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ПОБОЧНЫЕ ЭФФЕКТЫ ПРИ ПРИМЕНЕНИИ ГАМ-КОВИД-ВАК В ЧЕРНОГОРИИ

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SIDE EFFECTS FOLLOWING ADMINISTRATION OF THE GAM-COVID-VAC IN MONTENEGRO

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Резюме.

Введение: В Черногории вакцинация против инфекции COVID началась с использования Гам-КОВИД-Вак, который не был одобрен для экстренного использования до окончания клинических испытаний со стороны Управления по санитарному надзору за качеством пищевых продуктов и медикаментов и Европейского агентства по лекарственным средствам. Поэтому необходимо подчеркнуть побочные эффекты.

Методы: Данные были собраны для целей настоящего исследования из национальной формы сообщения о нежелательных явлениях для Гам-КОВИД-Вак, полученной от Учреждения здравоохранения Аптеки Черногории - Монтефарм, как носителя разрешения на эти вакцины.

Результаты: За период с 1 марта 2021 г. по 13 февраля 2022 г. после применения 16 756 доз вакцины Gam-COVID было всего зарегистрировано 220 случаев, т.е. 716 побочных эффектов. Средний возраст вакцинированных, сообщивших о нежелательных явлениях, составил 40,79 ± 11,35 лет. В общей сложности 79,55% женщин по сравнению с 20,45% мужчин сообщили о побочных эффектах после вакцинации. Наиболее частой побочной реакцией была температурная реакция (79,55%). Другими очень частыми побочными эффектами были: боль в месте инъекции (38,18%), головная боль (33,18%), миалгия (32,27%), недомогание (31,82%), лихорадка (30,45%), артралгия (22,73%), отек и покраснение в месте введения (15,91%). Менее распространенными побочными эффектами были тошнота, боль в конечностях, диарея, головокружение, утомляемость, боль в горле и herpes labialis. Серьезные побочные эффекты, отмеченные в 8 случаях, включали шум в ушах, тромбофлебит, гипотонию, боль в груди, учащенное сердцебиение и периферический цианоз и были связаны с некоторыми сопутствующими заболеваниями.

Выводы: После введения вакцины Гам-КОВИД у населения Черногории наблюдались побочные эффекты легкой и средней степени тяжести, с редкими серьезными эффектами преходящего характера, которые были связаны с определенными сопутствующими заболеваниями. По результатам данного исследования вакцина Гам-КОВИД подтвердила хороший профиль безопасности и высокую переносимость, о чем свидетельствует статистический анализ с отсутствием госпитализаций и летальных случаев.

Ключевые слова: инфекция COVID-19, вакцинация, Гам-КОВИД-Вак, побочные эффекты, сопутствующие заболевания, безопасность.

Abstract

Introduction: Vaccination against COVID infection began in Montenegro using Gam-COVID-Vac, which was not approved for emergency use before the end of clinical trials, by the Food and Drug Administration and the European Medicines Agency. Therefore, it is necessary to emphasize the harmful effects.

Methods: For the purposes of this research, data were collected from the national form for reporting adverse events for Gam-COVID Vac obtained from the Health Institution Pharmacy of Montenegro - Montefarm, as the holder of the license for these vaccines.

Results: For the period from March 1, 2021 to February 13, 2022, after the administration of 16,756 doses of the Gam - COVID vaccine, a total of 220 cases, or 716 side effects, were reported. The average age of vaccinated persons who reported adverse effects was 40.79 ± 11.35. A total of 79.55% of women versus 20.45% of men reported adverse effects after vaccination. The most common adverse reaction was pyrexia (79.55%). Other very common side effects were: injection site pain [38.18%], headache [33.18%], myalgia [32.27%], malaise [31.82%], fever [30.45%] , arthralgia [22.73%] and swelling and redness at the application site [15.91%]. Less common side effects were nausea, pain in extremities, diarrhea, dizziness, fatigue, sore throat, and herpes labialis. Serious side effects, noted in 8 cases, included tinnitus, thrombophlebitis, hypotension, chest pain, palpitations, and peripheral cyanosis and were associated with certain comorbidities.

Conclusions: After administration of the Gam - Covid vaccine, the population in Montenegro had mild to moderate AEs, with rare serious AEs of transient nature, which were associated with certain comorbidities. According to the results of this study, Gam-COVID vacc confirmed a good safety profile and high tolerability, as indicated by the statistics that there were no hospitalizations and no deaths.

Keywords: COVID-19 infection, vaccination, Gam-COVID-Vac, side effects, comorbidities, safety.

Introduction: In Montenegro, vaccination against COVID infection began with the use of Gam-COVID-Vac, which was not approved for emergency use before the end of clinical trials, by the Food and Drug Administration and the European Medicines Agency. Therefore, it is necessary to emphasize the adverse effects.

Methods: For the purpose of this study, there were collected data from national adverse events reporting form for Gam-COVID Vac obtained from the Health Institution Pharmacy of Montenegro - Montefarm, as the holder of permits for these vaccines.

Results: For the period March 1, 2021 to February 13, 2022, after administration of 16,756 doses of vaccine Gam - COVID, a total of 220 case reports, or 716 adverse effects were recorded. The mean age of vaccinated individuals who reported adverse effects was 40.79 ± 11.35 years. Totally, 79, 55% females versus 20, 45% males reported side effects post-vaccination. The most common adverse reaction was pyrexia [79.55%]. Other very common adverse effects were as follows: injection site pain [38.18%], headache [33.18%], myalgia [32.27%], malaise [31.82%], fever [30.45%], arthralgia [22.73%] as well as swelling and redness at the site of application [15.91%]. Less common adverse effects were nausea, pain in extremity, diarrhea, dizziness, fatigue, sore throat and labial herpes. Serious adverse effects were recorded in 8 cases including tinnitus, thrombophlebitis, hypotension, chest pain, palpitations and peripheral cyanosis related to specific comorbidities.

Conclusions: After the administration of Gam - Covid vaccine, the population in Montenegro experienced mild to moderate adverse effects, with rare serious transient adverse effects related to specific comorbidities. The data presented here on investigating Gam-COVID-Vac caccine verified good safety profile and high

tolerability evidenced by the statistics analysis as lacked COVID-19-associated hospitalizations or deaths.

Keywords: COVID-19 infection, vaccination, Gam-COVID-Vac, adverse effects, comorbidities, safety.

1 Introduction

SARS-CoV-2 virus infection, detected on December 31, 2019 in Wuhan (China), has rapidly widespread and caused a global pandemic of acute respiratory disease, defined as COVID-19 disease. A high rate of transmission and ability to mutate are the most distinctive characteristics of the SARS-CoV-2 virus, as indicated by data on registered cases of infection as well as the duration of the pandemic (9,14). From December 2019 until August 8, 2023. total of 695,063,811cases of infection plus 6,913,777 deaths were registered globally. Accordingly, COVID-19 has been a public health problem worldwide (33).

The pandemic has forced policy makers, health professionals, pharmaceutical industry and other organizations, at the level of diagnostics (development of fast and reliable diagnostic methods), treatment (application of effective therapeutic options, use of existing and synthesis of new drugs) and prevention (introduction of preventive measures, recommendations for protection and vaccination) to decree urgent confinements to combat, stop a rapid and massive contagion and reduce COVID-19 mortality (2).

