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ABSTRACT
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in the PhD program "Social Medicine and Organization of
by professional direction 7.4. Public Health
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On the subject:

EFFECTIVE MANAGEMENT OF PROCESSES MEDICINAL SAFETY

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The dissertation is 126 pages long, inclusive table of contents, bibliography and appendices. The literature used includes 92 sources.

The numbering of the tables, diagrams and figures in the auto-reference is preserved as it is in the dissertation.

The dissertation was discussed, accepted and directed for defense before a scientific jury by the Departmental Council of the Department of Health Policy and Management, Faculty of Public Health „Prof. Tsekomir Vodenicharov, MD, DSc" Medical University of Sofia.

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ABBREVIATIONS USED

ADR	Adverse Drug Reaction
BCP	Business Continuity Plan
BCP-DRP	Business Continuity and Disaster Recovery Plan
CA	Competent authorities
CAPA	Corrective and Preventive Actions
CCDS	Company Core Data Sheet
CIOMS	Council for International Organizations of Medical Sciences
CT	Clinical Trial
DHPC	Direct Healthcare Professional Communications
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EU QPPV	European Qualified person responsible for pharmacovigilance
EV	EudraVigilance
EVDAS	EudraVigilance Data Analysis System
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HCPs	Healthcare Professionals
ICSR	Individual Case Safety Report
ISO	International Organization for Standardization
KPI	Key Performance Indicators
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorisation Safety Studies

PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Check
QMS	Quality Management System
EU QPPV	Qualified Person responsible for Pharmacovigilance
RA	Regulatory Affairs
RMP	Risk Management Plan
SDEA	Safety Data Exchange Agreements
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
WI	Working Instruction
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XML	Extensible Markup Language

INTRODUCTION

"Pharmacovigilance", As per World Health Organization (WHO), "Pharmacoivigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems". The set of measures and activities undertaken in the process of development, authorization and post-marketing use of medicinal products, leading to the achievement of the lowest and at the same time acceptable level of risk, for the achievement of a given benefit, is called Drug Safety.

The monitoring of Drug Safety in the post-marketing period carries the correct term pharmacovigilance.

Medicines can affect the body in unwanted and harmful ways. These effects, called side effects or adverse reactions, are a risk of medicines.

By the time a new drug is approved for use, the active substance has been tested and the data allow or can be concluded that the benefits of the drug outweigh the risks.

However, once a drug is Marketing Authorisation, it is used in normal health conditions in many patients who may differ from the study population, for example by age or concomitant diseases.

It is therefore important to identify any new or changing drug risk as soon as possible and to take measures to minimize the risk and promoting safe and effective use.

EMA coordinates pharmacovigilance in the EU and operates services and processes in line with EU legislation. The EMA pharmacovigilance system manual describes how EMA performs, monitors and reports on its pharmacovigilance duties for human medicines.

The EMA Pharmacovigilance System Guide describes how the agency carries out, monitors and reports its pharmacovigilance obligations for medicines for human use. Individually, each EU member state has national legislation describing the specific drug safety processes in each individual member state.

Drug safety by pharmaceutical companies

The company that holds the medicines's marketing authorization has legal obligations to continuously collect data and conduct follow-up of medicines use.

In Bulgaria, the monitoring of drug safety (pharmacovigilance) was introduced in July 2012. All Holders of the Authorization for the Use of Medicinal Products (MAH) were obliged

to appoint a Qualified Person in Pharmacovigilance with appropriate qualifications and relevant medical education if possible - (QPPV), deputy QPPV, to develop and implement PSMF and Standard Operating Procedures (SOPs), to register in the European portal for reporting product information, for reporting Adverse Drug Reactions (ADRs), registration of QPPV in EV portal.

In addition, MAHs had to submit two documents related to Pharmacovigilance in the initial dossier for the registration of medicinal products: 1.8.1 - Summary of PSMF and 1.8.2 - RMP - Risk Management Plan for each medicinal product. To these two documents, the MAH declared that it has the necessary means to ensure the monitoring of drug safety. MAHs submitted to the Bulgarian Drug Agency (BDA), according to a special schedule developed by the BDA, Periodic Safety Reports (PSURs) in the first years until 2016, when all PSURs began to be submitted to the EMA in the PSUR Repository as PSUSA (single PSUR report) according to a special schedule developed by EMA.

The MAH had to provide sufficient autonomy and authority to the QPPV to be able to fulfill all its pharmacovigilance obligations.

Drug safety data must be submitted to the authorities in a timely manner, and any emerging concern about the benefit-risk balance must be reported immediately.

If necessary, the authorities may request further investigations, including official inquiries. There are regulatory procedures in place to update product information and implement other safety measures.

EU Pharmacovigilance System

The European Union's pharmacovigilance regulatory system includes:

- the competent authorities for the regulation of medicines in the Member States;
- The European Commission as the competent authority for medicinal products authorised centrally in the EU;
- European Medicines Agency, with responsibilities for centrally authorized products and coordination of the system.

Responsibilities within the system

The EU system performs the following tasks:

- Collection of data from all available sources, mainly case reports of individual patients and results of epidemiological studies and trials;
- Analyzing data and identifying signals of possible new or changing risks;

- Evaluation of Risk Management Plans, Case Reports, Study Reports, Periodic Safety Update Reports and Risk-Benefit Reviews submitted by MAH.

Coordination systems in EMA

The Agency assists the competent authorities of the Member States and coordinates the system, in particular by:

- EudraVigilance, the EU reporting and data storage system for case reports;
- the EU's early warning and incident management systems for timely and adequate responses to new safety data;
- the Pharmacovigilance Risk Assessment Committee (PRAC), which provides advice on all aspects of pharmacovigilance and risk management;
- ENCePP, the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance, to facilitate independent multicentre studies;
- good practices in Pharmaceutical Safety (GVP) and other standards;
- developing scientific networks to improve evidence for decision-making and the effectiveness of public health pharmacovigilance.

Pharmacovigilance in the European Medicines Agency

In line with Article 57 (1)(d) of Regulation (EC) No 726/2004 which provides the legal basis for the dissemination of information on adverse reactions (as well as, Directive 2001/83/EC, as amended, and Directive 2001/20/EC the EMA has developed the process of Policy an access of EudraVigilance, which has provided the stakeholders such as National Competent Authorities (NCA). In order to comply with its legal obligations related to the promotion and protection of public health by monitoring the safety of authorized medicinal products and to detect and confirm any change in their risk-benefit balance, the Agency operates a quality-assured pharmacovigilance system. The detailed operational requirements of all EMA pharmacovigilance tasks that make up the EMA pharmacovigilance system are the pharmacovigilance policies, which are part of EMA's integrated quality management system and can be found on the website of Agency. The EMA has a coordinating role in the functioning

of the EU Pharmacovigilance and cooperation system with the Member States and the European Commission.

The monitoring of Pharmacovigilance has become mandatory and the activities that each MAH must guarantee have increased a lot in recent years. This activity is important for the health system and is carried out worldwide. Pharmacovigilance has expanded beyond simply identifying adverse events.

However, there are numerous issues that must be addressed in ensuring the safety of medicines.

According to the World Health Organization, Pharmacovigilance is a science and activity related to the detection, evaluation and prevention of adverse reactions. The purpose and scope of Pharmacovigilance is broad and includes multiple components, such as medication errors, use of counterfeit or unauthorized products, lack of efficacy, drug interactions, and correct prescribing of medications.

The Pharmacovigilance process includes five main steps:

1. Collect, manage and analyse. This process group describes the collection, overall management and analysis, where applicable, of data, information and documents in relation to product safety.

2. Review and assess. This process group describes the overall review and analysis (e.g. by rapporteurs) of data, information and documents in relation to product safety.

3. Decide and act. This process group describes the overall coordination of decision-making through committees (e.g. PRAC, CHMP) and the coordination group (CMDh).

4. Communicate. This process group describes the overall coordination of safety communication.

5. Monitor. This process group describes the overall monitoring of implementation and impact of proposed regulatory actions. After definitively establishing the cause-and-effect relationship and with the patient's symptoms, the EMA or the Agencies of the Member country (MC) are notified of the findings made about the safety problem of a particular drug and the EMA or MC prepares a formal report known as RAR (Risk Assessment Reports) . In such cases, a Direct Healthcare Professional Communication (DHPC) letter is sent, which may be followed by a change in product information, Educational materials or a Post Marketing Safety Study (PASS) decision to be made by the MAH.

As seen, Pharmacovigilance is not just about reporting ADRs by patients and healthcare professionals, but that benefit-risk assessment is the most important driver of patient safety, not just the frequency of the types of adverse events. that less than 10% of all adverse events are

actually reported, yet MAHs are still drowning in a sea of reporting obligations. Effective safety systems can help MAHs meet this burden. It is important to note that medical effectiveness is even more important than operational effectiveness in the Pharmacovigilance process.

Due to ever-increasing pressure from regulators, pharmaceutical companies are forced to streamline various reporting procedures and ensure that safety reports are processed in an accurate and timely manner. This requires synchronizing adverse reaction reporting and other disparate reports, such as electronic submissions and document management tools. Pharmaceutical companies have changed their existing processes and systems to adhere to set protocols and standards. The EMA (European Medicines Agency) has introduced various structures and models for pharmaceutical companies and regulatory authorities to submit adverse event reports electronically in specific formats such as E2B (electronic safety reports). It is obvious that the mortality and morbidity costs of drugs are much higher than the costs of their development process. On average, 10% of approved drugs are withdrawn from the market due to serious side effects. Pharmaceutical companies spend approximately one billion dollars to develop a drug, and it can take many years. Although a significant amount of information on product efficacy can be obtained during the pharmaceutical drug development process, it is impossible to determine the complete safety profile of a product in premarket studies. Some drugs may be withdrawn from the market due to safety concerns related to the occurrence of severe side effects.

Post-marketing surveillance is vital to identify drug safety problems that were not discovered during pre-marketing studies. Thereafter, the primary source of safety information for newly approved drugs is post marketing surveillance of adverse reactions in both the community and clinical settings.

Healthcare professionals play a crucial role in the Pharmacovigilance system. They should have considerable knowledge and experience in the area of drug safety, to recognize, manage and report drug safety problems early. In addition, healthcare professionals should be well educated on the need and procedure for reporting of adverse events. They should have a combination of training and research skills in this field. Despite global concerns about Pharmacovigilance, there is still a lack of awareness and knowledge about Pharmacovigilance and reporting of ADRs among health professionals. Furthermore, recent studies have shown that ADRs are underreported, with only 2-4% of all ADRs and 10% of serious ADRs reported worldwide. It is recommended that healthcare professionals, especially medical doctors, pharmacists, and nurses, report any suspected adverse reaction, especially for newly authorized drugs and serious events.

Therefore, Pharmacovigilance assessment should be considered an integral part of the daily clinical practice of healthcare professionals.

They should be motivated to carry out the reporting and evaluation because they could be the most important participant in the Pharmacovigilance processes.

AIM, TASKS, MATERIALS AND METHODS OF RESEARCH

The aim of the present dissertation is to analyze the attitudes towards reporting of suspected adverse drug reactions mainly by medical doctors in the post-marketing period, i.e. after the medicinal product has received a Marketing Authorization and is used by the population.

To achieve the aim so set in the scientific research, the following tasks are planned to be solved:

1. To carry out a literature review of scientific publications and a specialized regulatory database on Drug Safety in Bulgaria and in the individual EU member states.
2. To study and systematize the various aspects and challenges for the participation of medical professionals in the monitoring of Drug Safety.
3. To analyze the regulatory dimensions and attitudes of physicians and other healthcare professionals to participate in Pharmacovigilance and tools that would improve reporting of ADRs.
4. To develop special informational materials for doctors to increase their awareness of the quality, efficacy of ADR reports for medicinal products.

In order to achieve the aim of the scientific research, they were following scientific methods of analysis were applied: documentary method, sociological method, mathematical-statistical analysis, graphic analysis.

The main materials used to achieve the aim and tasks of the dissertation work are survey cards for each of the conducted surveys according to Appendix 1.

The first survey – A voluntary, anonymous survey was conducted among medical doctors and nurses working in a large hospital in the city of Sofia to obtain information on whether they report observed ADRs, how they are already treating received ADRs, where they get objective information about medicinal products, whether sufficient efforts are being made to prevent the occurrence of ADRs. Do they receive PRAC and DHPC decisions and from whom?

Do they have scheduled procedures in their hospitals for ADRs. The survey was conducted in the period September 14 - 17, 2020. All doctors and nurses who were invited to participate in the survey agreed to answer the questions. Selection criteria: It included doctors from different specialties and nurses working in the emergency department.

Questionnaires were sent for completion to 50 medical doctors and 18 nurses, and subsequently 2 (2%) of the medical doctors declined to participate in the study. All nurses agreed to participate. Number of participants: A total of 48 medical doctors and 18 nurses participated in the study. Survey procedure: Creation of protocols and standard questionnaires to complete, one for medical doctors and one for nurses. Medical doctors were interviewed using a structured questionnaire that included demographic variables (age, gender, medical specialty) and asked thirteen questions for the purposes of the study. The last three questions were general questions about their drug safety awareness.

The first four questions were of specific interest: reporting, management, and review of ADRs observed throughout the hospital, review of ADRs observed in their medical unit, information on alerts generated by new alerts received by the DHPC or published by regulatory agencies or published in medical journals. A Likert scale (0-10 points) was used to evaluate the doctors' opinions.

The questionnaire designed for nurses was developed based on knowledge, attitudes and practices of ADR reporting, communication and based on an existing instrument aimed at general practitioners. It consists of three sections and a section with socio-demographic and occupational data.

The questionnaire consists of 11 multiple-choice questions and measures theoretical knowledge of drug safety in general and reporting of suspected ADRs. For example, for theoretical knowledge are: "the WHO definition of ADRs", "targets of drug safety", "limitations of pre-marketing drug studies". Each item consists of a statement or question with three possible answer options, of which only one is correct ("0 - wrong answer"; "1 - correct answer"). Correct answers are summed and converted to 11 points.

The attitudinal section of the questionnaire aims to measure attitudes towards under-reporting of suspected ADRs. Items are rated on a 5-point Likert scale ranging from “1-strongly disagree” to “5-strongly agree” An example item is: “Reporting ADRs is a bureaucratic process”, “I do not have time to report ADRs during his job", "the ADR report is the doctor's duty". Lower scores indicate a more positive attitude toward reporting ADRs.

The knowledge and reporting style section of the questionnaire aims to measure reporting skills and attitudes. For example: "I know where to find the ADR reporting form", "I

know how to complete and submit it", "I have a case of a reported ADR in the last year". Each item is separated by two possible answers: "0-no" or "1-yes".

The second study - was conducted only among doctors from all over Bulgaria.

With the assistance of the BLS, a developed questionnaire consisting of 20 questions with several sections was sent to 650 doctors from all over the country:

general information, reporting adverse reactions - general information, motivation for reporting adverse reactions, need for reminders and ways, how they receive new information about the risks of medicinal products, what training they have and whether they need further training, how they avoid adverse reactions, when they decide to prescribe a treatment, do they feel guilty if a certain adverse reaction could have been prevented, sources of reference for medicinal products and what are their suggestions for improving drug safety monitoring.

1. MATERIALS AND METHODS:

In order to achieve the objective of the scientific research, **scientific methods** of analysis were applied:

• ***Documentary method*** – review and systematization of the results obtained from questionnaires, normative acts and other literary sources for Bulgaria and the European Union, overview articles, reports of international organization, leading experts and competent authorities, and others – in order to identify specific challenges posed to pharmacovigilance.

