this country is the implementation of the OPeN project by HALMED. With its completion, this agency will automate capturing of pharmacovigilance data from various clinical information systems and enable data unification in the Croatian national ADR database, enhancing medical practice and improving the public health system at the same time, as well[69]. Opposite to healthcare professionals, annual ALIMS reports show that patients are much more likely to use an online application for ADR reporting. From the moment when e-application became available on the ALIMS website, the prevalence of this way of reporting is increasing among healthcare users in Serbia, so in 2019 it was as high as 87.5%, significantly more than in patients who used mail (10%) or e-mail (2.5%) for submitting the application[34]. Considering this, it seems that the main barrier to increasing the efficiency of electronic ADR reporting in Serbia is insufficient information on this way of submitting ADR reports. The results of a recent study among students at the Faculty of Medicine, University of Novi Sad, Serbia, supported this claim; despite the high level of knowledge about pharmacovigilance and its public health and clinical significance, students of medicine, pharmacy, dentistry and nursing science of this faculty mainly stated that they were not sufficiently familiar with the manner and possibilities of submitting reports on observed ADRs[70].

From 2010 until 2019, the majority of reported cases of ADRs in Serbia were related to females, and this trend is noticeable throughout the observed period (Table 3), but in different age groups of the population; the reports show a different way of age periodization, and the last one has been in use since 2016 (Table 4). The higher prevalence of ADRs in the female population is also noticeable in the surrounding countries, and female gender has often been described in the literature as a risk factor for the development of various forms of adverse reactions. As potential reasons for greater sensitivity of women to the use of drugs, the authors of various studies include polypharmacy, the specific influence of female sex hormones on the pharmacodynamic and pharmacokinetic properties of the drug, as well as physiological features of the female body such as body composition, plasma and tissue distribution, metabolizing enzymes and transporters, excretion potentials, and prolonged gastrointestinal transit[71-73]. However, a recent analysis of data from more than 18 million ADR reports included in Vigibase from 131 member states found that male reports were more likely to contain serious and fatal adverse events than females[74].

One submitted report always represents one case of ADR related to one patient, which is the reason why the same report may contain several observed ADRs that are suspected to be directly or indirectly caused by the use of one or more drugs[25-34]. Therefore, the total number of registered single ADRs, as well as the total number of suspected drugs is often higher than the total number of submitted ADR reports. When entered into the national database, reported ADRs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Distribution of reported reactions in certain MedDRA classes of organ systems (System Organ Class, SOC) during the 2010-2019 period is shown in Table 5.

Table 5. Distribution of reported adverse drug reactions (SOC classification) in Serbia during the 2010-2019 period

ADRs (SOC classification)	Year									
	2010	2011	2012	2013	2014*	2015	2016	2017	2018	2019
- General and administration site reactions	**341*** **	**423**	**512**	No data available	**398**	**426**	370	421	**640**	**549**
- Skin and subcutaneous tissue disorders	238	370	448		369	342	**417**	328	359	350
- Gastrointestinal disorders	190	251	291		254	325	250	**769**	353	273
- Neural disorders	134	201	225		184	195	156	215	220	220
- Respiratory, thoracic and mediastinal disorders	76	119	167		128	140	98	211	153	287
- Clinical trials	-	-	-		-	105	145	102	189	166
- Psychiatric disorders	80	97	138		85	74	73	169	97	85
- Musculoskeletal and connective tissue disorders	11	35	45		68	64	76	124	86	87
- Immune system disorders	-	13	27		58	64	59	53	34	36
- Vascular disorders	21	19	27		74	64	53	42	74	115
- Blood and lymphatic system disorders	75	78	95		78	60	80	66	77	112
- Injuries, poisonings and procedural complications	-	-	-		48	59	96	81	101	102
- Infections and infestations	-	-	-		74	53	133	69	83	88
- Reproductive system and breast disorders	14	23	23		35	51	47	28	27	39
- Cardiac disorders	57	102	120		61	50	43	54	73	65
- Metabolism and nutrition disorders	37	14	37		39	47	26	36	40	62
- Ophthalmic disorders	19	20	23		52	37	45	46	48	51
- Neoplasms – benign, malignant and indeterminate	9	9	16		19	32	52	35	60	117
- Disorders of the ear and labyrinth	9	10	18		19	25	20	18	20	28
- Disorders of the kidneys and urinary system	31	40	59		28	17	29	24	27	22
- Product problems	-	-	-		-	16	27	12	18	12
- Endocrine disorders	8	10	47		6	11	7	5	5	13
- Hepatobiliary disorders	31	14	21		16	11	12	9	12	22
- Pregnancy, puerperium and perinatal conditions	12	4	24		6	7	2	3	6	1
- Surgical and medical procedures	-	-	-		1	4	2	1	1	5
- Congenital, familial and genetic disorders	-	-	-		1	3	2	2	2	2
- Social circumstances	-	-	-		1	3	1	3	1	1
- Other	14	20	48		-	-	-	-	-	-
**Total:	1406	1872	2411		2238	2285	2321	2929	2806	2910

