JHPHS
Journal of Hospital Pharmacy and Health Services

Original Paper

Open Access

Adverse Event Reporting for Medications and Vaccines Before and During the COVID-19 Pandemic: An Observational and Retrospective Study

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Submitted: 06-02-2025 Resubmitted: 11-06-2025 Accepted: 13-06-2025

Double blind peer review

Abstract

Objective: Compare the profile of suspected adverse events (AE) reports associated with medicines and vaccines before and during the COVID-19 pandemic. **Method:** An observational, retrospective study was conducted using data extracted from the VigiMed database. Spreadsheets were reviewed and processed, starting with the exclusion of the lines that had incomplete and uninterpretable data on the following variations related to the patient, related to the AE, related to the medication/vaccine and related to the notifier. Following database extract, reports were categorized into two groups: Group 1 (G1), before the pandemic; and Group 2 (G2), during the pandemic. Categorical variables were compared using absolute and relative frequency. **Results:** There was no difference between the notification profiles in the two groups about the sex and age of the individuals affected by AE related to medicines and vaccines. The notifiers in G1 were predominantly pharmacists (77.5%) while in G2, it was the consumers (55.9%). With respect to the products that were the target of the notifications, in G1 the most prevalent classes were analgesics, antibiotics and antineoplastics. In G2, there were vaccines against COVID-19 and immunosuppressants. About reports of suspected fatal AE related to medicines and vaccines, the most prevalent products in G1 were antimicrobials and antiepileptics, while G2 included antineoplastics, COVID-19 vaccines and immunosuppressants. **Conclusion:** The comparative of AE to drugs and vaccines notifications revealed that the COVID-19 pandemic contributed to a change in the profile of the notifiers, as well as in the type of product targeted by the notifications most frequently reported. These findings highlight the landscape of pharmacovigilance during public health emergencies.

Keywords: adverse events, post-vaccination adverse event, drug-related adverse events, pharmacovigilance, database

Notificação de eventos adversos para medicamentos e vacinas antes e durante a pandemia de COVID-19:vum estudo observacional e retrospectivo

Resumo

Objetivos: Comparar o perfil das notificações de suspeita de eventos adversos (EA) relacionados a medicamentos e vacinas antes e durante o período da pandemia de COVID-19. **Métodos:** Foi realizado um estudo observacional e retrospectivo para análise do banco de dados gerado a partir do VigiMed. As planilhas foram analisadas e tratadas, a partir da exclusão das linhas que possuíam dados incompletos e não interpretáveis sobre as seguintes variáveis relativas ao paciente, relativas ao EA, relativas ao medicamento/vacina e relacionado ao notificador. A partir da extração do banco de dados, as notificações foram separadas em dois Grupos: o Grupo 1 (G1) antes da pandemia; e o Grupo 2 (G2) durante a pandemia. Cada variável categórica foi analisada por meio de cálculo de frequência absoluta e relativa. **Resultados:** Não houve diferença entre os perfis de notificação nos dois grupos em relação ao sexo e idade dos indivíduos acometidos pelos de EA relacionados a medicamentos e vacinas. Entretanto, em relação à prevalência dos notificadores no G1 a predominância foi de farmacêuticos (77,44%) e no G2 foram os consumidores os notificadores mais prevalentes (55,88%). Em relação aos produtos alvo das notificações, no G1 as classes mais predominantes foram os analgésicos, antibióticos e antineoplásicos. No G2, foram vacinas contra a COVID-19 e imunossupressores. Em relação às notificações de suspeita de eventos adversos relacionados a medicamentos e vacinas fatais, os produtos mais prevalentes no G1 foram os antimicrobianos e antiepiléticos, enquanto no G2 foram antineoplásicos, vacinas contra COVID-19 e imunossupressores. **Conclusão:** Desse modo, a comparação entre as notificações de EA relacionados a medicamentos e vacinas apontou que a pandemia de COVID-19 contribuiu para modificação no perfil dos notificadores, bem como no tipo de produto alvo das notificações.

