Arh. farm. 2025; 75: 465 – 479 *Review article/Pregledni rad*

Pharmacovigilance and Adverse Drug Reaction Reporting in Primary, Secondary, and Tertiary Healthcare: A Review of Practices, Challenges, and Recommendations

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Received: 11 February 2025; Revised in revised form: 19 June 2025; Accepted: 07 July 2025

Abstract

According to the World Health Organization, pharmacovigilance is a science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. Since the underreporting of adverse drug reactions (ADRs) remains a significant global issue, reporting ADRs is essential for the success of pharmacovigilance programs. By systematically monitoring and reporting ADRs at the primary, secondary, and tertiary levels of healthcare, pharmacovigilance plays a crucial role in protecting public health. In addition to facilitating the early identification and prevention of negative consequences, reporting also contributes to improving the quality of healthcare services. This article presents a narrative review aimed at synthesizing available literature and regulatory documents related to pharmacovigilance and ADR reporting across various levels of healthcare, with particular emphasis on the national context in Serbia and relevant international comparisons.

Key words: pharmacovigilance, adverse drug reactions, healthcare

https://doi.org/10.5937/arhfarm75-56709

Introduction

According to the World Health Organization (WHO), pharmacovigilance is a science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems (1).

The ultimate goal of pharmacovigilance is to protect public health by continuously monitoring medication safety after marketing authorization. This discipline is essential for the protection of public health, as it enables the identification and minimization of risks associated with medicine use, thereby reducing the incidence of adverse effects and improving overall patient safety (2).

To identify and minimize the risks related to medication usage, the national pharmacovigilance system of Serbia is established and maintained in large part by the Medicines and Medical Devices Agency of Serbia (ALIMS). In order to guarantee high-quality, safe, effective, and easily accessible medications and medical devices, the ALIMS was formed in 2004. According to the law, it reports its activity to the Government of the Republic of Serbia. The ALIMS is responsible for the evaluation and approval of medicines and medical devices, pharmacovigilance activities, and monitoring the quality and safety of medicinal products in use (3).

Pharmacovigilance plays a significant role in reducing unwanted side effects and helps predict potential adverse drug effects at the population level. Adverse drug reactions (ADRs) are receiving more attention in order for medications to be used properly in the treatment and prevention of illnesses (4).

Estimates show that between 5% and 10% of all hospitalizations may be caused by side effects of medicines, and many of these side effects can be prevented. Therefore, it is important that all actors in the healthcare system are aware of their role in this process. As a result, pharmacovigilance is crucial to guaranteeing the safe use of medications and reducing the hazards involved. By continuously monitoring and analyzing ADRs, this science contributes to patient health preservation and enhances the standard of healthcare (5).

Methods

This article presents a narrative review aimed at synthesizing available literature and regulatory documents related to pharmacovigilance and ADR reporting across different levels of healthcare, with particular emphasis on the national context in Serbia and relevant international comparisons.

A non-systematic literature search was conducted in the PubMed, Scopus, and Web of Science databases, covering the period from 2000 to 2025. The search terms included the combinations of the following keywords: “pharmacovigilance,” “adverse drug reactions,” “drug safety,” “reporting systems,” “primary healthcare,” “Serbia,” “clinical research,” and “regulatory frameworks.” In addition, official websites of regulatory agencies (e.g., ALIMS, WHO) were consulted to obtain up-to-date reports and guidance.

The inclusion criteria were as follows:

1. Peer-reviewed articles and official reports published in English or Serbian;
2. Publications relevant to ADR reporting practices in primary, secondary, or tertiary care;
3. Studies discussing national or international pharmacovigilance systems;
4. Articles addressing challenges or educational gaps in ADR reporting.

The included materials were selected based on their relevance and contribution to the discussion of pharmacovigilance practices and their applicability to the Serbian healthcare system.

The Role of Pharmacovigilance in Clinical Research

Pharmacovigilance plays a crucial role not only after a drug is marketed but also throughout the entire drug development process. Drug development begins with preclinical testing, which involves laboratory and animal studies to evaluate the safety, pharmacodynamics, pharmacokinetics, and toxicological profile of a potential drug. Upon obtaining promising preclinical results, the compound advances to clinical trials, conducted in four sequential phases (6, 7).

