

Covid – 19 Vaccine Adverse Reaction Reported To The Pharmacovigilane Unit Of Beira Interior In Portugal.

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Abstract

Coronavirus disorder 2019 is an acute respiratory ailment as a result of the intense acute respiration syndrome coronavirus 2. because the virus spreads rapidly, it has come to be a main public fitness emergency, which has brought about rapid vaccines improvement. but, vaccines can gift dangerous and accidental responses, which need to be notified to the countrywide Pharmacovigilance gadget.

The purpose of this study is to symbolize the adverse drug reactions (ADRs) of these vaccines notified within the place protected by the nearby Pharmacovigilance Unit (RPU) of Beira interior, in Portugal, between 1 and 31 December 2020. at some stage in this era, four vaccines had been administered: Comirnaty®, Spikevax®, Vaxzevria® and Jcovden®.

The RPU of Beira interior acquired 2134 notifications corresponding to 5685 ADRs, of which 20.34% (n = 434) of the notifications had been taken into consideration critical reactions. of these, 9.fifty two% (n = forty two) led to hospitalization and 0.forty five% (n = 2) led to death. among the ADRs notified, reactions at or across the injection web page, myalgia, headaches and pyrexia had been the most usually notified.

maximum ADRs had been resolved inside a few hours or days with out sequelae. those ADRs are in accordance with clinical trials, the summary of product traits (SmPC) of each vaccine and ADR notifications from other countries. however, in addition studies are had to verify these effects.

Keywords.

Destructive drug reactions, COVID-19 vaccines, mRNA vaccines, vaccines with a viral vector, pharmacovigilance, immunization, safty.

1) Introduction.

Coronavirus disorder 2019 (COVID-19) is an acute breathing disease resulting from the excessive acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first emerged in Wuhan in December 2019. Its transmission takes place with the aid of droplets, respiration secretions and direct contact [1,2].

Because the virus has a fast spread, it has come to be a serious public fitness emergency [2]. for the reason that vaccination can be used to save you infections or lessen the seriousness of a ailment, some strategies had

been studied to generate vaccines towards the brand new coronavirus, inclusive of vaccines primarily based on DNA and RNA [3,4].

Nucleic acid vaccines encompass mRNA with information towards coronavirus-particular structural proteins and do not comprise any viral proteins able to causing ailment. The mRNA is taken up by means of cells and translated right into a viral antigen, the spike protein. when recognized by the immune system as some thing overseas, antibodies are produced, and T cells are activated to assault the protein.If the vaccinated person later comes into touch with coronavirus, their immune device will apprehend the spike protein and be equipped to defend itself [5,6,7,8,9]. inside the eu Union (eu), at some stage in the observe period, 2 mRNA-based vaccines had been legal through the european medicines agency (EMA): Comirnaty® and Spikevax® [7,8,9].

Urther to mRNA vaccines, there is every other form of vaccine authorized for immunization in opposition to COVID-19: vaccines with a viral vector with out the capacity to copy. This sort of vaccine is constituted of another virus (e.g., adenovirus) that has been modified to incorporate data concerning the virus of hobby, so as to be delivered to human cells. The viral vector is a harmless virus and special from coronavirus, so it does no longer reason the disease.

That encodes the spike protein found in SARS-CoV-2. It then uses the cell's equipment to provide this glycoprotein which, when diagnosed by means of the immune system, ends in the manufacturing of antibodies and activation of T cells, as is in nucleic acid vaccines [10,11,12,13]. within the ecu, for the duration of the take a look at length, vaccines primarily based on viral vectors had been legal with the aid of the EMA: Vaxzevria® and Jcovden® [7,12,13].

Dangers. hence, because of the truth that there may be a restricted information of the healing profile of a few tablets, it is vital to continue to display their protection after marketing, thru several available methodologies, considered one of that is the notification of unfavorable drug reactions (ADRs) to the national systems of Pharmacovigilance (NPS), present round the sector, and created as a way to monitor the protection of medicines.The NPS cover all information related to ADRs and guarantee the safety of users who have contact with medicines, especially medicines recently introduced on the market. This is the case of vaccines used to immunize against COVID-19 [14,15].

In 1992, the SNF was created in Portugal, presently coordinated by INFARMED, I.P. in the early 2000s, the SNF became decentralized into 4 local Pharmacovigilance gadgets (RPU)-Norte, Centro, Sul and Açores-, with the purpose of publicizing the gadget and promoting notification, bringing the machine towards health professionals and sell the involvement of university centres. due to the fact that 2017,

the variety of RPUs in the SNF expanded, and there are currently 10 masking distinctive regions inside the united states.The RPU of Beira Interior is placed at the University of Beira Interior, in the interior of Portugal, covers the districts of Castelo Branco, Viseu and Guarda and involves some under reporting [16,17].

when the advent of ADRs is suspected, the manner of spontaneous notification thru an internet or paper form or by cellphone will become important. Spontaneous reporting is a voluntary pharmacovigilance methodology, which consists of reporting an ADR associated with a particular drug and a affected person, which can be with the aid of the affected person, a member of the family or a healthcare expert.Spontaneous reporting makes it feasible to detect ADRs that arise rarely or , producing an alert signal for subsequent epidemiological research [16].

therefore, pharmacovigilance, a science involved within the detection, assessment and prevention of ADRs, through the method of spontaneous reporting is an crucial step to evaluate the safety of vaccines used in the immunization towards COVID-19 [17,18,19,20].

accordingly, this observe had targets. the primary objective was to symbolize the ADRs associated with vaccines used within the immunization towards COVID-19, notified within the vicinity protected by means of the nearby Pharmacovigilance Unit of Beira indoors, in Portugal.the second one objective become to compare the consequences received with the protection records from studies finished in different international locations around the arena. this period changed into the problem of observe because it turned into the preliminary duration in which the vaccines authorized in the eu started to be administered to the Portuguese populace.

2. Substances And Methods.

This paintings is a retrospective observational have a look at. The information underneath analysis were accumulated thru spontaneous notifications despatched to the Portuguese NPS by way of healthcare professionals, patients or member of the family. The Portuguese database is “Portal RAM” which is coordinated by the country wide Authority of drugs and fitness products, I.P. (INFARMED). the quest was performed in this database considering the international not unusual Denomination of each vaccine (Comirnaty®, Vaxzevria®, Spikevax® and Jcovden®), study duration (1–31 December 2021) and the area covered by the RPU of Beira interior, in Portugal.

Statistical evaluation of the facts acquired changed into performed the usage of the Microsoft office Excel 365 tool. in this device, the information have been prepared in line with the variables below observe and had been later represented in tables and appropriate pix.

It's far vital to note that each notification concerns a single affected person. however, more than one ADR and seriousness criteria may be related to each notification. Of the 2145 notifications received, best 2134 have been studied due to the dearth of records in eleven notifications.

it is also important to mention that this work did no longer require previous authorization from the Ethics Committee, because the sufferers’ personal data became now not used.

2.1. populace.

2.2.1. Characterization of the Notification source.

Notifier Characterization.

ADRs can be notified via specialists in the pharmaceutical enterprise, sufferers, circle of relatives contributors or healthcare experts. The healthcare specialists taken into consideration are categorized as physicians, pharmacists, nurses or different healthcare professionals. these experts play a critical position in reporting ADRs, with the goal of reducing the poor outcomes associated with them. Bearing in mind that this have a look at only focuses on a nearby unit, there aren't any notifications from the pharmaceutical enterprise, due to the fact that those experts notify at once to the RAM portal, and no precise vicinity is assigned to them.

District of origin.

For the look at, simplest the RPU of Beira indoors turned into taken into consideration, which covers three districts: Castelo Branco, Guarda and Viseu. This area corresponds to approximately seven hundred,000 population and about 8000 healthcare professionals (docs, nurses and pharmacists). as a consequence, the notifications had been analyzed in line with the district of foundation.

2.2.2. Demographic.

Characterization of the population.

The evaluation became executed via characterizing the notifications through age and gender. In phrases of age, eight age groups were considered: five to eleven years old; 12 to 17 years antique; 18 to 24 years old; 25 to forty nine years vintage; 50 to sixty four years old; sixty five to 79 years old; ≥ 80 years; and unknown. Gender changed into labeled as male, female or unknown.

2.2.3 Characterization of destructive Drug Reactionss.

Characterization by Administered Vaccine.

Notified ADRs were categorized based totally at the associated vaccine. handiest four vaccines were considered: Comirnaty, Spikevax, Vaxzevria, and Janssen as they have been the vaccines authorized for management in Portugal throughout the look at duration.

Analysis of ADRs.

The description of each ADR is executed by way of the notifier, which is later coded in keeping with the scientific Dictionary for Regulatory sports (MedDRA) terminology. MedDRA is an worldwide medical terminology advanced in 1994 via the international conference on Harmonization (ICH). prior to the creation of this dictionary, there has been no global medical terminology, so the lifestyles of a couple of terminologies created numerous troubles in the evaluation of information associated with pharmaceutical merchandise. on this way, there has been a need to create an worldwide clinical terminology, so that you can facilitate communicate among the various fitness professionals, and the crossing of information concerning pharmaceutical products [21].