Palavras-chave: Eventos adversos, Eventos adversos pós-vacinação, Eventos adversos a Medicamentos, farmacovigilância, Banco de dados

Introduction

Pharmaceutical products are inputs that promote health and quality of life. Among these, medicines are essential for which help to prevent or control symptoms, thereby delaying the progression of diseases and diagnoses, and vaccines, which act to prevent various illnesses. However, medicines and vaccines can cause users to suffer undesirable effects, known as adverse events (AEs).[1] Any unwanted medical occurrence after vaccination, which may or may not have been caused by vaccination, is called a post-vaccination adverse event (PVAE) while drug-related adverse events (DAEs) are any injury or damage caused to the patient by the drug-related intervention. The incidence of AEs has increased in both cases in all spheres of healthcare.[2-4]

When AE related damage is considered serious, it can lead to hospital admissions, prolonged hospital stays, increased morbidity and mortality, as well as having a direct impact on potentially avoidable costs for health systems.[5,6] Hence, health bodies are continuously striving to reduce AE. In Brazil, initiatives such as the patient safety sectors, the implementation of the National Patient Safety Program and the promotion of various basic protocols, such as the "Protocol for Safety in the Prescription, Use and Administration of Medicines", there has been an incentive for health professionals to report any suspicion of AE.[7]

Reporting to the pharmacovigilance system is a tool for mitigating the negative impacts of DAEs, since the analysis of reports makes it possible to characterize factors related to the incident.[8] Information on notifications of DAEs related to medicines and vaccines in Brazil is stored in a database system managed to the National Health Surveillance Agency (ANVISA).[9] Although reports do not always confirm the occurrence of an DAE and are therefore considered suspected, they can generate warning signs and hypotheses about the safe use of medicines and vaccines.[9,10] Therefore, careful analysis of pharmacovigilance databases is an essential strategy to prevent the occurrence of DAEs.

The COVID-19 pandemic has had a significant impact on the routine of health services and medication-use behaviors.[11] With reduced access to health services to meet primary demands, the introduction of new pharmaceutical products and, especially, and widespread dissemination of information on the population, the patterns of prescription and use of medicines and vaccines may have been impacted.

Given the substantial public health implications of PVAE, DAEs and the pandemic scenario, it is important to verify information on notifications of AEs to drugs and vaccines before and during the COVID-19 pandemic. This data collection can identify key indicators to enhance patient safety strategies. Therefore, this study aimed to compare reports of suspected AE related to medicines and vaccines before and during the COVID-19 pandemic.

Methods

Research design

The research is an observational, retrospective study, conducted between June 2021 and November 2022, based on the comparison of an AE related to medicines and vaccines notification database.

Data extraction and comparison

The data was extracted from the Brazilian Open Data Portal - National Health Surveillance Agency (https://dados.gov.br/dataset/notificacoes-em-farmacovigilancia). The data was accessed free of charge on the website which allows the visualization of data received by VigiMed, a system for monitoring AE, made available by Anvisa. The study samples consisted of notifications of suspected AE to medicines and vaccines reported since the implementation of VigiMed in 2018.

The database was extracted on April 12, 2022, in csv format, from the spreadsheet called "Notifications", in which all the data relating to a notification is grouped into just one line. The spreadsheet was processed by deleting rows with incomplete and uninterpretable data (e.g., blank fields or entries containing symbols). The following variables were considered: Patient-related (age at the time of occurrence, biological sex, pregnant or lactating), AE-related (description of the AE, severity, severity assessment classifications, clinical evaluation, outcomes), Medication/Vaccine-related (Name of the suspect product) and Notifier-related (patients, health professionals, companies, health services, among others).

After processing the data, the spreadsheet was subdivided into two groups: Group 1 (G1) consisted of data recorded from 12 December 2018 through 19 March 2020, whereas Group 2 (G2) contained data obtained from 20 March 2020 to 12 April 2022. Details on patient information, the AE, the suspected drug/vaccine and the notifier were included in the comparative of the groups. Reports were categorized according to VigiMed's classification system:[12]

- Spontaneous notifications: Voluntary submissions by healthcare professionals or the public, reporting suspected AEs related to medicines and vaccines.
- Study notifications: AEs identified in clinical trials or research studies.
- Other notifications: Reports not fitting spontaneous or study classifications.
- Unspecified notifications: Cases where the notifier did not define the report type.

