https://doi.org/10.31925/farmacia.2023.2.25 **ORIGINAL ARTICLE**

PERCEPTIONS OF FRONTLINE HEALTHCARE PROFESSIONALS ON COVID-19 VACCINATION

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Abstract

Emerging infectious diseases (EIDs) and their determinants are attracting increasing attention from scientists, with approximately 75% of EIDs being zoonotic. Among these pathogens are viruses belonging to the *Coronaviridae* family. Until 2002, CoVs were primarily studied for scientific or veterinary purposes. However, the world's view on the virulence of CoVs changed in 2002 when a zoonotic betacoronavirus named SARS-CoV appeared in southern China and caused a global epidemic with over 8,000 cases. Ten years later, in the Middle East, another zoonotic betacoronavirus, MERS-CoV, emerged and caused 2,521 cases. A new highly contagious CoV named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in 2019, causing the largest pandemic of the modern era known as coronavirus disease 2019 (COVID-19). Vaccination is one of the most effective methods to reduce the risk of severe illness, hospitalization, and death. The main objective of the study was to evaluate the acceptability of the COVID-19 vaccine among healthcare workers, describe the main adverse reactions, and identify the need for medication administration based on the severity of the adverse reactions manifested.

Rezumat

Bolile infecțioase emergente și factorii determinanți ai acestora atrag din ce în ce mai mult atenția oamenilor de știință, aproximativ 75% dintre acestea fiind zoonotice. Printre acești agenți patogeni regăsim virusuri aparținând familiei *Coronaviridae*, care până în 2002, au fost studiate în principal în scopuri științifice sau veterinare. Cu toate acestea, viziunea lumii asupra acestora s-a schimbat în 2002, când un beta-coronavirus zoonotic numit SARS-CoV a apărut în sudul Chinei și a provocat o epidemie globală cu peste 8.000 de cazuri. Zece ani mai târziu, în Orientul Mijlociu, un alt beta-coronavirus zoonotic, MERS-CoV, a apărut și a provocat 2.521 de cazuri. Un nou coronavirus extrem de contagios, denumit SARS-CoV-2, a apărut în 2019, provocând cea mai mare pandemie din epoca modernă, boala fiind cunoscută sub numele COVID-19. Vaccinarea este una dintre cele mai eficiente metode de reducere a riscului de îmbolnăvire severă, spitalizare sau deces. Obiectivul principal al studiului a fost evaluarea acceptabilității vaccinului COVID-19 în rândul personalului medical, descrierea principalelor reacții adverse și identificarea necesității administrării de medicamente în funcție de gravitatea reacțiilor adverse manifestate.

Keywords: COVID-19, SARS-CoV, vaccination, health care workers

Introduction

The pandemic caused by the SARS-CoV-2 virus has had, and continues to have, a profound impact on people's daily lives, including widespread job losses, mental health issues, social isolation, and overwhelming demands on healthcare professionals [1-3]. Statistical data shows that no other infectious disease, not even the Spanish flu of the 1900s, has had such a significant impact on the global economy [4]. The current pandemic has also highlighted the existing inequalities in health-care and exposed the fragility of global supply chains. Overall, this global pandemic has demonstrated the need for global preparedness and coordination to respond to future outbreaks [5-7].

Vaccines have proven to be the best way to prevent the spread of infectious diseases and, thanks to modern technologies, several vaccines for combating the COVID-19 pandemic have been developed. One year after the identification of the first case of COVID-19, the first vaccine was granted emergency use authorization, which caused controversy among the population regarding the vaccine's effectiveness and safety due to its short development time [8].

In mid-December 2020, the United States Food and Drug Administration (FDA) granted emergency use

authorization for the use of Comirnaty (Pfizer/ BioNTech) and Spikevax (Moderna) vaccines [9, 10], as there was sufficient evidence that both vaccines could be effective in combating the COVID-19 pandemic, followed by authorization from the European Medicines Agency (EMA). This led to the astonishingly rapid development of several vaccines for a single infectious disease in less than a year. The Comirnaty vaccine has the following administration schedule: two injections in the upper arm muscle, spaced 21 days apart, with the possibility of a booster dose at 4 months depending on the population group (healthcare workers, elderly, etc.). The Spikevax vaccine is also administered in two doses, spaced 28 days apart, with the same booster dose schedule.

On February 15, 2021, the AstraZeneca/Oxford vaccine (Vaxzevria), a non-replicating viral vector vaccine isolated from chimpanzees, produced by the Serum Institute of India and SKBio, received emergency authorization [11]. The vaccination schedule consists of administering two separate doses, at an interval of 4 - 12 weeks. This was followed by the JCOVDEN vaccine (Ad26.COV2.S) on March 12, 2021, created by Janssen Pharmaceuticals (Johnson & Johnson), which is a recombinant human adenovirus that encodes the full length of the spike protein of the SARS-CoV-2 virus, producing antibodies against the infection [12], and is the only vaccine administered in a single dose.

During the COVID-19 pandemic, health care workers (HCWs) have played a vital role in providing medical care and treatment to infected with SARS-CoV-2 patients and in educating the public about the severity of the diseases and providing guidance on how to prevent its spread [13, 14].

Vaccinating healthcare workers against COVID-19 is considered a global priority because they are at an increased risk of exposure also helps to protect the healthcare system from being overwhelmed by a large number of personnel falling ill or needing to be in quarantine [15, 16]. Healthcare workers who have been vaccinated are less likely to develop a severe form of the disease or require hospitalization, allowing them to continue to provide care to patients. In addition, vaccinating HCWs is beneficial for their patients, the entire national healthcare system, and society as a whole, as it can help to control outbreaks of infection in hospitals [17].

The COVID-19 vaccination campaign started in Romania on 27 December 2020. The vaccination was implemented in phases (1st phase – health and social services staff, 2nd phase – population at risk and those employed in the essential sectors, 3rd phase – general population). A total of 41% of the population received at least one dose of the COVID-19 vaccine [18].