MedDRA terms are hierarchically organized into: machine organ class (SOC); excessive stage organization term (HLGT); excessive degree phrases (HLT); preferred time period (PT) and lowest stage time period (LLT), with the SOC level being the widest and maximum comprehensive and the LLT stage being the maximum specific [21].

Accordingly, the ADRs had been to start with grouped in keeping with the SOC group, and sooner or later, they were prepared in keeping with the PT time period.

Description in the precis of Drug traits (SmPC).

As a way to verify the preceding descriptions of the ADRs underneath take a look at associated with the vaccines, the SmPC of each vaccine changed into used, grouping the information into 2 categories: “described in the SmPC” and “not described in the SmPC”.

Regarding ADRs not described, they were grouped into 2 parameters: “diploma of Causality Studied” and “diploma of Causality no longer studied”. Causality is attributed by way of an expert from the regulatory authority or the pharmaceutical business enterprise, in ADRs considered critical, and from the records furnished during the notification.

Ultimately, the ADRs for which the degree of causality became studied were grouped into 6 classes: Definitive, likely, viable, unlikely, Conditional, Unclassifiable [22].

Seriousness and Seriousness criteria.

regarding the seriousness, notifications have been grouped into severe and non-severe primarily based at the notifier’s assessment and/or nearby Pharmacovigilance. subsequently, severe ADRs were grouped by means of seriousness criteria.

There was also the characterization of ADRs related to the seriousness standards “Hospitalization”, “life risk” and “loss of life”, according to age and related vaccine brand.

An ADR is taken into consideration critical if it “effects in transient or everlasting disability, reasons a congenital abnormality, consequences in hospitalization or prolongation of hospitalization, causes dying or is lifestyles-threatening, or fulfills any other clinically important condition” [23].

Evolution of ADRs..

Information were grouped into the following classes: treatment, remedy with collateral damage, in recuperation, loss of life and Unknown, based at the records provided via the notifier.

Characterization of Notifications with the final results “loss of life” with phrases Belonging to the IME listing.

Finally, the characterization of the notifications that culminated in demise changed into executed, deliberating the presence of phrases belonging to the vital medical events (IME) list.

with a view to facilitate the type of ADRs, as well as help in the analysis of notifications submitted to the national Pharmacovigilance structures, Eudravigilance created a listing of scientific phrases considered critical, known as the IME list, based totally at the definitions adopted with the aid of the ICH. crucial scientific events are events that won't at once lead to loss of life or hospitalization however compromise the man or woman's lifestyles or require clinical or surgical intervention so one can avoid the consequences listed in the definition of seriousness ADR [24]. with a view to facilitate the type of ADRs, as well as help in the analysis of notifications submitted to the national Pharmacovigilance structures, Eudravigilance created a listing of scientific phrases considered critical, known as the IME list, based totally at the definitions adopted with the aid of the ICH. crucial scientific events are events that won't at once lead to loss of life or hospitalization however compromise the man or woman's lifestyles or require clinical or surgical intervention so one can avoid the consequences listed in the definition of seriousness ADR [24].

3 Consequences.

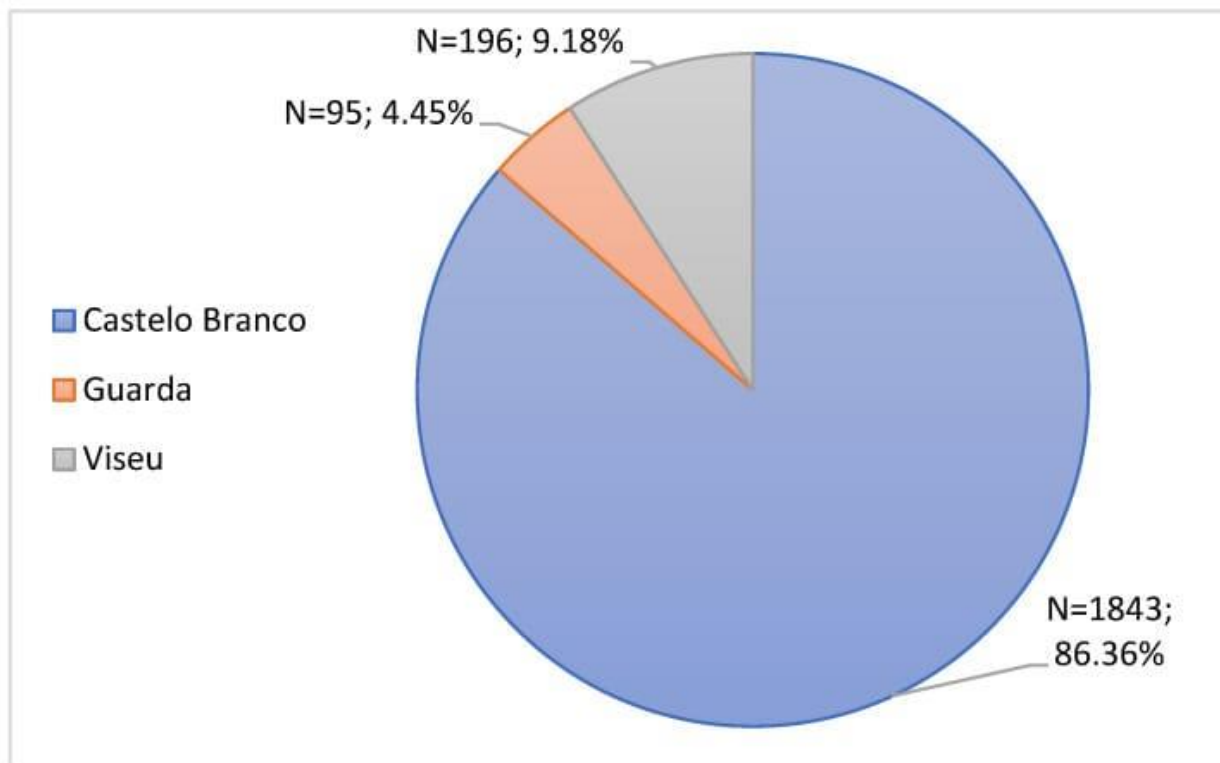
As mentioned above, the number of notifications to be analyzed, after the reproduction and annulled notifications have been withdrawn, changed into 2134.

3.1. Characterization of the Notification source.

3.1.1. Notifier Characterization.

In this have a look at, the type of notifier who submitted the notification became analyzed. via parent 1, it's miles possible to look at that most notifications were submitted by way of the pharmacist (eighty two.15%, n = 1753), followed by way of the person or other non-healthcare professional (6.47%, n = 138) and later the medical doctor (6.09%, n = one hundred thirty). Nurses had a notification rate of four.87% (n = 104), and finally, other healthcare specialists submitted handiest 0.forty two% (n = nine) of the notifications.

Figure 1.

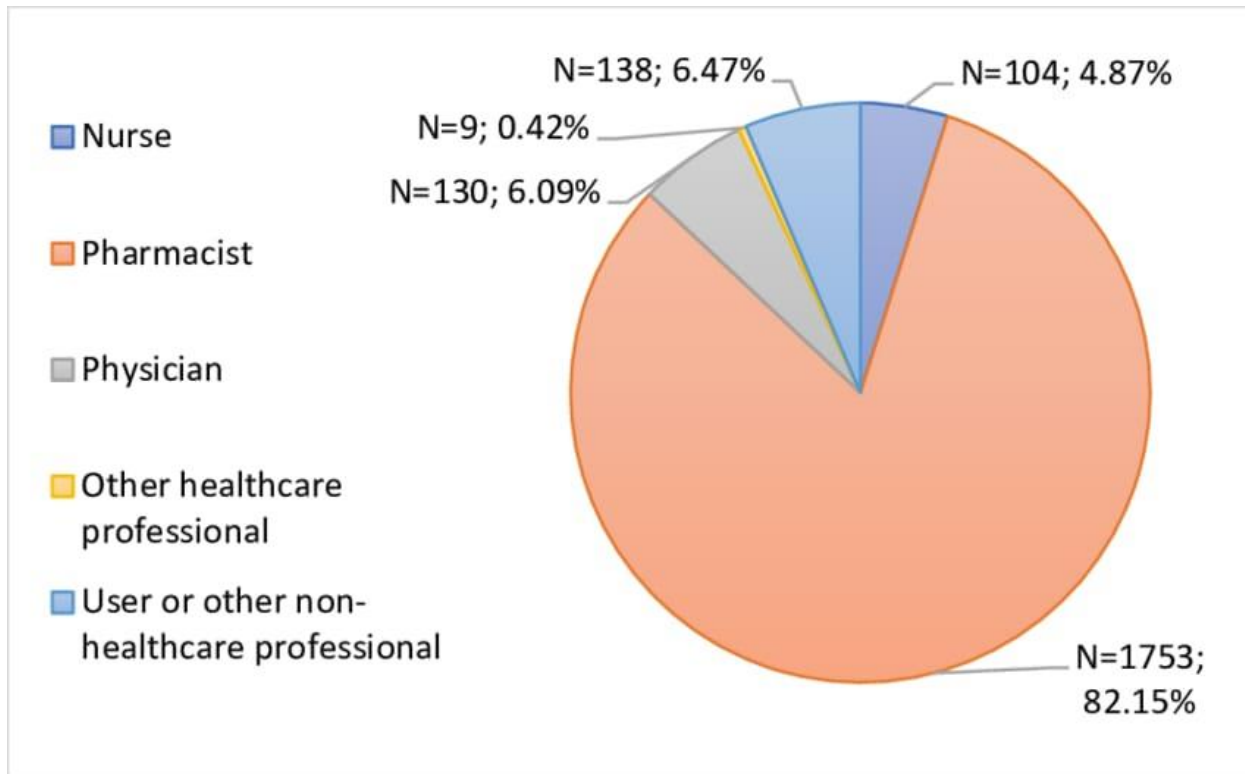


Characterization of notifications by means of kind of notifier.