*Revised SOC classification; **including vaccines; ***most numerous ADRs in each year are bold; ADRs = adverse drug reactions; SOC = System Organ Class

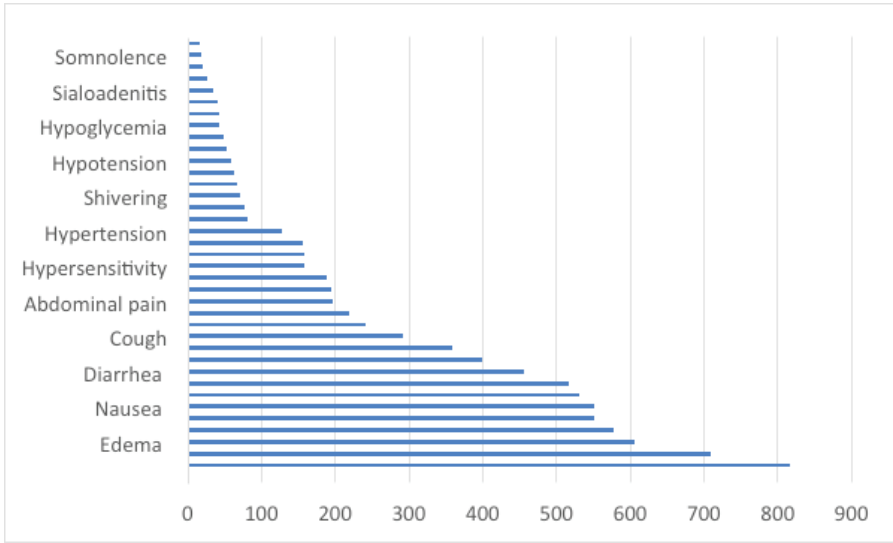

Fig. 3. List of reported adverse drug reactions including vaccines in Serbia during the 2010–2019 period.

The list of ADRs reported in Serbia from 2010 to 2019 mostly correlate with the list of ten most common ADRs in general (nausea, somnolence, diarrhea, vomiting, skin rash, heart rhythm disorders, skin itching, various unpleasant manifestations at the site of parenteral drug administration, hyperkalemia and drug fever, in descending order)[7]. Based on the analysis of ALIMS annual reports, the most commonly reported ADR in the 2010-2019 period was erythema (817 cases), followed by rash (710 cases), edema (606 cases), fever (577 cases), administration site reactions and nausea (551 cases both), urticaria (530 cases), skin itching (516 cases), diarrhea (455 cases), and headache (399 cases) (Fig. 3). These results are not surprising, considering most of the listed ADRs have been continuously reported in large numbers in Serbia for years. The listed ADRs are usually easily noticeable, most of them are clearly time-related to the use of a certain drug and transient, but significantly reduce the patient's quality of life, although they are not classified as severe ADRs by regulations. However, it should be noted here that the absence of any reported case of administration site reaction and urticaria in 2017, any case of fatigue in 2012, or vomiting in 2017 and 2019, as the reactions that are most frequently registered in the region and worldwide, certainly indicates inconsistency in their reporting rather than the objective possibility of the complete absence of these reactions in one calendar year.

Analyzing data published in ALIMS reports, it can also be noticed that some ADRs were reported only in certain annual reports, while they were not present in others (34 cases of sialadenitis and 16 cases of parotitis in 2010, 26 cases of asphyxia in 2011, 21 cases of tremor and 19 of somnolence in 2014, 42 cases of hypoglycemia in 2015, 42 cases of infection in 2016, 66 cases of constipation and 40 cases of insomnia in 2017), which is most likely related to clinical trials of certain drugs. For isolated cases of not common ADRs, it would certainly be important to indicate in the report whether they relate to the same drug and the same formulation, whether they were reported by the same marketing license holder or spontaneously by healthcare professionals and/or patients from the same or different healthcare institutions, as well as whether they were reported during a clinical trial of a new drug or it is a drug that is already on the market. Only in this way, information on isolated cases of unusual ADRs can be useful both to the public and healthcare professionals, which is already the practice of reporting in the surrounding countries. For example, in its 2020 report, HALMED warned the public that a number of suspected ADRs had been received for the new formulation of Euthyrox®75. It should be noted that the ALIMS reports registered a very small number of ADRs that are listed in the literature as potentially most dangerous[6]; from 2010 to 2019, only 195 cases of various forms of bleeding, 82 cases of heart rhythm disorders, and 59 cases of hypotension were reported. However, this information should also be considered carefully, having in mind the previously mentioned