The selection and research of the scientific publications was carried out using certain keywords(drug product, pharmacovigilance, adverse drug reaction, physician, medical specialist, spontaneous reporting, drug information, pharmaceutical legislation, risk minimization measure, benefit/risk ratio, rationale drug use), and searching the scientific databases: PubMed, Scopus, Google Scholar, ScienceDirect for a period of more than 20 years (1993 – 2022). Eleven keywords were used in English (drug product, pharmacovigilance, adverse drug reaction, physician, medical specialist, spontaneous reporting, drug information, pharmaceutical legislation, risk minimization measure, benefit/risk ratio, rationale drug use) and Bulgarian (medicinal product, drug safety, adverse drug reaction, doctor, medical professional, spontaneous reporting, drug information, risk-minimizing agent, benefit/risk ratio, rational drug use) languages. With their help, 88 scientific publications were selected. They were selected, reviewed and included in the Literature review of the dissertation work.

- ***Sociological method*** - Two direct individual surveys. The survey card was distributed by e-mail, and the answers were received in the same way, according to Appendix 1. When additional clarifications were needed, they were again requested and received electronically.
- ***Statistical methods*** used in the processing and presentation of survey results:

o Statistical analysis: For descriptive analysis, continuous variables are described by mean, standard deviation (SD), median, and range.

o Categorical variables were described as percentages and statistical differences were assessed by the χ 2 test. Significance was determined at the 0.05 level (two-fold).

o Statistical analysis was performed using the statistical package SPSS version 14.0.

- General research methods.

RESULTS AND DISCUSIONS

1. Analysis of the results of the sociological survey among doctors

Statistical analysis: For the descriptive analysis, continuous variables were described by the mean, standard deviation (SD), median, and range. Categorical variables were described as percentages and statistical differences were assessed by the χ 2 test. Significance was set at the 0.05 level (two-fold).

Study Participant Demographics: Study Participant Demographics are categorized based on gender distribution, age distribution and occupational status. The average age of the study participants was 46 years. Out of 48 of the respondents (n = 48, 100%) have master's in medicine and practicing General Medicine (GP), followed by neurology specialists working in a hospital ward -18.33%, 15% by cardiologists and 4.17% by endocrinologists.

Table 1. Gender distribution of respondents (n = 48)

Gender	**Frequency**
Male gender	41.50%
Female	58.50%

Table 2. Age distribution of respondents (n = 48)

Age (in years)	**Frequency**
31 – 40 years	20.75 %
41 – 50 years	41.50 %
51 – 60	37.75 %

Table 3. Distribution by medical specialty of respondents (n = 48)

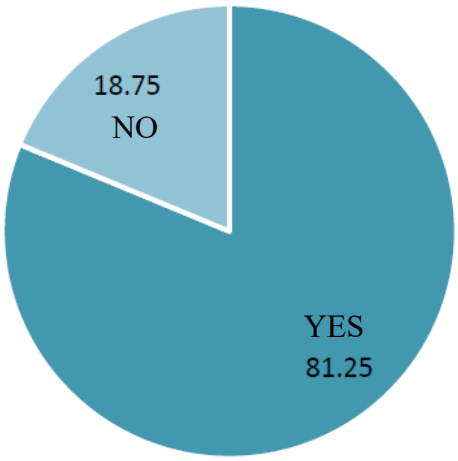
Medical specialty	**Frequency**
General medicine	62.5%
Neurology	18.33%

Cardiology	15.00%
Endocrinology	4.17%

Physicians' opinions and awareness of drug safety and ADRs were explored through a survey, the results of which are presented in the following figures.

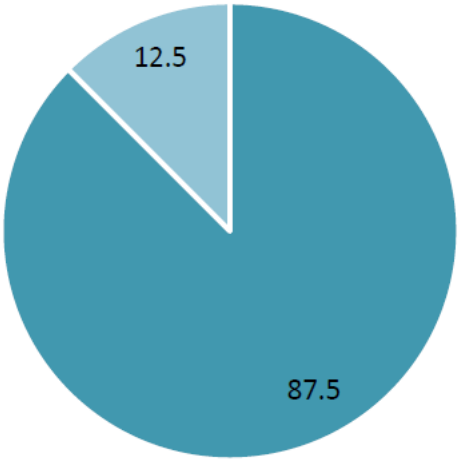
Fig. 6. Is ADR reporting required?

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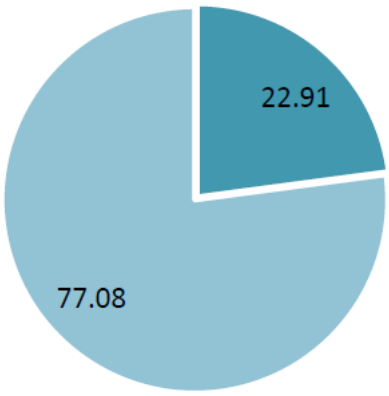
According to 39 (81.25%) of the surveyed physicians, only serious side effects should be reported. All of them are of the opinion that non-serious side effects should not be reported. 19 of the doctors (18.75%) do not think that ADRs should be reported at all, because they are already known, and nothing depends on their reports.

Fig. 7. Does ADR reporting take a long time?



Many of medical doctors acknowledged that the reason for underreporting ADRs was related to a lack of education and training. 40 (83.33%) categorically answer that such programs are necessary, and 8 of the respondents (16.66%) believe that they are unnecessary.

Fig. 8. Does the reporting of ADRs improve patient health outcomes and is there a visible result of reporting in your opinion?

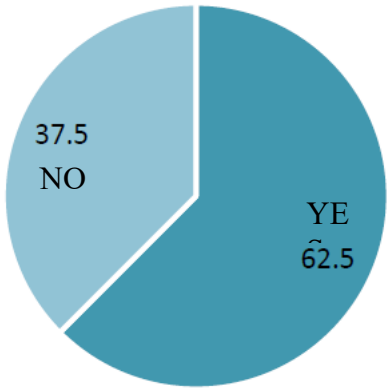


The question aims to obtain information about the opinion of health professionals about the benefits of reporting ADRs and what their observation is in their patients. Only 8 categorically positive answers were received without any opinion or justification being expressed.

In 40 of the respondents (77.08%), the negative answer was accompanied by an expressed opinion such as «I do not understand how my reporting will improve the health of patients», «I do not see how the report can affect the patient's condition» or «Reporting of ADR does not change the safety of the medicinal product itself».

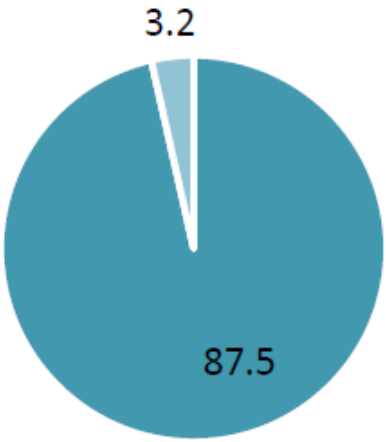
Reporting ADRs is a commitment that takes too much time for 42 of the respondents (87.5%), especially when they have to provide additional information about ADRs, and time is not a problem for 8 of the doctors (12.5%).

Fig. 9. Do you think that reporting to NLR is your duty?



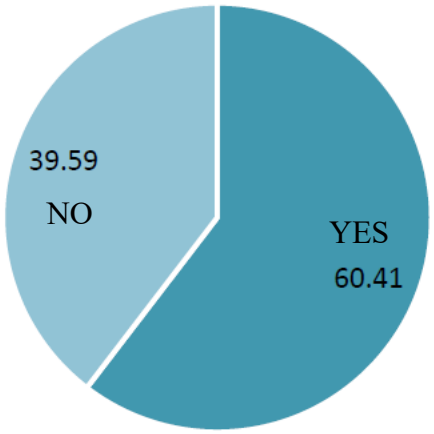
31 (62.5%) responded positively, while the remaining 17 (37.5%) surveyed participants did not consider this to be their duty. The high percentage of medical workers who are not aware of the ADR, which obliges all medical professionals to report ADRs, is indicative.

Fig. 10. Do you think educational programs on drug safety and ADR reporting have needed?



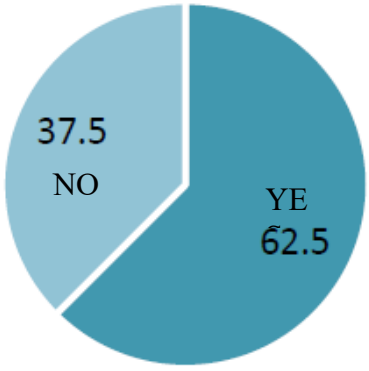
Many of medical doctors acknowledged that the reason for underreporting ADRs was related to a lack of education and training. 40 (83.33%) categorically answer that such programs are necessary, and 8 of the respondents (16.66%) believe that they are unnecessary.

Fig. 11. Do you think the reporting of ADRs should be made mandatory?



29 (60.41%) answered yes to this question, 19 respondents (39.58%) gave negative answers.

Fig. 12. Measures when receiving "Direct Communication" letters

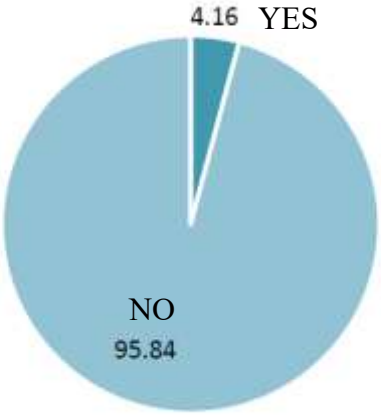


There are 30 doctors (62.5%) who take adequate measures upon receiving such letters. The "no" answers are of interest, as one part explains the inattention to these letters with

lack of time - 6; they think that it is just another advertising material, and they don't read it - 7 or they leave it for later and then forget about it.

The next question No. 1 of Questionnaire 1 according to the Appendix 1b is related to the ADR database and to what extent medical professionals have information about it and whether they use it. The results are shown in Fig.13.

Fig. 13. Do you use EMA to access the Eudravigilance database?
46 (95.83%) of the respondents do not know that such an EU database "Eudravigilance



database" exists and only two of the respondents (4.16%) are aware of their access to it and sometimes make inquiries on various occasions.

2. Analysis of the results of the sociological survey among nurses according to the First questionnaire survey

Statistical analysis: For the descriptive analysis, continuous variables were described by the mean, standard deviation (SD), median, and range. Categorical variables were described as percentages and statistical differences were assessed by the χ 2 test. Significance was found at the 0.05 level (two-fold). Statistical analysis was performed using the statistical package SPSS version 14.0.

Study Participant Demographics: Study Participant Demographics are categorized based on gender distribution, age distribution and years of work experience.

The aim of the research in nurses was focused on their knowledge of the meaning of 'reporting ADRs'. ADR reporting is a sequential process where the reporter recognizes a

possible ADR, locates, and completes the reporting form and submits it to the pharmacovigilance system or the MAH.

Data from Survey 1, Appendix 2, obtained from the survey, showed in 2019-2020 that nurses declared that they "reported a suspected ADR" when they simply "reported" it verbally to the doctor, to the senior nurse or noted in the record it in the patient's clinical sheets.

All nurses surveyed were female. The distribution by age groups is as follows: Table 5

from 22 to 32 years old 4 ppl.

from 33 to 43 years 9 ppl. and from

44 to 54 years 5 ppl.

The distribution by years of work experience shows the following: from 1 to 2 years, the number of respondents is 4; from 3 to 10 years – 6; from 11 to 20 years - 5 and over 20 years - 3.

All interviewed nurses work in the emergency department of a metropolitan hospital.

Table 4. Gender distribution of respondents (n = 18)

Gender	**Frequency**
Male gender	0%
Female	100%

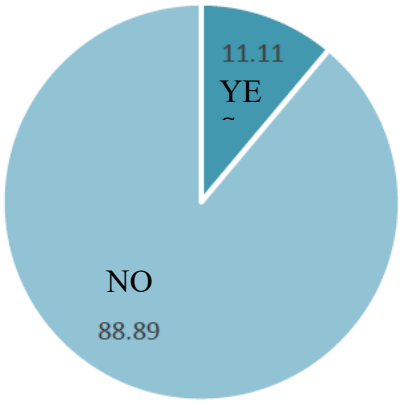
Table 5. Age distribution of respondents (n = 18)

Age (in years)	**Frequency**
22-32 years	22.22 %
33-43 years	50.00 %
44-54 years	27.78%

Table 6. Distribution by number of years of work experience of the respondents (n = 18)

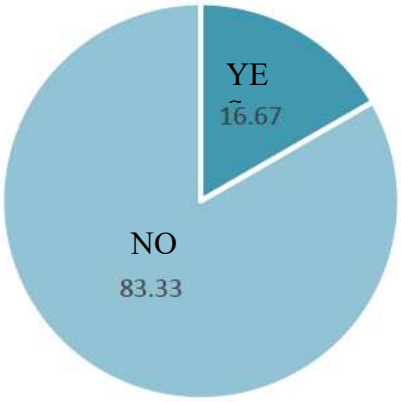
Years of work experience	**Frequency**
From 1 to 2 years	16.67%
From 3 to 10 years	44.44%
From 11 to 20 years	27.78%
Over 20 years	11.11%

Fig. 14. Do you know what the WHO definition of ADR is?



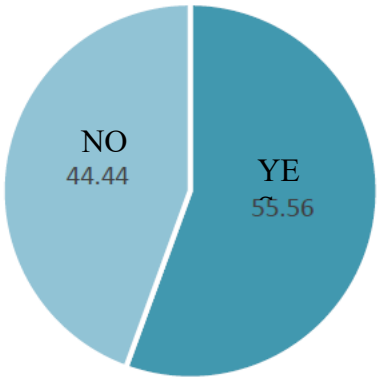
Only two of the nurses surveyed (11.11%) gave a definition of an adverse reaction that came close to that given by the WHO. The remaining 16 (88.89%) could not give any definition.

Fig. 15. Do you know what pharmacovigilance is and what it deals with?



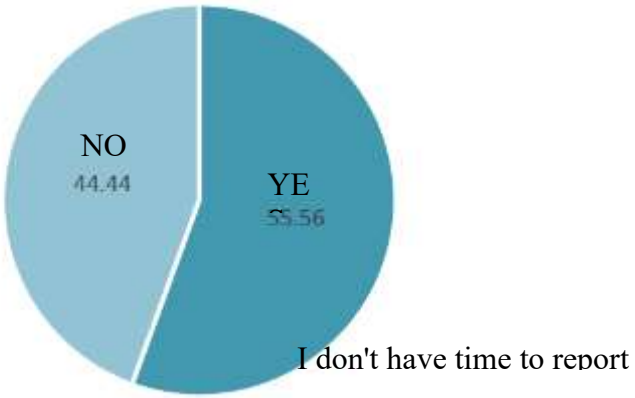
Only 3 of the respondents answered "yes" (16.67%), the remaining 15 nurses (83.33%) had no idea of the concept of pharmacovigilance and what its essence is.

Fig. 16. Have you had training in pharmacovigilance and how to recognize and report ADRs?