After identification of SARS-CoV-2 genome sequence, pharmaceutical companies have designed and developed considerable number of COVID-19 vaccines using either previously available vaccine production technologies or new scientific approaches and methods. By the end of 2020, more than 280 different COVID-19 vaccines were in some stages of development. In addition, according to the World Health Organization (WHO), 63 vaccines and more than 172 candidate vaccines were in preclinical development (6, 18). Vaccines, along with all drugs, are subject to legal regulations for placing the drug on the market, which, among other things, involves providing documentary evidence of pharmaceutical-chemical-biological testing, pre-clinical or pharmacological-toxicological testing as well as clinical trials of drugs, which prove quality, efficacy and drug safety. Assuming the urgent need to prevent the spread of COVID-19 infection plus the fact that the

development of new drugs / vaccines is an enduring process (around 10 years), conventional procedures for approving the marketing of COVID-19 vaccines could not be followed. Nevertheless, the WHO and the European Medicines Agency (EMA), in public health emergencies, such as pandemics, may also authorize the use of certain medicines that do not comply with regulatory legal procedures for placing on the market if presented data indicate that the benefits outweigh the risks. Depending on the regulatory process for the evaluation and approval of vaccines, certain vaccines against COVID-19 in the clinical trial phase, received emergency use approval before the completion of all three phases of clinical trials (8, 10). Therefore, this fact is of particular importance for collecting enough scientific evidence on adverse events (AE), recording, evaluating and monitoring the AE of the vaccinated population.

The first registered cases of SARS-CoV-2 virus infection in Montenegro were confirmed on March 17, 2020. By August 8, 2023, there were 292,510 infected and 2,828 deaths cases (0.97%) as a result of COVID-19 infection. The vaccine that first arrived and with which the vaccination started in Montenegro on March 1, 2021, was Gam - COWD-Vac, produced by FSBI "NRCEM N.A. N.F. Gamaleya", Russian Federation '. The vaccine was developed as a vector vaccine. It is meant to be given as two doses (Gam-COVID-Vac component I and Gam-COVID-Vac component II) with different adenovirus-based viral vectors (serotypes 26 and 5) administered 21 days apart. Then other vaccines arrived continuously (chronological overview):

- March, 16, 2021 - Vero Cell, SARS CoV-2 vacc manufacturer Beijing Institute of Biological Products Co., Beijing, China
- March, 30, 2021 - AstraZeneca (Vaxzevria®) Vaccine, manufactured by AstraZeneca Nijmegen B.V., Netherlands
- May, 4, 2021. - Comirnaty® Vaccine, manufactured by Pfizer BioNTech, Belgium

- October, 29, 2021. - CoronaVac, COVID-19 Vaccine (Vero Cell) Inactivated (SINOVAC) manufactured by Sinovac Life Sciences Co., Beijing, China
- January, 24, 2022. - COVID-19 Vaccine Moderna®, manufactured by Rovi Pharma Industrial Services, S.A., Spain

Amongst all procured vaccines in Montenegro, WHO issued emergency use approval at the time only for Comirnaty®, Vaxzevria® and Moderna® vaccines. Vaccines from the Chinese manufacturer Beijing were approved almost two months after their use (May 7, 2021), while vaccines from the Russian Federation are still not approved for use. Nevertheless, based on the Law on Medicinal Products ('Official Gazette of Montenegro', No. 080/20), Article 8, the Government of Montenegro in cases of emergencies and other special situations, takes measures to supply medicines and prescribes special procedures and conditions for granting approval for the procurement and sale of medicines (34).

According to the WHO, Gam – COVID vaccine used in Montenegro against COVID-19 infection was not approved for emergency use. Therefore, it is necessary to emphasize AEs, compare recorded AEs with those in the summary of product characteristics as well as with the results of clinical studies, and establish a possible association between AEs and premorbid background, which is the main goal of this study. The results of this study will provide useful information to vaccine recipients in terms of expected AEs in a specific population depending on individual characteristics such as age, sex, as well as existing medical conditions.

2 **Materials and methods**

Process of a comprehensive adverse drug reaction (ADR) monitoring and reporting in Montenegro is defined by the Rulebook on the Manner of Collecting of Data and Reporting and Monitoring AEs to Medicines for Use in Human Medicine (46/2014). According to this Rulebook, monitoring the safety of medicines in the market and detecting any changes in the benefits and risks of their application is

done by establishing a pharmacovigilance system by two entities - license holders and the Institute of Medicines and Medical Devices of Montenegro (CInMED) (28). CInMED is an independent, national regulatory authority in the field of medicines and medical devices, responsible for monitoring AEs in Montenegro. In order to exchange information in the field of pharmacovigilance, CInMED is in the partnership with WHO Safe Use Program and cooperates with its Uppsala Monitoring Center (UMC), the European Medicines Agency (EMA) and other professional and regulatory bodies in European Union and other countries.

Adverse events are reported in safety reports of individual cases of AEs (ICSR) in the form of a standardized international form (CIOMS I) for the ICSR report, issued in 1990 by CIOMS and the working group of the Council of International Organizations for Medical Sciences. The form includes information about the patient (age, sex), disease records, information on the details of adverse events (beginning, duration, severity, and outcome) and administrative details (source of the AE report and association with the vaccine received).

Every single report of adverse events by healthcare professionals, pharmaceutical companies and patients is forwarded by CInMED to the qualified person responsible for the pharmacovigilance of the marketing authorization holder, i.e. the importer / distributor, with the protection of the reporter's data. The authority responsible for pharmacovigilance monitors the safety profile and all safety issues related to licensed vaccines and is obliged to forward the report of suspected AEs after vaccination to vaccine manufacturers in order to be included in global safety documents. Applications from CInMED are entered into the VigiFlow database, processed in such a way that the data on the suspected vaccine and the reactions expressed are coded using the MedDRA dictionary. VigiFlow supports data exchange of safety information with internal and external stakeholders in different formats such as Excel, xml/ICH E2B and provides secure, controlled and easy sharing of adverse event reports to WHO through VigiBase, WHO’s global database

of reported potential side effects of medicinal products, EMA (EudraVigilance) and other systems such as DHIS2 and Vigilance Hub.

For the purpose of this study, we collected data from national adverse events reporting form for vaccines against COVID-19 infection - Gam-COVID component I and Gam-COVID component II. The data were obtained from the Health Institution Pharmacy of Montenegro Montefarm, as the holder of permits for these vaccines. All collected data were placed in appropriate files - DBF (data base file), inserted into Excel operating program and formed tables that for all analyzed vaccines contained age, sex, medical conditions, side effects, the relationship between side effects and vaccines and the source of application. The recorded AE are, in relation to the prevalence, expressed as a percentage and the obtained data are compared with the data from the approved summaries (Table 1) (29). For other AE, an association with available study results was sought. Electronic databases - PubMed, Embase, Cochrane Library and Google Scholar - were searched using the descriptors "Gam-COVID", "adverse effects" and "safety" in English, without time limit.