Given their critical role in controlling the COVID-19 pandemic, it is important to understand the perception of HCWs regarding vaccination and the acceptance of the vaccine. The main objective of our study was to evaluate the acceptability of the COVID-19 vaccine among healthcare workers, describe the main adverse reactions and identify the need for medication administration based on the severity of the adverse reactions manifested.

Materials and Methods

This study was conducted in the National Institute of Infectious Diseases "Prof. Dr. Matei Balș", the reference centre for the management of public health alerts in Romania (avian influenza, severe acute respiratory syndrome (SARS), pandemic influenza, Ebola alerts) and nominated as a hospital dedicated to the treatment of COVID-19 patients (Ministry of Health Order 550/2020) [19]. The research on health-care personnel's perception regarding COVID-19 vaccination was conducted from January 2022 to April 2022 at the National Institute of Infectious Diseases "Prof. Dr. Matei Balș". The study was conducted using a questionnaire consisting of 21 questions, designed to include specific data on the situations encountered by healthcare personnel during the pandemic, as well as data on the safety and efficacy of COVID-19 vaccines available in Romania at the time of the study. The questionnaires were physically distributed to healthcare personnel who cared the COVID-19 patients and subsequently collected to enter the responses into the database.

To assess readability, clarity, and average response time, the questionnaire was distributed to 10 randomly selected individuals within the institute. For evaluation, the volunteers were offered a scale from 0 to 5, where: 0 = confusing; 1 = very difficult; 2 = difficult; 3 = standard; 4 = easy; and 5 = very easy. These 10 participants were not included in the final results.

The 21-question questionnaire was divided into four sections as follows: general participant information (9 questions), information about SARS-CoV-2 infection (3 questions), information about COVID-19 vaccination status (3 questions), information about COVID-19 vaccines administered and locale/systemic post-vaccination adverse reactions as were described in the manufacturers the Summary of Product Characteristics (SmPC) (6 questions).

The general data category also included 2 questions regarding the participants' overall vaccination status, aimed at highlighting their general opinion on vaccination. The 2 questions referred to the administration of mandatory childhood vaccines in the past and whether they have ever received the flu vaccine.

To evaluate the COVID-19 vaccination status of healthcare personnel, the following questions were included in the questionnaire: "Have you been vaccinated against COVID-19?"; "What is the reason why you have not been vaccinated against COVID-19?"; and "Do you intend to get vaccinated in the near future?".

To evaluate the status regarding SARS-CoV-2 infection the following questions were included in the questionnaire: "Have you been infected with the Sars-Cov-2 virus?"; "If yes, what was the date of the positive test?"; and "What clinical form of COVID-19 did you develop?".

The evaluation of post-vaccination adverse events was analysed by including in the questionnaire all AEs reported by manufacturers in the Summary of Product Characteristics [20-23].

The obtained data were coded, validated, and analysed using Microsoft Office Excel (macOS) version 16.67 and GraphPad Prism Version 9.5.1 (528). The statistical significance of the data was calculated using the Chi-square test and One sample t and Wilcoxon test. We used a robust ANOVA version to compare our datasets because some of the samples in our study were too small for a classical approach. The results of the applied statistical tests present a confidence interval of 95%.

Results and Discussion

350 questionnaires were distributed to the medical staff who cared for the COVID-19 patients. 307 (87,7%) were fully completed and analysed.

Of the 307 participants in the study, 78.2% were women (reflecting some degree of the overrepresentation of females in the healthcare sector in Romania in general and in the institute in particular (91.2%) [19] and the overall average age of the participants was 41 years. 39.1% graduated from university as their last form of education, while 13.03% completed high school as their last form of education. Regarding occupational status, according to the collected data, 24.48% of the participants were doctors, 19.40% were nurses, and 15.47% were resident doctors. 75.16% reported not having any chronic illness, 6.60% had hypertension, and 6.92% had an autoimmune disease. The complete general data of the participants are illustrated in Table I.

Table I

Characteristics of study participants, National Institute of Infectious Diseases "Prof. Dr. Matei Balș" (n = 307

Characteristic	Number of participants	%
Gender		
Woman	240	78.18
Man	67	21.82
Age (years)		
23 - 29	53	17.26
30 - 39	89	28.99
40 - 60	158	51.47
> 60	7	2.28
Weight (kg)		
40 - 50	30	9.77
51 - 70	155	50.49
71 - 90	91	29.64
> 90	31	10.10
High (cm)		
145 - 165	149	48.53
166 - 180	124	40.39
> 180	34	11.07
Last form of school graduated		
Highschool	40	13.03
Undergraduate degree	62	20.20
Bachelor degree	120	39.09
Master/PhD degree	85	27.69
Employment		
Nurse	42	13.68
Medical assistant	84	19.40
Physician	106	24.48
Medical resident	67	15.47
Other	8	1.85
Chronic diseases		
Diabetes	4	1.26
Hypertension	21	6.60
Heart failure	2	0.63
Asthma	8	2.52
Cancer	1	0.31
Autoimmune disease	22	6.92
Immunosuppressive diseases (leukaemia, lymphomas, transplant, etc.)	0	0.00
Haematological diseases	0	0.00

Characteristic	Number of participants	%
Neurological diseases	0	0.00
No chronic disease	239	75.16
Other	21	6.60
Flu vaccine administered before		
Yes	252	82.08
No	55	17.92
Other vaccines administered in childhood		
Yes	284	92.51
No	4	1.30
I don't know	19	6.19
COVID-19 vaccination status		
Dose 1	298	97.07
Dose 2	285	92.83
Dose 3	144	46.90

In the present study, the majority of the participants were vaccinated in childhood (92.51%) and 82.08% received the flu vaccine at least once.

Interpreting data on COVID-19 vaccination status

Large majority of the participants have been vaccinated against COVID-19 (97.07%). Among the 2.93% unvaccinated, the reasons for the decision not to vaccinate were varied, as illustrated in Table II. It can be observed that some of the unvaccinated individuals plan to get vaccinated.