Phase I studies involve a small number of healthy volunteers or patients and primarily aim to assess the safety, tolerability, and optimal dosage of the drug. Phase II trials are conducted on a larger patient population to further evaluate efficacy and monitor side effects. Phase III trials involve an even broader patient population and are intended to confirm therapeutic efficacy, compare the new drug with standard treatments, and identify any less common ADRs. Although these phases are rigorously controlled, they have limitations in detecting rare, long-term, or population-specific ADRs. This limitation highlights the critical role of Phase IV – post-marketing surveillance – during which pharmacovigilance systems monitor the drug's safety profile in real-world settings and broader populations. Through spontaneous reporting, observational studies, and risk management plans, Phase IV enables the detection of previously unknown ADRs and helps regulatory authorities take timely action when necessary (6, 7).

The tragic incident involving thalidomide prompted the establishment of systematic monitoring and reporting of adverse events. Between 1957 and 1961, thalidomide, a sedative used to treat nausea in pregnant women, caused 10,000 to 15,000 cases of phocomelia, or severe limb abnormalities. This disaster highlighted not only the need for stricter regulations on drug testing before market authorization but also underscored the importance of ongoing safety monitoring after drugs are marketed. Consequently, the WHO Programme for International Drug Monitoring was established in 1968, and Serbia (then Yugoslavia) joined as the 18th member in 1974. This tragedy deeply impacted the medical community and shaped modern pharmacovigilance practices aimed at preventing similar incidents in the future (8).

In preclinical studies, it is often difficult to predict side effects that may occur during the initial phases of clinical trials. For example, an analysis of 30 Phase I studies

conducted between 1993 and 1998 showed that the incidence of side effects was similar in patients receiving a placebo and those taking an active drug, with headache being the most commonly reported adverse event. These effects were mostly subjective and could not have been identified in animal models. In contrast, some side effects, such as constipation and abnormal liver function tests, were observed in animals but occurred only in subjects receiving the active compound (6, 7).

The significance of pharmacovigilance during clinical trials has grown, especially with the increasing complexity of novel therapies, including biologics and gene therapies. It is now widely recognized that safety monitoring must begin in the earliest phases of human research, rather than only after marketing authorization (6, 7).

In the Republic of Serbia, the Law on Medicines and Medical Devices, along with accompanying regulations, imposes strict obligations on sponsors and investigators to report adverse drug reactions (ADRs) occurring during clinical trials. Serious and unexpected ADRs must be promptly reported to the ALIMS and relevant ethics committees, in accordance with international standards such as the International Council for Harmonisation Good Clinical Practice (ICH-GCP). These legal provisions are designed to protect trial participants and ensure the timely management of emerging safety data. Moreover, the ALIMS oversees the implementation of pharmacovigilance plans within clinical trial protocols, ensuring adherence to reporting requirements and timelines (3, 9).

Many countries, including Serbia and member states of the European Union, have progressively strengthened their pharmacovigilance regulations, aligning them with international standards such as ICH-GCP and EU pharmacovigilance legislation. These developments reflect the ongoing regional variations in regulatory frameworks while underscoring a shared global commitment to enhancing safety monitoring systems (9, 10).

While Serbia has developed a robust legal framework for pharmacovigilance in clinical trials, other regions are still in the process of developing and refining their safety monitoring capabilities. For example, the clinical research sector in the Middle East and North Africa (MENA) is relatively young, with pharmacovigilance practices still evolving and varying significantly across countries due to differences in healthcare infrastructure, regulatory focus, and availability of modern diagnostics and therapies (11).

In light of the increasing participation of MENA countries in regional and multinational clinical trials, Cheaib identified key areas needing reform to establish effective pharmacovigilance systems. Challenges include regulatory ambiguity in accelerated reporting, lack of causality-based reporting criteria, and overburdening of regulatory authorities with non-informative cases. Moreover, despite global emphasis on real-time safety data, many local regulators still do not require continuous updates to cumulative safety profiles. As highlighted by Cheaib, priority should be given to improving trial-specific reporting (including for pregnancy and fatal events) and establishing local pharmacovigilance protocols aligned with international standards (11).