Data on the total number of vaccinated persons with the first, second and third dose of analyzed vaccines were collected from the electronic database of the Institute of Public Health of Montenegro, relying on the calculated percentage of reported AE to vaccines.

This study included all AEs reported to the import license holder, Montefarm, following the administration of any of the three doses Gam - COVID - Vac in the period between March 1, 2021 and February 13, 2022.

3 **Results**

For the period March 1, 2021 to February 13, 2022, a total of 8,302 people had received Gam - COVID vaccine their first dose, 8,136 the second doses and 318 the third dose. Gam - COVID - Vac component I was used as the first and third dose and Gam - COVID - Vac component II as the second dose. In the mentioned period,

a total of 16,756 doses of Gam - COVID vaccine were administered, namely 8,620 Gam - COVID - Vac component I and 8,136 Gam - COVID - Vac component II.

98% of vaccinated with the first dose also received the second dose though only 3.9% of the population received the third dose. Public Health Institute recommended mRNA vaccines as the third dose, for reasons of well-documented immunity, especially in persons over 60 years of age which resulted in small coverage with the third dose of the Gam - COVID vacc. As for the age structure of the vaccinated, the largest percentage of the vaccinated population was in older than 50 years of age (65.9%) (Graph 1).

After receiving of 16,756 doses of vaccine Gam - COVID, a total of 220 case reports, or 716 AE, were reported, equivalent to a reporting rate of 13,1 case reports and 42,7 AE per 1000 doses received. Out of 220 reports of AE, 184 related to Gam - COVID - Vac component I, and 36 to Gam - COVID - Vac component II. The mean age of vaccinated individuals who reported AE was 40.79 ± 11.35 ranged between 21 and 81 years with a median of 39 (Figure 1). Statistically significant gender difference in the percentage was reported, 20, 45% in males vs 79, 55% in females (Table 2).

Of the total number of individuals (220) who reported AEs, 8.64% (n=19) had at least one medical condition recorded in the CIOMS form. The most common condition was hypertension (3.18%, n=7), followed by myocardial infarction (1.36, n=3), obesity (1.36%, n=3), thyroid disorder (0.91%, n=2), thrombophilia (0.91). %, n=2) and thrombophlebitis (0.91%, n=2). Among other medical conditions, insulin resistance (0.45%, n=1), obstructive chronic bronchitis (0.45%, n=1), lupus (0.45%, n=1), angina pectoris (0 .45%, n=1), and one person had multiple comorbidities – overlap autoimmune hepatitis/primary biliary cirrhosis, Sjogren's syndrome, celiac disease and chronic gastritis.

Case reports were submitted by health professionals, 219 from doctors and one from a pharmacist. The biggest number of applications refers to the population under 60 years of age (96.4%) (Graph 2).

Local and systemic AE after Gam-COVID-Vac component I and Gam-COVID-Vac component II are presented in Table 3. The most common adverse reaction was pyrexia reported with 175 of vaccinated individuals (79.55%). The range in body temperature was 37.1 to 40°C and most often occurred 8-12 hours after vaccination. The estimated median total duration of pyrexia was 1 to 36 hours. Other very common AE were: injection site pain (38.18%), headache (33.18%), myalgia (32.27%), malaise (31.82%), fever (30.45%), arthralgia (22.73%) and swelling and redness at the site of application (15.91%). Less common AE after administration of these vaccines were nausea (8.64%), pain in extremity (7.27%), diarrhea (4.55%), dizziness (4.09%), fatigue (3.64%), sore throat (1.82%) and herpes labialis (1.36%).

Rarely reported AE, recorded in one or two vaccines included paresthesia (tongue, lips and face), cough, hoarseness, neutropenia, bronchospasm, metallic taste in the mouth, swelling of the nasal mucosa, face and neck, heaviness in the body, supraclavicular lymphadenopathy and renal pain.

Among rare AE, serious AE were recorded in 8 cases including tinnitus, thrombophlebitis, hypotension, chest pain, palpitations and peripheral cyanosis.

Very common AE were in a significantly higher percentage of population younger than 50 years of age (pyrexia 87% vs 52%, fatigue 36% vs 17%, arthralgia 27% vs 8%) while dizziness, pain in extremity and gastrointestinal discomfort (nausea, diarrhea) were more common in the population older than 50 years of age. Local AE were lower in males and systemic reactions of pyrexia (86% vs 53%) and headaches (37% vs 18%) were much more common in females, while other AE were similar (Graphics 3 and 4).

The difference in reported AE after the application of Gam Covid Vacc component I and component II mainly included rare effects, and of the frequent AE, higher temperature appeared in a significantly higher percentage after the application of the first dose (Gam - COVID -Vac component I). However, pyrexia and fever were reported in a higher percentage after the application of the second dose. AE such as skin reactions at the application site and arthralgia were lower after the second dose, while site pain, headache, malaise and myalgia were more common after Gam-COVID-Vac component II administration (Graph 5).

4 **Discussion**

Based on the experience with the COVID infection, we are aware that vaccines are the most effective means of achieving control over the pandemic. Given the pandemic circumstances of the COVID infection, the urgent actions for vaccine synthesis, the short time frame for efficacy and safety testing, and their urgent approval for use before the completion of all three phases of clinical trials, there are public concerns about the efficacy and safety of vaccines against the COVID infection. Of particular importance is the dataset related to vaccines that for some reason have not yet been approved by the Food and Drug Administration and the European Medicines Agency. Therefore, it is necessary to collect evidence-based information on the effectiveness and safety of vaccines. In terms of efficacy, the highest clinically confirmed efficacy (>90%) against COVID infection, in preventing symptoms and reducing the risk of severe forms of COVID and death (11), was shown by mRNA vaccines, BNT162b2 Comirnaty® (~95%) and mRNA -1273 Moderna (~94%) and adenovirus vaccine Gam-COVID vacc (~92%) (7). However, AEs play a key role in public confidence in vaccination.

The first vaccine against COVID infection that was administrated in Montenegro je Gam-COVID. According to the recommendations of the National Immunization Advisory Body of Montenegro, health professionals (who came into contact with infected persons and their contacts), along with the elderly and those

with chronic diseases had priority for the administration of the first limited quantities of vaccines. Accordingly, most health workers were vaccinated with Gam - COVID vaccine. The high rate of reports (13.1 / 1000 doses) and reported AE to Gam - COVID vaccine (42.7 / 1000 doses) is the result of professional responsibility and self-developed awareness of health professionals about the importance of the vaccines safety monitoring. These data are in agreement with the results of studies where the rate of reporting AE after vaccination of health care workers is higher (4, 26) compared to the rate of reporting AE after vaccination of general population (1).

According to the results of this study, a significantly higher number of AE reports were related to women compared to men (80.45% vs 19.55%), which is in line with the results of observational studies on AE, in general, for all vaccines against COVID infections (4, 23, 26).