Table II

Data on COVID-19 vaccination status

Question	n	%
Vaccinated against COVID-19		
Yes	298	97.07
No	9	2.93
What is the reason why you have not been vaccinated against COVID-19		
Medical issues	2	22,22
Phyisician's recommendation	1	11.11
Personal beliefs	2	22.22
I believe the vaccine does not protect me	1	11.11
I believe the vaccine causes severe adverse reactions	1	11.11
I believe the SARS-CoV-2 virus poses no risk to my health	0	0.00
Others	2	22.22
Do you intend to get vaccinated in the near future		
Yes	2	22.22
No	7	77.78

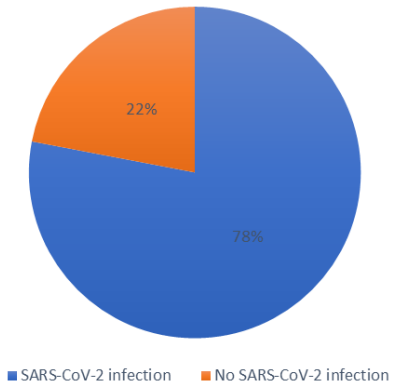

Figure 1.

The graphical distribution of unvaccinated individuals by status of previous infection with SARS-CoV-2

In Figure 1, we have illustrated the graphical distribution of unvaccinated individuals by status regarding confirmed previous infection with SARS-CoV-2. It can be observed that nearly all unvaccinated participants have experienced the disease and still chose not to protect themselves from it.

Analysis of data regarding previous infection with SARS-CoV-2

It is expected that healthcare personnel have experienced COVID-19 at least once, taking into account prolonged exposure to the virus before the development of the vaccine. Thus, one of the purposes of this study was to evaluate the status regarding SARS-CoV-2 infection to be able to correlate this data with data on the manifestation of adverse reactions after vaccination or with re-infection after vaccination. Of the total participants in the study, approximately half have experienced COVID-19 (49.84%), and 10.42% reported that they do not know if they have been infected, as can be seen in Table III.

Table III

Status regarding previous infection with SARS-CoV-2

Confirmed infection with SARS-CoV-2	Number	Percent (%)
Yes	153	49.84
No	122	39.74
I don't know	32	10.42

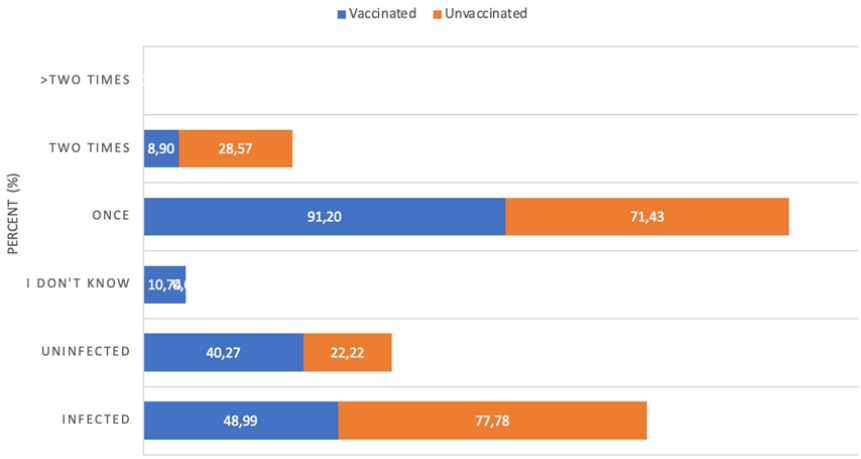

Figure 2.

Distribution of vaccinated and unvaccinated individuals regarding SARS Cov2 infection status (n = 307)

Based on current research, there is no statistically significant difference ($p > 0.05$) between vaccinated and unvaccinated individuals in terms of the number of times they get ill with COVID-19. Thus, while both vaccinated and unvaccinated individuals can still get infected with COVID-19, vaccination significantly reduces the risk of severe illness and hospitalization. We have illustrated the comparative analysis between vaccinated and unvaccinated individuals regarding confirmed SARS-CoV-2 infection and the number of episodes of infection in Figure 2. None of the participants experienced more than 2 times the COVID-19 infection.

For assessing the severity of the disease, the same scale as described in previous chapters was used. Among those who had been infected with the virus, over half (53.59%) had a mild form of the disease that did not require hospitalization, and nearly 10% re-ported being asymptomatic (7.84%). Approximately 10% had a moderate form that required hospitalization (9.80%), and only one person had a severe form that required admission to the ICU (0.65%).

As expected, the data collected in this study showed that the majority of individuals had contracted the disease before the development of the vaccine (44.44%), with a slight increase in the number of cases in 2022 (32.03%), as shown in Figure 3. In the case of the percentage of people infected in the year 2020, we can observe statistically significant differences between the year when a COVID vaccine was not available and after the development of vaccines ($p < 0.05$).

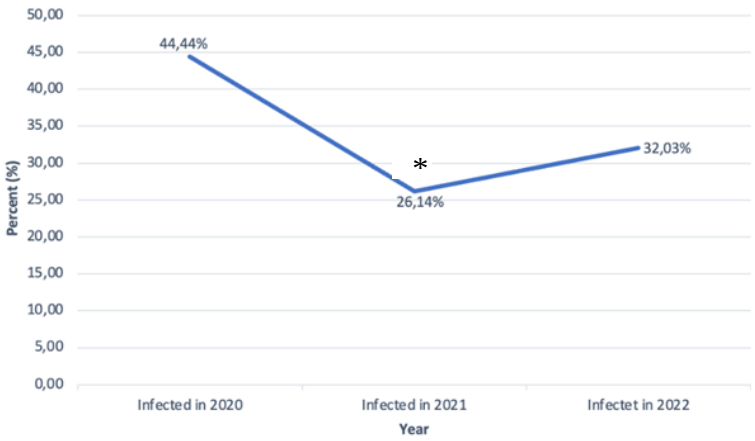

Figure 3.