3.1.2. District of foundation.

For the observe, best the RPU of Beira interior became taken into consideration. through figure 2, it's far feasible to observe that maximum notifications presented Castelo Branco as the district of origin (86.36%, n = 1843), accompanied via Viseu (nine.18%, n = 196) and eventually Guarda (four.45%, n = 95).

Figure 2.



Characterization of notifications via District of beginning of notification.



3.2. Demographic Characterization of the populace.

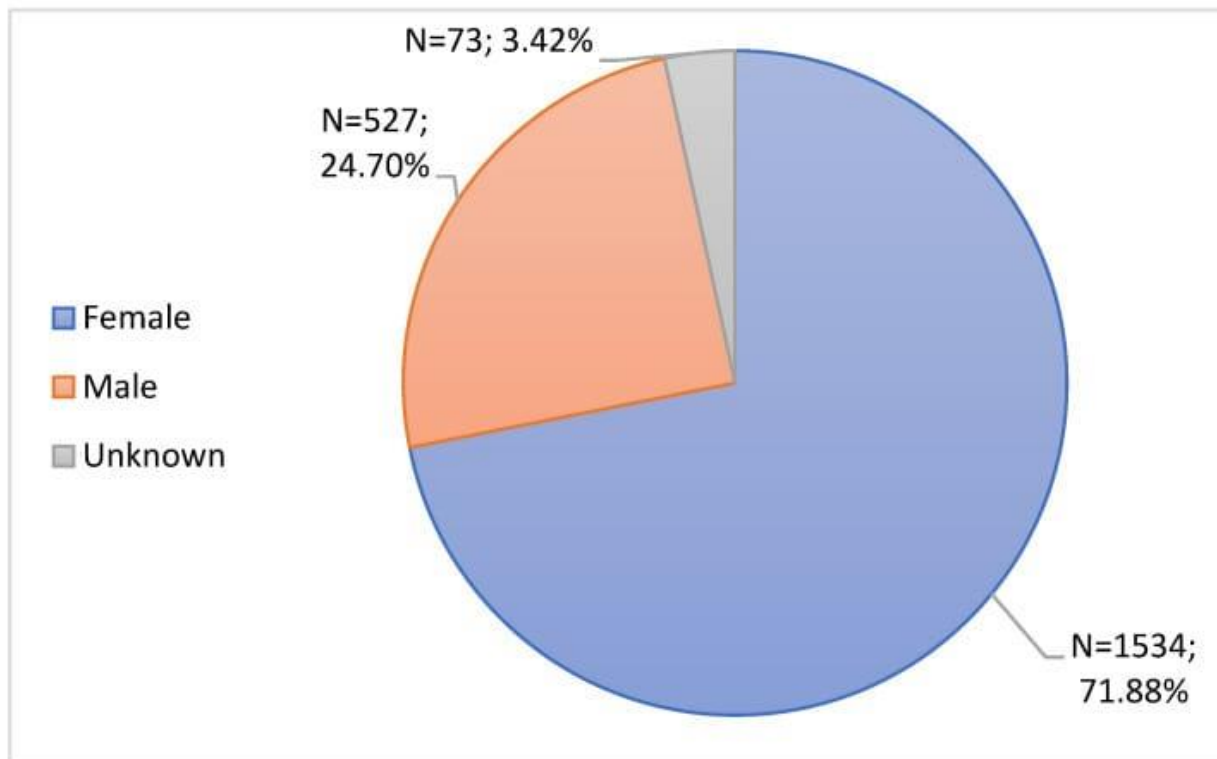
The notifications have been characterised as to the age and gender of the patients, as may be visible in table 1 and determine 3, respectively.

Table 1.

Distribution of notifications via age organization.

Notification Year	AGE GROUP						Total
	Oct/14	15-19	20-34	35-49	50-64	65-79	
2014	0	2	5	4	4	0	15
2015	2	5	6	10	4	2	29
2016	0	2	8	2	5	2	19
2017	0	10	8	14	7	1	40
2018	2	3	11	17	6	4	43
2019	0	5	20	27	17	6	75
Total	4	27	58	74	43	15	221

Figure 3.



Characterization of notifications in line with Gender.

Reading table 1, it is feasible to confirm that maximum notifications had been associated with sufferers elderly between 25 and forty nine years (fifty seven.64%, n = 1230), observed by using patients aged among 50 and sixty four years. (26.90%, n = 574).

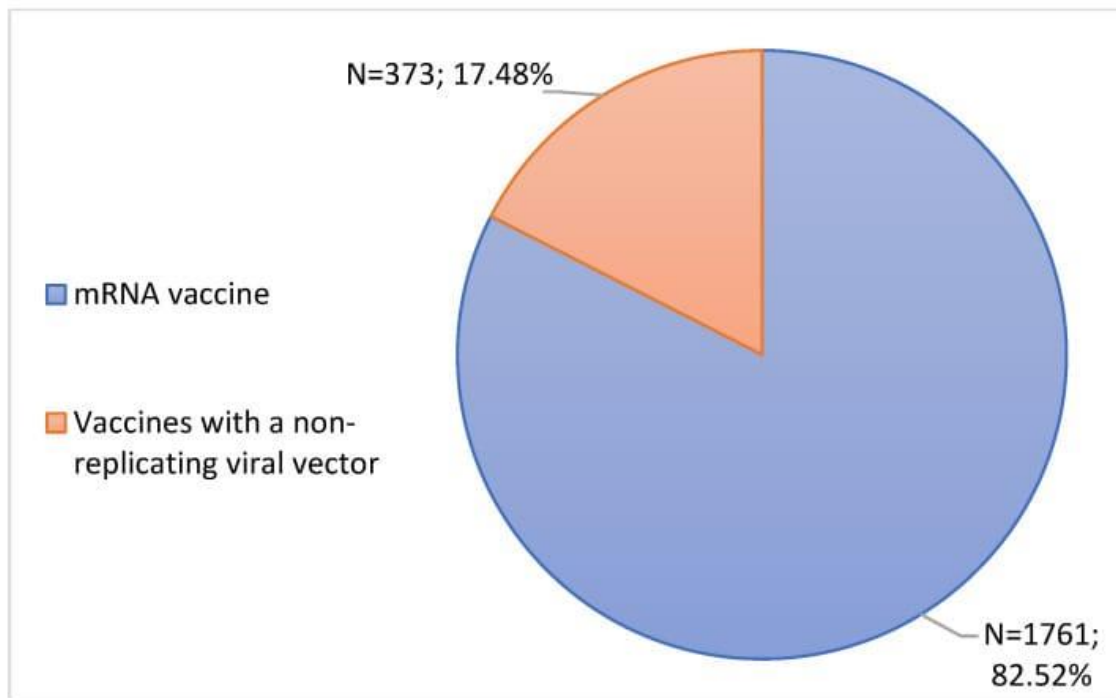
Concerning gender, notifications have been grouped into lady, male and unknown. The female gender supplied the maximum notifications, accounting for 1534 (seventy one.88%) out of 2134 overall notifications.

3.3 Characterization of negative Drug Reactions.

3.3.1. Characterization via Administered Vaccine.

Throughout the observe duration, only 2 forms of vaccines have been administered–mRNA vaccines and non-replicating viral vector vaccines. it's far crucial to be aware that every notification issues a single vaccine. consistent with discern four, mRNA vaccines have been highlighted (82.52%, n = 1761). In turn, vaccines with a non-replicating viral vector had a notification charge of 17.48% (n = 373).