Regarding age, AE were significantly more common in young people than in older adults, as found in other studies. The old population was vaccinated with the first vaccine, Gam - COVID vaccine as a high risk group. Out of the total number of administered doses (16,756 doses), 45.9% of the population over 60 years of age (7725 people) received the vaccine and only 3.6% (8 people) reported AE; 3.3 % after the first dose and 5.5% after the second dose. According to a study by Montalti et al (24) 43.7% population aged 60 and over reported AE after the first dose of Gam - COVID vaccine plus 60% after the second dose which is not in agreement with these results. Difference can be explained by a significantly higher percentage of vaccinated persons 60 years of age and older (76.1%) compared to the same age population of this study (45.9%).

Regarding AE after the first and second doses of Gam - COVID vaccine, the results are controversial. In the observational study by Montalti et al (24), side effects increased after the second dose and in the study by Babamahmoodi et al (4), side effects significantly decreased after the second dose compared to the first. In this study, a much higher number of reports were related to the first dose compared

to the second dose (5.1% vs 1%) but the number of side effects in relation to the number of reports was slightly higher after the second dose received (3.4% vs 3.2%). This variability in results may be due to the different Gam - COVID vacc component I and Gam - COVID vacc component II vectors.

The most common AE in this study included pyrexia, fever, application site reactions, headache, musculoskeletal pain, general weakness (fatigue and tiredness), consistent with the data collection and the results of a randomized controlled trial of phase 3 efficacy and safety Gam - COVID vaccine (21), in which the most common AE included influenza - like condition, application reaction, headache and asthenia. The frequency of AE, such as - injection site reaction, headache, fever, arthralgia, nausea, diarrhea, in this study is similar to the results of a study on AE after Gam - COVID vaccine in healthcare workers in Iran (4).

The emphasis of the study was placed on AEs not recorded in the summary of characteristics of the Gam-COVID vacc, with a special focus on AEs that occurred in persons with present comorbidities, in order to determine whether there is an association of AEs with a premorbid background.

The recorded AEs in this study, which are not found in the summary of characteristics, and characterized as rare and serious, occurred in the largest percentage as a consequence of the medical conditions of the participants.

Obesity is a serious health concern that increases the risk of many other health conditions. In this study, specific AEs were recorded in three subjects who had an increased body mass index. The primarily observed swelling of the face and neck, recorded in a woman (37 years old, BMI 28.16), was found to be lymphedema. Enlargement of lymph nodes is one of the possible reactions after vaccination, which was somewhat more pronounced in this person due to being overweight, as a significant risk factor for the development of lymphedema. Enlargement of lymph nodes is one of the possible reactions after vaccination, which was somewhat more

pronounced in this person due to being overweight, as a significant risk factor for the development of lymphedema (22). Kidney pain that manifested itself 12 hours after the administration of the second dose of the vaccine and lasted 24 hours, in a 22-year-old man with a BMI of 31.79, the doctor registered the link with the vaccine as "probable". This condition is probably a consequence of obesity, as one of the most significant risk factors for kidney disease is a high body mass index. (17). An obese man (43 years old, BMI 32.22) developed herpes labialis, which the doctor did not associate with the vaccine. Research indicates a connection between obesity and herpes simplex virus infection (13), that fat tissue can participate in the body's immune responses (15)

After administration of the first dose of Gam-COVID vacc, thrombosis was recorded in two women, aged 56 and 65 years. Both women had thrombophlebitis in their medical history with other comorbidities (a 65-year-old woman had hypertension, and a 56-year-old woman had hypertension and thyrotoxicosis). Thrombosis was reported in three cases in the phase 3 study (21), two cases in the vaccine group and one case in the placebo group. Research results indicate that a possible cause of thrombosis in vector vaccines is an immune response to the vector, which leads to heparin-induced thrombocytopenia, which leads to the formation of antibodies directed against the complex of platelet factor 4 with heparin (12). However, in this study, the reporters do not link the manifested reaction to the vaccine, precisely because of thrombophlebitis as a registered medical condition in the medical history of these two patients. That hypertension and thyroid disorders do not affect thrombophlebitis is confirmed by cases that had these medical conditions and only mild, common effects from AE.

More serious adverse reactions after vaccination with the first and second doses of Gam-COVID vacc were noted in a 44-year-old woman with multiple comorbidities - overlap autoimmune hepatitis/primary biliary cirrhosis, Sjogren's syndrome, celiac disease, and chronic gastritis. After the first dose, the more serious

AEs included tinnitus and hypotension, resulting in collapse, and after the second dose, palpitations and hypotension, lasting 48 hours. Studies indicate that Sjogren's syndrome can develop hyper orthostatic hypotension (30), vestibular symptoms, such as dizziness and tinnitus (25) as well as autonomic nervous system dysfunction that affects the cardiovascular system (16). But it is not known if the vaccine temporarily "enhanced" this medical condition or if it interacted with the therapy, because the patient with another autoimmune disease, lupus, had only a slightly elevated temperature (37.3°C) from AE. Given that the patient had several comorbidities, it is assumed that she was also taking a large number of medications that the doctor did not list in the formulary.

Other patients included in this study, who had a history of serious medical conditions – insulin resistance, chronic obstructive bronchitis, myocardial infarction and thrombophilia, had the expected and short-term AEs (pyrexia, fever, pain at the application site) in a milder form.

Tinnitus, which was reported by another female case after the administration of the first dose of Gam - COVID vacc, has not been reported in studies with this type of vaccine. Cases of tinnitus after administration of vector-based vaccines (Vaxzevria®) and mRNA (Comirnaty®) have been reported in the literature (27,32). However, during the last two years, the number of people who developed tinnitus after vaccination has been increasing. The mechanism of tinnitus formation is still unknown it is possible that it occurs as a consequence of a hypersensitivity reaction with an abnormal autoimmune response or vasculitis (27). Also, study results indicate that the vaccine interacts with pre-existing risk factors for tinnitus and that there is a link between glaucoma and tinnitus, with glaucoma patients having a 19% higher chance of developing tinnitus (3). A report of a metallic taste (which was present for 21 days), accompanied by chest pain, pyrexia, fever, gastrointestinal complaints and myalgia in a 33-year-old woman was submitted by a doctor with the

comment that the person was probably infected with a COVID infection during the period when she was vaccinated.

Peripheral cyanosis of the fingers appeared 9 hours after vaccination and lasted half an hour, in a 51-year-old woman with no history of Raynaud's phenomenon. There have been cases in the literature in which Raynaud's phenomenon occurred after m-RNA-based COVID vaccines (BNT162b2-Comirnaty® and mRNA-1273- Spicevax®) and adenovirus vaccines (Vaxzevria®). The link between COVID vaccines and cyanosis has not yet been clarified, because the occurrence of Raynaud's phenomenon has also been reported after vaccination against human papillomavirus, hepatitis B and diphtheria-tetanus. But the authors point to the possibility that the spike protein may act as an additional trigger in the development of Raynaud's phenomenon (20).

Mild chest pain, which lasted 1 hour, accompanied by fever and malaise also occurred in a 51-year-old woman after the second dose. This short-term pain can be psychological in nature.

Oral paresthesias, especially of a short-term, transient nature, as described in this study where two cases of paresthesia lasting 1 minute were recorded, are most often the result of psychogenic disorders (fear, anxiety, depression,...) (5).