problems in the activities of ADR monitoring and reporting in Serbia. It would be certainly useful for the improvement of clinical practice in Serbia to include reports on the number of cases that met at least one criterion for consideration of any ADR as serious. Those criteria include immediate death or endangerment of the life of the user of the drug, occurrence of the need of hospitalization or its prolongation due to drug use, causing permanent and/or severe disability of the drug user, causing congenital defects or anomalies of the newborn whose mother was user of a certain drug, or another medically significant serious condition[6,74]. As potentially serious are also considered ADRs listed in the Important Medical Event List, which are classified in the last listed criterion, i.e., in the category of medically significant serious conditions[76].

Table 6 shows representation of certain groups of suspected drugs (excluding vaccines) that have been associated with ADRs in Serbia in the 2010-2019 period, as determined by the initial reporter. An overview of the groups of suspected drugs is given in the ALIMS annual reports according to the Anatomical Therapeutic Chemical Classification (ATC), an internationally accepted classification system for medicines that is maintained by the WHO. ATC codes are assigned by the WHO to all active substances contained in medicines, based on their therapeutic indication.

A review of the data from Table 6 shows that drugs from group L (Antineoplastics and Immunomodulators) were the most represented ATC group from 2013 to 2019, with the exception of 2018, when it was the second most common. Given the known specificity of

*Table 6. Suspected drugs in Serbia during the 2010–2019 period (Anatomical Therapeutic Chemical classification)**

Drug group	Year										Total
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	
A Alimentary tract and metabolism	30	40	47	46	33	154	80	55	97	95	677
B Blood and hematopoietic organs	25	36	32	29	74	155	89	92	112	131	775
C Cardiovascular system	71	**175**	184	152	105	145	101	116	148	175	1372
D Skin and subcutaneous tissue	3	4	2	6	43	24	20	11	9	4	126
G Genitourinary system and sex hormones	25	33	48	49	105	98	46	46	31	40	521
H Hormonal preparations for systemic use, excluding sex hormones and insulins	17	20	21	5	17	15	52	29	23	25	224
J Antibiotics for systemic use	**98****	152	167	158	114	191	206	215	**455**	287	2043
L Antineoplastics and immunomodulators	83	113	165	**361**	**341**	**323**	**447**	**315**	268	**516**	**2932**
M Musculoskeletal system	37	55	77	71	113	55	40	41	56	45	590
N Nervous system	92	121	**204**	144	173	123	123	190	96	123	1389
P Antiparasitic products, insecticides and similar remedy	-	-	-	1	10	4	5	3	4	0	27
R Respiratory system	30	55	3	26	36	46	35	49	101	170	551
S Sensory organs (eye and ear)	3	2	43	10	29	7	5	3	3	9	114
V Other	32	35	6	14	52	19	41	11	36	25	271
Total	546	841	1032	1032	1245	1359	1290	1179	1408	1645	11577

*Excluding vaccines; **the largest number of reports on suspected drugs in a year is bold