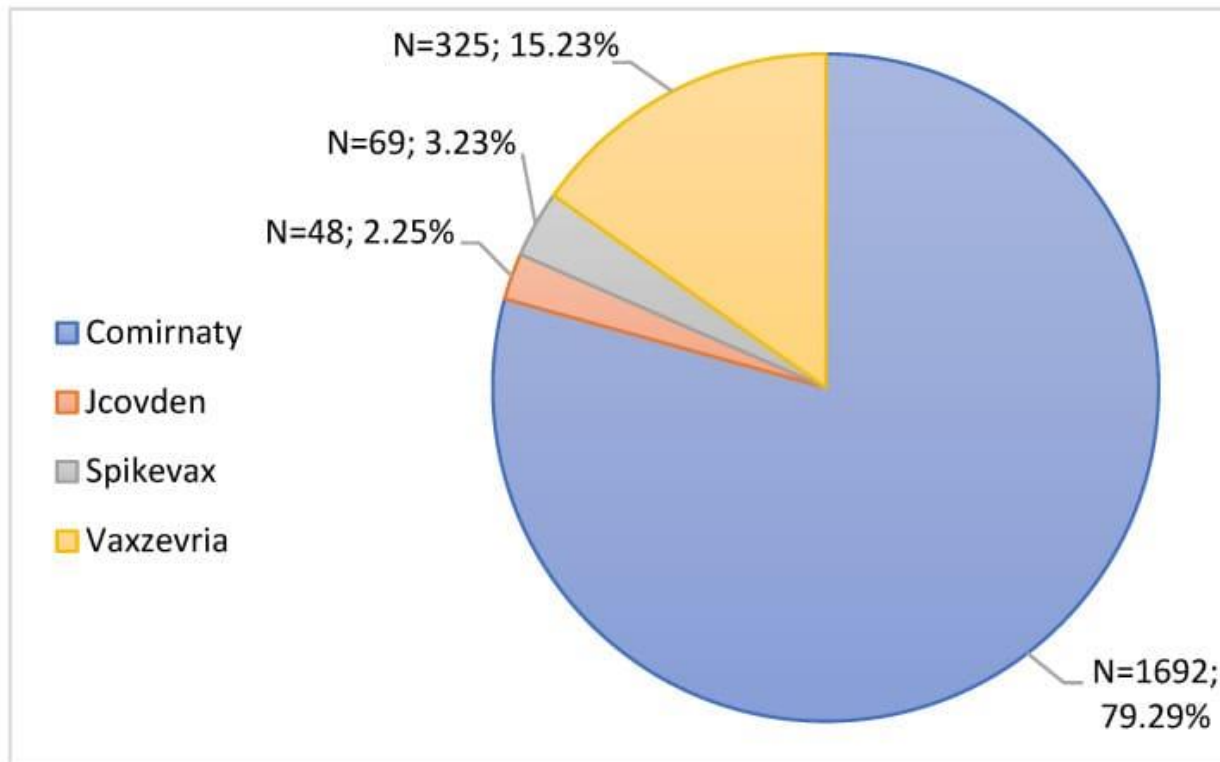
Figure 4.



Characterization of notifications in step with the form of vaccine.

eventually, the ADRs have been prepared into four lessons, in line with the logo call of the administered vaccine. studying figure 5, it's far viable to take a look at that maximum of the notifications submitted were associated with the Comirnaty vaccine (79.29%, n = 1692), followed with the aid of the Vaxzevria vaccine with 325 notifications (15.23%). The Spikevax vaccine had a notification fee of three.23% (n = 69), and ultimately, the Jcovden vaccine became associated with 2.25% (n = forty eight) of the notifications submitted.

Figure 5.



Characterization of notifications according to the brand name of the vaccine.

3.3.2. analysis of negative Drug Reactions

on this look at, the notifications sent to the nearby Pharmacovigilance Unit of Beira interior were first of all characterized in line with the SOC category of the MedDRA dictionary. The 2134 notifications had been prepared into 5685 SOC reactions, which means that there had been, on common, about three SOC reactions for each notification.

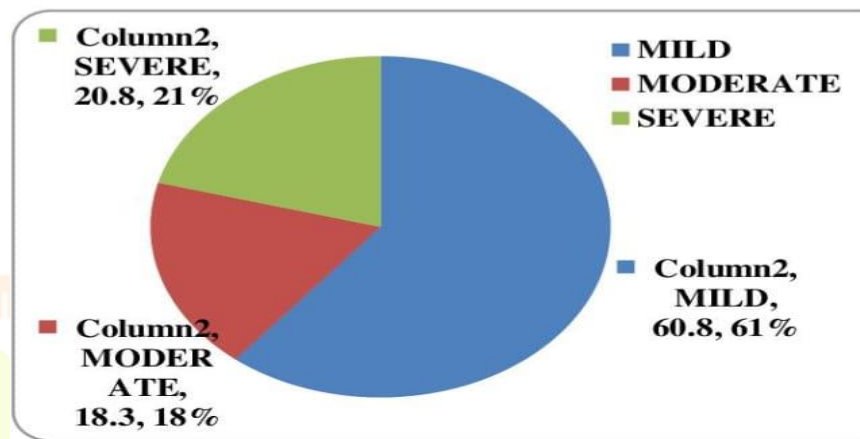
via desk 2, it's miles feasible to finish that the 3 SOC businesses most regularly notified had been “widespread disorders and administration web site situations”, “apprehensive machine problems”, and “Musculoskeletal and connective tissue issues”, imparting the following frequencies 2454 (43.17%), 1048 (18.forty three%) and 1015 (17.85%), respectively. The least notified SOC agencies had been “pregnancy, puerperium and perinatal situations”, constituting 0.02% (n = 1) of the notifications, and “Social instances”, with zero.04% (n = 2).

Research Through Innovation

Table 2.

No.	WHO-Code	System organ classes	No. of ADR
1	0410	Central and pns disorder	20
		Ataxia	13
		Giddiness	5
		Drowsiness	2
2	0100	Skin and appendages disorder	94
		Rashes	64
		DRESS syndrome	1
		Erythroderma	5
		Steven- Johnson syndrome	12
		Toxic epidermal necrolysis	5
		Fixed drug eruption	6
		Lichenoid eruption	2
3	1810	Body as a whole generalise disorder	3
		Gingival hyperplasia	2
		ECG abnormality	1
4	0600	GIT disorders	2
		Acute pancreatitis	2

Severity of ADRs



After the evaluation through SOC businesses, the ADRs notified to the URF of Beira indoors have been categorised in line with the PT phrases. The results are proven in table three. The “other reactions” category encompassed unfavorable reactions with a notification fee $\leq 1\%$.

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Table 3.

Characterization of destructive Drug Reactions in step with the desired time period

Type	Number of cycles of adverse drug reactions	%
Blood/Bone marrow	351	71.5
Neutrophils <1500/mm ³	297	60.5
Hemoglobin <10 g/dL	52	10.6
Platelets <75,000/mm ³	73	14.9
Gastrointestinal	56	11.4
Mucositis/Stomatitis	22	4.5
Diarrhea	33	6.7
Vomiting	10	2.0
Heartburn	1	0.2
Neurological	27	5.5
Neuropathy (motor and sensory)	24	4.9
Dizziness	2	0.4
Encephalopathy	1	0.2
Infection	21	4.3
Metabolic/Laboratory	8	1.6
Allergic/Immunology	6	1.2
Dermatology/Skin	6	1.2
General cardiac	4	0.8
Constitutional symptoms	3	0.6
Renal/Genitourinary	3	0.6
Pain	3	0.6
Hepatobiliary/Pancreas	1	0.2
Musculoskeletal/Soft tissues	1	0.2
Vascular	1	0.2
Total	491 ^(*)	100

* The “different reactions” class encompasses unfavourable reactions with a notification price ≤1%.

thru table three, it's miles feasible to conclude that the three ADRs most often notified had been “reaction at or across the site of management”, “Myalgias”, and “Headache”, with the following frequencies 1147 (20.18%), 751 (thirteen.21%) and 608 (10.69%), respectively.

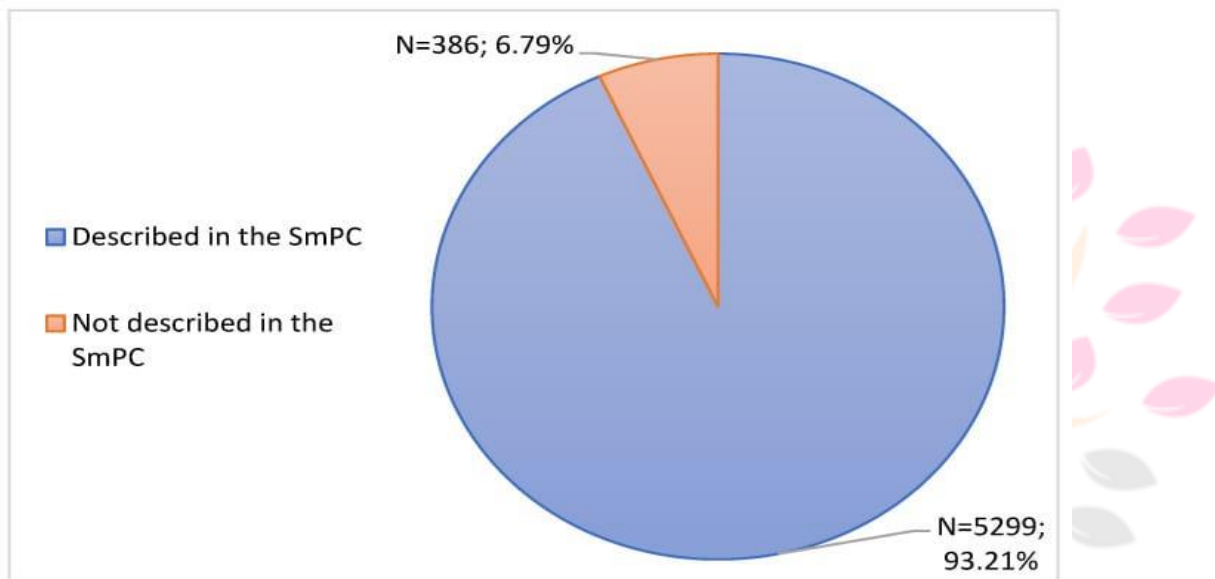
regarding the “different reactions” category, it covered ADRs with a low reporting price, including miscarriage, anaphylactic shock, seizures, respiration misery and syncope.