The spreadsheet was processed, organized and restructured in Excel (Microsoft, Redmond), and the data in each categorical variable was compared by calculating absolute and relative frequencies. The frequency of each piece of data was used as the denominator of the comparison, thus building the profile of AE reported by VigiMed.

Ethics approval

Ethical approval was not required as the data were neither confidential nor commercially sensitive obtained in this study.

Results

Number of notifications

The initial dataset comprised 110,569 notifications, of which 76,079 (69%) were excluded due to incomplete data (Figure 1). From the 34,490 notifications included in the study, an important increase in the number of notifications in G2 (31,861 notifications) was observed compared to G1 (2,629 notifications) (Table 1).

Type of notification

Spontaneous reports constituted the predominant notification type in both periods (Table 1). However, G2 demonstrated increased reporting through alternative channels, particularly study reports (98.5% of which were submitted by pharmaceutical companies).

Table 1. Profile of notifications included in the study reported for G1 (December 12, 2018, to March 19, 2020) and G2 (March 20, 2020, to April 12, 20s22)

	Number of notifications	
	Group 1 (n = 2,629)	Group 2 (n = 31,861)
Variables	n (%)	n (%)
Types of Notifications		
Spontaneous notifications	2,586 (98.4%)	24,043 (75.5%)
Study notification	11.0 (0.4%)	5,132 (16.1%)
Other	32.0 (1.2%)	2.6 (8.3%)
Not available by notifier (unknown)	0	39.0 (0.1%)
Profile of notifiers		
Pharmacists	2,036 (77.5%)	6,001 (18.8%)
Consumers (Other non-health professional)	322 (12.2%)	17,805 (56.0%)
Other healthcare professional	208 (8.0%)	2,544 (8.0%)
Doctor	44 (1.67%)	5,375 (16.9%)
Attorney	19.0 (0.7%)	136 (0.5%)
Biologic sex		
Female	1,499 (57.0%)	19,750 (62.0%)
Male	1,130 (43.0%)	11,991 (37.6%)
Unknown	-	120 (0.4%)
Fatal cases by biologic sex		
Female	19 (50%)	1,391 (46%)
Male	19 (50%)	1,635 (54%)
Age of the patients		
0-19 years old	445 (16.9%)	3,171 (10.00%)
20-59 years old	1,335 (50.7%)	18,308 (57.5%)
60-105 years old	849 (32.3%)	10,382 (32.6%)
Severity		
Threatens life	281 (10.7%)	2081 (6.5 %)
Congenital anomaly or malformation at birth	3 (0.1%)	53 (0.2%)
Hospitalization/Prolongation of hospitalization	657 (23.0%)	6606 (20.7%)
Persistent or significant disability	104 (3.9%)	2171 (6.8%)
Other clinically significant effect	1541 (58.6 %)	17883 (56.1%)
Resulted in death	43 (1.6%)	3067 (9.6)
Degree of Severity		
Not serious	0	1 (00.01%)
Serious	2,629(100%)	31,860 (99.99%)

Note: When reporting the Gravity/Severity option in Vigimed, it offers the option "resulted in death" regarding the impact of the AE, however, in the outcome option (Table 2) there is also the option "resulted in death" regarding the outcome of the AE, not always when reported in severity was it reported in outcome.

Profile of notifiers

Differences were observed in the profile of the groups' notifiers before and during the COVID-19 pandemic (Table 1). According to the data presented, in G1, pharmacists were the ones who made the most notifications (77.44%). Whereas in G2, consumers or other non-health professionals comprised the largest group of notifiers (55.88%). In addition, about 81.5% of the notifications associated with COVID-19 vaccines were made by consumers and this coincided with the emergence of these vaccines.

Notifications by biological sex and age

Both groups showed female predominance in reporting (Table 1), though the biological sex disparity was more pronounced in G2 (24.4% difference vs. 14% in G1). The comparison of fatal adverse event reports revealed proportional differences between sexes in the study periods. (outcomes), G1 exhibited no difference between females and males, but in G2, males comprised a greater proportion of fatal cases (54%) (Table 2).