Distribution of the number of infected persons by year (* $p < 0.05$)

The increase in the number of cases in 2022 could be due to the fact that 44.89% of them have not received the complete vaccination schedule. Among those infected in 2020, approximately one third (27.94%) were infected during March-April-May, when very little was known about this new coronavirus. 22.05% of those infected in 2020 experienced reinfections either in 2021 or 2022.

Data on administered COVID-19 vaccines and post-vaccination adverse reactions

Depending on the type of vaccine, COVID-19 vaccines can cause a range of mild or major adverse reactions (ARs) after the first or second dose, as stated by manufacturers in the SmPC (Summary of Product Characteristics). Some of the most common ARs include: pain, redness, or swelling at the injection site, fever, tiredness, headache, muscle aches, nausea, vomiting, itching, chills, muscle pain and joint pain. In rare cases, anaphylactic shock may occur. In general, adverse reactions are under-reported by both patients and healthcare professionals. When we have a new vaccine, it is important to have active monitoring of adverse reactions, as is our study.

Out of the 298 participants vaccinated against COVID-19, less than half have completed the full vaccination schedule (48.32%). Considering the faster availability in Romania of the Pfizer/BioNTech vaccine compared to other vaccines, the need for rapid vaccination of healthcare personnel has led to the predominantly chosen use of this vaccine, as shown by the data collected from the questionnaires (89.60%) (Table IV). Based on the statistical analysis of the data, there is a significant difference between individuals who got vaccinated with vaccines developed based on RNAm technology and those who got vaccinated with adenovirus vaccines ($p < 0.0001$). The data collected suggests the that the difference between these two groups is highly significant and not likely to occur by chance alone.

The complete data regarding the AEs reported and their duration for each dose are illustrated in Table V.

Table IV

Data on administered COVID-19 vaccines

Question	Answer	Number	Percent (%)
Vaccinated with complete schedule (3 doses)?	Yes	144	48.32
	No	154	51.68
What vaccine did you get vaccinated with?	Pfizer/BioNTech	267	89.60
	Johnson & Johnson	15	5.03
	Moderna	6	2.01
	Oxford/AstraZeneca	26	8.72

Table V

Complete data on AEs divided by dose and persistence

Adverse reaction (n)	Dose 1					Dose 2					Dose 3				
	Yes	No	Duration			Yes	No	Duration			Yes	No	Duration		
			< 1 day	1 - 3 days	> 3 days			< 1 day	1 - 3 days	> 3 days			< 1 day	1 - 3 days	> 3 days
Redness at the injection site	115	183	57	45	13	97	188	53	31	13	45	99	22	15	8
Swelling at the injection site	74	224	28	36	10	73	212	28	37	8	38	106	16	16	6
Pain at the injection site	233	65	87	120	26	203	82	47	128	28	101	43	35	52	14
Fever > 38°C	47	251	36	10	1	52	233	31	14	7	14	130	10	3	1
Fatigue	137	161	80	45	12	126	159	64	43	19	51	93	21	21	9
Headache	95	203	61	28	6	77	208	40	28	9	41	103	21	18	2
Chills	69	229	52	13	4	72	213	49	17	6	28	116	18	9	1
Nausea	29	269	27	1	1	33	252	24	7	2	18	126	15	3	0
Vomiting	11	287	11	0	0	14	271	12	1	1	5	139	4	1	0
Diarrhoea	14	284	11	3	0	15	270	12	2	1	6	138	4	2	0
Muscle pain	111	187	39	59	13	114	171	42	50	22	51	93	16	26	9
Joint pain	47	251	23	20	4	50	235	27	19	4	19	125	8	8	3
Insomnia	28	270	22	3	3	23	262	14	5	4	9	135	2	6	1
Malaise	63	235	40	17	6	63	222	41	15	7	34	110	20	8	6
Lymphadenopathy	17	281	9	4	4	20	265	12	5	3	21	123	4	11	6
Allergic reaction (anaphylactic shock)	2	296	2	0	0	0	285	0	0	0	2	142	2	0	0
Other reactions	17	281	17	0	0	30	255	29	0	1	7	137	7	0	0

n = number of participants

Evaluation of AEs manifested after the administration of dose I. Among the 298 participants vaccinated against COVID-19, 84.23% received the Pfizer/BioNTech vaccine. The participants' choices regarding the type of vaccine are listed in Table VI.

Table VI

The total number of vaccinated individuals by vaccine type

Vaccine dose I	n	Percent (%)
Pfizer/BioNTech	251	84.23
Johnson & Johnson	15	5.03
Moderna	6	2.01
Oxford/AstraZeneca	26	8.72

n = total number of participants

The adverse reactions reported after the first dose are listed in Table VII. The most reported AR for all 4 vaccine products was pain at the injection site, followed by redness and swelling at the injection site [24]. Anaphylactic shock-type allergic reaction was reported only for the Pfizer/BioNTech and Oxford/ AstraZeneca vaccines. 92.31% of those vaccinated with Oxford/AstraZeneca reported fatigue after the first dose. Among other adverse reactions, participants reported: skin allergy, dizziness, physical asthenia, abdominal pain, high blood pressure, swollen lymph nodes, spinal pain, drowsiness, and irritability. In the case of the vaccines developed using the technology mRNA, no statistical difference ($p > 0.05$) has been observed regarding the occurrence of adverse reactions after administering the first dose of the vaccine. The same trend was observed in the case of adenovirus-type vaccines ($p > 0.5$).