3.3.3. Description within the summary of Drug traits (SmPC)

The ADRs had been analyzed in phrases of their prior information. for that reason, the SmPC of the respective vaccines beneath take a look at turned into used for in addition characterization in: “defined inside the SmPC” and “now not defined in the SmPC” [25,26,27,28].

via figure 6, it is possible to affirm that 5299 ADRs have been defined within the SmPC (ninety three.21%), amongst which it's miles feasible to spotlight “reaction at or around the administration web page”, “Myalgias”, “Arthralgias”, “Pyrexia” and “headaches”. 386 ADRs had been no longer described in the SmPC (6.79%).

Figure 6.

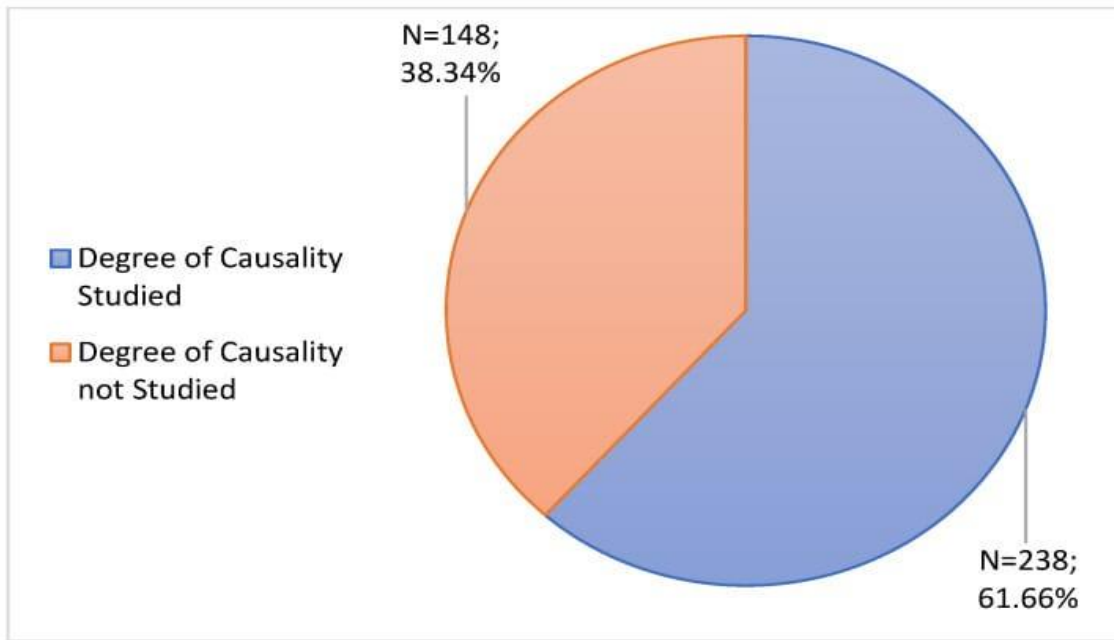


Characterization of negative Drug Reactions according to the description in the SmPC.

ADRs not defined inside the SmPC have been grouped in line with 2 classes: “degree of Causality Studied” and “degree of Causality now not studied”. The class of “degree of Causality Studied” acquired the maximum prominence (61.66%; n = 238) (parent 7).



Figure 7.



Study of Causality.

The ADRs for which the diploma of causality become studied were grouped into 6 categories: “Definitive”, “likely”, “viable”, “not going”, “Conditional”, and “Unclassifiable”. in step with desk 4, it's far feasible to look at that most ADRs had been categorised as “possible” (n = 118, forty nine.fifty eight%). a hundred ADRs (forty two.02%) have a “possibly” diploma of causality and 18 (7.fifty six%) were classified as “unlikely”. The degree of causality that was less prominent turned

Table 4.

Characterization of adverse Drug Reactions in keeping with the degree of causality attributed.

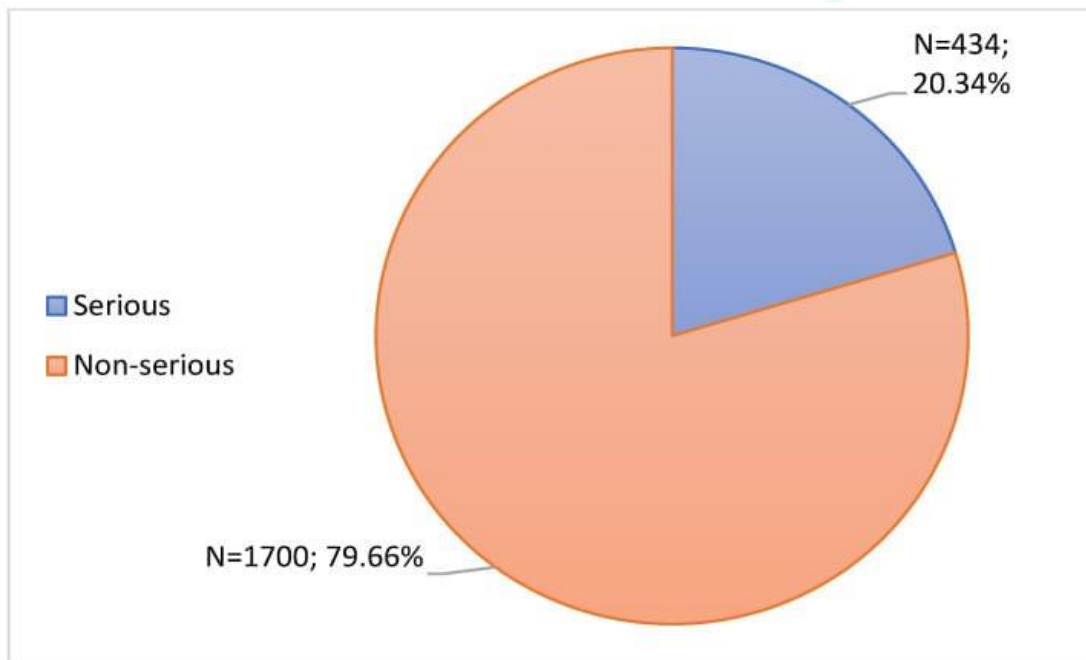
Type of ADRs	Characteristics	Examples
Type A	-Dose-related -Related to a pharmacological action of drug -Predictable from known pharmacology	-Nephrotoxicity caused by aminoglycosides -Anticholinergic effects of tricyclic antidepressants
Type B	-Not dose-related -Uncommon -No relation to a pharmacological action of the drug	-Penicillin- induced urticaria -Anticonvulsant hypersensitivity syndrome reaction
Type C	-Uncommon -Long term exposure of drugs	-Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Type D	-Prolonged exposure to a drug	-Tardive dyskinesia caused by antipsychotic medication
Type E	-Termination of treatment	-Tachyphylaxia

3.3.4.Seriousness and Seriousness standards

Seriousness

in this have a look at, the 2134 notifications have been in addition characterized in keeping with seriousness. among those notifications, 1700 notifications have been taken into consideration non-critical (seventy nine.sixty six%) as they did no longer satisfy any of the criteria mentioned in Seriousness and Seriousness standards segment. In turn, 434 notifications were considered extreme, representing 20.34%, as may be seen in determine eight.