Regarding age, the highest notifications were recorded for 20-59 years old individuals in both groups (50.77% - G1; 57.46% - G2). When the notifications with suspected fatal AEs related to medicines and vaccines were evaluated, both G1 and G2 had a predominance of elderly people (60-120 years), 68.42% and 53.98%, respectively.

Table 2. Profile of interventions and outcome of notifications reported for G1 (December 12, 2018, to March 19, 2020) and G2 (March 20, 2020, to April 12, 2022)

	Number of notifications	
	Group 1 (n = 2,629)	Group 2 (n = 31,861)
Variables	n (%)	n (%)
Outcome		
Recovered/Resolved	1873 (71.2%)	12031 (37.8%)
In recovery/Solving	421 (16.0%)	4570 (14.3%)
Fatal/Death	38 (1.4%)	3047 (9.5%)
Recovered/Resolved with sequelae	25 (1.0%)	662 (2.1%)
Unknown	108 (4.1%)	6435 (20.2%)
Not Recovered/Unresolved/ Ongoing	164 (6.2%)	5116 (16.0%)
Actions		
Dose increase	27 (1.0%)	330 (1.0%)
Medication withdrawal	1529 (58.1%)	10123 (31.8%)
Dose reduction	137 (5.2%)	743 (2.3%)
Not applicable	482 (18.3%)	8756 (27.5%)
No dose change	357 (13.6%)	5877 (18.4%)
Unknown	97 (3.7%)	6032 (18.9%)
Unknown	-	120 (0.4%)

Note: When reporting the Gravity/severity option in Vigimed, it offers the option "resulted in death" regarding the impact of the AE, (Table 1) however, in the outcome option there is also the option "resulted in death" regarding the outcome of the AE, not always when reported in severity was it reported in outcome.

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Profile of reported AE to medicines and vaccines

In the data extraction, each line of the database table corresponds to a notification, which may contain one or more AE or suspected drugs. Thus, the most reported AE in G1 were: pruritus, exanthema, dyspnea, nausea, erythema, hyperemia, vomiting, facial erythema, diarrhea, and neutropenia. In G2, the most reported were headache, pyrexia, off-label use, COVID-19, ineffective drug, dyspnea, fatigue, nausea, pain and pruritus (Table 3).

Regarding severity classification, 'other clinically significant effect' and 'hospitalization/prolonged hospitalization' were the most frequently reported in both groups. However, the ranking order of other severity notifications differed, given the distinct contexts in which they were recorded. An increase in notifications associated with 'resulted in death' and 'persistent or significant disability' was observed in G2. Adverse events related to 'COVID-19' represented the fourth most frequently reported outcome and were the leading cause in records of suspected fatal cases (Table 3).

Profile of the most reported medicines and vaccines

The total number of drugs reported in G1 and G2 were 4,503 and 70,376, respectively. In G1, the drugs with the highest number of notifications included analgesics (dipyrone, morphine, tramadol) and antineoplastics (oxaliplatin, paclitaxel and carboplatin). On the other hand, in G2, which represents the profile of notifications during the pandemic, COVID-19 vaccines were the most notified for AE, along with some immunosuppressant drugs (infliximab and secukinumabe) (Table 4).

The comparison of the profiles of drugs reported as suspected causes of fatal DAE revealed a higher prevalence of medications routinely used in primary health care, such as antibiotics, antihypertensives, and antiepileptics in G1. In contrast, G2 showed a predominance of antineoplastic agents, as well as vaccines used to COVID-19 and immunosuppressants (Table 4).