Overall, pharmacovigilance serves as a fundamental pillar of clinical research ethics and regulatory compliance, playing a key role in the development of safer and more effective therapies (12).

Adverse Drug Reactions: Classification and Clinical Relevance

ADRs encompass a wide range of unwarranted and unintended effects that may occur during standard use of medications for therapeutic, prophylactic, or diagnostic purposes (5). According to the WHO, these reactions may vary from mild symptoms such as nausea, dizziness, or skin rashes to severe outcomes including hospitalization, disability, or even death. A particular category of ADRs, termed serious adverse reactions, is defined as adverse reactions that result in death; that are life-threatening; that require hospitalization or prolongation of existing hospitalization; that result in persistent or significant disability or incapacity, or cause a birth defect (13). Although pharmacotherapy has advanced significantly, the recognition and systematic monitoring of ADRs developed only later, partly due to the earlier underestimation of the potential harm caused by drugs and the complexity of establishing causal links (14, 15).

A side effect must be distinguished from an adverse event. Unlike adverse events, which are merely temporally associated with drug intake, side effects are both causally and temporally related to drug intake (5).

According to the mechanism of occurrence, side effects were originally divided into Types A and B, later expanded to include Type C. Presently, there are 5 types (16). These include:

1. Type A is characterized by dose-dependent reactions that are generally predictable and are a consequence of the pharmacological action of the drug.
2. Type B is characterized by phenomena that are not dose-dependent, often unpredictable, and, most importantly, they are not related to the pharmacological activity of the drug.
3. Type C is a dose-dependent phenomenon. It is characterized by a precisely predicted time of the onset of symptoms, and this is usually a consequence of the cumulative effect of the drug itself.
4. Type D is an unusual reaction of the organism itself to the drug. It often occurs only after a certain time and is not dose-dependent.
5. Type E is characterized by all those adverse reactions that occur after the discontinuation of the therapy, so it is necessary to reintroduce the drug and gradually reduce the dose until complete cessation (16).

Previous research indicates that reports of preventable adverse reactions are rare, with significant variability across healthcare sectors and hospital units (17). As these reports often underestimate the true incidence, caution is needed when interpreting such data. Nevertheless, incident reporting remains valuable for uncovering previously

unrecognized events and identifying risks associated with harmful drugs, ultimately helping in the reduction of the occurrence of common adverse effects (17).

The Importance of Reporting Adverse Drug Reactions in Primary, Secondary, and Tertiary Healthcare Institutions

Reporting ADRs is a crucial component of patient safety in primary, secondary, and tertiary healthcare, and should be emphasized when discussing the importance of pharmacovigilance within the healthcare system. This activity enables the following:

1. Increasing drug safety: By actively reporting ADRs, patients and healthcare providers can help identify potential risks and enhance drug safety in routine practice.
2. Improving healthcare quality: Providing information about ADRs contributes to a better understanding of the effects of drugs, which can lead to improvements in the way they are prescribed and treated.
3. Regulation and supervision: Through systematic reporting, healthcare institutions can implement more effective measures for monitoring and controlling drugs, thereby reducing the risk of serious complications.
4. Education and awareness: Increasing the understanding of the significance of reporting ADRs can encourage more patients and healthcare professionals to actively participate in the process, which will contribute to a better overall health status of the population (18, 19).

To provide a clearer understanding of the structure of responsibilities in pharmacovigilance and the flow of ADR reporting, Figure 1 illustrates how information is communicated across different levels of healthcare – from general practice, through clinical centers, and ultimately to the national regulatory agency.