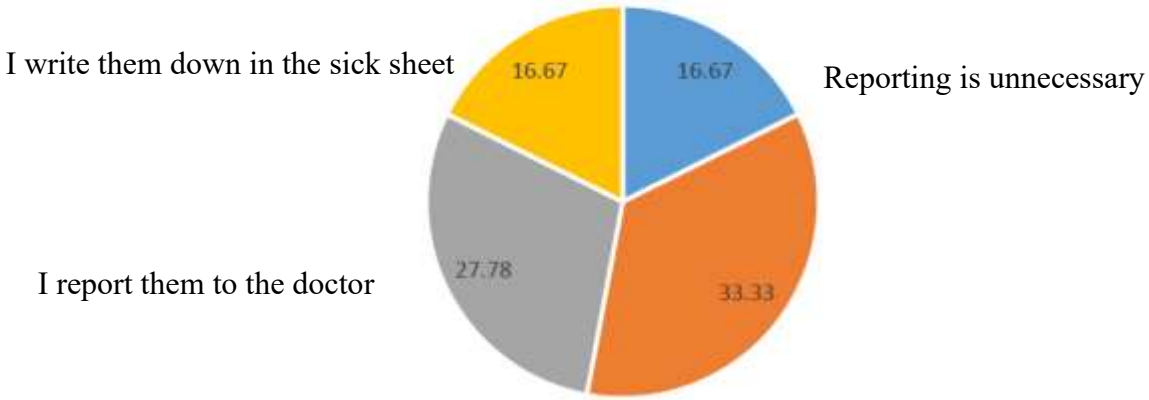
The majority - 10 of the respondents (55.56%) had training related to the reporting of adverse reactions. The remaining 8 (44.44%) did not attend such training.

Fig. 17. Do you think you should report ADRs?



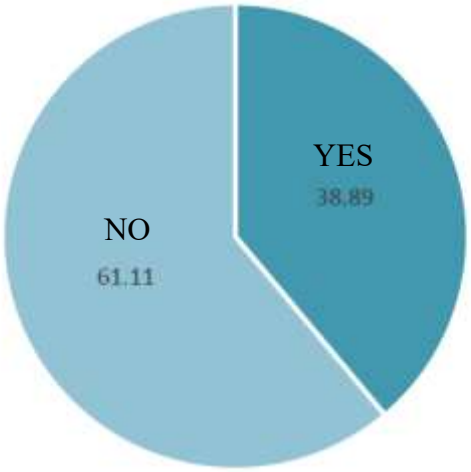
Ten of the nurses (55.56%) believed they should report ADRs. The remaining 8 (44.44%), have shared that they should not.

Fig. 18. Do you report ADRs and how?



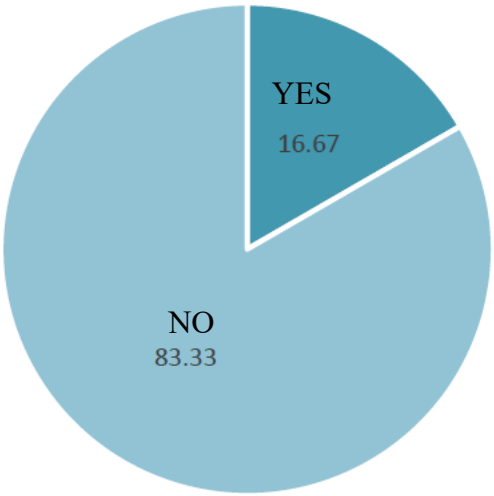
Nurses have specific interpretations of reporting ADRs and when analyzing their responses these interpretations form quite an interesting picture. 5 nurses believe they have 'reported a suspected ADR' when they simply 'report' it to the doctor, the senior nurse or when they simply record it in the patient's clinical sheets - 3. Lack of time to report ADRs is the answer in 6 of the respondents, and 4 consider it unnecessary to report.

Fig. 19. Do you know where to find an ADR reporting form?



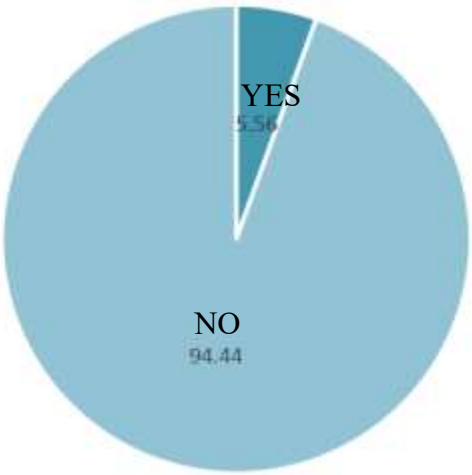
11 of the respondents answered "no" (61.11%); 7 answered "yes" (38.89%).

Fig. 20. Do you know how to fill out the NPR form?



The answers to this question correlate with those of the previous one: only 3 can complete the form (16.67%) and the remaining 15 (83.33%) cannot cope with the filling.

Fig. 21. Do you have an ADR reported this year?



Of all the nurses surveyed, only one (5.56%) had a report on ADR this year, and the remaining 17 (94.44%) have not reported an ADR this year.

Analysis of reports received in the BDA.

An analysis was made of the reports received in BDA [1] by medical specialists for the last 4 years and the data from the reports of adverse reactions received in three other European Medicines Agencies - the Czech Republic, Poland and Ireland.

Table 7. Adverse reactions reported by medical professionals in the Czech Republic, Poland and Ireland5. Year/ Country, Czech Republic, Poland, Ireland

Year	Czech Republic	Poland	Ireland
2016	1 822	1 822	1 822
2017	2,058	2,058	2,058
2018	2 027	2 027	2 027
2019	1 736	1 736	1 736

According to the BDA data, for three years in a row there has been a trend towards an increase in reports of ADRs. The majority of reports received were made by healthcare professionals (doctors, pharmacists, nurses, dentists) directly or through Marketing Authorization Holders (MAHs), as seen in the last year 2018; in 2019 patient reports also increased [1].

2016 – 187 (23%)

2017 – 745 (62%)

2018 – 1,224 (71.70%)

2019 - 1,345 (69.62%)

The information obtained from the conducted survey fully corresponds to the results of the reported ADRs in IAL obtained from four consecutive annual reports of IAL 2016, 2017, 2018 and 2019. Against the background of the number of reports from medical specialists from 3 randomly selected other European countries, the difference is obvious in the number of reports and the lack of commitment of Bulgarian medical specialists in the processes of monitoring drug safety.

Table 8 Adverse reactions reported by medical specialists in Bulgaria [1] Total amount of reports/year. Primary reports Secondary reports

Year	Total number of reports/year	Primary reports	Secondary reports
2019	2,669 (2,640 valid)	1,932 (73.18%)	708 (26.82%)
2018	2,354 (2,309 valid)	1,707 (73.93%)	602 (26.07%)
2017	1,200 (850 valid)	850 (71%0	350 (29%)
2016	1,176 (1,176 valid)	799 (68%)	337 (32%)

Although the survey was conducted with a small number of physician and nurse participants, its results indicate a rather alarming trend of lack of personal commitment among physicians and nurses to report, prevent, and manage ADRs.

Their attitudes towards reporting ADRs appear to be good, but targeted educational strategies on how to report could improve the ADR reporting process.

Currently, **medical doctors** reporting of ADRs is voluntary, but many responded that it should be mandatory.

Reporting ADRs is the responsibility of healthcare professionals to increase patient safety and reduce the cost of their treatment.

Awareness-raising measures are needed to overcome this attitude towards pharmacovigilance processes, especially since they are direct participants in this process.

The finding of the study showed that the awareness of reporting ADRs and knowledge about reporting them was very poor among the responding medical practitioners. The ultimate goal of drug safety is to prevent patients from being unnecessarily affected by a negative consequence of drug therapy. The goal can only be achieved with proper reporting of ADRs by medical professionals.

This study points to the need for educational programs for healthcare professionals to be aware of the need to report ADRs and the need for pharmacovigilance in general.

The results for nurses emphasize the need to encourage them to learn, as well as to have a personal attitude towards the safety of the patients entrusted to them.

According to our findings, the underestimation of ADRs among nurses may be mainly due to a lack of knowledge and a concern for patient safety in their work.

On the other hand, nurses do not consider reporting ADRs as an activity that they are expected to do independently; nurses tend to inform the doctor about suspected ADRs and for him to decide to report it or to reflect the ADR symptoms in the hospital chart. Misinterpretation of the meaning of "reporting" may be due to ignorance about the ADR reporting activity and the need for training is obvious and should be addressed in these aspects.

The need to participate in specific training courses is strongly perceived among nurses, they are willing to develop their knowledge and competence in reporting ADRs.

Recently, a critical and systematic review of strategies to promote ADR reporting showed that 87% borrow educational materials such as presentations and other materials [7]. This means that training courses or other educational initiatives should be used as a lever for motivation and positive attitudes, for changing routine practices and taking initiative.

3. Analysis of the results of the sociological survey among doctors from all regions of the Republic of Bulgaria

The survey was conducted only among the physicians from all over Bulgaria. With the assistance of the Bulgarian Medical Association (BMA), a questionnaire was sent to 650 physicians from all over the country, consisting of 20 questions with several sections: general information, reporting adverse reactions - general information, motivation for reporting adverse reactions, need for reminders and ways they receive new information about the risks of medicinal products, what training they have and whether they need further training, how they avoid adverse reactions when deciding to prescribe treatment, do they feel guilty if a particular adverse reaction could have been prevented, reference sources for the medicinal products and what are their proposals for improving the monitoring of drug safety.

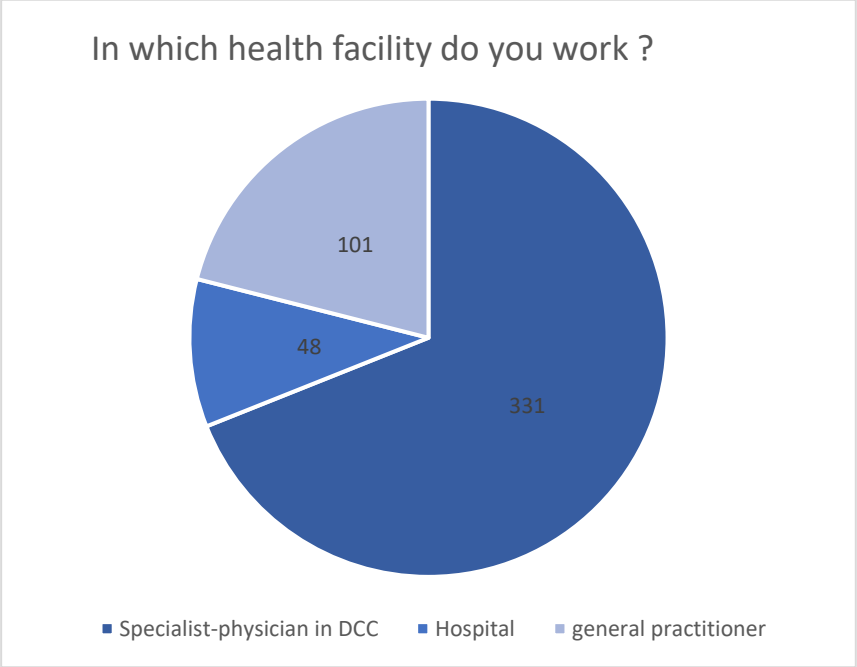
Exclusion criteria included inadequately completed questionnaires and physicians unwilling to participate in the study. Validated completed questionnaires with answers to each question were 480.

3.1. Demographics

The physicians who answered the questionnaire have a long professional experience. 77% of them have a minimum of 10 years of experience in their profession.

The main workplace of most physicians is in Diagnostic Consultative Center (DCC), with 69 % of respondents being specialist-physicians, 10% working in a hospital and 21% working as general practitioners in pre-hospital care.

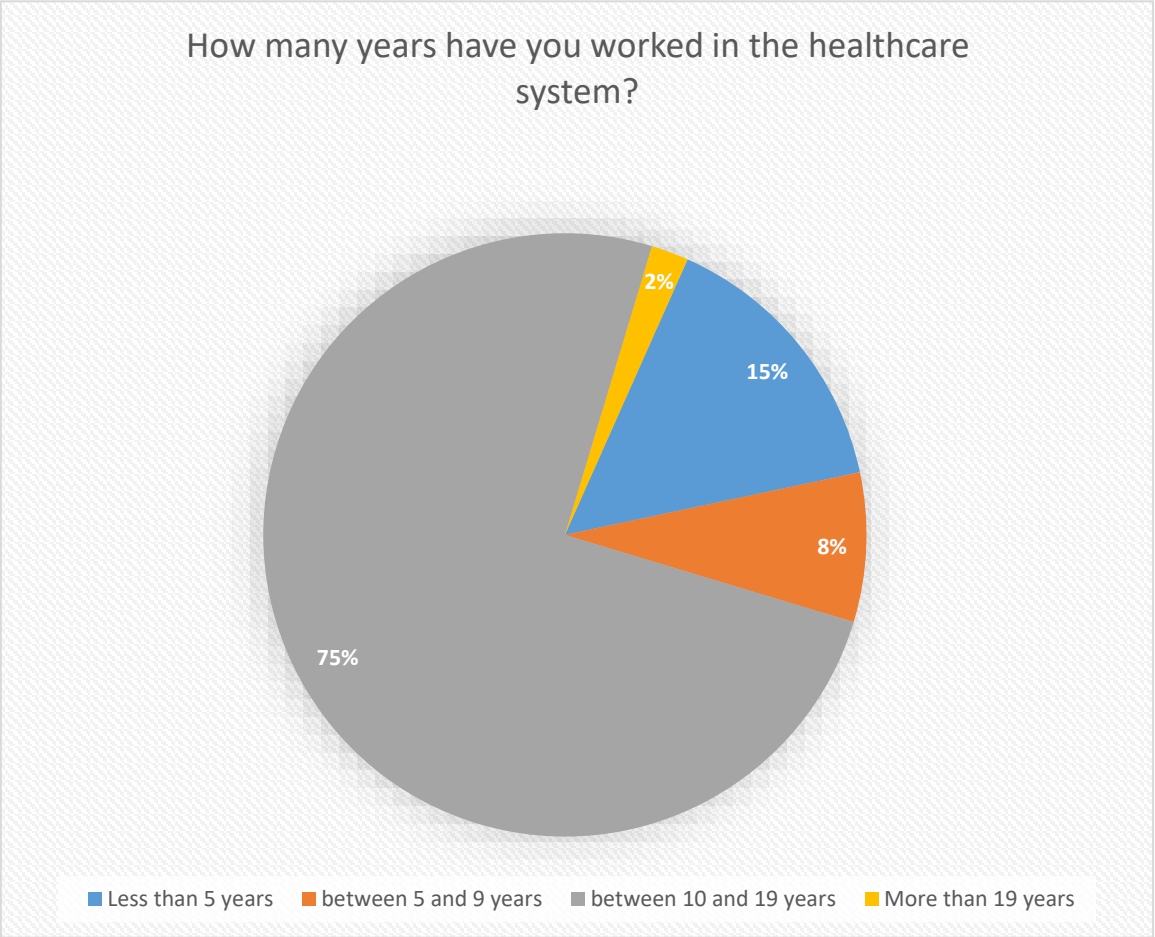
Fig. 22. What healthcare facility do you work at?



Specialist physician in DCC - 331 (69%); Hospital – 48 (10%); General practitioner - 101 (21%);

The main workplace of the majority of physicians is in the DCC, as a specialist physician and it is 69%. 10% work in a hospital setting and 21% of respondents work as general practitioners in pre-hospital care.

Fig. 23. How many years have you worked in the healthcare system?



75% of physicians have a minimum of 10-19 years of experience, 15% have less than 5 years of experience, 8% have between 5 and 9 years of experience, and 2% have more than 19 years of experience.