Table VII

Comparison of adverse reactions among the 4 vaccines

Adverse event (%)	Vaccine product received			
	Pfizer/BioNTech (n = 251)	Johnson & Johnson (n = 15)	Moderna (n = 6)	Oxford/AstraZeneca (n = 26)
Redness at the injection site	39.84	20.00	66.67	30.77
Swelling at the injection site	25.10	13.33	66.67	19.23
Pain at the injection site	78.49	80.00	83.33	73.08
Fever > 38°C	9.96	26.67	16.67	65.38
Fatigue	39.84	60.00	66.67	92.31
Headache	28.29	33.33	33.33	65.38
Chills	19.12	20.00	16.67	65.38
Nausea	8.37	20.00	0.00	19.23
Vomiting	3.19	6.67	0.00	7.69
Diarrhoea	3.98	0.00	0.00	15.28
Muscle pain	32.27	66.67	16.67	73.08
Joint pain	14.74	13.33	33.33	23.08
Insomnia	7.57	40.00	0.00	11.54
Malaise	17.93	13.33	0.00	61.54
Lymphadenopathy	5.98	0.00	0.00	7.69
Allergic reaction (anaphylactic shock)	0.4	0.00	0.00	3.85
Other reactions	5.18	6.67	16.67	7.69

Evaluation of AEs manifested after the administration of second dose. For the analysis of data regarding adverse reactions (ARs) manifested after the administration of the second dose, the individuals who received only one dose of the JCOVDEN vaccine were excluded from the calculation, leaving a total of 285 participants. Of the 15 individuals who received the JCVODEN vaccine, only 2 continued the vaccination schedule by receiving a booster dose of Pfizer/AstraZeneca. The total number of individuals vaccinated with the second dose according to the type of vaccine is presented in Table VIII.

Table VIII

The total number of people vaccinated with the second dose according to the vaccine

Vaccin dose II	n	Percent %
Pfizer/BioNTech	253	88.77
Moderna	6	2.11
Oxford/AstraZeneca	26	30.59

Based on this data, we conducted a comparative analysis of the adverse reactions manifested after the second dose of the three vaccines, and the data is shown in Table IX and Figure 4. Following the analysis, it can be observed that the most reported adverse reaction for all three vaccines is pain at the injection site, followed by fatigue, muscle pain, and redness at the injection site. After the second dose, no person reported an anaphylactic shock allergic reaction. An increase of more than 10% was identified for the category of other adverse reactions after administering the Oxford/AstraZeneca vaccine (19.23%). From the category of other adverse reactions, in addition to those reported for the first dose that continued to manifest after the second dose, participants also reported neuralgia sciatica, extremity and perioral paraesthesia, tachycardia, and dry cough. A significant statistical difference ($p < 0.05$) was detected between the

Pfizer/BioNTech and Oxford/AstraZeneca vaccines regarding adverse reactions: pain at the injection site, tiredness and muscle pain as it can be seen in Figure 4.

Table IX

Comparison of adverse reactions after the second dose among the 3 vaccines

Adverse reaction (%)	Vaccine		
	Pfizer/BioNTech	Moderna	Oxford/AstraZeneca
Redness at the injection site	34.49	66.67	23.08
Swelling at the injection site	26.09	66.67	11.54
Pain at the injection site	72.73	83.33	53.85
Fever > 38°C	17.00	33.33	26.92
Fatigue	43.87	66.67	42.31
Headache	26.88	50.00	23.08
Chills	26.09	33.33	15.38
Nausea	11.07	0.00	19.23
Vomiting	3.95	0.00	15.38
Diarrhoea	5.93	0.00	0.00
Muscle pain	40.71	50.00	30.77
Joint pain	18.18	33.33	7.69
Insomnia	8.70	0.00	3.85
Malaise	23.72	33.33	3.85
Lymphadenopathy	7.11	0.00	7.69
Allergic reaction (anaphylactic shock)	0.00	0.00	0.00
Other reactions	9.88	0.00	19.23

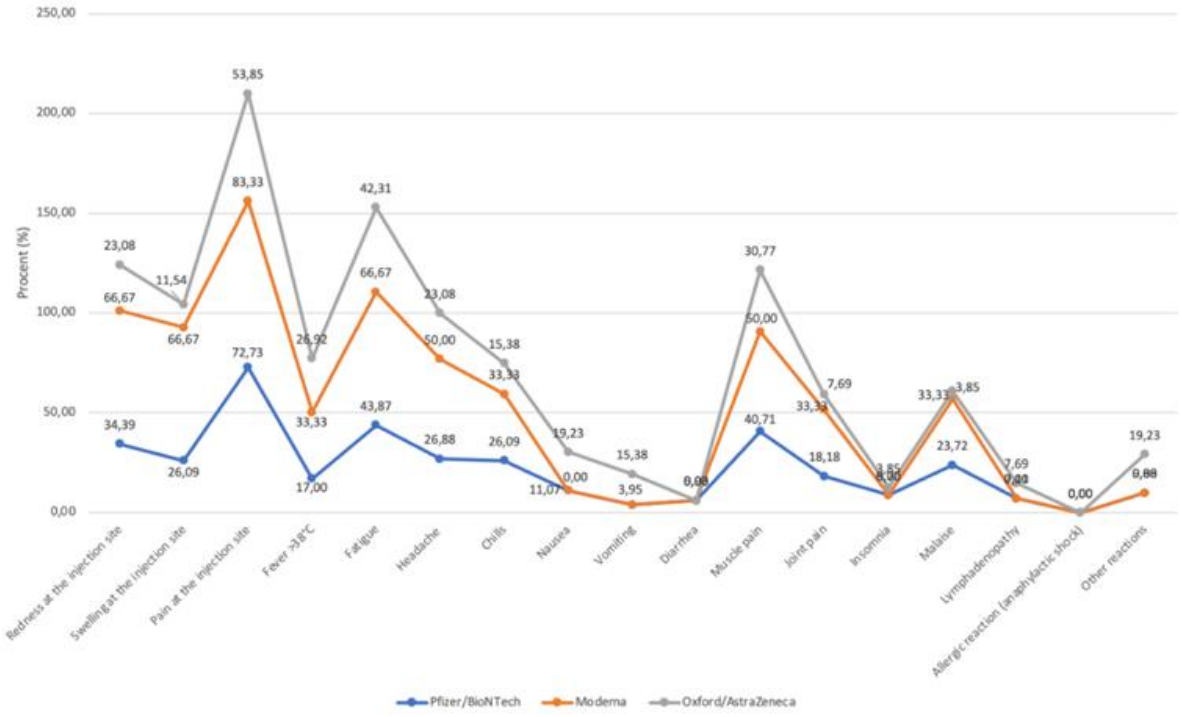

Figure 4.