Table 3. Profile of the TOP 10 AE to drugs and vaccines reported for G1 (December 12, 2018, to March 19, 2020) and G2 (March 20, 2020, to April 12, 2022)

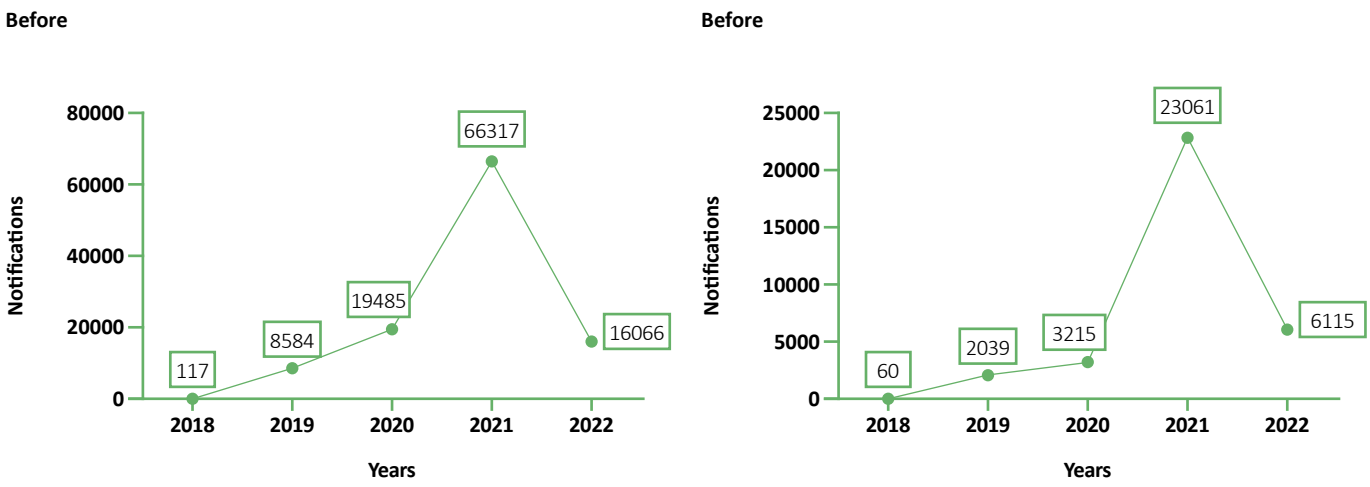
Number of notifications	
Group 1 (n = 4953)	Group 2 (n = 138747)
n (%)	n (%)
Pruritus (319- 6.44%)	Headache (2809- 2.020%)
Rash (216-4.364%)	Fever (2352- 1.697%)
Dyspnea (193- 3.899%)	Off-label use (2085- 1.50%)
Nausea (128- 2.586%)	COVID-19 (2074- 1.495%)
Erythema (125- 2.52%)	Ineffective medicine (1865- 1.334%)
Hyperemia (122- 2.546%)	Dyspnea (1861- 1.34%)
Vomiting (112- 2.326%)	Fatigue (1781- 1.24%)
Facial flushing (99- 2.01,995)	Nausea (17.26- 1.24%)
Diarrhea (94- 1.89%)	Pain (1618- 1.162%)
Neutropenia (92- 1.85%)	Pruritus (1471- 1.061%)

Note: Some recorded adverse events are not actually described as an AE. However, this occurrence may be justified because the notification form is filled out directly by the notifier.

Table 4. Profile of the TOP 10 Profile of the most reported medicines and vaccines reported for G1 (December 12, 2018, to March 19, 2020) and G2 (March 20, 2020, to April 12, 2022)

Number of notifications	
Grupo 1 (n = 4503)	Grupo 2 (n =70376)
n (%)	n (%)
Dipyrone (130- 2.88%)	ioNTech vaccine, Pfizer (2888- 4.10%)
Morphine (114- 2.53%)	COVID-19 vaccine AstraZeneca (2685- 3.41%)
Vancomycin (111- 2.546%)	Infliximab (1353- 1.92%)
Oxaliplatin (77- 1.70%)	Secukinumab (1316- 1.879%)
Paclitaxel (72- 1.659%)	CoronaVac (1303- 1.85%)
Warfarin (70- 1.55%)	Losartan potassium (1254- 1.788%)
Carboplatin (70- 1.55%)	Metformin (814- 1.15%)
Ondansetron (66- 1.465%)	Cetuximab (808- 1.14%)
Omeprazole (65- 1.44%)	Levothyroxine (717- 1.01%)
Tramadol (62- 1.437%)	Prednisone (657-1.00.93%)

Figure 1: Number of adverse drug event reports per year in VigiMed, before and after data processing 2018-2022.