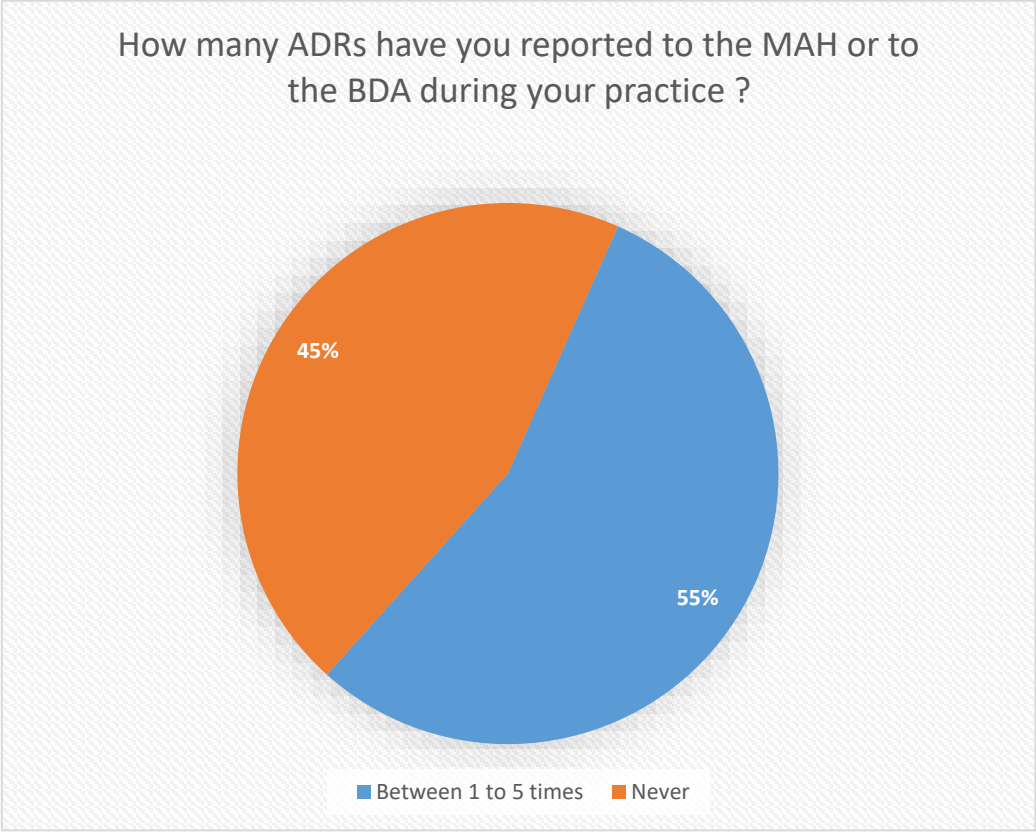
The majority of physicians (360, 75%) are in the age group with accumulated professional experience between 10 and 19 years. Another interesting group are those physicians who have less than 5 years of experience. There are 72 recently graduated physicians. These two groups are expected to be the most active in reporting adverse reactions.

3.2. Experience and knowledge of reporting Adverse Drug Reactions

Physicians' knowledge and perception of the safety profile of drugs is essential. They should be aware of the potential occurrence of unexpected side effects and report suspected side effects to drug regulatory authorities to facilitate the detection and evaluation of drug safety signals. They should be aware that no medicinal product is completely or absolutely safe for all

patients, with different types of diseases. They should always practice prescribing different drugs with some degree of uncertainty.

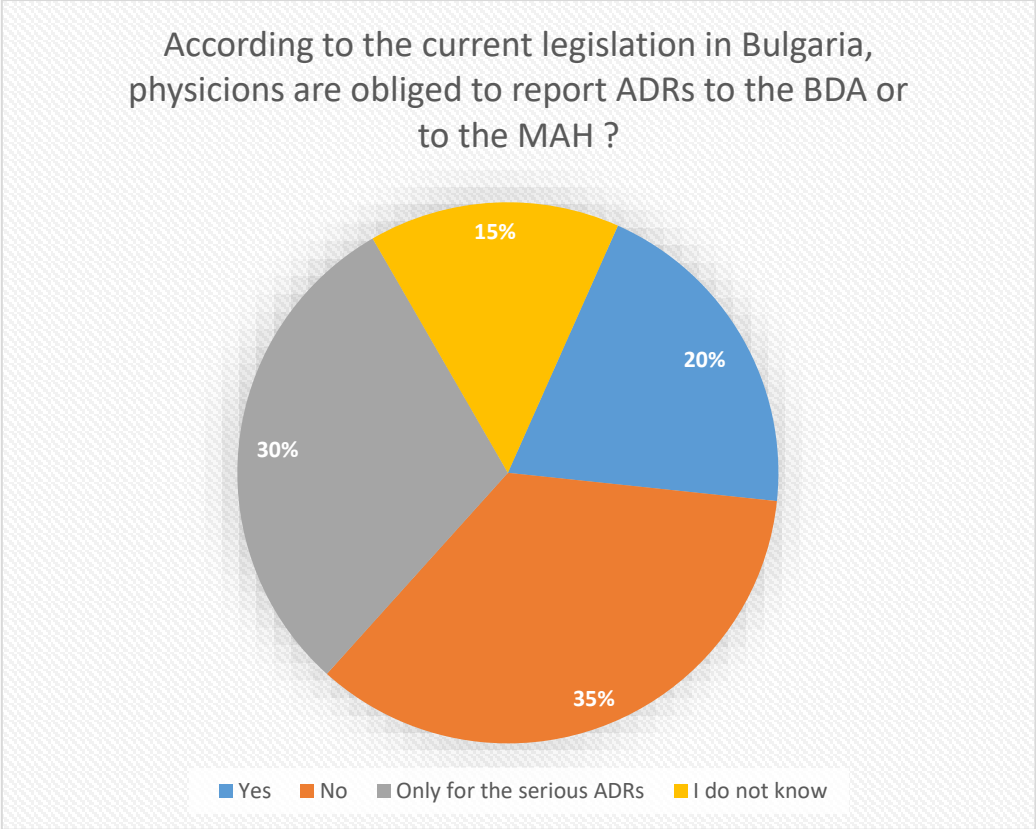
Fig. 24. How many of Adverse Reactions have you reported to a Marketing Authorization Holder or to Bulgarian Drug Agency during your practice?



45% of physicians responded that they had not reported any ADRs during their career, and the rest (55%) had reported ADRs one to five times.

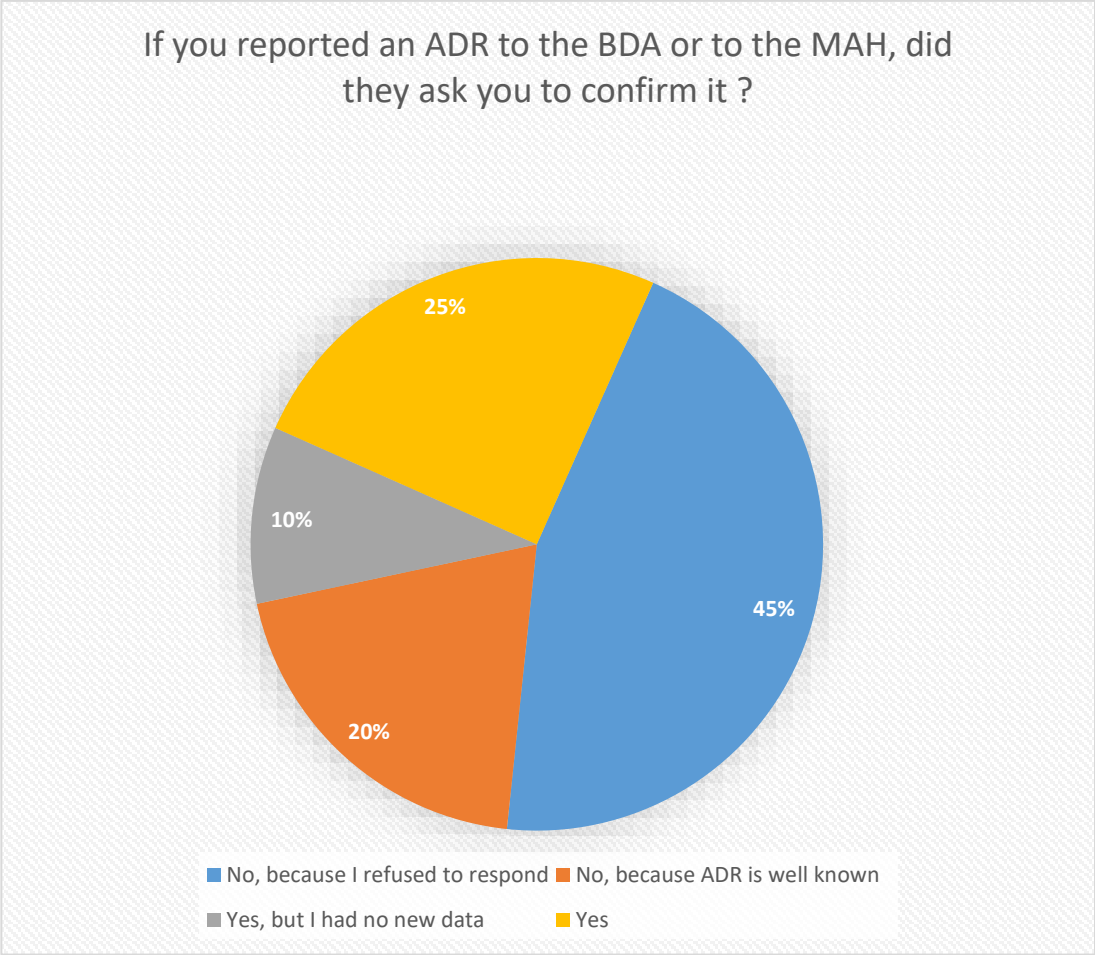
216 physicians reported between 1 and 5 ADR cases, 264 responded that they never reported an ADR. The fact that most physicians never reported ADRs is concerning.

Fig. 25. Please answer whether, according to the current legislation in Bulgaria, physicians are obliged to report suspected adverse reactions to the Bulgarian Drug Agency and to the Marketing Authorization Holder?



Only 20 % (96) are aware of their obligation to report all ADRs, 35% (168) responded that no ADRs should be reported, 30% (144) responded that they are obligated to report only serious adverse reactions, and 15% (72) of physicians do not know. As can be seen, the % of

physicians who are aware of this duty is too low, and the % of physicians who answered that they do not know is quite high.

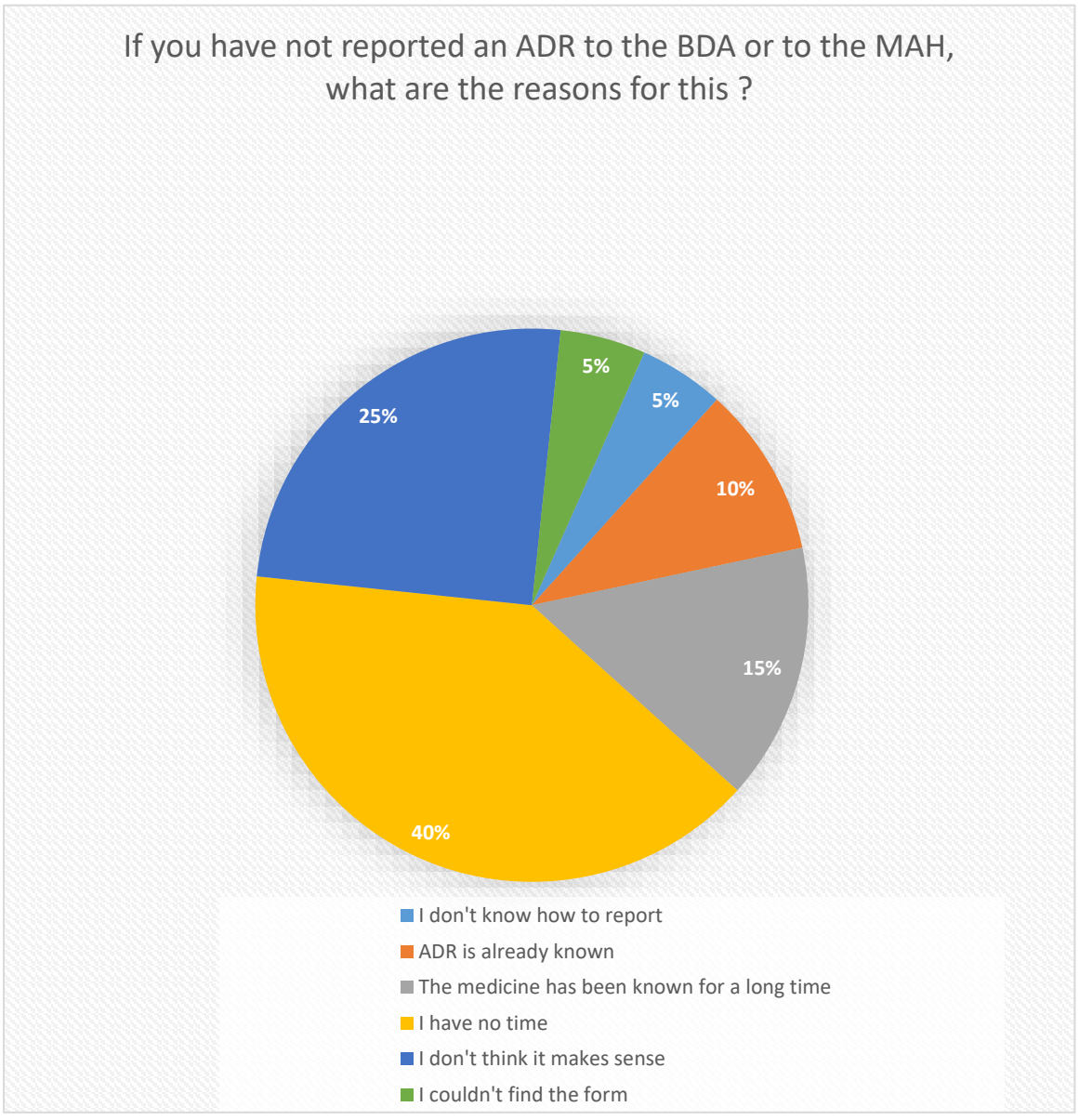


From the responses of the surveyed physicians, it appears that the majority of them were asked to confirm ADRs: 216 (45%) were asked to confirm ADRs, but refused to answer; 96

(20%) answered that they were not sought, because the ADR is well known; 48 (10%) were asked for confirmation but had no new data and 120 (25%) of the physicians answered "Yes".