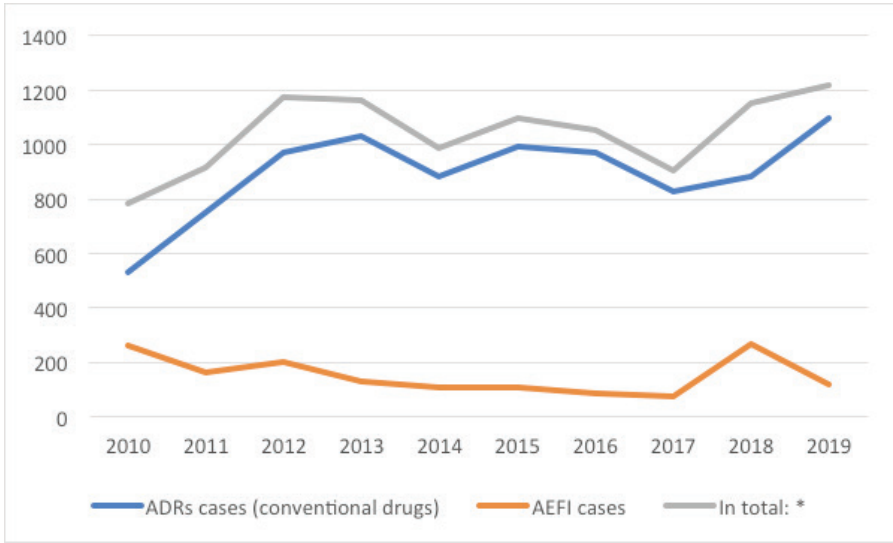

Fig. 4. Share of AEFI in the total number of reported ADRs in Serbia during the 2010–2019 period.

*Total number of reported ADRs represent the number of adequately documented cases that met the criteria for entry into the national ADR database and forwarding to the Uppsala Monitoring Center (UMC); ADR = adverse drug reaction; AEFI = adverse event following immunization.

the safety profile which implies the expected occurrence of numerous ADRs, the highest prevalence of drugs from the L group is certainly not surprising. This is supported by the fact that the L group of drugs is at the very top of the list of suspected drugs not only in Serbia, but also in the already mentioned countries in the region, Croatia and Montenegro. Even though Croatia has a smaller population, and therefore less people suffering from malignant diseases than Serbia, HALMED registered 1242 suspected drugs from the L group in 2019, and 1451 in 2020. In recent years, CALIMS has also recorded an increase in the number of suspected drugs from this ATC group in its annual reports, explaining it with the education of prescribing physicians and raising awareness of the importance of reporting ADRs to these drugs[54]. After the L group, according to the total number of suspected drugs in the observed period, the J group (Antibiotics for systemic use) follows, which was the most represented group in the ALIMS report from 2018. The globally known decades-long problem of irrational use of antibiotics has not escaped Serbia either[77,78], where the health authorities have significantly tightened the regulations regarding prescribing and sale of antibiotics in recent years. Although these regulations have resulted in a more rational use of antibiotics in Serbia, there is reasonable doubt that strict legal regulations have led to (un)intentional concealment and biased presentation of the actual number of antibiotic-related ADRs, especially non-life-threatening ones. The number of ADR reports and suspected drugs from this group is constantly increasing, but compared to the reports in neighboring countries, it would be objective to expect them to be significantly more represented. In comparison, 287 ADRs to suspected drugs from group J were registered in Serbia in 2019, and in Croatia almost three times more at the same time (779 ADRs). In addition, ALIMS has registered a large number of reports on drugs from the ATC group C (Cardiovascular system as the third most common in 2018 and 2019), and also from the R group (Respiratory system), with an evident increase in the number of suspected drugs since 2018. Besides, the ATC group R was one of the four most represented groups in 2019 for the first time since the beginning of using the ATC classification in Serbia.

According to current international recommendations, annual reports of the national pharmacovigilance centers always show side effects of vaccines separately from reactions to conventional drugs. Understandably, total number of registered adverse events following immunization (AEFI) is always expected to be lower, so the structure of reported ADRs in Serbia is also very similar to other countries. Considering reported AEFI, most of them have been forwarded from health institutions to ALIMS by Dr Milan Jovanović Batut Institute of Public Health of Serbia, which together

with ALIMS monitors safety of the vaccines on the market in the Republic of Serbia. In the 2010-2019 period, the total number of appropriately reported AEFI varied significantly (72-198 cases), with two unusual increases in 2010 (255 cases in total) and 2018 (262 cases in total) (Fig. 4). Given the long-standing global vaccinal crisis that threatens to jeopardize vaccination as one of the most important preventive health measures, the availability of AEFI reports is an extremely important tool in the battle against the anti-vaccinal movements around the world, including Serbia. Members of these movements often post unverified or inaccurate information about vaccines and their 'harmful' effects on human health *via* the internet and social networks, thus spreading the irrational fear of AEFI. Because of this, Lombardi *et al*. conducted a study in 2019 with the aim of characterizing AEFI in general population, in terms of prevalence and preventability, and defining predictors of their seriousness, especially in children population. Results showed that "AEFI were very rare; the vast majority of them was non-serious and, despite the claims of anti-vaccination movements, the simultaneous administration of vaccines was safe and did not influence the risk of reporting a serious AEFI, particularly in children"[79].