In this study, reported adverse effects were mild or moderate, and no serious AEs considered vaccine-related were reported, which is consistent with the results of observational and survey studies with low sample size. Recorded serious AEs were not related to the vaccine but to comorbidities. Medical conditions that require caution and monitoring of the patient after vaccination are obesity, thrombophlebitis and Sjogren's syndrome. It is safe to use Gam-COVID vacc in patients with lupus, hypertension, thrombophilia, insulin resistance, chronic obstructive bronchitis and thyrotoxicosis.

Although it still does not have approval for use by the Food and Drug Administration and the European Medicines Agency, compared to other approved vaccines against COVID infection, Gam-COVID vacc has a much lower rate and incidence of AEs. It belongs to one of the three most effective vaccines, with the difference that highly effective mRNA vaccines lead to rare but very serious clinical manifestations such as acute myocardial infarction, Bell's palsy, cerebral venous sinus thrombosis, Guillain–Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, thrombosis with thrombocytopenia syndrome, lymphadenopathy, appendicitis, herpes zoster reactivation, neurological complications, and autoimmunity (e.g., autoimmune hepatitis and autoimmune peripheral neuropathies) (31). In order to improve future vaccines, studies are being conducted that try to clarify the mechanisms of the occurrence of side effects after the administration of vaccines against COVID infection. The results of these studies will provide evidence as to whether there is a clear association between these effects and vaccines and, if so, which vaccine components and/or platforms are responsible for these reactions (19).

5 **Conclusion**

According to the results of this study, Gam-COVID vacc confirmed a good safety profile and high tolerability, as indicated by the statistics that there were no hospitalizations and no deaths. After administration of the Gam - Covid vaccine, the population in Montenegro had mild to moderate AEs, with rare serious AEs of a transient nature, which were associated with certain comorbidities. The most common side effects were in accordance with the data from the summary of drug characteristics and the results of the randomized controlled trial phase 3 trials. These included fever, site reaction, headache and musculoskeletal pain. The most important variables in the prevalence of AEs were age, sex, and premorbid background. AEs were significantly more frequent in women and the younger population and slightly more pronounced in patients with certain medical conditions.

Future studies on the safety of the Gam - COVID vaccine should focus on the population with comorbidities, who have an increased risk of infection with COVID-19, in order to prove whether there is an association of the vaccine with adverse effects or with a premorbid background and reliably assess and prevent risk of AEs.

Vaccination is the most effective form of protection against COVID-19 and should be continued to reduce the risk of severe infection and death. Rapid identification of potential health risks and effective measures to reduce them is the basis for restoring, gaining and strengthening the general population's trust in vaccination. That is why support, improvement and strengthening of the pharmacovigilance as well as cooperation at the global level are necessary.

Limitation of the study

This study is limited by the small sample size and insufficiently complete data from the CIOMS form (therapy, comorbidities).

Acknowledgments

Thanks to all the doctors who professionally and quickly sent detailed reports on adverse events.

ТАБЛИЦЫ

Table 1. Adverse effects Gam-COVID-Vac from the approved summaries.

Таблица 1. Побочные эффекты после применения вакцины Gam-COVID-Vac согласно утвержденным обзорам.

AE **Побочные эффекты**	**Symptoms** **симптомы**
General injection site disorders and reactions	Very common and common - hyperthermia
	Very common and common - injection site pain
	Very common and common - injection site swelling
	Very common and common - asthenia
	Very common and common - pain
	Very common and common - malaise
	Very common and common - pyrexia
	Very common and common - decreased appetite
Nervous system disorders	Common - Nervous system disorders
	Rare - Dizziness, syncope
Musculoskeletal disorders	Very common and common - arthralgia, myalgia
Respiratory, chest, and mediastinal disorders:	Common - oropharyngeal pain, nasal congestion, sore throat, rhinorrhea
Gastrointestinal disorders	Common - nausea
	Common - vomit
	Common - dyspepsia
Lab test and instrumentation data	a) Divergent deviations of immunological status indicators
	increased count of T-lymphocytes
	increase in the percentage of lymphocytes
	decreased count of natural killer cells
	increased count of CD4-lymphocytes
	decreased count of CD4-lymphocytes
	increased count of B-lymphocytes
	decreased count of B-lymphocytes
	increased count of natural killer cells
	increased count of CD8 lymphocytes
	increased level of immunoglobulin E (IgE) in the blood
	increase in the CD4/CD8 ratio
	decrease in the CD4/CD8 ratio
	increased level of immunoglobulin A (IgA) in the blood

	decrease in the percentage of CD8 lymphocytes
	b) Abnormalities in the complete blood count
	increase in the percentage of lymphocytes
	decrease in the hematocrit
	increased count of lymphocytes and monocytes
	increase in the erythrocyte sedimentation rate
	increased platelet count
	decreased count of neutrophils
	decreased platelet count
	c) Deviations in common urine analysis
	erythrocytes in the urine

Побочные эффекты	**симптомы**
Общие нарушения и реакции в месте инъекции	Очень часто и часто — гипертермия.
	Очень часто и часто — боль в месте инъекции.
	Очень часто и часто — отек в месте инъекции.
	Очень часто и часто — астения.
	Очень часто и часто — боль
	Очень частое и распространенное – недомогание
	Очень часто и часто — пирексия.
	Очень часто и часто — снижение аппетита.
Расстройства нервной системы	Часто — расстройства нервной системы.
	Редко — головокружение, обморок.
Скелетно-мышечные нарушения	Очень часто — артралгия, миалгия.
Нарушения со стороны органов дыхания, грудной клетки и средостения:	Часто — боль в ротоглотке, заложенность носа, боль в горле, ринорея.
Желудочно-кишечные расстройства	Часто – тошнота
	Часто — рвота
	Часто – диспепсия
Данные лабораторных испытаний и приборов	а) разнонаправленные отклонения показателей иммунологического статуса
	увеличение количества Т-лимфоцитов
	увеличение процента лимфоцитов
	уменьшение количества естественных клеток-киллеров
	увеличение количества CD4-лимфоцитов
	снижение количества CD4-лимфоцитов
	увеличение количества В-лимфоцитов
	снижение количества В-лимфоцитов
	увеличение количества естественных клеток-киллеров
	увеличение количества лимфоцитов CD8
	повышение уровня иммуноглобулина Е (IgE) в крови

	увеличение соотношения CD4/CD8
	снижение соотношения CD4/CD8
	повышенный уровень иммуноглобулина А (IgA) в крови
	снижение процента CD8-лимфоцитов
	б) Отклонения в общем анализе крови
	увеличение процента лимфоцитов
	снижение гематокрита
	увеличение количества лимфоцитов и моноцитов
	увеличение скорости оседания эритроцитов
	увеличение количества тромбоцитов
	снижение количества нейтрофилов
	снижение количества тромбоцитов
	в) Отклонения в общем анализе мочи
	эритроциты в моче

Table 2. Demographic characteristics of individuals vaccinated with Gam – COVID vac (component I and component II) with reported AE.

Таблица 2. Демографические характеристики лиц, вакцинированных вакциной Gam-COVID (компонент I и компонент II) с зарегистрированными НЯ.