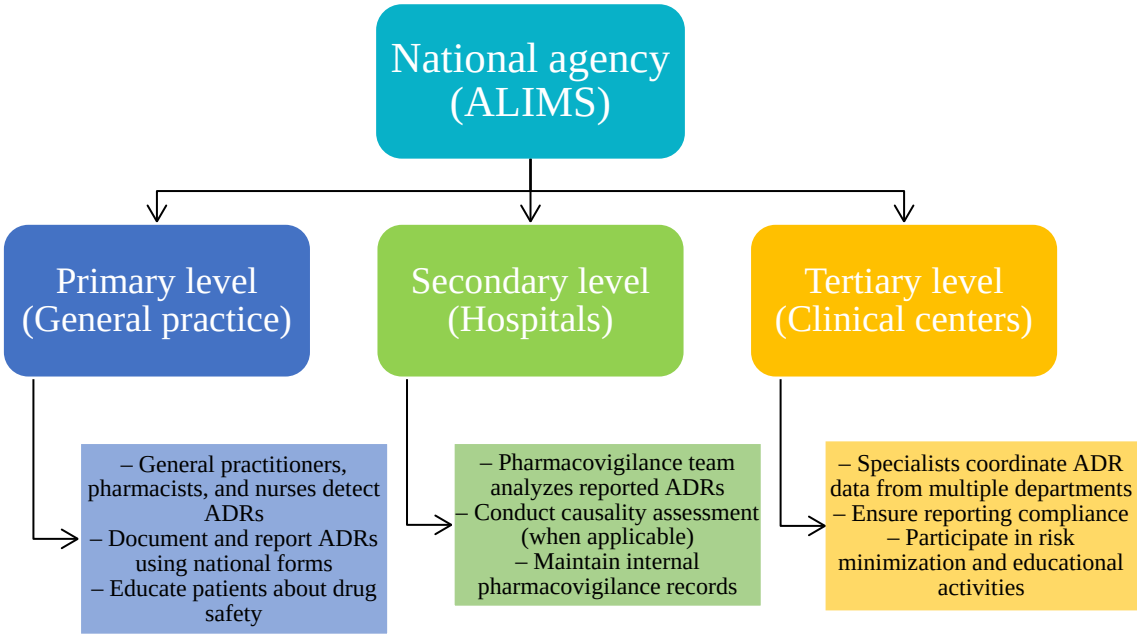

Figure 1. Flowchart of pharmacovigilance responsibilities and ADR reporting across different levels of healthcare

Slika 1. Dijagram toka odgovornosti u farmakovigilanci i izveštavanja o neželjenim reakcijama na lekove na različitim nivoima zdravstvene zaštite

A study conducted in China to assess the future needs of existing systems investigated the current status of pharmacovigilance and ADR reporting in healthcare institutions (4). As a research method, a cross-sectional survey was employed. In all 31 Chinese provinces, 10,063 physicians, nurses, and pharmacists from primary, secondary, and tertiary hospitals participated in the study. In March 2020, the study was carried out on behalf of the National Center for Monitoring Adverse Drug Reactions in China. The participants' sociodemographic traits, their knowledge of the pharmacovigilance system, and the state of hospital ADR reporting were the three areas that were evaluated. The following results were obtained: healthcare professionals had already heard of the term pharmacovigilance (89.40%) and were familiar with the subject of reporting (68.47%), content (65.94%) and scope (64.83%) of pharmacovigilance. Most hospitals sent responsible specialists (87.64%) and departments (86.25%) to monitor ADR reporting. A total of 58.66% of tertiary, 45.25% of secondary and 38.90% of primary institutions retrieved unwanted medicines from the hospital information system. Moreover, 53.09% of tertiary healthcare institutions, 38.93% of secondary and 23.89% of primary institutions established an automatic prescription verification system to warn of the risk of ADRs. Healthcare professional reports (99.92%) and patient feedback (77.99%) were included in the majority of hospital reports on ADRs. The study authors concluded that Chinese healthcare professionals generally have a good awareness of pharmacovigilance,

and pharmacovigilance is relatively more advanced in China compared to other developing countries (4).

A study evaluating the pharmacovigilance and ADR reporting behaviors, attitudes, and knowledge of medical staff (physicians and pharmacists) at an Egyptian hospital discovered that, in addition to obstacles to reporting ADRs, there were poor levels of general knowledge (median: 40%) and behaviors (median: 50%) about pharmacovigilance and reporting ADRs (20). Nonetheless, attitudes were mostly favorable. The difficulty in detecting whether ADRs had occurred was the primary obstacle to reporting them (42.3%). The results indicate that the significant discrepancy between experienced and reported ADRs may be reduced by having a better grasp of pharmacovigilance and ADR reporting. Appropriate ADR reporting must be created in order to evaluate the efficacy of personalized medicine (20).