Interventions and outcome of notifications

In the VigiMed system, the severity classification includes the option 'resulted in death' to characterize the impact of the adverse event (Table 1). Notably, although the outcome field (Table 2) also contains the designation 'resulted in death' for the final outcomes of adverse events, this was not consistently reported in both the severity and outcome fields.

After the AE were identified, several actions were taken, with both groups reporting "withdrawal of medication" as the most prevalent action. It is important to note that there was a considerable increase in the number of notifications in which the intervention was "unknown", accounting for 3.69% in G1 and 18.93% in G2 (Table 1).

Although 99% of notifications were identified as serious, in both groups, only 1.44% of those in G1 and 9.56% of those in G2 had a "death" as the outcome. In both groups, the outcome "Recovered/ Resolved" was the most frequently reported (71.24%- G1; 37.76%- G2).

Discussion

The high number of incomplete notifications evidenced in this study can be explained by the fact that filling in the form on VigiMed is the sole responsibility of the notifiers and ANVISA has no control over the completeness of filling in all the fields. Although some data is mandatory, there is a lack of standardization of responses.

As regards the increase in notifications made during the pandemic period, this it may be related to the change in the notifier profile, the increase in the use of medicines during this period, the discovery of new drugs and vaccines and the increase in the development and dissemination of knowledge about pharmacovigilance during the beginning of the pandemic period.[13-16]

Notification of increased number of "study reports" during the pandemic period can be explained by the emergency use of vaccines against COVID-19. Owing to the severity of the disease and associated high rate of mortality, there was a need to release vaccines in Phase III studies, and new AE to medicines and vaccines associated with their use were reported subsequently.[13,14] Furthermore, pharmaceutical companies are required by law to collect and monitor all AE.[15,16]

Regarding pharmacists who have made most notifications on G1, this result can be explained by the fact that pharmacists are the ones to majorly work with medicines and are responsible for pharmacovigilance activities in hospitals. Another crucial point is their recurrent participation in clinical trials in pharmaceutical institutions.[17] Conversely, in G2, the predominance of notifications by other health professionals and consumers may be attributed to the high level of self-medication in Brazil by the public apprehension. The search for solutions to combat COVID-19 has led to widespread speculation based on the off-label use of medicines, without robust scientific evidence proof of clinical effectiveness and safety, which has contributed to the development of adverse reactions.[11] This finding is supported by the literature, as healthcare professionals were identified as the primary reporters in other countries: the Netherlands (2015: 40%), Portugal (2015: 65%), and Germany (2015: 87.71%). [18]

Moreover, the predominance of the notifications associated with COVID-19 vaccines has increased. Were made by consumers may be associated with the widespread dissemination of negative information about vaccine usage due to which part of the population was afraid of its use and may have been proactive in reporting the AE.[11,22] Globally—including the US and Europe—post-pandemic efforts emphasized reporting suspected vaccine-related AEs via electronic systems. EudraVigilance data showed 77.6%-82.7% of early vaccination cases involved AEs, demonstrating consumer reporting's critical role in ensuring vaccination safety worldwide. [19-21]

A factor potentially contributing to the higher frequency of notifications by consumers could be the implementation of the "citizen and health professionals" module in VigiMed, which allows notifications to be made directly, without requiring prior registration on the ANVISA website, in a simplified way, in contrast, the previous system (Notivisa) restricted access exclusively to registered users.[8] Furthermore, the prevalence of AE reports in female in both groups may be attributed to increased health awareness, leading to increased medication use and more frequent engagement with health systems.

In addition, up until the day the database was extracted, according to the Vacinometro website, 736,627 doses of COVID-19 vaccines had been administered to the general population and suspected cases of AE related to medicines and vaccines were recorded in only 1% (n=7,423) of these individuals.