	Gam – COVID vacc I dose		Gam – COVID vacc II dose		Total	
Age	Reported cases (n)	Percent-age (%)	Reported cases (n)	Percen-tage (%)	Reported cases (n)	Percent-age (%)
20-30	35	19,02	8	22,22	**43**	**19,55**
31-40	63	34,24	13	36,11	**76**	**34,55**
41-50	48	26,09	5	13,89	**53**	**24,09**
51-60	32	17,39	8	22,22	**40**	**18,18**
61-70	4	2,17	2	5,56	**6**	**2,73**
71-80	0	0,00	0	0,00	**0**	**0,00**
81-90	2	1,09	0	0,00	**2**	**0,91**
Total	184	100,00	36	100,00	**220**	**100,00**
Average value ± SD	40,85 ± 11,26		40,44 ± 11,97		**40,79 ± 11,35**	
Min- max	21 - 81		22 - 65		**21 - 81**	
Gender						
Male	37	20,11	6	16,67	**45**	**20,45**
Female	147	79,89	30	83,33	**175**	**79,55**

	Гам – COVID вакцина I доза		Гам – COVID вакцина II доза		Всего	
Возраст	Зарегистрированные случаи (n)	Процент (%)	Зарегистрированные случаи (n))	Процент (%)	Зарегистрированные случаи (n)	Процент (%)
20-30	35	19,02	8	22,22	**43**	**19,55**
31-40	63	34,24	13	36,11	**76**	**34,55**
41-50	48	26,09	5	13,89	**53**	**24,09**
51-60	32	17,39	8	22,22	**40**	**18,18**
61-70	4	2,17	2	5,56	**6**	**2,73**
71-80	0	0,00	0	0,00	**0**	**0,00**
81-90	2	1,09	0	0,00	**2**	**0,91**
Всего	184	100,00	36	100,00	**220**	**100,00**
Среднее ± с.о.	40,85 ± 11,26		40,44 ± 11,97		**40,79 ± 11,35**	
Min- max	21 - 81		22 - 65		**21 - 81**	
Пол						
Мужской	37	20,11	6	16,67	**45**	**20,45**
Женский	147	79,89	30	83,33	**175**	**79,55**

Table 3. Local and systemic AE Gam - COVID –Vac component I and component II.

Таблица 3. Местные и системные НЯ после применения вакцины Gam-COVID-Vac, компонент I и компонент II.

AE	Gam - COVID component I (N = 184)	Gam - COVID component II (N = 36)	Total	
	Number and percentage N (%)	Number and percentage N (%)	N=220	%
Local adverse events				
Injection site pain	67 (36,41)	17 (47,22)	**84**	**38,18**
Injection site swelling, erythema	31 (16,85)	4 (11,11)	**35**	**15,91**
Systemic adverse events				
Pyrexia	153 (83,15)	22 (61,11)	**175**	**79,55**
Headache	59 (32,07)	14 (38,89)	**73**	**33,18**
Fatigue	7 (3,80)	1 (2,78)	**8**	**3,64**
Malaise	56 (30,43)	14 (38,89)	**70**	**31,82**
Myalgia	57 (30,98)	14 (38,89)	**71**	**32,27**
Fever	52 (28,26)	15 (41,67)	**67**	**30,45**
Arthralgia	44 (23,91)	6 (16,67)	**50**	**22,73**
Nausea	16 (8,7)	3 (8,33)	**19**	**8,64**
Pain in extremity	14 (7,61)	2 (5,56)	**16**	**7,27**
Diarrhoea	8 (4,35)	2 (5,56)	**10**	**4,55**
Dizziness	7 (3,80)	2 (5,56)	**9**	**4,09**
Oropharyngeal pain	2 (1,09)	2 (5,56)	**4**	**1,82**
Herpes simplex	3 (1,63)		**3**	**1,36**
Tinnitus	2 (1,09)		**2**	**0,91**
Thrombophlebitis	2 (1,09)		**2**	**0,91**
Hypotension	1 (0,54)	1 (2,78)	**2**	**0,91**
Chest pain	1 (0,54)	1 (2,78)	**2**	**0,91**
Paresthesia	2 (1,09)		**2**	**0,91**
Cough	1 (0,54)		**1**	**0,45**
Dysphonia	1 (0,54)		**1**	**0,45**
Neutropenia	1 (0,54)		**1**	**0,45**
Dyspnoea	1 (0,54)		**1**	**0,45**
Palpitations		1 (2,78)	**1**	**0,45**
Metallic taste	1 (0,54)		**1**	**0,45**

Peripheral cyanosis	1 (0,54)		**1**	**0,45**
Nasaloedema	1 (0,54)		**1**	**0,45**
Face Swelling	1 (0,54)		**1**	**0,45**
Feeling of heaviness	1 (0,54)		**1**	**0,45**
Lymphadenopathy		1 (2,78)	**1**	**0,45**
Renal pain		1 (2,78)	**1**	**0,45**

НЯ	**Gam – COVID, компонент I (N = 184)**	**Gam – COVID, компонент II (N = 36)**	**Всего**	
	Количество и процент N (%)	**Количество и процент N (%)**	**N=220**	**%**
Местные нежелательные явления				
Боль в месте инъекции	67 (36,41)	17 (47,22)	**84**	**38,18**
Отек в месте инъекции, эритема.	31 (16,85)	4 (11,11)	**35**	**15,91**
Системные нежелательные явления				
Пирексия	153 (83,15)	22 (61,11)	**175**	**79,55**
Головная боль	59 (32,07)	14 (38,89)	**73**	**33,18**
Усталость	7 (3,80)	1 (2,78)	**8**	**3,64**
Недомогание	56 (30,43)	14 (38,89)	**70**	**31,82**
Миалгия	57 (30,98)	14 (38,89)	**71**	**32,27**
Высокая температура	52 (28,26)	15 (41,67)	**67**	**30,45**
Артралгия	44 (23,91)	6 (16,67)	**50**	**22,73**
Тошнота	16 (8,7)	3 (8,33)	**19**	**8,64**
Боль в конечностях	14 (7,61)	2 (5,56)	**16**	**7,27**
Диарея	8 (4,35)	2 (5,56)	**10**	**4,55**
Головокружение	7 (3,80)	2 (5,56)	**9**	**4,09**
орофарингеальная боль	2 (1,09)	2 (5,56)	**4**	**1,82**
Простой герпес	3 (1,63)		**3**	**1,36**
звон в ушах	2 (1,09)		**2**	**0,91**
Тромбофлебит	2 (1,09)		**2**	**0,91**
Гипотония	1 (0,54)	1 (2,78)	**2**	**0,91**
Боль в груди	1 (0,54)	1 (2,78)	**2**	**0,91**
Парестезия	2 (1,09)		**2**	**0,91**
Кашель	1 (0,54)		**1**	**0,45**
Дисфония	1 (0,54)		**1**	**0,45**
Нейтропения	1 (0,54)		**1**	**0,45**
Одышка	1 (0,54)		**1**	**0,45**

Сердцебиение		1 (2,78)	**1**	**0,45**
Металлический привкус	1 (0,54)		**1**	**0,45**
Периферический цианоз	1 (0,54)		**1**	**0,45**
отек носа	1 (0,54)		**1**	**0,45**
Отек лица	1 (0,54)		**1**	**0,45**
Чувство тяжести	1 (0,54)		**1**	**0,45**
Лимфаденопатия		1 (2,78)	**1**	**0,45**
Почечная боль		1 (2,78)	**1**	**0,45**

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РИСУНКИ

Figure 1. Age structure of those vaccinated with the first, second and third dose of Gam-COVID vacc.