3. 3. Failure to report of Adverse Drug Reactions

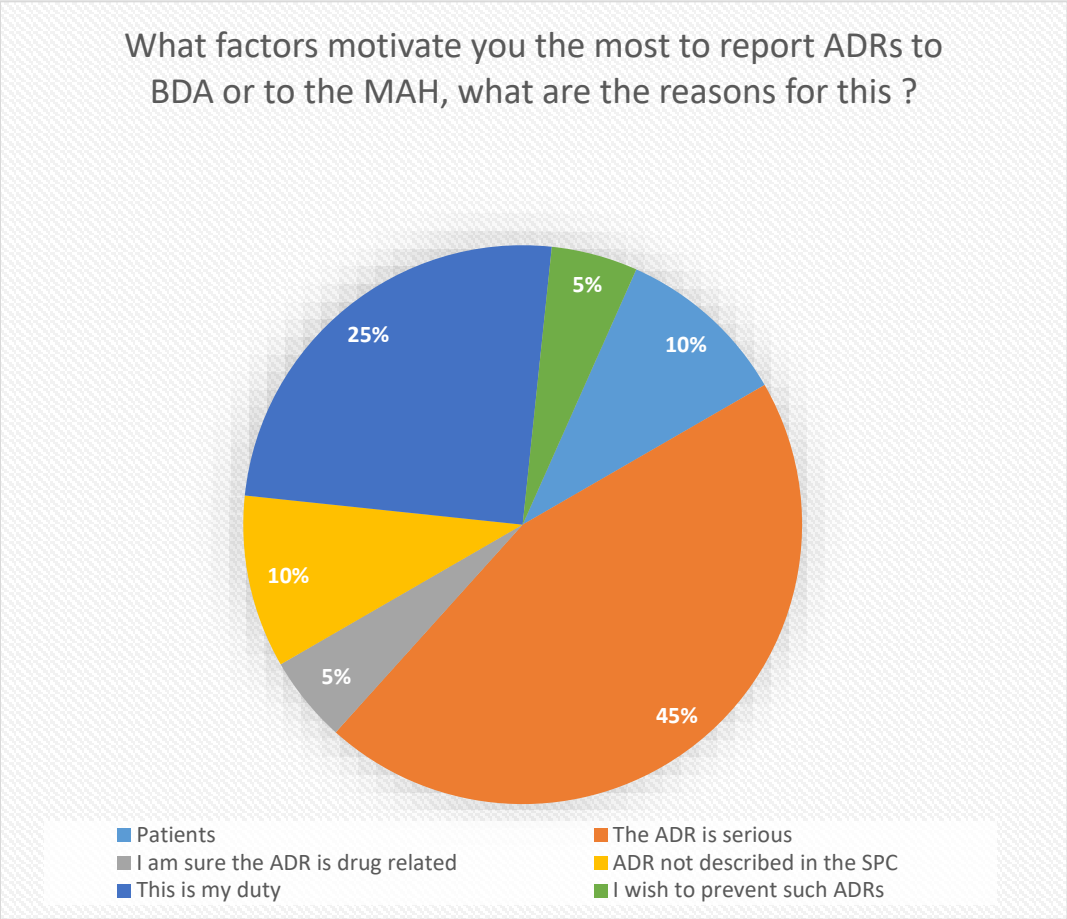
Fig. 28. If you have not reported an Adverse Reaction to the BDA or to the MAH, what are the reasons for this? (Choose one or more reasons)



To this question, a disturbingly high proportion of the surveyed physicians answered that they do not have time 192 (40%), and according to 120 physicians (25%), there is no point in reporting the ADR. A relatively small number of physicians answered that they were not aware (24%) and as many respondents answered that they could not find the form. The other two answers show that physicians do not know the drug safety processes well: 48 (10%)

answered that the drug reaction is already known and 72 (15%) answered that the drug has been known for a long time.

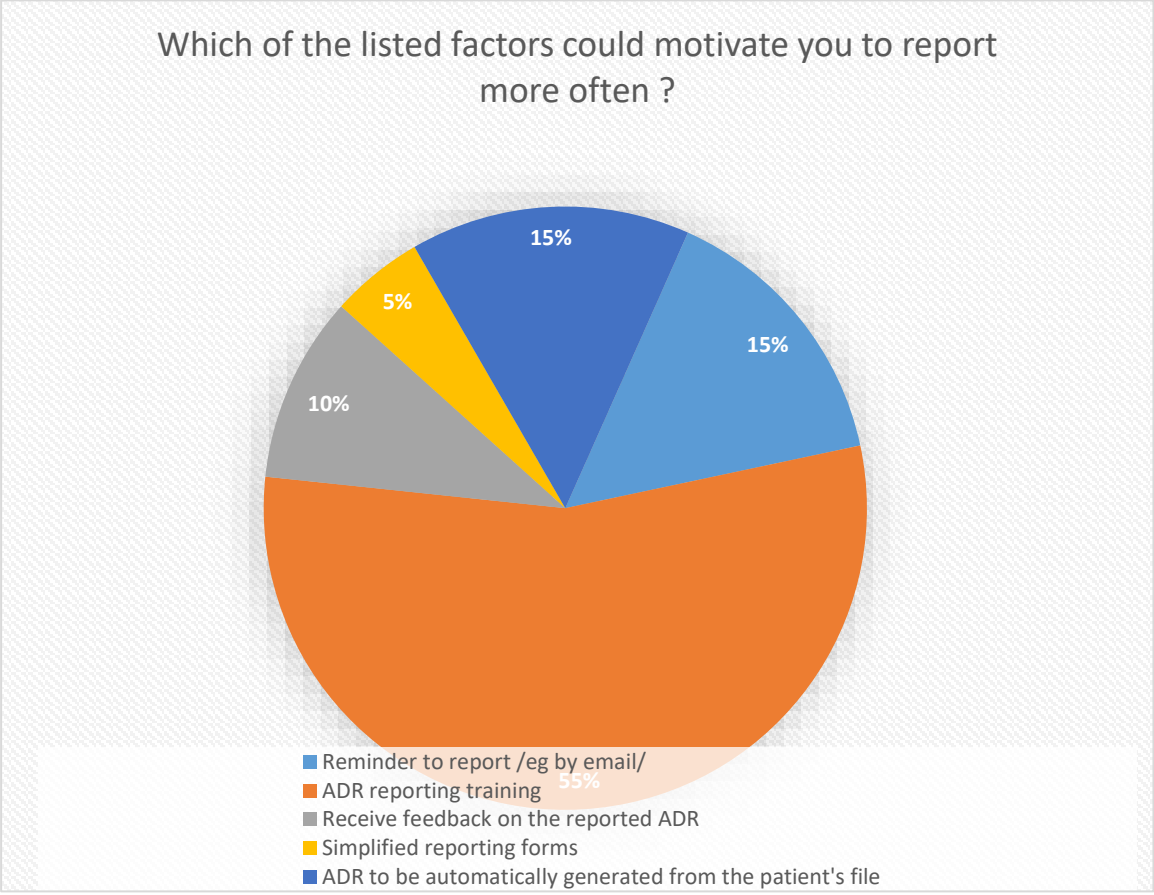
Fig. 29. What factors motivate you most to report a suspected adverse reaction to the Bulgarian Drug Agency or to the Marketing Authorization Holder, what are the reasons for this?



According to 120 (25%) of the respondents, the motive for reporting ADR is that they accept it as their duty. 216 (45%) responded that the reason they reported an ADR was because it was serious. Only 24 (5%) physicians answered that the reason for reporting was their certainty about the connection of the ADR to the medicinal product, and so many answered that they wanted to prevent such ADRs. 48 (10%) stated as a motive the patient and that the ADR is not described in the SPC.

3.4. Improving the reporting of adverse drug reactions

Fig. 30. Which of the listed factors could motivate you to report more often?



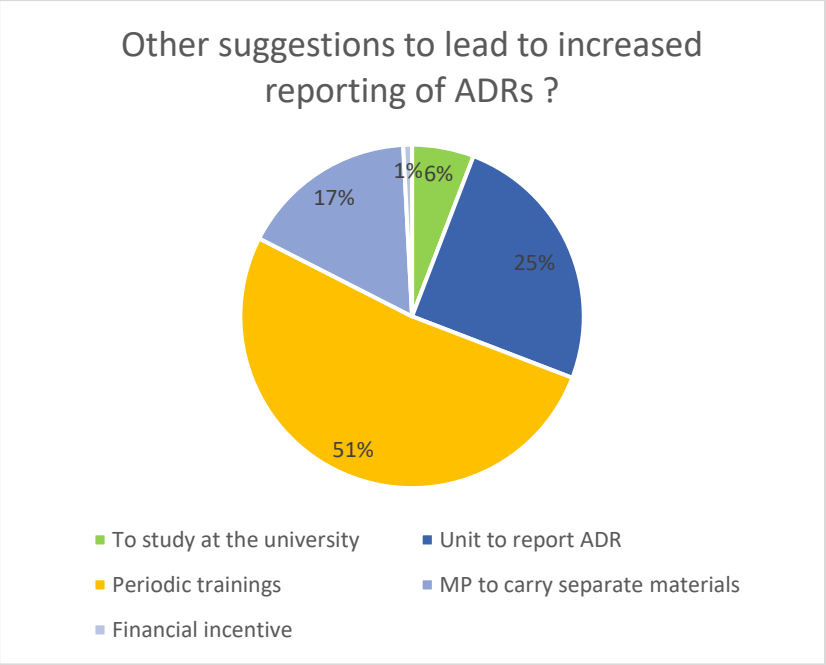
As expected, more than half of the respondents answered that training on reporting ADRs would motivate them to report more often 264 (55%), another 72 (15%) indicated the need for an e-mail reminder.

The motive for another 48 (10%) is to receive feedback on their reported ADR and 24 (5%) wish the reporting format to be simplified. Of interest is the response of 72 (15%) of the

physicians who responded to the survey that ADRs should be automatically generated from the patient's file. On the last response for other incentives, only 3 physicians indicated a financial incentive, which is a negligibly low proportion.

Fig. 31. Do you have other suggestions that could lead to increased activity in adverse reaction reporting?

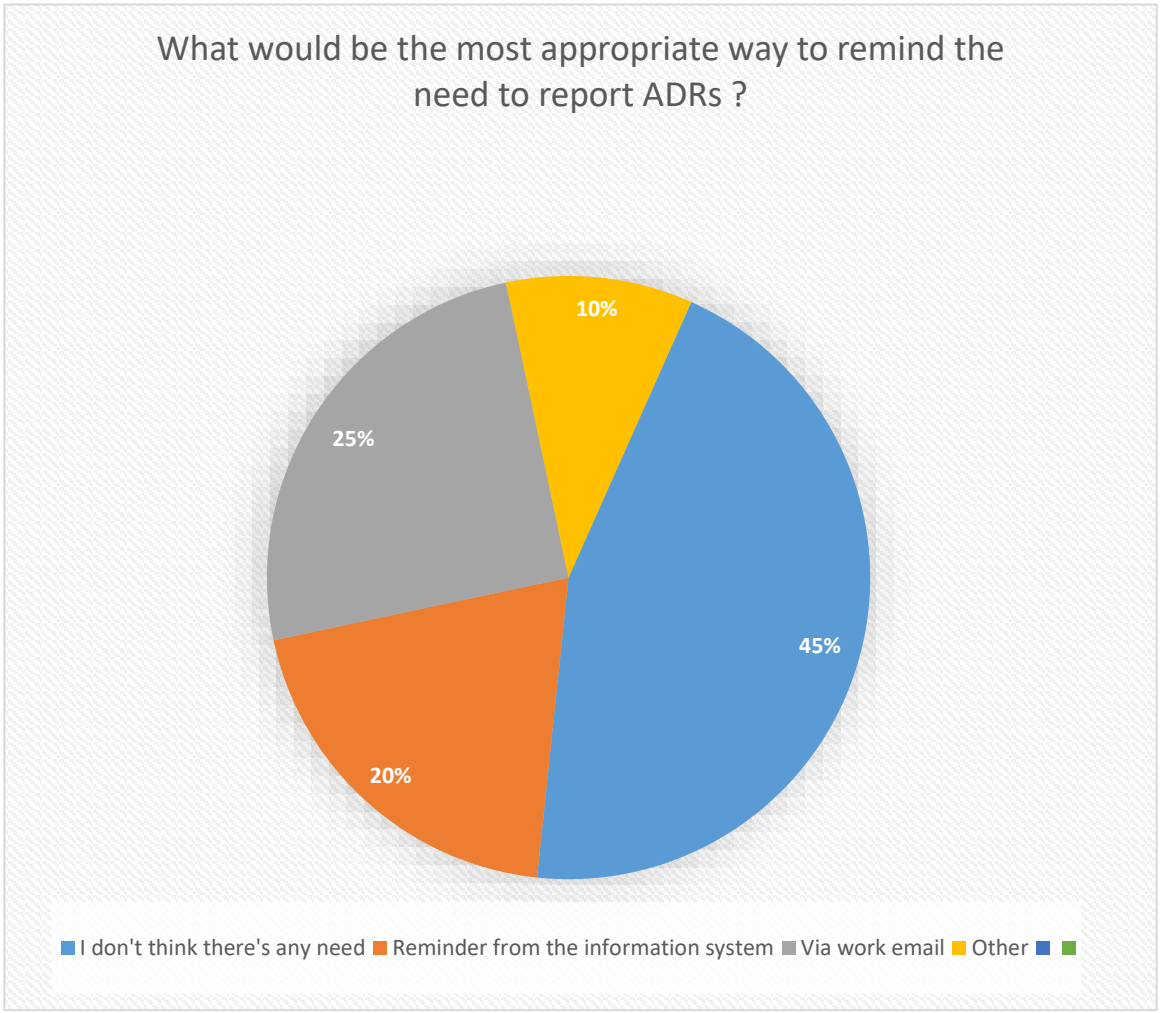
(If you have, please list them.)



Various responses were received to this question, e.g. that pharmacovigilance training should be studied together with pharmacology at university - 28 (5.83%) of the responses, 120 (25%) of the respondents believed that medical leaders institution should create a unit to deal with ADR reporting using the data from the patient's file because the physicians themselves do not have time for this, 248 (51.67%) of the physicians that periodic training should be organized on the new trends in the reporting of ADRs, 80 (16.67%) physicians suggest that during the visit of the medical representatives to provide as a separate material, the form for reporting ADRs with relevant explanations to it and new information about the safety of their medicinal

products. Only 4 (0.83%) of the physicians indicated that there should be a financial incentive from the MAH.