Graphical representation of the comparison of adverse reactions manifested for each vaccine after the administration of the second dose ($p < 0.05$ Pfizer/BioNTech *versus* Oxford/AstraZeneca vaccines regarding adverse reactions: pain at the injection site, tiredness and muscle pain)

Evaluation of AEs manifested after the administration of third dose. Among the 298 participants vaccinated against COVID-19, approximately half are fully vaccinated (144, 48.32%). Of these, only one person received all 3 doses with the Moderna vaccine, while 89.58% received all 3 doses with the Pfizer/BioNTech vaccine. The percentage distribution of people vaccinated with the third dose of Pfizer/BioNTech vaccine is shown in Table X.

The of post-vaccination adverse reactions after the third dose showed that after the administration of the Moderna vaccine, only local reactions (redness, swelling, pain at the injection site) persisted, while for the Pfizer/BioNTech vaccine, adverse events were reported at

a similar rate to the first 2 doses. Anaphylactic shock was again reported for the Pfizer/BioNTech vaccine (1.40%). Among the other adverse reactions, in addition to those reported for the second dose that continued to occur after the third dose, participants also reported seizures and syncope. Detailed adverse reactions after vaccination with Pfizer/BioNTech vaccine are listed in Table XI.

Table X

The percentage distribution of individuals fully vaccinated

Third dose/booster dose	N = 144	%
Pfizer/BioNTech	143	99.31
3 doses with Pfizer/BioNTech	129	89.58
1 booster dose with Pfizer/BioNTech	14	9.72

Table XI

Comparison of adverse reactions after the third dose

Adverse reaction (%)	Pfizer/BioNTech (n = 143)
Redness at the injection site	30.77
Swelling at the injection site	25.87
Pain at the injection site	69.93
Fever > 38°C	9.09
Fatigue	34.97
Headache	27.97
Chills	18.88
Nausea	12.59
Vomiting	3.50
Diarrhoea	4.20
Muscle pain	34.97
Joint pain	13.29
Insomnia	6.29
Malaise	23.08
Lymphadenopathy	13.99
Allergic reaction (anaphylactic shock)	1.40
Other reactions	4.90

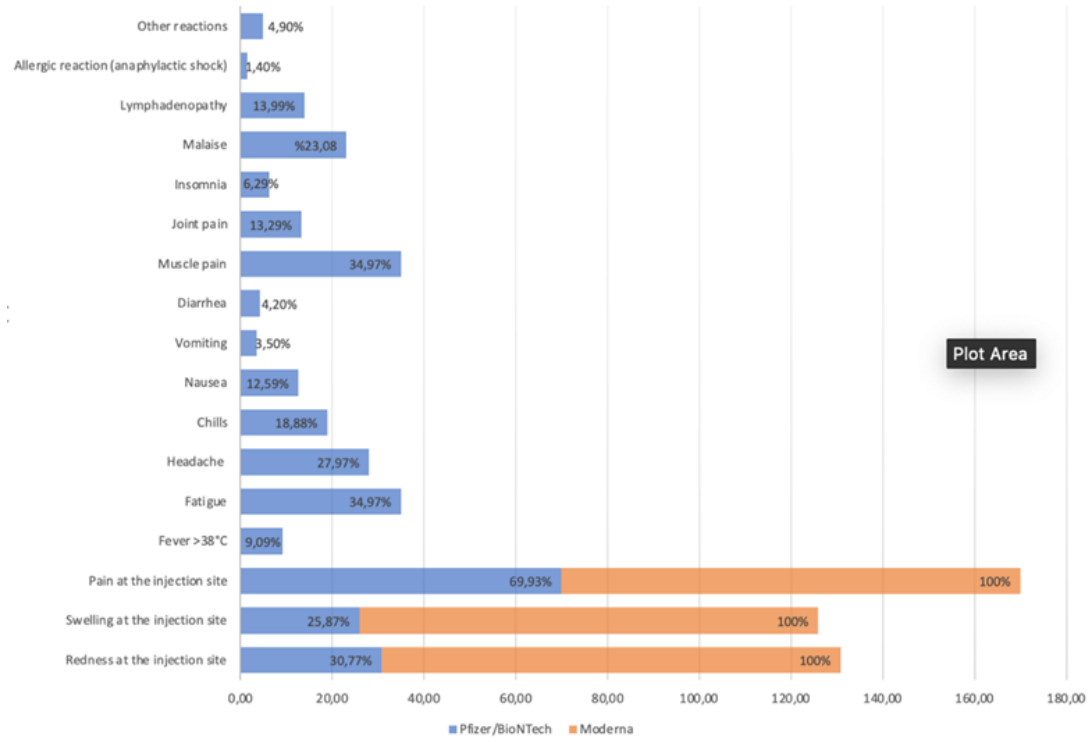

Figure 5.

Reported adverse reactions after the third dose, by vaccine product (n = 144)

Interpretation of data regarding the co-administration of drugs or other vaccines simultaneously with the COVID-19 vaccine

According to the data in presented in Table I, out of the total of 307 participants in the study, 75.16% reported not having any chronic illness. For the rest, we analysed the medication they were taking for the chronic conditions they reported at the same time as receiving the COVID-19 vaccine to evaluate a possible correlation between adverse reactions after vaccination and chronic medication. Table XII shows the complete data on pre-existing chronic diseases according to COVID-19 vaccination status. Table XIII shows the data on chronic medication administered by COVID-19 vaccinated individuals concurrently with each vaccine dose. A statistical difference was observed between vaccinated and unvaccinated individuals ($p < 0.05$).