The significance of AEFI reporting can certainly be understood in the context of the current COVID-19 pandemic, which in the last two years has caused a public health crisis of unprecedented proportions. Along with different health and social problems, as well as millions of deaths around the world, the global spread of this disease will be remembered for the appearance of the so-called infodemic[80,81], a rapid flow and availability of a large amount of misinformation, especially those related to the treatment and safety of available vaccines. Even more than in regular situation, pharmacovigilance should be the most important and reliable source of all drug safety information and education in a public health crisis, equally for patients, health professionals, and the general public[82]. In order to contribute to the development of collective immunity as quickly and efficiently as possible, the Serbian health authorities were among the first in the world to start mass vaccination of the population against COVID-19 in January 2021, firstly with vaccines made by Pfizer-BioNTech (Germany/USA) and Sinopharm (China), and soon after with almost all available types of COVID-19 vaccines. Unfortunately, the infodemic has caused a public health 'damage' in Serbia, as well; despite exceptional efforts of the ALIMS to provide all necessary information on the safety of available vaccines against COVID-19, the overall response to vaccination is still unsatisfactory.

Conclusion

In organizational and technical terms, the Republic of Serbia has a well-developed system of pharmacovigilance, created on the basis of a proven reliable system of the former SFR Yugoslavia. However, based on the analysis of ADR monitoring and reporting activities in the 2010-2019 period, it can be concluded that Serbia is still far from the expected standards set by the WHO in this aspect of healthcare. The practice of pharmacovigilance is not aimed at finding 'bad' drugs and does not necessarily mean the existence of problems in the quality or formulation of a particular drug but helps increase the safe use of medicines based on monitoring its action and effectiveness in a real situation. A key element of the reliability and efficiency of the national pharmacovigilance system of any country is systematic and organized education of health science students and healthcare professionals on the ADR monitoring and reporting, its importance for public health, but also obtaining valuable information that will help them in rational prescription, application, and distribution of drugs. Identification and elimination of factors that hinder effective implementation of pharmacovigilance activities, organization of continuing education programs for healthcare professionals, more precise definition of activities and responsibilities in this professional area, as well as raising awareness of the importance of spontaneous ADR reporting among healthcare professionals and the general population will certainly contribute to improving the safety of drug use in the Republic of Serbia.

Acknowledgment

The Ministry of Education and Science of the Republic of Serbia (grants number 41012 and 172050) and Provincial Secretariat for Higher Education and Scientific Research of the Autonomous Province of Vojvodina (grant number 142-451-3176/2020-02) supported this scientific work.

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Sažetak

FARMAKOVIGILANCIJA U SRBIJI: DESETOGODIŠNJA FARMAKOEPIDEMIOLOŠKA ANALIZA

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Farmakovigilancija kao znanost i skupina aktivnosti vezanih za otkrivanje, prikupljanje, analizu, razumijevanje i sprječavanje nuspojava lijekova (NPL) predstavlja važnu aktivnost u regulatornom sustavu lijekova bilo koje zemlje. Definiranjem povećane sigurnosti bolesnika kao glavne svrhe prijavljivanja nuspojava, dobro osmišljen nacionalni sustav farmakovigilancije postiže svoj krajnji cilj, a to je zaštita javnog zdravlja. U organizacijskom i tehničkom smislu Republika Srbija ima dobro razvijen sustav farmakovigilancije utemeljen na provjerenom sustavu bivše SFR Jugoslavije, a provodi ga Nacionalna agencija za lijekove i medicinska sredstva Srbije (ALIMS), koja organizira sve aktivnosti usmjerene na jačanje nacionalnog sustava praćenja i izvješćivanja o NPL. Za razliku od susjedne Hrvatske i Crne Gore sa sličnim sustavima farmakovigilancije, Srbija se tek nedavno približila standardu Svjetske zdravstvene organizacije od 200 izvještaja na milijun stanovnika unatoč značajnom povećanju od 180 izvješća o neželjenim reakcijama na milijun stanovnika u 2019. godini (ukupno 1251). S obzirom na to, ovaj je rad imao za cilj pružiti kritički uvid u praksu farmakovigilancije u Srbiji kroz farmakoepidemiološku analizu desetogodišnjeg razdoblja praćenja i izvješćivanja o neželjenim reakcijama na lijekove.

Ključne riječi: *Nuspojave lijekova; Praćenje i izvješćivanje o nuspojavama lijekova; Lijek pod sumnjom; Nuspojave cjepiva*