Рисунок 1. Возрастная структура вакцинированных лиц после применения первой, второй и третьей дозы вакцины Gam-COVID.

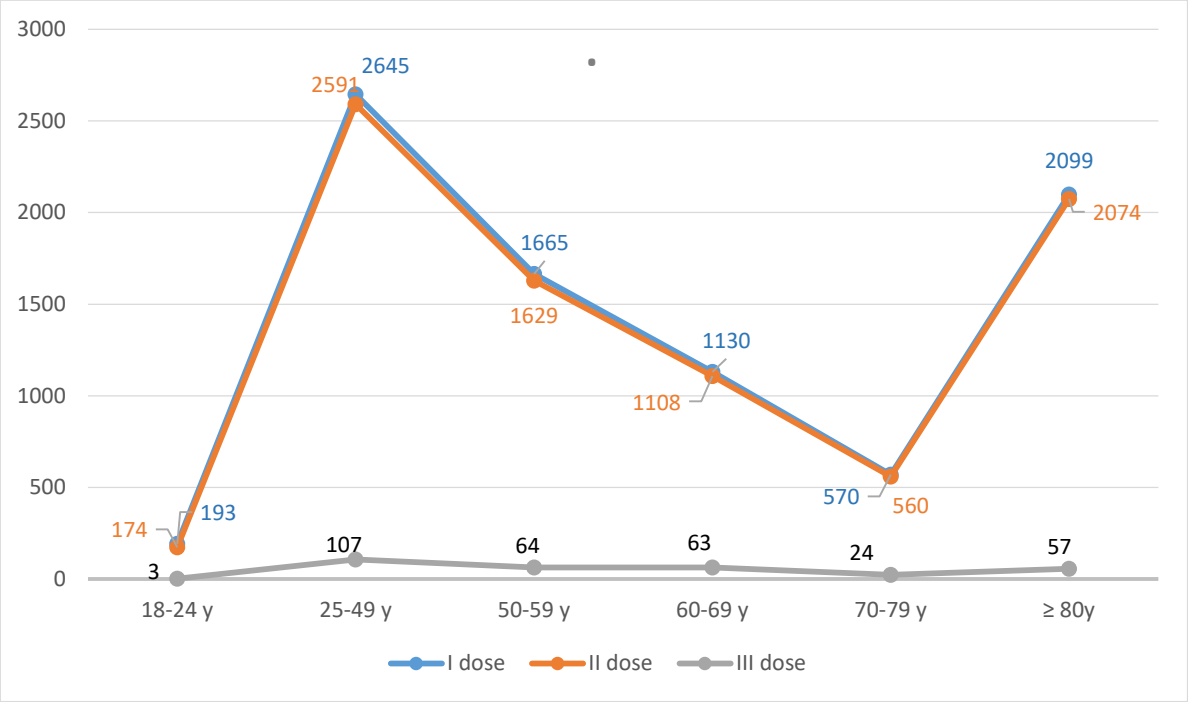

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Figure 2. Age distribution of the study sample of AE to Gam-COVID vac in Montenegro.

Рисунок 2. Возрастное распределение исследуемой выборки НЯ после применения вакцины Gam-COVID в Черногории.

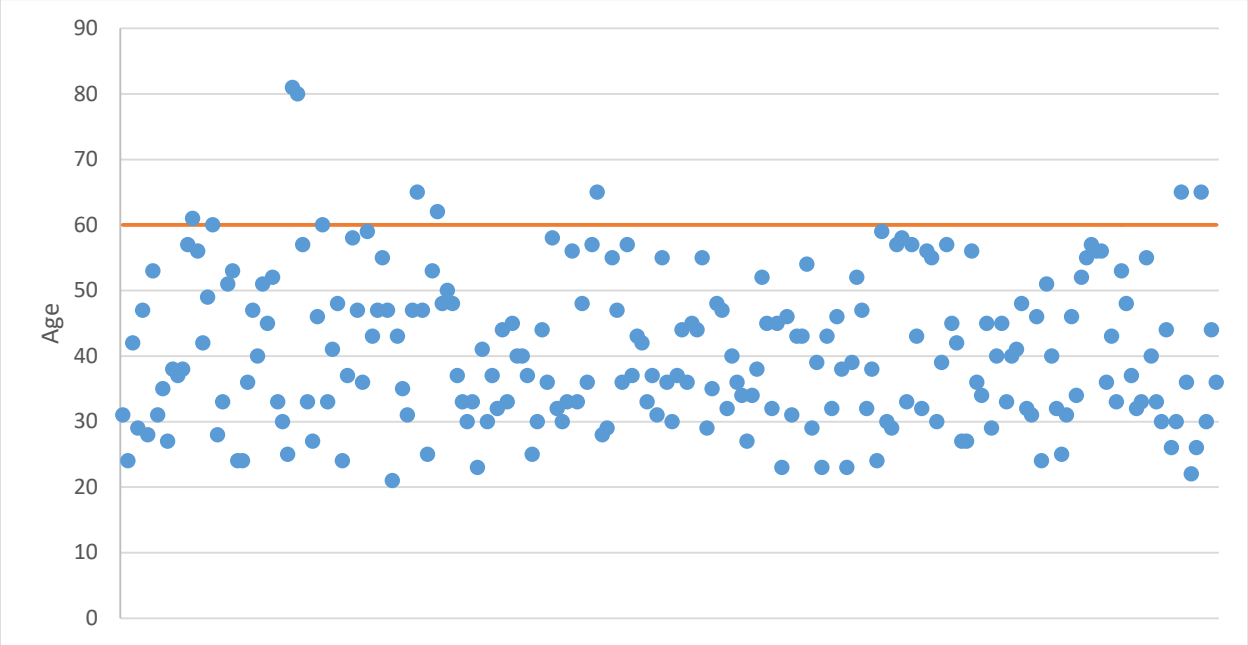

Figure 3. Sex group-graded the most common systemic vaccination reactions.

Рисунок 3. Наиболее распространенные системные реакции на вакцинацию в зависимости от пола лиц.

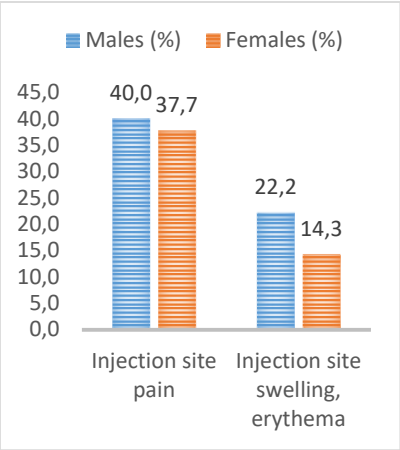

Figure 4. Sex group-graded the most common systemic vaccination reactions.