Since underreporting of ADRs is still a significant issue globally, reporting spontaneous ADRs is essential to a successful pharmacovigilance program (21). A research that aimed to assess the attitude, knowledge, and practice of healthcare workers regarding pharmacovigilance, along with barriers and factors to encourage reporting of adverse events in tertiary care hospitals, was conducted in Pakistan in 2020 among a sample of 669 healthcare workers. A convenient sample technique was used to gather data from physicians, nurses, and pharmacists working in seven tertiary care hospitals between July 2019 and March 2020 as part of a cross-sectional study based on a questionnaire. Overall, healthcare professionals showed poor knowledge (79.5%) about adverse event reporting and pharmacovigilance, but 73.5% of pharmacists were more knowledgeable compared to 18.7% of physicians and 13.8% of nurses. Moreover, 95.6% of doctors, 94.4% of nurses, and 75.5% of pharmacists showed poor reporting practices. However, the majority of healthcare workers showed a generally positive attitude (94%) towards reporting side effects. The most frequently mentioned barriers were the unavailability of reporting forms (92.5%), the lack of a professional environment for discussing side effects (82.5%), and the lack of training (81.8%), while the most common factors to encourage the reporting of side effects were mandatory reporting (85.9%) and the provision of guidelines and training for the management of side effects medicine (84.3%). Health workers' professional status was found to be significantly correlated with their overall knowledge, attitude, and practice, while their knowledge and practice of pharmacovigilance and their reporting of side effects were found to be moderately positively correlated (16). The conclusion was that there is a general lack of knowledge and poor reporting practices among healthcare workers about reporting side effects and pharmacovigilance. Therefore, this study suggests that all stakeholders should devise strategies for proper education and training of healthcare professionals in this area to improve overall patient safety and safe medication use (21).

When it comes to the importance of pharmacovigilance for primary care workers, physicians play an important role in recognizing and reporting side effects, which is important for national pharmacovigilance centers to record and evaluate these concerns and take the necessary actions to maintain patient safety related to the use of medicines.

The purpose of national pharmacovigilance centers is for clinicians to understand their functions, including monitoring, investigation, and evaluation of adverse event reports, along with periodic assessments of drug use and risk through multiple sources (19).

While descriptive data provide valuable insight into pharmacovigilance practices, a critical examination of underlying challenges and the potential for digital innovation is necessary to guide future improvements (22).

Critical Analysis of Pharmacovigilance Reporting Challenges and Opportunities

Despite the progress in pharmacovigilance systems worldwide, several persistent challenges limit the effective reporting of ADRs. Understanding the root causes of underreporting, particularly in low- and middle-income countries (LMICs), is essential for improving patient safety and optimizing pharmacovigilance strategies (23).

Root Causes of Underreporting

Underreporting remains a major obstacle due to multiple factors. Healthcare professionals often lack sufficient knowledge about pharmacovigilance and ADR reporting procedures. Fear of legal repercussions, blame, or professional consequences discourages open reporting. Additionally, complex and time-consuming reporting processes, absence of feedback from regulatory bodies, and insufficient integration of reporting systems contribute to low reporting rates (15, 23).

Barriers to ADR Reporting in Low- and Middle-Income Countries

LMICs face specific challenges, including limited healthcare infrastructure, scarcity of trained pharmacovigilance personnel, weak regulatory frameworks, and financial constraints. Cultural and hierarchical barriers may inhibit frontline healthcare workers from reporting ADRs. Moreover, inadequate national guidelines and low public awareness further impede effective pharmacovigilance adoption (24, 25).

Effectiveness of National Systems in Signal Detection

The capability of national pharmacovigilance centers to detect safety signals depends on the volume and quality of data, as well as analytical resources. Advanced data management systems and standardized reporting improve signal detection; however, many countries still struggle with fragmented data, inconsistent reporting, and insufficient analytical capacity, delaying timely safety interventions (26).