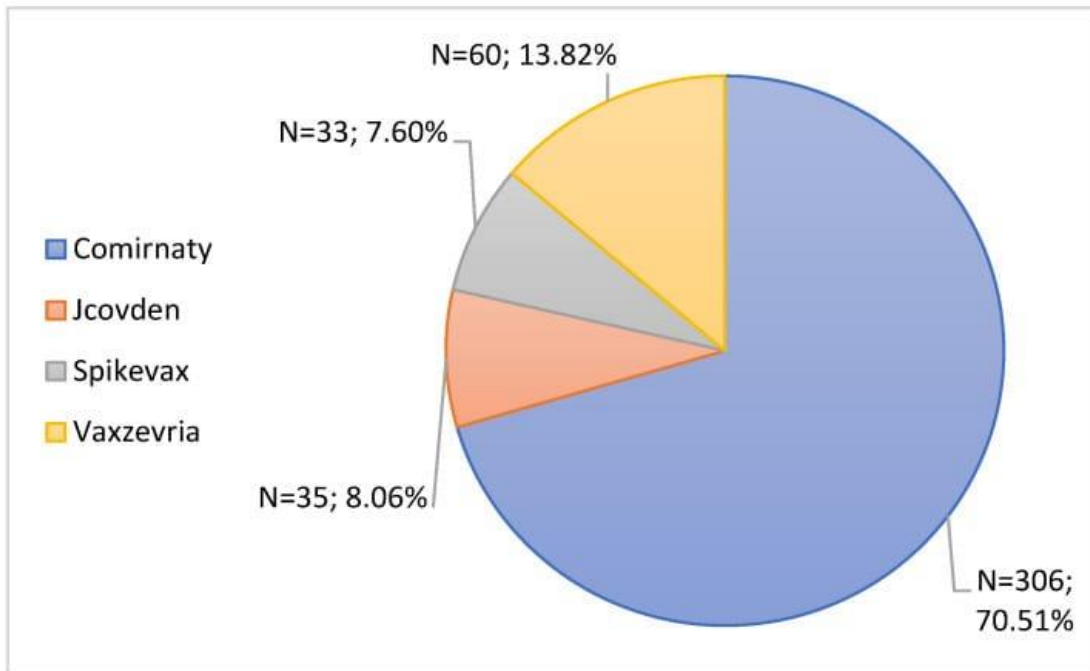
Figure 8 .



Characterization of notifications according to seriousness.

in the end, the 434 notifications considered severe have been prepared in keeping with the brand of vaccine administered. determine 9 suggests that maximum ADRs taken into consideration serious belonged to the Comirnaty vaccine (70.51%, n = 306), followed by way of the Vaxzevria vaccine with 60 extreme ADRs (13.82%). The Jcovden vaccine had 35 extreme notifications (eight.06%) accompanied via Spikevax with 33 notifications (7.60%).

Figure 9.



Characterization of significant notifications according to the logo call of the vaccine administered.

Seriousness Criteria

ADRs considered extreme had been grouped by using seriousness into five criteria: “Clinically vital”, “incapacity”, “Hospitalization”, “existence hazard” and “demise”. some serious notifications had multiple seriousness criteria, with a complete of 441 seriousness standards notified for 434 severe notifications.

The seriousness standards “Clinically vital” had notable prominence, with a percent of 64.63% (n = 285), accompanied by using “disability” (24.04%, n = 106). Then came the standards “Hospitalization” with nine.fifty two% of great notifications, which corresponds to 42 notifications. finally, the standards “existence danger” and “demise” regarded with 6 and a pair of notifications (1.36% and 0.45%), respectively, as can be seen in figure 10.

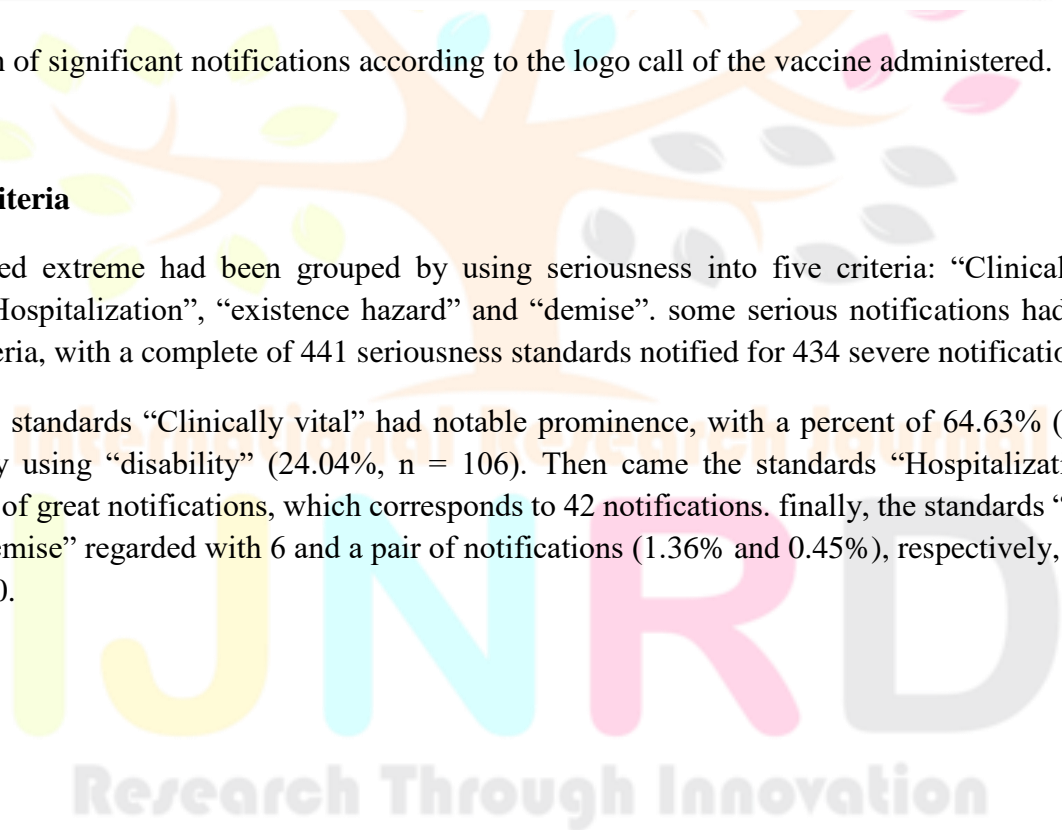
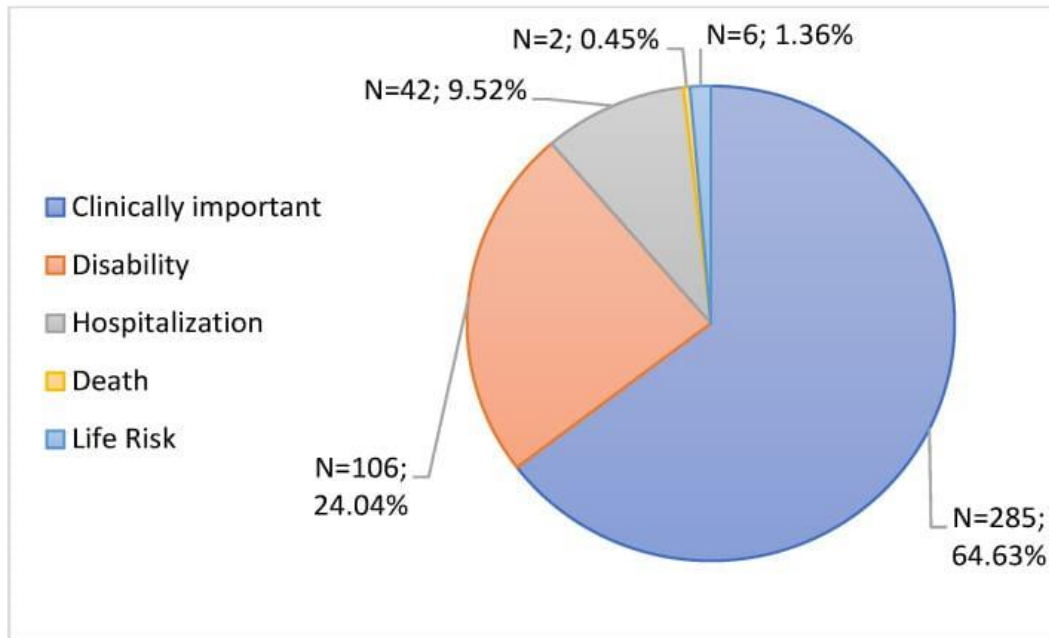


Figure 10.

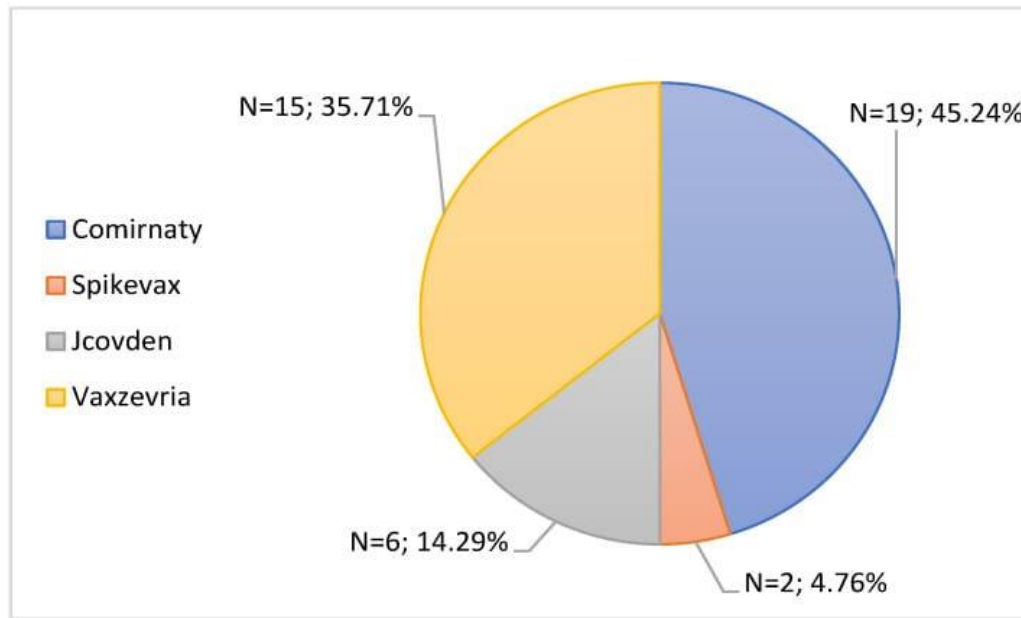


Characterization of significant notifications in keeping with the seriousness criteria.