Due to the impact of the pandemic "COVID-19" related to AE related to medicines and vaccines was the most cited notification when it came to AE registered as a suspected fatal case. In view of the above, it is worth mentioning that "COVID-19" should not be reported as an AE or reaction, but rather the development or worsening of the disease or its symptoms because of the use of medicines or vaccines. The high rate of this notification likely reflects the notifiers' difficulty in understanding the definition of AE and the incorrect filling in of the mandatory fields according to what is requested, due to a lack of knowledge in using the platform.[11]

Changes in the reporting profile of medicines and vaccines from G1 to G2 coincided with the introduction of therapeutic strategies prioritized for the prevention and treatment of COVID-19, its risk factors and consequences. This observation demonstrates that the pandemic has, in fact, affected the profile of reports of suspected AE. Brazil has also seen the incitement of discourse from the "anti-vaccine movement", which has sparked questions about vaccine safety and efficacy.[23] Anti-vaccination campaigns have gained traction in the media and following the announcement of the development of the COVID-19 vaccine, there had been a 383% increase in the sharing of dubious news on the subject. The anti-vaccination movement is among the top ten global health risks, also causing the re-emergence of preventable diseases that have already been eradicated, such as polio.[28,29]

Thus, although they are among the main products to be notified, the results suggest that COVID-19 vaccines are safe and effective, a fact corroborated by the decrease in cases and severity of the disease.[17,22,30]

JHPHS
Journal of Hospital Pharmacy and Health Services

Some recorded adverse events are safe and are not actually described as an AE related to medicines and vaccines. However, this occurrence may be justified due to the fact that the notification form is filled out directly by the notifier and that it is necessary for the person to have knowledge about pharmacovigilance and how to report, to reduce subjectivity.

The high prevalence of notifications in which the intervention was "unknown" and increase in the absence of action taken in the event of a suspected AE may reflect the predominance of consumer-reported cases in G2. This contrasts with standard clinical practice, where healthcare professionals are expected to implement appropriate measures to mitigate or prevent AE progression when identified.

Regardless of the classification of the outcome of the notifications (Death; Recovered/Resolved), Marques *et al*. and Dubrall *et al*. indicated respectively a prevalence of 55.6% and 66.9% prevalence of severe AEs related to medicines and vaccines over non-severe AEs related to medicines and vaccines, with death cases being 10.9% and 5.5%, respectively. However, when evaluating on a global scale, only 1.34% of cases resulted in death.[23]

Despite all the evidence presented, the study's information is based on suspicions of AE. In this sense, the study has some limitations: the study did not estimate the underreporting rate; the lack of completeness in mandatory information on AE; absence of comparison of the direct relationship between drugs/vaccines and their respective AE. Since this is a database extraction, it is difficult to determine whether a drug or vaccine was being used at the time, or whether it was often used concomitantly with other products.

As strengths, the reporting of AE related to medicines and vaccines is relevant to patient safety, as their comparison makes it possible to generate indicators that lead to the early identification of possible problems resulting from the use of medicines. Furthermore, in view of the harmful nature of AE related to medicines and vaccines, comparison of the national database is a pharmacovigilance tool that makes it possible to assess the safety profile and helps to identify factors that are associated with the cause of a particular AEs related to medicines and vaccines.

Conclusion

From this comparative study, it was possible to observe that the COVID-19 pandemic has affected the profile of notifications of AE related to medicines and vaccines, with changes in the number, type of notifier and profile of the products targeted by the notifications. Such information on notifications can help in future multifactorial correlations on AEs, which will contribute to actions for the safe use of medicines and vaccines in clinical practice and in health care processes. Moreover, future studies should be systematically conducted to evaluate potential temporal variations in adverse event reporting patterns during the post-pandemic period, which may provide critical insights for pharmacovigilance systems.

Funding Sources

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Contributors

Project conception (R.L.R, E.R.A.P, V.A.C, D.T.S). Data extraction, interpretation, and manuscript drafting (R.L.R, E.R.A.P). Final critical review of the manuscript (V.A.C, D.T.S). All authors approved the final version of the manuscript and are responsible for all the information contained within.

Acknowledgements

The authors would like to acknowledge the Postgraduate Program in Biosciences at the Federal University of Vale do São Francisco and the Geriatrics and Gerontology Study Group (GREGG) for support during the research.

Conflicts of Interest Declaration

The authors have no relevant financial or non-financial interests to disclose.

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