Role of Digital Solutions and Automation

Emerging digital technologies are reshaping pharmacovigilance by enabling more efficient and accurate data collection and analysis. Electronic reporting platforms, mobile applications, and telehealth tools facilitate timely ADR reporting. Artificial intelligence and machine learning offer enhanced capabilities for signal detection and risk prediction. Nevertheless, challenges such as data privacy, interoperability issues, and the need for specialized training remain critical for widespread adoption (24).

Table I Comparison of Pharmacovigilance Systems, Barriers, and Enablers in Selected Countries

Tabela I Poređenje sistema farmakovigilance, prepreka i podsticajnih faktora u različitim zemljama

Country	Main Barriers to ADR Reporting	Facilitators and Enablers	Digital Innovations and Automation
China	Complex reporting processes, training gaps	National monitoring centers, automated prescription verification systems	Electronic reporting, AI-driven data analysis
Egypt	Low awareness, fear of consequences	Generally positive attitudes among healthcare workers	Early stages of digital adoption, need for training
Pakistan	Lack of education, unavailability of forms	Mandatory reporting policies, training programs	Initial implementation of digital systems
Serbia	Low reporting practices, limited awareness	ALIMS oversight, publicly accessible reports	Gradual digitalization, online reporting portals
Other LMICs	Limited infrastructure, weak regulations	International collaborations, capacity-building initiatives	Variable digital adoption, mostly low

Through the National Centre for Pharmacovigilance, ALIMS conducts all planned efforts aimed at bolstering the pharmacovigilance system and the regulatory system of pharmaceuticals, including post-registration surveillance of side effects in Serbia. Bosnia and Herzegovina, Montenegro, and Croatia all have similar pharmacovigilance legislation. While the annual reports on the monitoring and reporting of ADRs of Bosnia and Herzegovina are still inaccessible to the general public, those from Serbia, Croatia, and Montenegro are publicly accessible on the websites of the national agencies for medications and medical devices (27).

According to the latest reports from the ALIMS website (3), the number of ADR reports in Serbia has remained relatively stable in recent years. In 2019, a total of 1,251 ADR cases were reported, while in 2023, the number was slightly lower at 1,209 reports. Despite this slight decrease, these figures indicate a continued effort to maintain and improve pharmacovigilance reporting practices. However, Serbia still aims to reach the WHO standard of 200 ADR reports per million inhabitants to strengthen its national pharmacovigilance system (3, 28).