Then, the ADRs with seriousness criteria “Hospitalization”, “lifestyles threat” and “death”, were characterised in keeping with affected person’s age and related vaccine brand.

To start with, there was a characterization of the 42 notifications with the seriousness standards “Hospitalization” in step with the emblem of vaccine administered and age, and the outcomes can be found in determine eleven and table five, respectively. regarding the emblem of the related vaccine, the Comirnaty vaccine turned into chargeable for most hospitalizations (forty five.24%, n = 19), accompanied by Vaxzevria answerable for 35.seventy one% (n = 15). The Jcovden vaccine become associated with 14.29% (n = 6) of notifications with the seriousness criteria Hospitalization, and eventually, Spikevax originated 4.seventy six% (n = 2) of hospitalizations.

Figure 11.



Characterization of great notifications with the seriousness criteria “Hospitalization”, in step with the logo of vaccine administered.

Table 5.

Age Group	Frequency	Percentage (%)
(5–11)	0	0.00
(12–17)	0	0.00
(18–24)	2	4.76
(25–49)	13	30.95
(50–64)	7	16.67
(65–79)	12	28.57
≥80	7	16.67
Unknown	1	2.38
Total	42	100.00

studying desk 6, most hospitalizations have been related to sufferers elderly between 25 and 49 years (30.ninety five%, n = thirteen), accompanied by patients elderly among 65 and 79 years (28.fifty seven%, n = 12).

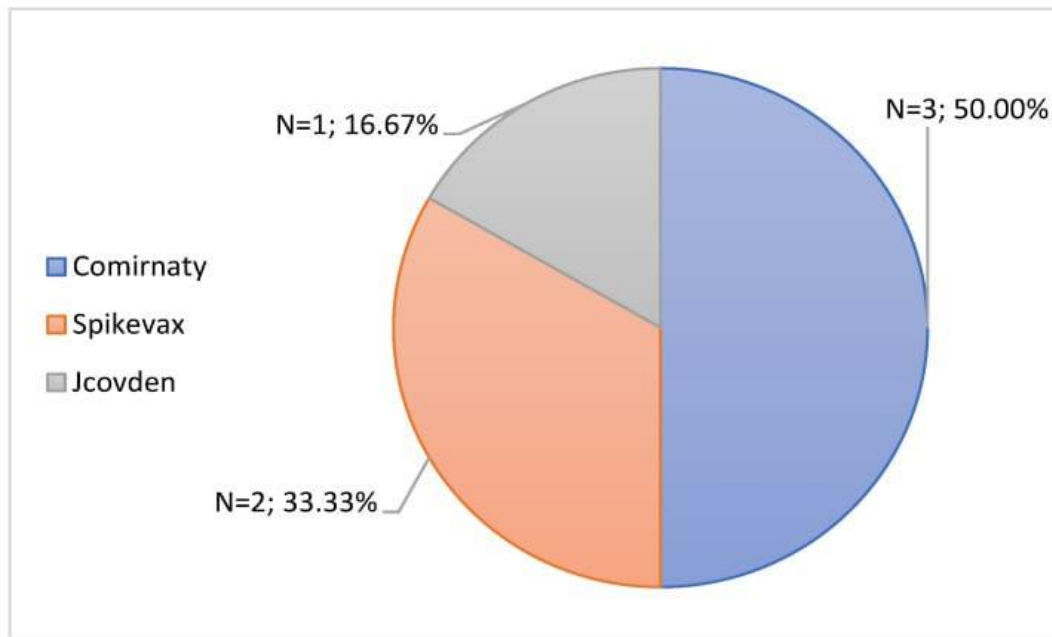
Table 6.

Characterization of great notifications with the seriousness criterion “lifestyles threat”, according to the associated age.

Age Group	Frequency	Percentage (%)
(5–11)	0	0.00
(12–17)	0	0.00
(18–24)	1	16.67
(25–49)	3	50.00
(50–64)	1	16.67
(65–79)	0	0.00
≥80	1	16.67
Unknown	0	0.00
Total	6	100.00

in the end, the 6 notifications with the seriousness standards “lifestyles threat” have been characterized, and the effects are observed in determine 12 and table 7. In figure 12 it is feasible to have a look at that the vaccines chargeable for this seriousness standards were the Comirnaty vaccine, the Spikevax vaccine and the Jcovden vaccine, each answerable for three, two and one case, respectively. In truth, the most prominent vaccine turned into Comirnaty, the most administered vaccine in Portugal [29].

Figure 12.



Characterization of great notifications with the seriousness standards “existence risk”, in step with the logo of vaccine administered.

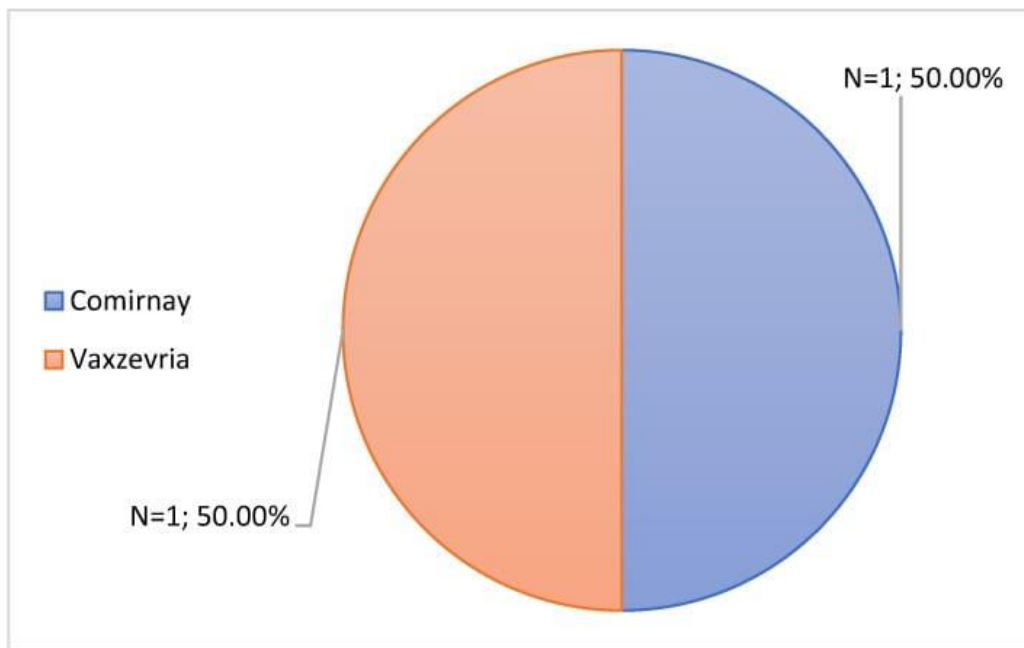
Table 7.

Evolution of Adverse Drug Reactions	Frequency	Percentage (%)
Cure	5361	94.30
Cure with collateral damage	9	0.16
In recovery	6	0.11
Death	6	0.11
Unknown	303	5.33
Total	5685	100.00

concerning the age agencies associated with the seriousness criteria “lifestyles chance”, it’s possible to study thru the table 6 that the age organization with the most instances turned into the group from 25 to forty nine years vintage (50.00%, n = three). The age companies from 18 to 24 years old, 50 to 64 years old and ≥eighty years vintage had been related to a unmarried case of “life danger”.

subsequently, the 2 notifications related to the seriousness criteria “loss of life” were characterized. In determine thirteen it’s feasible to take a look at that the vaccines responsible for this seriousness criteria were the Comirnaty and the Vaxzevria vaccine, each answerable for one case. these sufferers were 76 and eighty four years antique, respectively.

Figure 13.



Characterization of great notifications with the seriousness criteria “demise”, according to the emblem of vaccine administered.

3.3.5. Evolution of unfavourable Drug Reactions

another important parameter to be evaluated is the evolution of the patient’s clinical circumstance, whose information permit us to apprehend the viable risks to the affected person’s life after the administration of the drug in people (table 7).

Of the 5685 ADRs notified, 5361 (ninety four.30%) resolved within a few hours or days without the arrival of collateral damage, 9 (zero.sixteen%) led to the appearance of collateral harm, 6 (zero.eleven%) ADRs sufferers were in healing on the time of reporting and in 6 (0.eleven%) ADRs the result become death. In 5.33% of the ADRs (n = 303), it become not feasible to obtain statistics concerning the final results of the response.