Рисунок 4. Наиболее распространенные системные реакции на вакцинацию в зависимости от пола лиц.

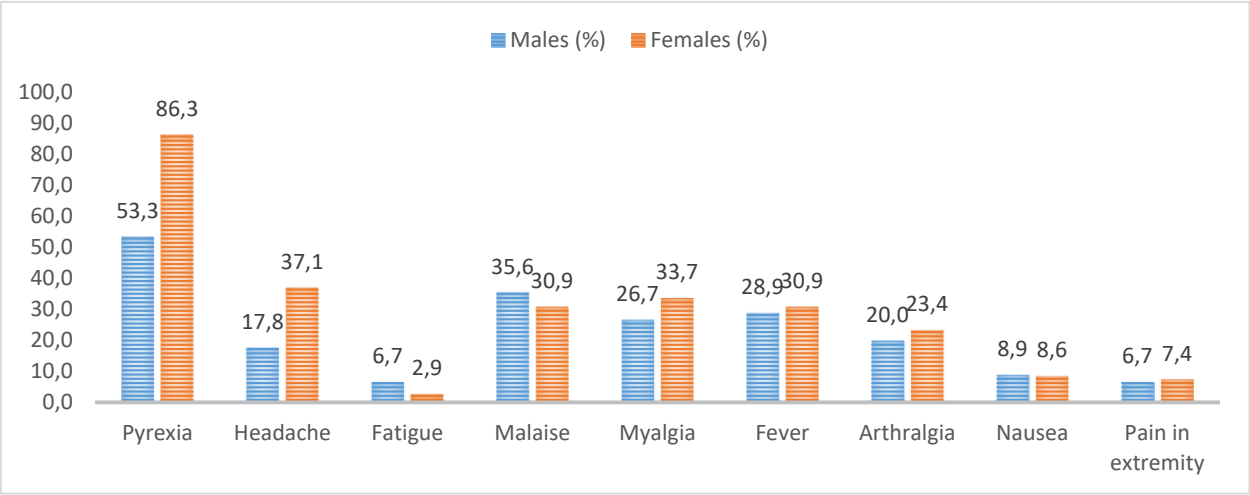

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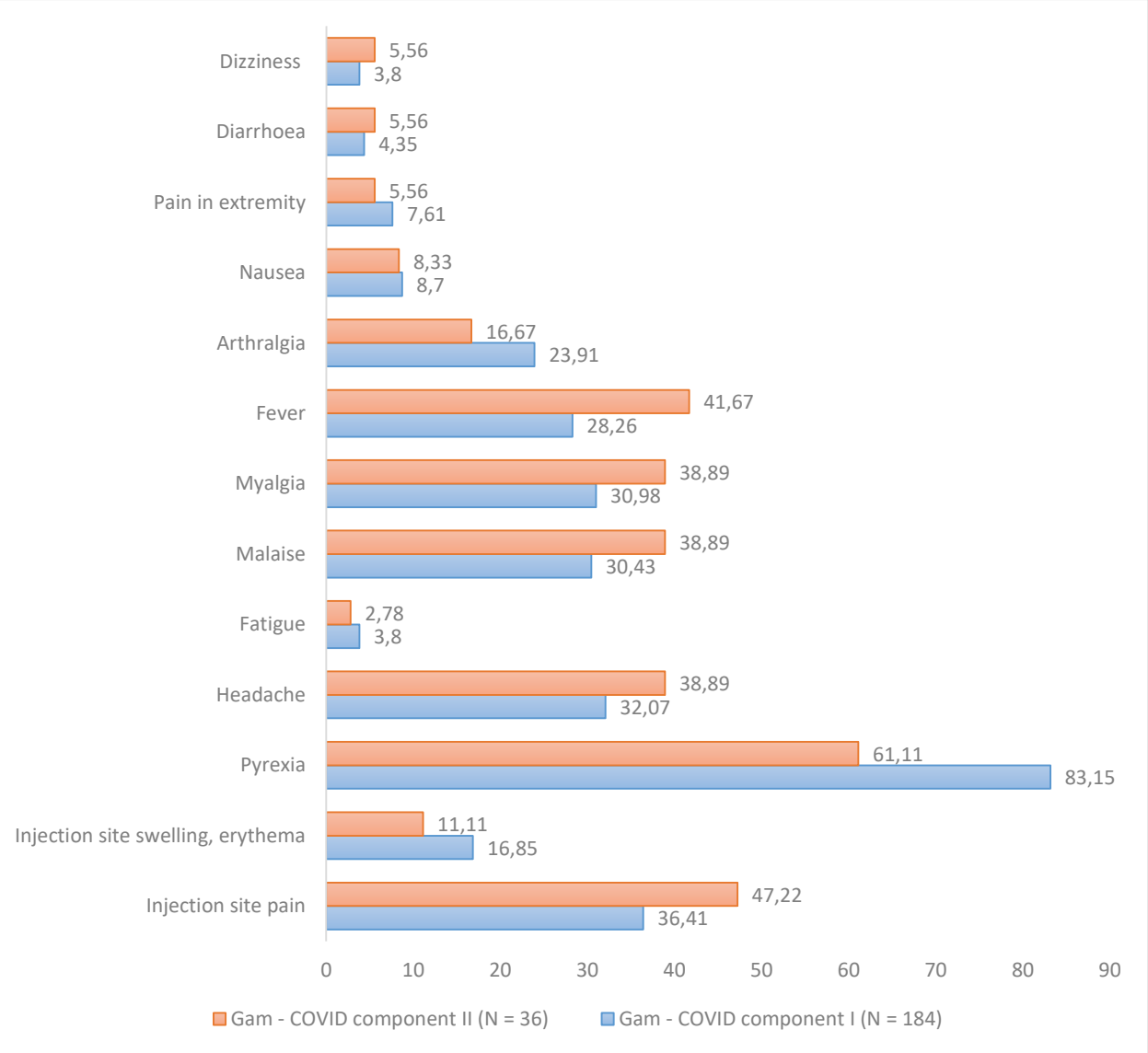
Figure 5. AE of Gam-COVID –Vac component I, and Gam-COVID –Vac component II.

Рисунок 5. НЯ после применения вакцины Gam-COVID-Vac, компонент I, и Gam-COVID-Vac, компонент II.



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

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Блок 3. Метаданные статьи

ПОБОЧНЫЕ ЭФФЕКТЫ ПРИ ПРИМЕНЕНИИ ГАМ-КОВИД-ВАК В ЧЕРНОГОРИИ

SIDE EFFECTS FOLLOWING ADMINISTRATION OF THE GAM-COVID-VAC IN MONTENEGRO

Сокращенное название статьи для верхнего колонтитула:

ПОБОЧНЫЕ ЭФФЕКТЫ ГАМ-КОВИД-ВАК В ЧЕРНОГОРИИ

SIDE EFFECTS OF THE GAM-COVID-VAC IN MONTENEGRO

Ключевые слова: инфекция COVID-19, вакцинация, Гам-КОВИД-Вак, побочные эффекты, сопутствующие заболевания, безопасность.

Keywords: COVID-19 infection, vaccination, Gam-COVID-Vac, side effects, comorbidities, safety.

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