Table XII

Chronic pre-existing diseases according to COVID-19 vaccination status

	Vaccinated		Unvaccinated	
	Chronic disease		Chronic disease	
	n	%	n	%
Yes	63	21.14	6	66.67
No	235	78.86	3	33.33

Table XIII

Medication administered concomitantly with the COVID-19 vaccine

	Vaccinated							
	Chronic disease		Concomitant medication					
			D1		D2		D3	
	N	%	n	%	n	%	n	%
Yes	63	21.14	20	6.71	19	6.67	10	6.94
No	235	78.86	278	93.29	266	93.33	134	93.06

From the data obtained, it was observed that only 3.02% of the total vaccinated persons with the first dose administered another vaccine at the same time. Of these, only one person received the pneumococcal vaccine, while the rest received the flu vaccine. During the administration of the second dose of the COVID-19 vaccine, no participant received another vaccine at the same time. A significant increase was identified in the case of the administration of the third dose of the COVID-19 vaccine, with 11.11% of the total of 144 persons receiving the flu vaccine at the same time. The complete data regarding the administration of another vaccine at the same time as the COVID-19 vaccine, according to the dose, are illustrated in Figure 6.

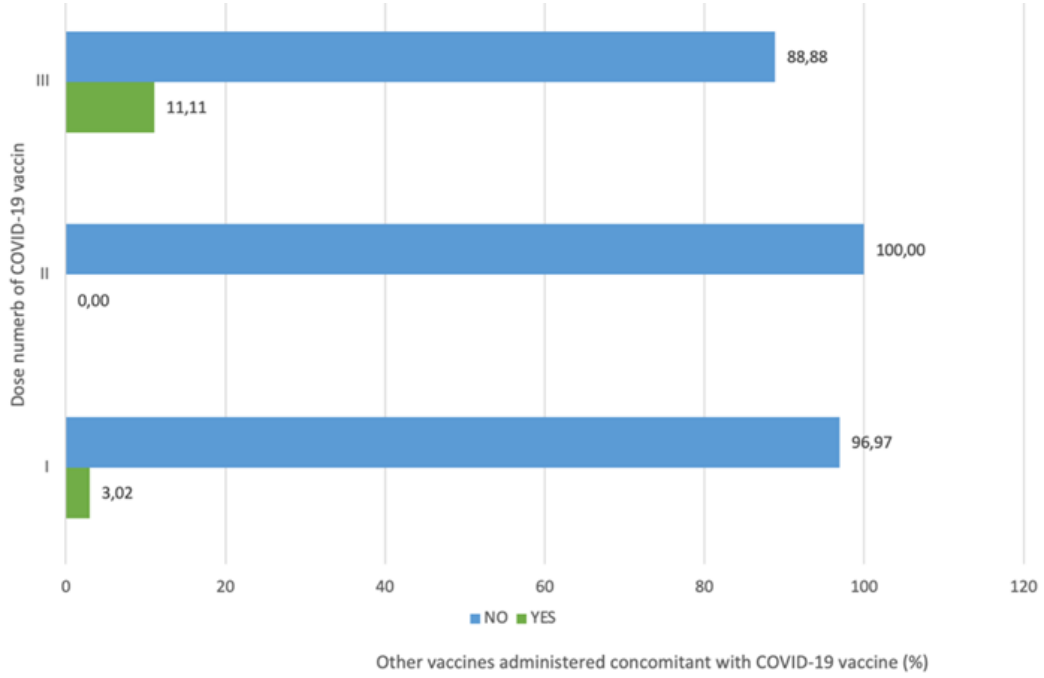

Figure 6.

Comparative analysis regarding the administration of other vaccines simultaneously with the COVID-19 vaccine

Analysis of data regarding medication administered for the treatment of adverse reactions (AR) manifested

To analyse the need for medication to alleviate adverse reactions, the extracted data on the total number of

vaccinated individuals according to dose and the total number of individuals who experienced adverse reactions were used. The data can be found in Table XIV.
The adverse reactions manifested according to dose and the duration of each adverse reaction were illustrated in Table V, based on the following measurement scale: < 1 day, 1 - 3 days and > 3 days. Based on this data, we calculated the average adverse reactions by dose, the complete data being presented in Table XV.

Table XIV

The total number of people who experienced adverse reactions

	Dose 1	**Dose 2**	**Dose 3**
Total number of vaccinated participants	298	285	144
Total number of participants who experienced AE	261	238	121
Percent (%)	87.58	83.51	84.03

Table XV

Comparative duration of adverse reactions for each dose

Duration (days)	**Dose 1**	**Dose 2**	**Dose 3**
	Total number of participants		
< 1	35	31	13
1 - 3	24	24	11
> 3	6	8	4

Regarding the duration of adverse reactions, it can be observed in Figure 7 that for each dose, the majority persisted for less than 1 day. There is a similarity between all three doses, namely that relatively few people had reactions lasting more than 3 days, and reactions lasting 2 days rank second statistically. At the same time, dose 3 has the highest number of cases of reactions among participants, in all three categories of duration. No statistically significant difference was identified regarding the duration of adverse reactions among the three vaccine doses ($p > 0.05$).