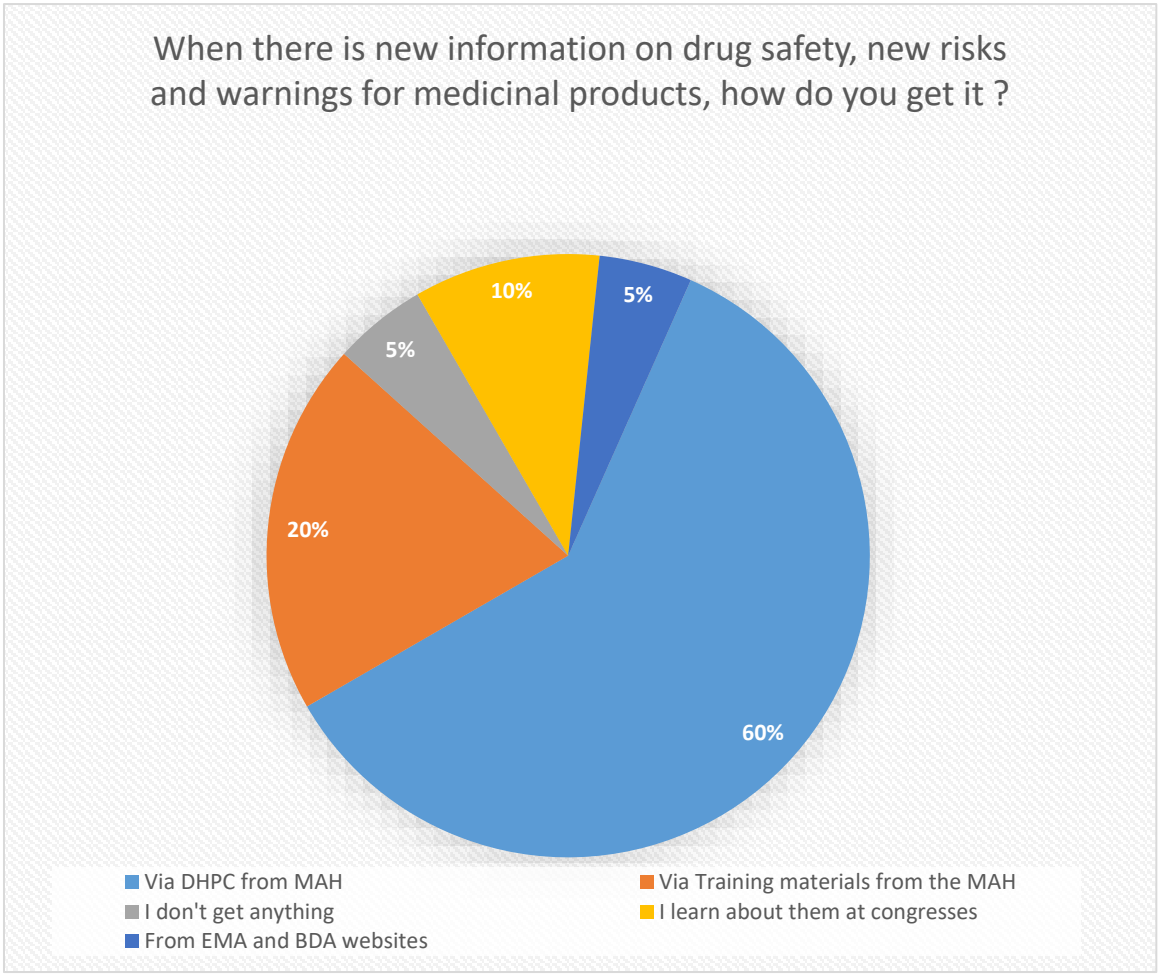
Fig. 32. What would be the most appropriate way to remind the need to report Adverse Reactions



A significant proportion of physicians 216 (45%) felt that there was no need for a reminder to report ADRs, 96 (20%) responded that through the patient information system used in their daily practice (e.g. pop-up) would be the most effective reminder option to report ADRs, 120 (25%) responded that periodic reminders should be sent via work email, 48 (10%)

responded 'Other', responding that medical representatives should remind them to report ADRs on their visits or provide reminder flyers.

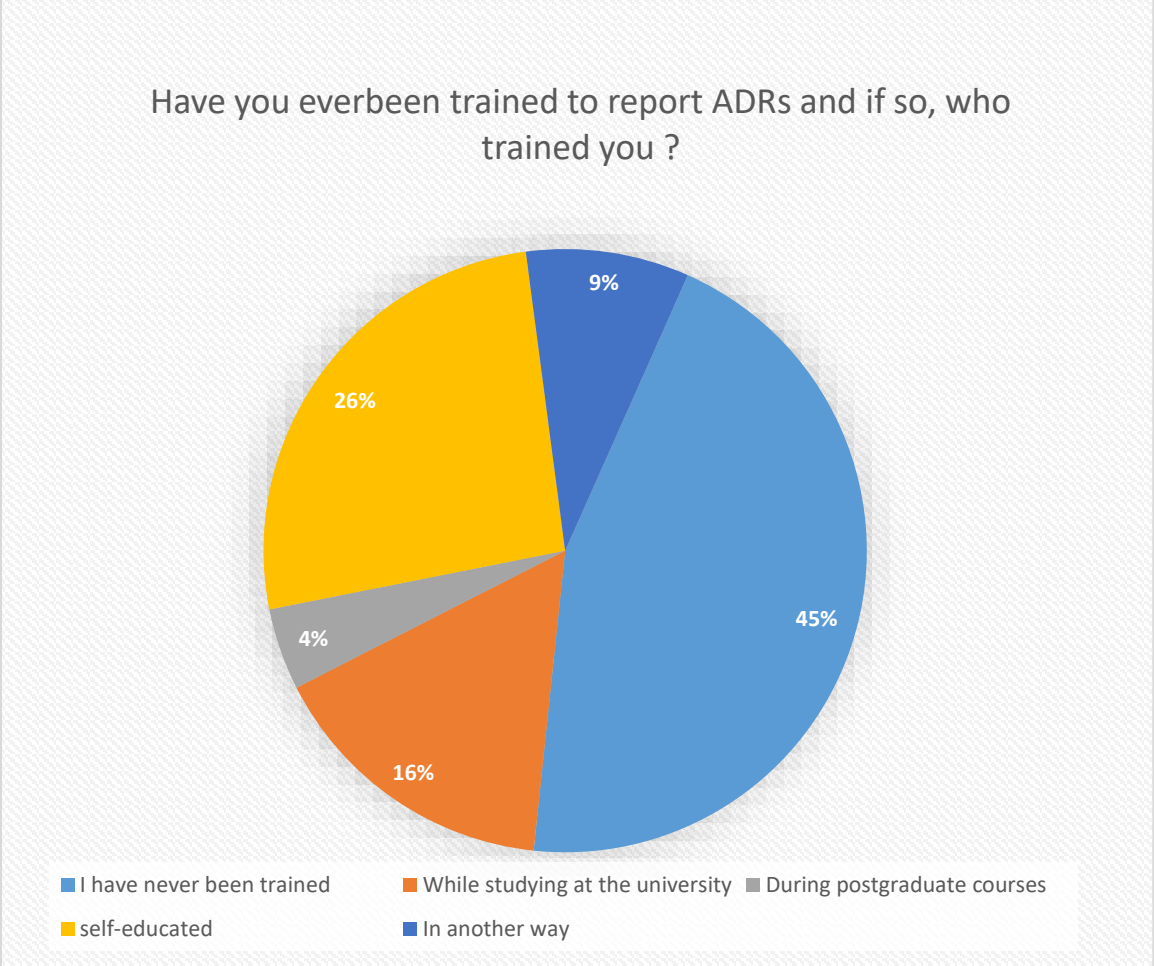
Fig. 33. When there is new information on Drug Safety, new risks, and warnings for medicinal products, how do you get it?



288 (60%) of the respondents answered that they learn the new information about the safety of medicinal products by receiving it from the MAH via the so-called letter for DHPC, 96 (20%) received Training materials from the MAH. A small number of respondents answered that they do not receive anything - 24 (5%). 24 (5%) indicated that they found this type of

information from the BDA or EMA website and 48 (10%) learned about it at medical congresses.

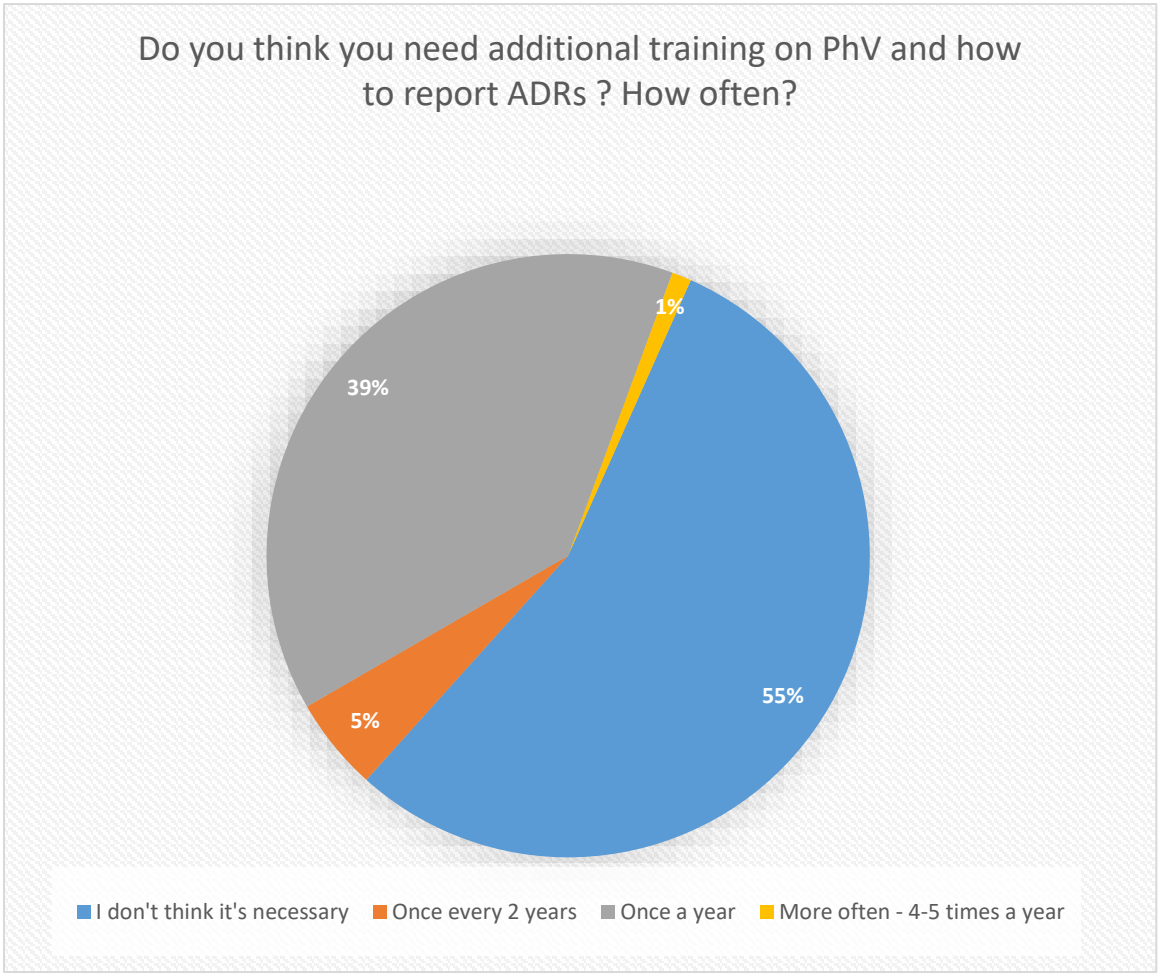
Fig. 34. Have you ever been trained to report adverse reactions and if so, who trained you?



I have never been trained - these are the answers of 216 (45%), which means that about half of the study group should not know how to report ADRs, 76 (15.83%) received training during the study, and 21 (4.38%) of the respondents were trained during postgraduate courses.

Another 125 (26.04%) answered that they were self-educated /without specifying in what way/, 42 (8.75%) indicated as an answer "In another way", again without specifying which way.

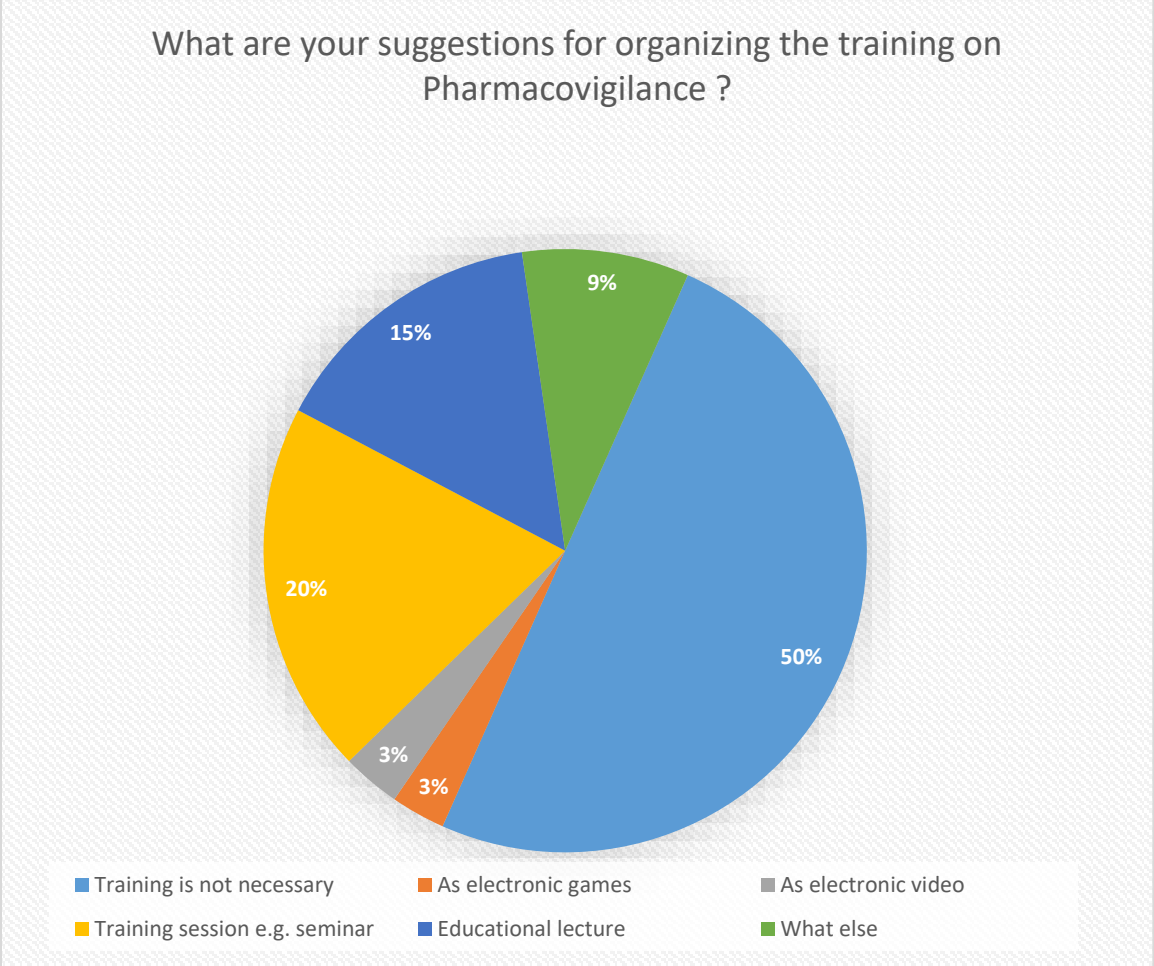
Fig. 35. Do you think you need additional training on pharmacovigilance and how to report ADRs? How often?



Slightly more than half of the respondents 264 (55%) to this question answered that there is no need for additional training on pharmacovigilance and ADR reporting against the background of low reporting by respondents, 24 (5%) indicated that they would be trained once

a 2 years, and 187 (38.90%) prefer the training to be once a year and only 25 (1.04%) of the respondents would like the training to be more frequent, e.g. 4-5 times a year.

Fig. 36. What are your suggestions for organizing the training on pharmacovigilance?