3.3.6. Characterization of Notifications with the final results “death” with terms Belonging to the important clinical events list

In general, 2 notifications had been received that culminated in demise, similar to a total of 6 ADRs, of which 5 have been on the IME list. via table eight, it's far feasible to see that the 6 ADRs associated with the outcome “death” belonged to three SOC corporations, among which the “Cardiac issues” group become extra distinguished.

Table 8.

dating among the destructive Drug Reactions of the notifications that improved to loss of life with the terms belonging to the Import scientific occasion (IME) listing.

System Organ Class Group	IME List Terms
Cardiac disorders (3)	Acute myocardial infarction (2); Cardiogenic shock (1)
Renal and urinary disorders (1)	Acute kidney injury (1)
Metabolism and nutrition disorders (1)	Hyperkalaemia (1)

those 2 cases acquired a causality examine by means of the regulatory authority, with a conclusion of an unlikely causal relationship, i.e., there was no causal dating among ADR and the related vaccine.

4. Discussion

This look at allowed the characterization of the notifications of ADRs related to vaccines used in the immunization towards COVID-19, notified to the Pharmacovigilance Unit of Beira interior, in Portugal, inside the term between December 2020 and December 2021.

to begin with, the form of notifier who submitted the notification became analyzed. thru records analysis, it become determined that pharmacists had the very best notification rate. The user or different non-healthcare professional also contributed to enhancing the safety profile of vaccines, accompanied later by means of physicians. according to the graph “Evolution of ADR Notifications obtained within the SNF, with the aid of foundation, 1992–2021”, made available by means of INFARMED, over the years, the most important notifier of ADRs has been the pharmaceutical enterprise [30]. inside the 12 months 2021, the enterprise became the biggest notifier, observed via physicians and later by means of pharmacists. The outcomes obtained on this study are not according with the INFARMED graph, supplying the pharmacist as the finest notifier of ADRs related to vaccines used within the immunization against COVID-19. that is associated with the fact that the pharmaceutical offerings of 2 hospital facilities set up pharmacovigilance protocols and were later worried in gathering statistics from patients after the management of these vaccines, consequently increasing the notification charge acquired through pharmacists. however, in general, the results received inside the have a look at support the reality that healthcare specialists are more and more aware about the want to notify suspected ADRs, so that you can improve the safety profile of drugs. As stated within the Notifier Characterization section, the reality that this look at targeted only on a local unit explains why we did not acquire ADRs notified by using the pharmaceutical industry, as these experts notify them directly at the ADR portal, with out a unique vicinity being assigned to them.

regarding the district of starting place of the notification, it changed into determined that most notifications offered Castelo Branco because the district of origin, accompanied by using Viseu and finally Guarda.

among the analyzed facts, the age institution with the very best notification fee, the various businesses considered, was the organization from 25 to forty nine years antique, followed by means of patients elderly among 50 and sixty four years old. those facts are in accordance with the file “Pharmacovigilance file: monitoring the protection of vaccines towards COVID-19 in Portugal. records obtained until 01/31/2022.”, which shows that the age companies 25 to forty nine years vintage and 50 to 64 years antique had the very best wide variety of ADR notifications on the national stage [29]. This fact may be because of the greater quantity of vaccines being administered in those two age businesses, further to being age corporations with more capacity to recognize an ADR. it is also critical to point out that, according to the records referring to the resident populace in Portugal by means of age institution, those are the age companies with the biggest population [31]. concerning gender, the population become basically girl, and these statistics are supported by the aforementioned record [29]. normally, the lady gender is the only that most notified to any drug, because of the greater susceptibility to broaden ADRs, compared to the male gender, in all likelihood because of the physiological differences among both sexes. additionally, it may be associated with girls’s more attention to their health and indicators evolved by way of their frame [29,32,33]. international research additionally confirm the aforementioned information concerning the age companies and gender with the highest notification quotes of vaccine-associated ADRs [34,35].

in the end, ADRs have been analyzed consistent with the type and logo of the vaccine administered. on this take a look at, during the evaluation duration, mRNA vaccines had been the most notified. maximum of the notifications submitted were related to the Comirnaty vaccine, followed via the Vaxzevria vaccine. In reality, these statistics had been in agreement with the INFARMED Pharmacovigilance file, which indicates that the

majority of ADRs notified in Portugal correspond to mRNA vaccines [29]. It ought to be cited that those consequences may be because of the truth that those have been the maximum administered vaccines in Portugal in addition to in the eu and the us [36,37]. The identical file mentions that the vaccine with the highest variety of ADR notifications become Comirnaty, followed by way of the Vaxzevria vaccine, which boosts the facts in discern five available in phase three.3.1. of the outcomes [29]. these information are corroborated by using EMA facts, which suggest that these have been also the most ADR vaccines suggested in Europe [38]. in step with data from the centers for disorder control and Prevention, the Comirnaty vaccine become the vaccine with the most ADRs said within the u.s. [39].

The 3 most regularly notified SOC organizations have been “fashionable problems and administration web page situations”, “nervous device problems”, and “Musculoskeletal and connective tissue issues”. consequently, in regards to “wellknown problems and management website changes”, it is easy to see why they represented the most frequent SOC institution, given that this organization encompassed non-specific signs that affect diverse websites in the body, together with fashionable malaise or fatigue, as well as ADRs often associated with the administration of any vaccine, which include ache, swelling, itching or bruising at the injection web site.those signs and symptoms are generally mild and temporary. As for the second one organization, “worried gadget sicknesses”, they blanketed signs which includes complications, migraines and convulsions. The 0.33 most notified institution became “Musculoskeletal and connective tissue disorders”, which included myalgias, arthralgias and pain within the extremities. It is straightforward to understand why it changed into a number of the 3 most notified companies, as SARS-CoV-2 binds to host cells through the spike glycoprotein, thru the ACE2 receptor [40].This receptor is determined inside the epithelial cells of the pulmonary alveoli and in the enterocytes of the small intestine, in addition to within the skeletal muscle and important nervous system, which can be associated with myalgias. moreover, some other phenomenon related to myalgias is the “cytokine storm”, wherein interleukin-6 plays a key role in inducing the manufacturing of prostaglandin E2, associated with irritation and ache [40].The vaccines used to immunize in opposition to COVID-19, in spite of now not containing the virus in their constitution, have statistics that encodes the spike protein, recognized by means of the immune device, and able to inflicting an inflammatory reaction, via a huge production of pro-inflammatory cytokines, which results in the advent of myalgias and other musculoskeletal signs [41,42].

those facts are according with the aforementioned Pharmacovigilance file [29]. in line with the file “Rapporto sulla Sorveglianza dei vaccini anti-COVID-19”, issued by the Agenzia italiana del farmaco, the 3 most frequently notified SOC corporations were the “widespread disorders and administration website conditions”, “frightened system problems”, and “Musculoskeletal and connective tissue disorders” which are in accordance with the outcomes acquired thru this take a look at [43].

Following the evaluation with the aid of SOC companies, the ADRs have been categorised in step with the PT phrases. The three maximum often notified ADRs have been “response at or around the injection web page”, “Myalgias”, and “Headache”. these information are in agreement with the information from the maximum often notified SOC companies referred to inside the preceding paragraph (“standard problems and administration website online disorders”, “frightened device issues”, and “Musculoskeletal and connective tissue disorders”).injection web site” being the various 3 maximum frequently said ADRs is associated with the way in which the vaccines are administered. This group belongs to the SOC group “fashionable disorders and administration web page conditions”...

regarding the notified ADRs, the regulatory authority classified them with a diploma of causality “improbable”, primarily based on the history that the patients had, which intended that the vaccines were now not the reason of loss of life for both patients. these records are in settlement with numerous studies that

indicated that the cases of demise that took place in sufferers after vaccination towards COVID-19 have been now not related to the vaccines administered, being not anything extra than mere twist of fate [51].

4.1. boundaries

This examine had a few boundaries, among which we can highlight the fee of under reporting of suspected ADRs, i.e., no longer all ADRs that passed off had been notified to the national Pharmacovigilance system, which may additionally have took place, for example, due to loss of time or lack of know-how concerning the existence of the “Portal RAM” [16,17] every other hassle is related to the truth that a few notifications presented a loss of statistics, making their study tough. moreover, the truth that the Comirnaty vaccine is the maximum administered vaccine in Portugal, leading to the general public of ADRs pronounced being related to this vaccine, may additionally have biased the results obtained, because the vaccines under observe have been not administered in the equal variety of sufferers, making it greater hard to examine the effects.

4.2. Strengths of examine

The strengths of our examine covered a big pattern size wherein it became feasible to represent several parameters related to the suggested ADRs. additionally, it become the primary take a look at accomplished in Portugal, to our information, over a long length related to statistics corresponding to the first, 2d and third doses.

5. Conclusions

The notification of suspected ADRs turned into in particular associated with not unusual and non-serious reactions (e.g., pyrexia, fatigue, myalgia and reaction at or around the injection site), that is according with medical trials, in the vaccine SmPCs and in ADR notifications of vaccines from different countries. In fashionable, ADRs resolved within some hours/days without any outcomes, which confirms a good safety profile of the COVID-19 vaccines. despite the consequences acquired, in addition research are had to affirm these statistics.

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