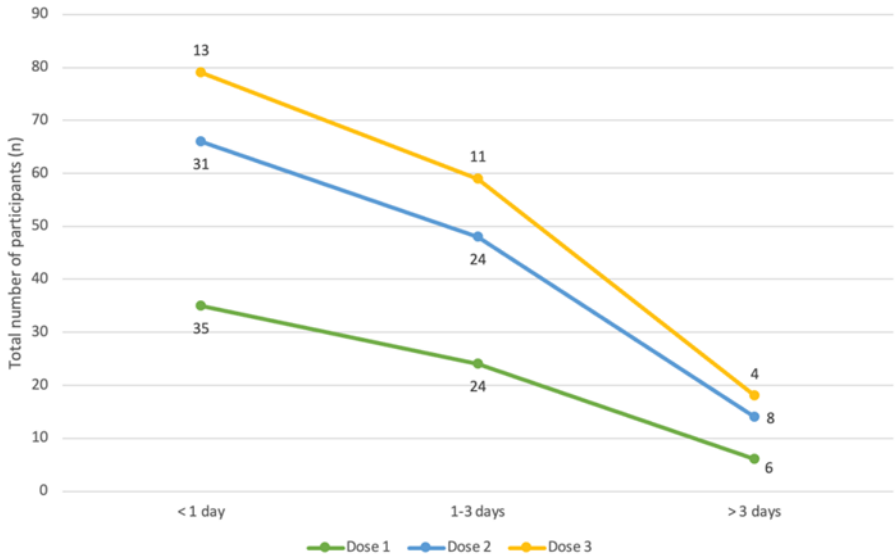

Figure 7.
Duration of adverse reactions after each dose of COVID-19 vaccine

The classes of medication that we considered relevant for alleviating post-vaccination COVID-19 AR were: anti-inflammatory drugs, analgesics, antipyretics, and the possibility of using any other necessary medication for relief.
Although most people experienced AR, almost all of them considered them not severe enough to require medication. Figure 8 shows a trend after the administration of the first dose, when the intensity of AR was higher and medication was needed.

Vaccination of healthcare workers against COVID-19 is considered a global priority, as they are at a higher risk of exposure to the virus due to close contact with infected patients. The data collected in the study conducted at the National Institute of Infectious Diseases "Prof dr Matei Balș" showed positive results of the vaccination campaign, with over 90% of the HCWs being vaccinated against COVID-19.
Vaccination is one of the most effective methods of protection against COVID-19 by reducing the risk of

severe illness, hospitalization, and death. This is the conclusion we reached based on the data collected in this study, where we identified that the majority of healthcare workers were infected in 2020 when the vaccine was not yet available, with a substantial reduction in the number of cases in 2021 and 2022. Additionally, the data showed that in 2021 and 2022, no one required hospitalization due to COVID-19.

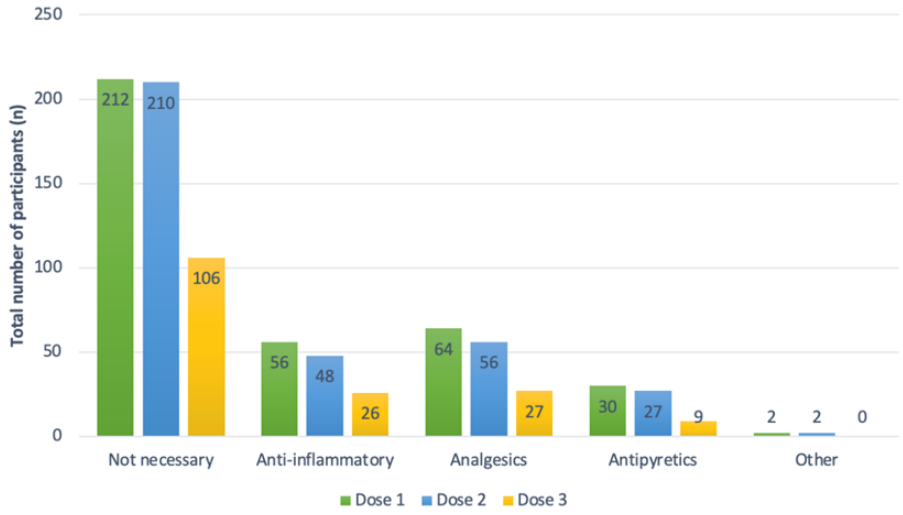

Figure 8.
Administration of medications to alleviate adverse reactions, by dose rank

One of the major conclusions identified in this study relates to post-vaccination adverse events, where we identified the following reactions that are not included in the Summary of Product Characteristics (SmPC): radialgia for Cominarty vaccine; syncope for Cominarty vaccine; hypertension for Spikevax vaccine and tachycardia for Spikevax vaccine.

Regarding the frequency of the most common adverse reactions included in the SmPCs, the data obtained in our study are consistent with the data mentioned by the manufacturers in the summary of product characteristics [20-24].

From the ANOVA analysis, we obtained a significant difference in ADRs duration after the first dose of the vaccine ($p < 0.005$). The same trend was identified for ADRs after the second dose but with a higher value ($p < 0.05$) and with a small difference after the third dose ($p < 0.05$).

From the analysis of adverse reactions, a trend was observed after the administration of the first and second doses, with the highest number of adverse events reported for the Vaxzevria vaccine and the highest number of gastrointestinal adverse events reported for this vaccine. These adverse events may also be due to the co-administration of medication or other vaccines.

From the data obtained, it was observed that during the administration of the third dose of the vaccine, more people received the flu vaccine at the same time, as it coincided with the flu season, and adverse reactions after the administration of the third dose cannot be entirely attributed to the COVID-19 vaccine.

In addition to the risks associated with exposure to the SARS-CoV-2 virus, healthcare workers are exposed to viral infections every day, with the most common annual epidemic in Romania being caused by the influenza virus. Influenza and COVID-19 are both respiratory illnesses caused by viruses, with some similar symptoms such as fever, cough and difficulty breathing. This can make it difficult to distinguish between the two illnesses and may lead to confusion and difficulties in establishing appropriate treatment. The worst-case scenario we can think of is having both influenza and COVID-19 at the same time, which can lead to much more severe symptoms. That is why it is extremely important for healthcare workers to receive the flu vaccine, and vaccination campaigns are regularly carried out in each institution.

Taking into account all the above-mentioned factors, we considered it of major importance to include in the study the analysis of co-administration of another vaccine at the same time as the COVID-19 vaccine, but no statistical difference has been identified ($p > 0.05$).

The limitations of our study are related to the timing of the vaccination campaign and the timing of the study. Another limitation is the smaller number of participants who were vaccinated with vaccines other than Pfizer/BioNTech vaccine.

Conclusions

The present study addressed a current topic at the international level, being among the first research in Romania on this field: the perception of healthcare workers regarding vaccination against COVID-19. The results obtained in this study showed that the large majority of participants were vaccinated with at least two doses. The study provides new information on adverse reactions after vaccination and arguments

for the importance of prioritizing the vaccination of healthcare workers.

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Conflict of interest

The authors declare no conflict of interest.

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