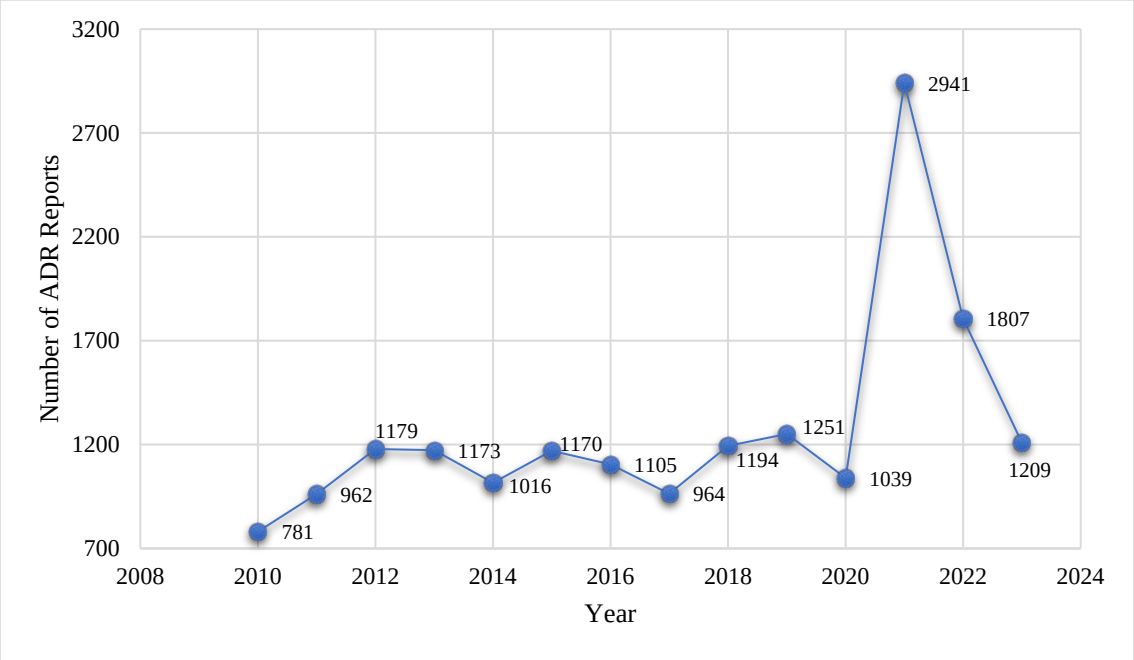

Figure 2. **Trend of reported ADRs in Serbia (2010–2023), based on data from the ALIMS**

Slika 2. **Trend prijavljenih neželjenih reakcija na lekove u Republici Srbiji (2010–2023), na osnovu podataka ALIMS-a**

Most doctors understand the importance and relevance of pharmacovigilance in clinical practice. However, the awareness of specific pharmacovigilance programs and practical aspects, such as where and what to report in terms of ADRs, remains low (19, 29). Therefore, to raise awareness and improve the quality of ADR reporting, educational and training initiatives are necessary. Lectures, small interactive learning groups, and hands-on demonstrations in real clinical settings can all contribute to achieving this goal (29, 30).

Conclusion

Effective pharmacovigilance across all levels of healthcare – primary, secondary, and tertiary – is essential for ensuring patient safety and improving the quality of medical care. The consistent reporting of ADRs enables the early detection of potential drug-related risks, contributing to safer medication use and informed clinical decision-making.

Despite the progress, significant challenges remain, including insufficient awareness, underreporting, and logistical barriers, especially in low- and middle-income countries. Digital innovations and targeted educational initiatives show promise in addressing these gaps but require widespread implementation and continuous support.

For Serbia, strengthening the pharmacovigilance system depends on increasing healthcare professionals' knowledge and engagement, simplifying reporting procedures, and promoting patient involvement. Ultimately, a robust pharmacovigilance framework

not only safeguards individual patients but also enhances public health by fostering rational drug use and minimizing the incidence of preventable adverse events.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This research received no external funding.

Author contributions

A.R.: Conceptualization, Writing – original draft, Visualization; **E.M**.: Conceptualization, Visualization, Writing – review & editing; **T.S.**: Conceptualization, Visualization, Writing – review & editing, Supervision.

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Farmakovigilanca i prijavljivanje neželjenih reakcija na lekove u primarnoj, sekundarnoj i tercijarnoj zdravstvenoj zaštiti: pregled praksi, izazova i preporuka

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Kratak sadržaj

Prema Svetskoj zdravstvenoj organizaciji, farmakovigilanca je nauka i skup aktivnosti koje se odnose na otkrivanje, procenu, razumevanje i prevenciju neželjenih reakcija na lek, kao i drugih problema u vezi sa lekom. Budući da je nedovoljno prijavljivanje neželjenih reakcija na lekove još uvek značajan globalni problem, prijavljivanje neželjenih reakcija na lekove predstavlja ključni element za uspešan program farmakovigilance. Sistemskim praćenjem i prijavljivanjem neželjenih reakcija lekova na primarnom, sekundarnom i tercijarnom nivou zdravstvene zaštite, farmakovigilanca ima ključnu ulogu u očuvanju javnog zdravlja. Osim što olakšava rano prepoznavanje i izbegavanje negativnih posledica, prijavljivanjem neželjenih reakcija doprinosi se i poboljšanju kvaliteta zdravstvenih usluga. Ovaj rad predstavlja narativni pregled koji ima za cilj sintezu dostupne literature i regulatornih dokumenata vezanih za farmakovigilancu i prijavljivanje neželjenih reakcija na lekove na različitim nivoima zdravstvene zaštite, sa posebnim osvrtom na nacionalni kontekst Srbije i relevantna međunarodna poređenja.

Ključne reči: farmakovigilanca, neželjene reakcije na lekove, zdravstvena zaštita