Completely consistent with the answers to other questions, the respondents indicated as an answer to this question that they had no suggestions, because in their opinion, training in Pharmacovigilance 240 (50%) was not necessary. Another 14 (2.92%) answered that they prefer learning in the form of electronic games, and 15 (3.13%) prefer learning in the form of electronic video. More serious training, such as a training session e.g., seminar, 96 (20%) of the respondents answered and 72 (15%) preferred training in the form of an educational lecture. As an answer "What else" are the answers of 43 (8.90%) of the respondents and the answers are

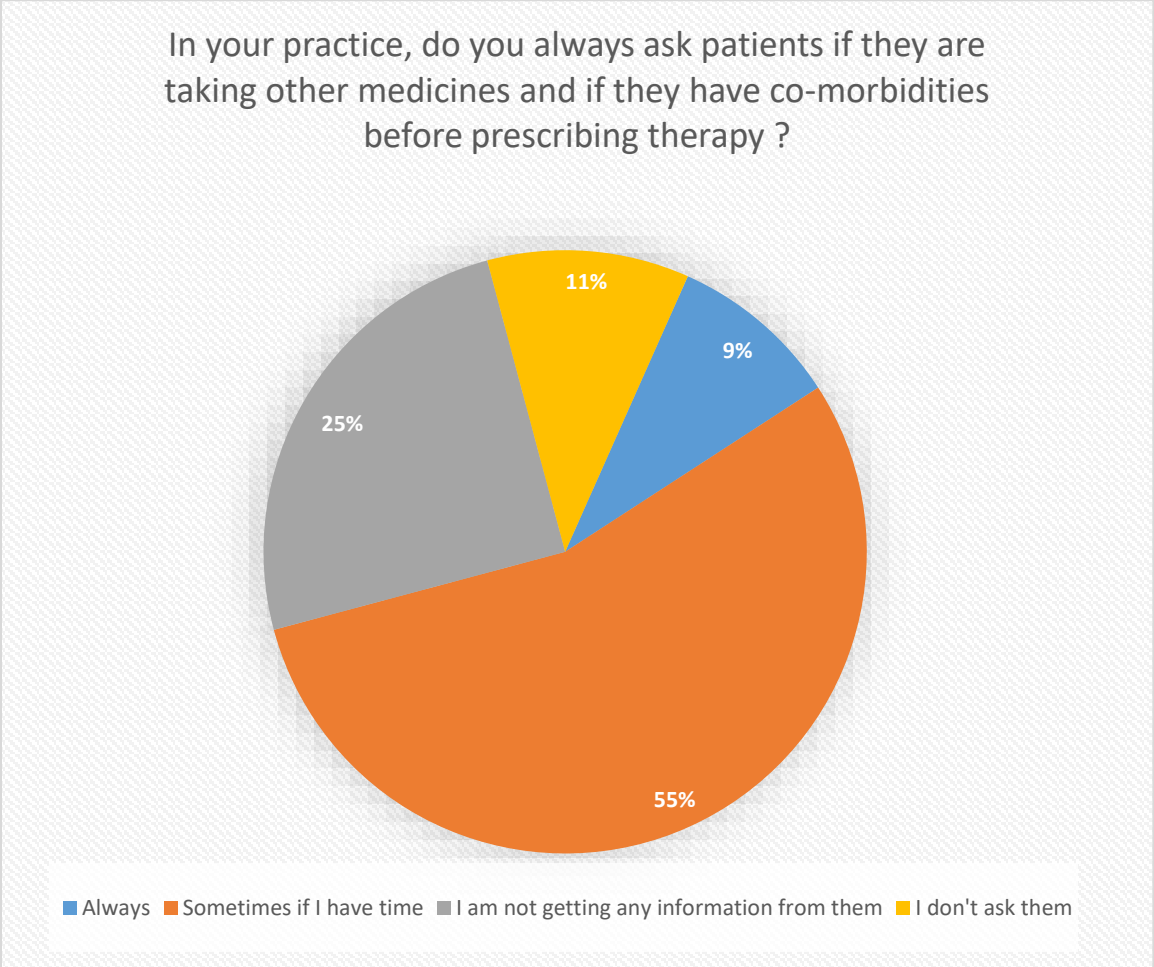
different such as e.g., training to recognize ADRs, to be trained how to report, to clarify the ADR reporting format, to promote a culture of ADR reporting.

Fig. 37. Are you have been trained in how to approach to prevent an adverse reaction?



Respondents answered as follows: 10 (48%) were trained and 432 (90%) were never trained for this.

Fig. 38. In your practice, do you always ask patients if they are taking other medicines and if they have co-morbidities before prescribing therapy?



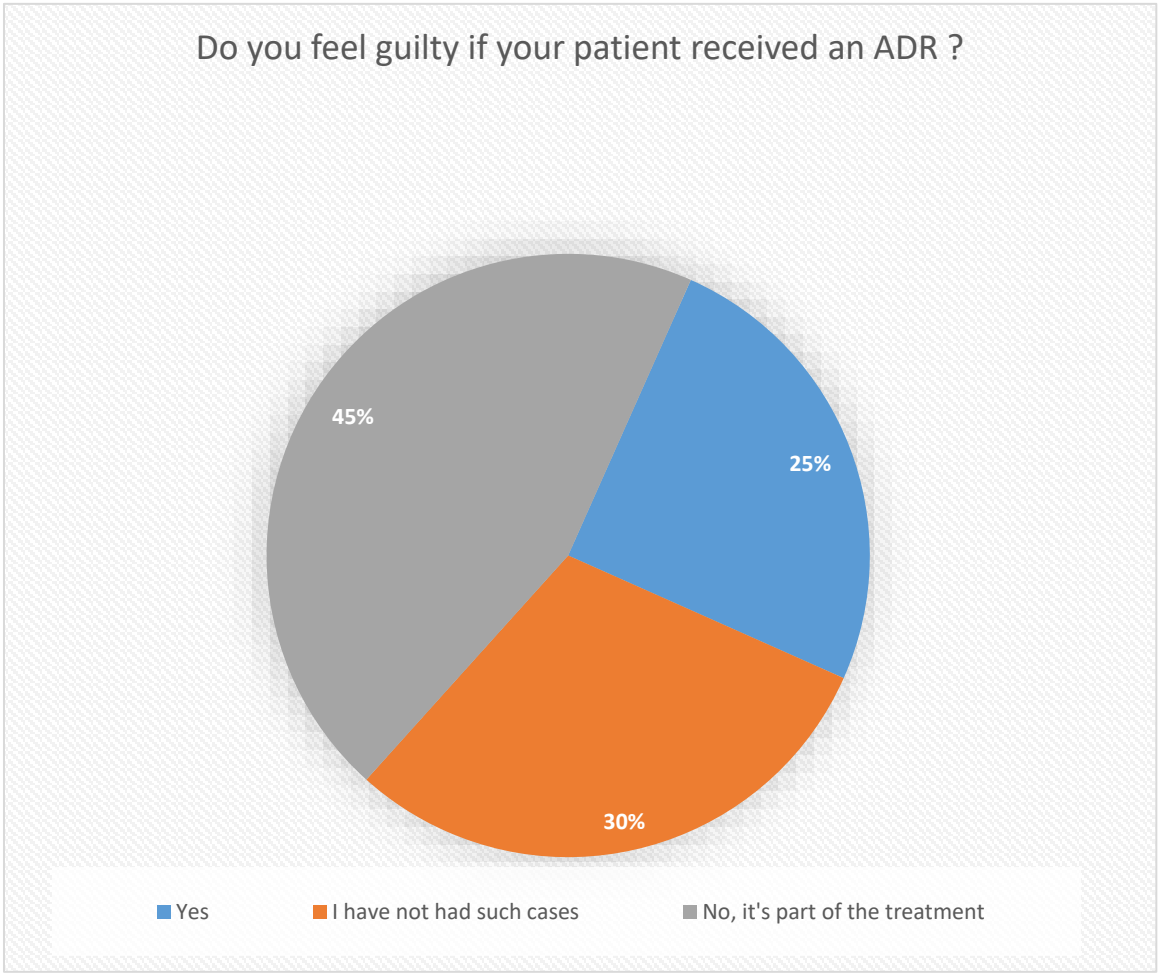
Unfortunately, the answers to this question are very worrying, as only 44 (9.17%) of the respondents always find time to ask them to their patients. From the information that is obtained, severe ADRs leading to death, hospitalization, prolongation of hospital stays, serious ADRs such as e.g., Stevens-Johnson syndrome, Toxic epidermal necrolysis, also known as Lyell's syndrome, anaphylactic shock, Severe kidney, liver and serious heart diseases, diabetes mellitus, hypertension, risk factors for thrombosis leading to cerebrovascular damage, etc.

Most of the respondents 264 (55%) answered "Sometimes, if I have time", 120 (25%) of the respondents answered that they cannot get information from the patient / do not know

the name of the drugs, the dose, do not report all accompanying diseases/, which takes a lot of the physician's time.

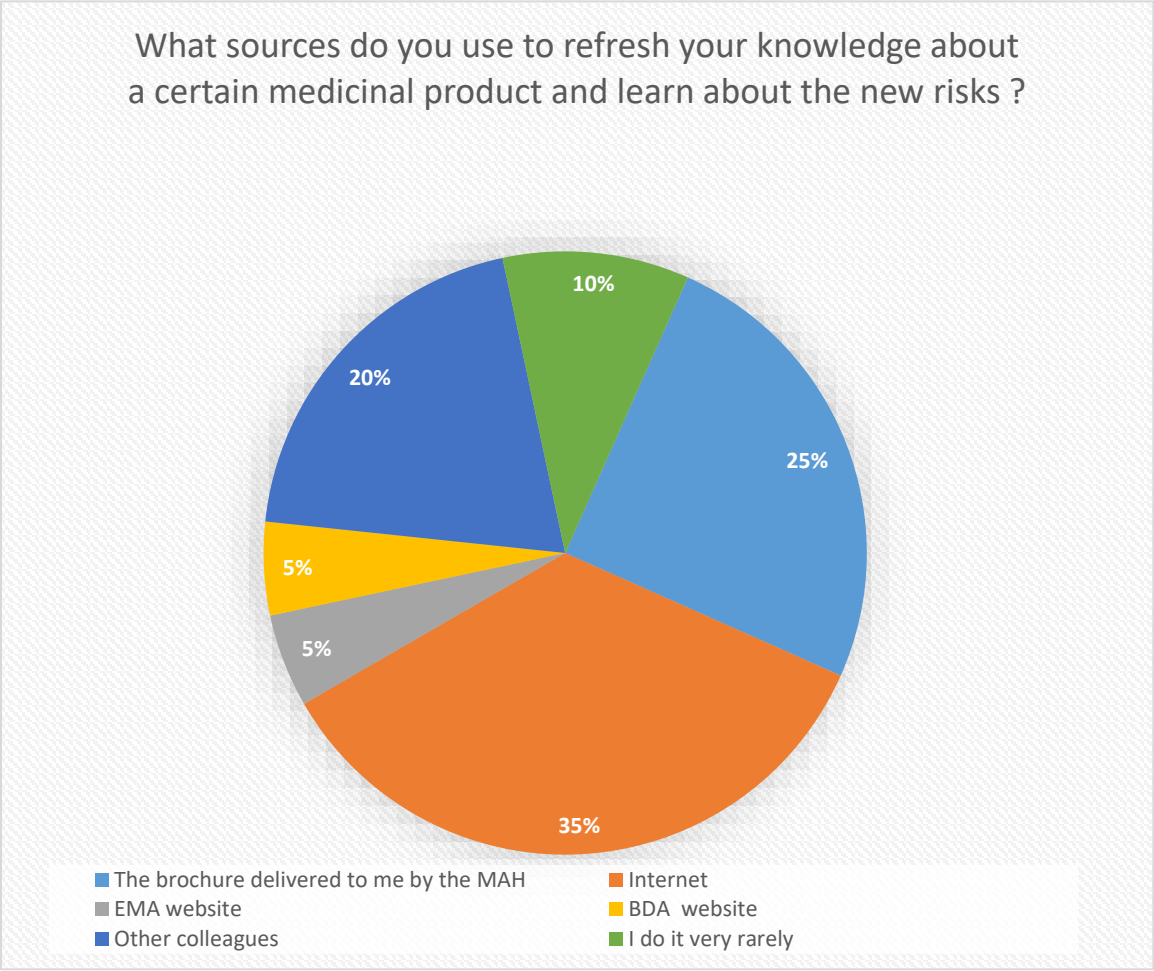
52 (10.83%) answered that they are not asked, without explaining why.

Fig. 39. Do you feel guilty if your patient received an adverse reaction?



120 (25%) of the respondents answered positively, another 144 (30%) answered that they did not have such cases in their practice, and the largest percentage 216 (45%) answered that this is part of the therapy and they do not experience regret.

Fig. 40. What sources do you use to refresh your knowledge about a certain medicinal product and learn about the new risks?



As can be seen, the surveyed physicians use different sources for information about the medicinal products and possible new risks - 120 (25%) do so by using the brochure received from the MAH. A large percentage of respondents turn to the Internet - 168 (35%), 24 (5%)

each turn to the EMA or BDA websites, 96 (20%) talk to another colleague and only 48 (10%) answer that they do it very rarely.

The final question was open-ended, asking respondents to share and suggest how the pharmacovigilance process could be improved, and it was their choice to answer or not.

Fig. 41. Please share what are your suggestions on how to improve the process of tracking the Pharmacovigilance?

/Question of your choice/

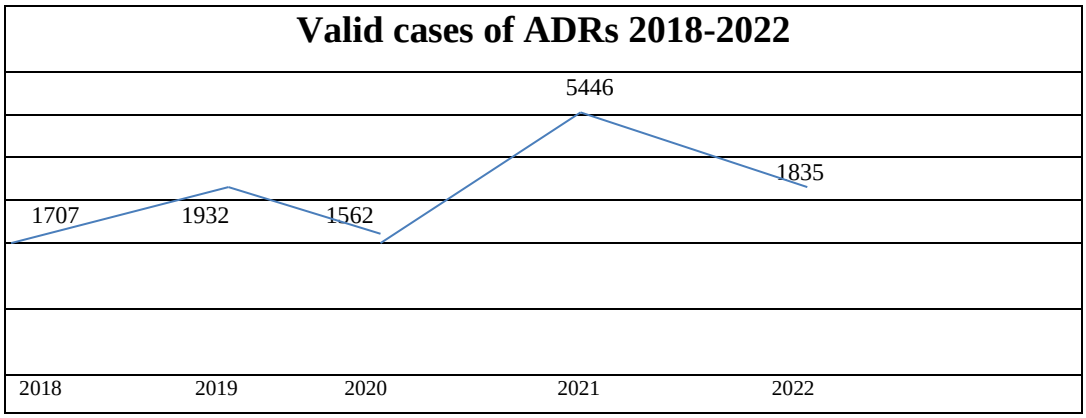
Not all of those who answered the remaining questions made any suggestions, but those who answered wrote down quite a few suggestions, of which the most well-founded were the following:

- **Training once a year for Pharmacovigilance** under in the form of seminars or in any other proper way.
- MAHs to produce a special **attractive, not very large, brochure - 1-3 pages,** reminding us to report ADRs and the most important risks in certain groups of patients, which can also be sent by email.
- A lecturer on Pharmacovigilance should also be invited **to the annual congresses.**

The survey revealed that the majority of physicians agreed that monitoring and reporting ADRs is beneficial to patients. About 55% of the surveyed respondents have between 1 and 3 ADRs reports, and 40% do not have time. 30% of physicians know that reporting ADRs is their duty, 40% do not have time to report ADRs, and 31% of surveyed respondents expressed a neutral response to the same question. The majority - 55% of the surveyed respondents believe that all unknown ADRs should be reported. A positive attitude was found among the majority of physicians that they need a detailed drug safety curriculum. 45% were not trained in Pharmacovigilance. 55% do not think there is a need for training, 90% of physicians have not been trained how to prevent possible ADRs.

According to BDA data for four consecutive years 2018 - 2022, there is a tendency to increase the reports on ADRs [2]. The majority of reports received were made by physicians.

In 2022, 1,835 reports of adverse drug reactions were received from the territory of Bulgaria, of which 1,772 reports were evaluated as valid.

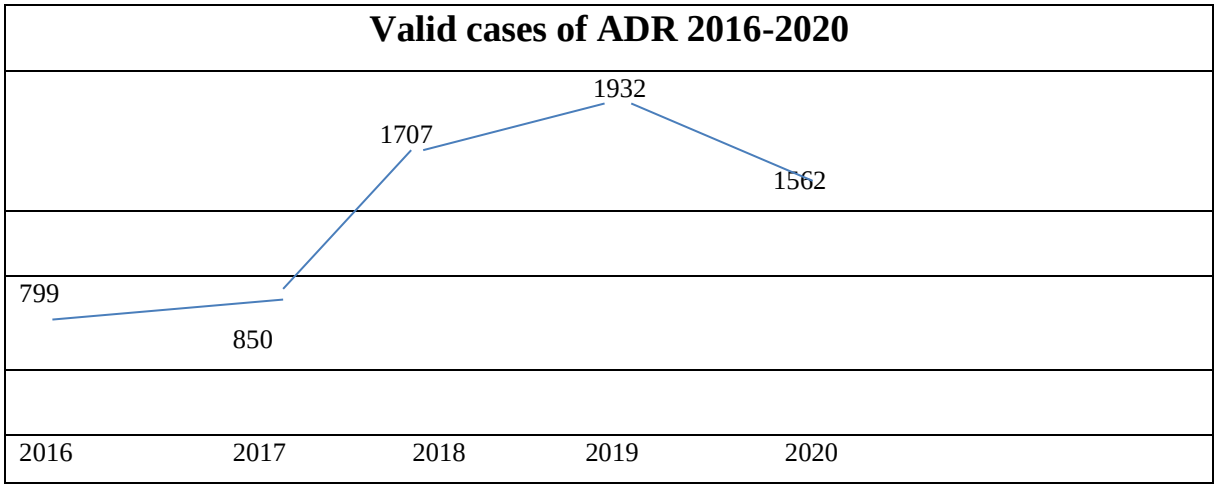


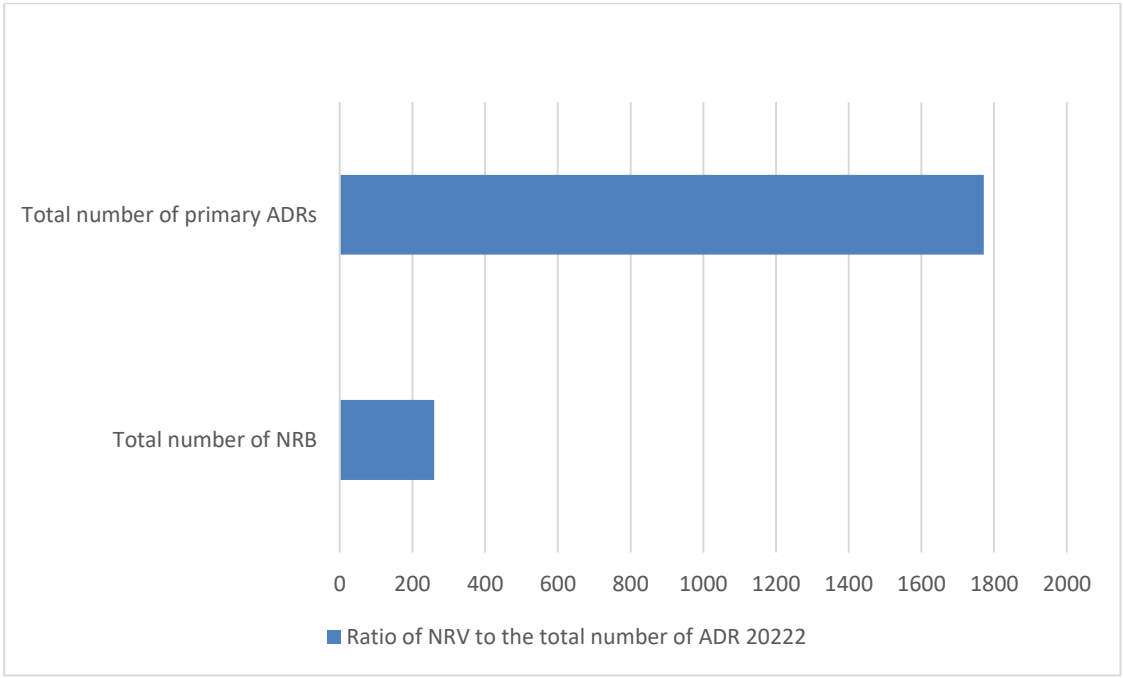
Ratio of received ADR reports by severity and expectation for 2022						
serious expected					311	
serious unexpected					436	
nonserious expected						550
nonserious unexpected						475

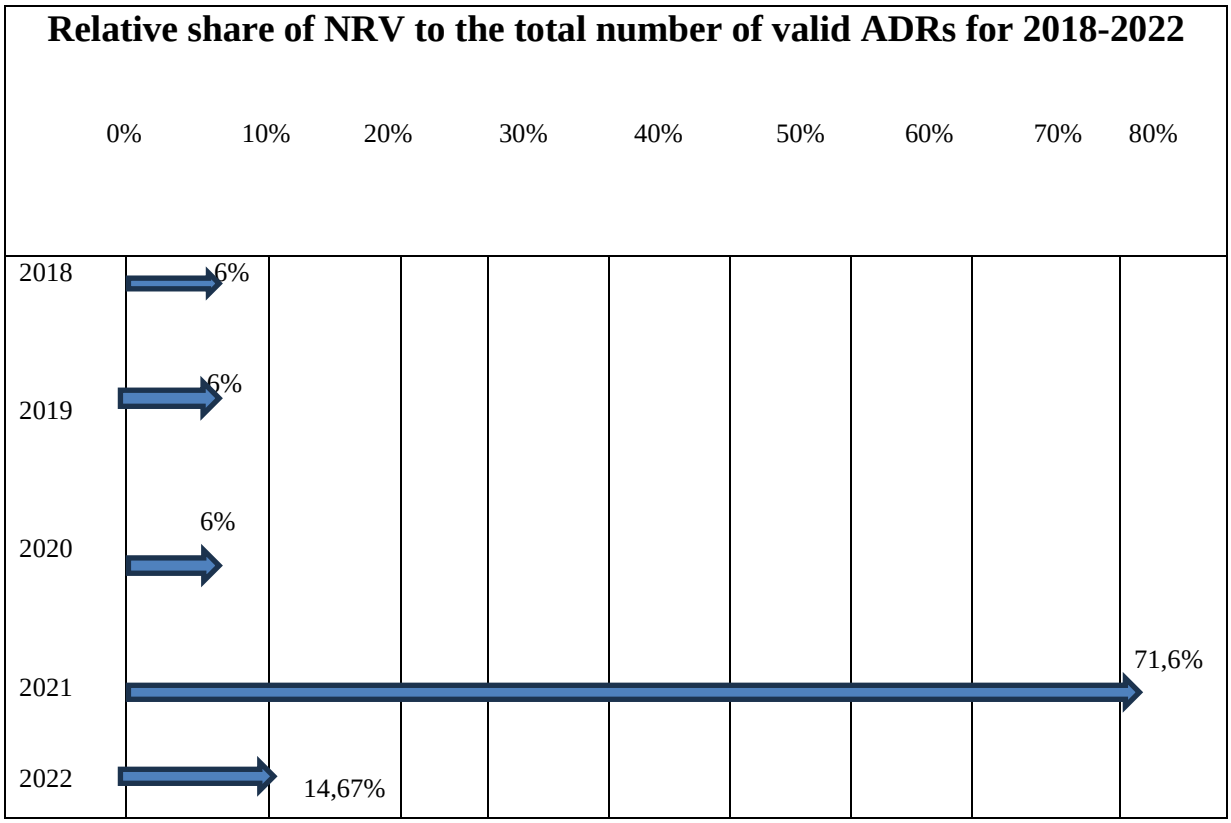
In 2022, 260 valid reports of adverse reactions after administration of vaccines were made on the territory of Bulgaria. Of these, 238 for vaccines against COVID-19 and 22 reports of adverse post-vaccination reactions after administration of other vaccines. These messages

constitute 14.6 % of the total number of valid primary messages. 227 were made by non-medical professionals and 33 by medical professionals.

The graph presents the dynamics in communication activity for the last 5 years.







The most valid ADRs were in 2021, when the peak of COVID-19 and the new vaccines against the disease had begun.

The information obtained from the conducted survey fully corresponds to the results of the reported ADRs in BDA obtained from four consecutive annual BDA reports of 2019, 2020, 2021 and 2022 [2].

The results show a physician's unsatisfactory attitude towards the reporting of ADRs. The practice of reporting ADRs is low among physicians, although many of them have had

patients who received ADRs in the course of their work and some of them have been trained to report ADRs - 45%.

Their attitudes towards ADR reporting appear to be good, but targeted educational strategies on how to report can improve the ADR reporting process.

Currently, physician reporting of ADRs is voluntary, but many responded that it should be mandatory.

Reporting ADRs is the responsibility of physicians to increase patient safety and reduce the cost of their treatment.

Awareness-raising measures are needed to overcome this attitude towards pharmacovigilance processes, especially since they are direct participants in this process.

The finding of the study showed that the awareness of reporting ADRs and knowledge about reporting them was very poor among the responding medical practitioners. The ultimate goal of pharmacovigilance is to prevent patients from being unnecessarily exposed to a negative consequence of drug therapy. The goal can only be achieved with proper reporting of ADRs by medical professionals.

CONCLUSION

ADRs remain a serious problem for the Bulgarian healthcare system and for patients. They affect both children and adults, causing morbidity as well as mortality.

The reporting rate of ADR in Bulgaria is below 1% compared to the global rate of 5% [9]. The success of the ongoing pharmacovigilance in the country depends on the active participation of health professionals such as Physicians, nurses and pharmacists [10-12].

In both surveys, 67.08% of the surveyed Physicians gave a positive response regarding their awareness of pharmacovigilance. Half of the participants (45.25%) agree that reporting ADRs is necessary, but at the same time, only 22.91% of them believe that it somehow improves public health. They are not convinced that the reporting of ADR leads to any visible results.

A significant number of the surveyed licensed Physicians do not perceive reporting ADRs as part of their duties (62.5%), but at the same time, 83% of them feel guilty if their patient has an ADR that could have been avoided. A relatively high percentage of the surveyed Physicians (37.5%) do not implement the necessary risk minimization activities when they receive Direct Healthcare Professional Communication (DHPC) letters.

Only 4.16% of the surveyed Physicians benefited from the access given by the EMA to the Eudravigilance database and only 4.16% were aware of the decisions of the Drug Safety Committee at the EMA.

83.33% gave a positive answer to the question of whether they believe that educational programs for drug safety and ADR reporting are necessary, which testifies to the awareness of the lack of theoretical and practical training on the matter.

Respondents' attitudes towards ADR reporting appear to be good, but targeted educational strategies on how to report could not improve the ADR reporting process.

Currently, reporting of ADRs by Physicians is voluntary, but many responded that it should be mandatory.

Reporting ADRs is the responsibility of Physicians to increase patient safety and reduce the cost of their treatment.

Awareness-raising measures are needed to overcome this attitude towards pharmacovigilance processes, especially since they are direct participants in this process.

Physicians should be aware that no medicinal product is completely or absolutely safe for all people, in different geographic regions, at all times. They should always practice with a degree of uncertainty in mind, especially these days when there are more and more different medicines on the market with different safety and efficacy profiles.

Furthermore, recent studies have shown that ADRs are underreported by healthcare providers, especially in developing countries. It is reported that only 2-4% of all adverse reactions and 10% of serious ADRs are reported worldwide. Physicians are strongly encouraged to report any suspected drug adverse reaction, especially suspected Adverse Drug Reactions,

and Serious Events of newly approved drugs. Therefore, drug safety assessment should be considered an integral part of daily clinical practice for Physicians [14, 17].

The reporting of spontaneous adverse reactions is the foundation of pharmacovigilance and is required to generate hypotheses about the potential harms of drugs that need further evaluation. Spontaneous reporting is very useful for identifying very rare or delayed reactions that cannot be detected during the short period of the clinical trial. The safety of a drug can be monitored and investigated more in-depth after its approval and throughout its life cycle [9].

Physicians' understanding of the safety profile of drugs is essential. They should be aware of the potential for unexpected adverse drug reactions and report suspected adverse reactions to drug regulatory authorities to facilitate the detection and evaluation of drug safety signals. This is the only way to preserve the health of their patients or reduce the risk of using their prescribed medicinal products. Also, hospitalization or prolongation will be avoided, and it will save a significant public financial resource.

RECOMMENDATIONS

To the Medical Universities and Associations of doctors, nurses and pharmacists (BLS, BAPZG, BFS)

This study points to the need for educational programs for healthcare professionals to be aware of the need to report ADRs and the need for pharmacovigilance in general. The need to participate in specific training courses is strongly perceived among nurses, they are willing to develop their knowledge and competence in reporting ADRs.
A critical and systematic analysis of promotion strategies the NLR reporting showed that 87% borrow educational materials such as presentations and handouts. This means that training courses or others educational initiatives to be a lever for motivation and positive attitudes, for changing routine practices and taking initiative.

To the Bulgarian Drug Agency

To conduct appropriate trainings for the reporting of ADRs. To undertake regulatory changes and other actions by the BDA.
All healthcare professionals should be aware that so-called Direct Healthcare Professional Communication (DHPC) Letters are the result of their reporting and they should read this communication carefully. On the other hand, MAHs must promptly inform medical professionals about a change in product information related to safety.

CONTRIBUTIONS

Scientific contributions

For the first time, this work examines in detail the role of all participants in the followup processes of Pharmacovigilance

Special attention is paid to the important responsibilities of medical professionals, as participants who prescribe the drugs and have direct patient monitoring. Practitioners are the main component of the ADR Reporting System.

For the first time, the entire Pharmacovigilance has been systematized, considering all aspects of the drug safety management system.

Contributions with a practical focus

Based on the in-depth scientific research and analysis of the results of the sociological research, an information brochure was developed with the aim raising awareness and stimulating the activity of medical professionals to report ADRs. The recommendations of the interviewed medical specialists have also been taken into account:

- 80 (16.67%) doctors suggest that during the visit of the medical representatives, they should provide as a separate material the ADR reporting form with relevant explanations to it and new information about the safety of their medicinal products.
- When asked what their suggestions are how the process of tracking the In order to improve medication safety (this was a matter of their choice), the respondents suggested the following:
- The second most respondents reasonably had a recommendation for MAHs to prepare a special attractive, not very large, brochure - 1-3 pages, to remind them to report ADRs and the most important risks in certain groups of patients, which could also be sent by email .

LIST OF SCIENTIFIC PUBLICATIONS

1. **Topalova V**., D. Sidzhimova, T. Benisheva. Socially-significant aspects of side effects of drugs among elderly people.VIII International scientific and practical conference "Forms and methods of social work in various spheres of life". October 3-5, 2019, Ulan-Ude, village 250-251

2. **Topalova V**., D. Sidzhimova, T. Benisheva. Adverse drug reaction alert management. Sp. Health Policy and Management, no. 4, 2019, pp. 58-63

3. **Topalova V**., D. Sidzhimova, T. Benisheva. Attitudes of healthcare professionals to report adverse drug reactions. Sp. Health Policy and Management, no. 1, 2020, pp. 28-35

4. Benisheva T., **V. Topalova,** D. Sidjimova. Pharmacovigilance ‑ Role and Importance. Basic & Clinical Pharmacology with Toxicology. ARSO. 2021, p. 446 ‑ 449

5. Sidjimova D., T. Benisheva, **V. Topalova**, V. Petkova. Medical Doctor's Attitude to the Adverse Drug Reactions Reporting in Bulgaria. Pharmacy. Received 9 November 2023 ♦ Accepted 14 November 2023. Journal Impact Factor: 1.1 ISSN 2603-557X (online)