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Adverse drug events among older adults in Brazil before and after the onset of the COVID-19 pandemic

Eventos adversos a medicamentos entre idosos no Brasil antes e após o início da pandemia da COVID-19

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ABSTRACT

Introduction: Harm resulting from adverse drug events (ADE) is among the most frequent in the world. Therefore, its monitoring is essential, especially among older adults, who are at greater risk of suffering such type of harm. Additionally, the COVID-19 pandemic, its high incidence among older adults and frequent use of off-label medications have reinforced the importance of monitoring ADE in this population. **Objective:** To describe the suspected ADE among older adults in Brazil before and after the beginning of the COVID-19 pandemic. **Method:** A description of suspected ADEs reported in the VigiMed system of the National Health Surveillance Agency was carried out, involving older adults (age ≥ 65 years) in the pre- (01/2019 to 03/2020) and post-onset of the pandemic period (04/2020 to 06/2021). The difference between the proportion of severe ADE between the periods was evaluated using Pearson's chi-square test. **Results:** 57,167 suspected ADE were reported in the global period evaluated; 22.2% involved older adults. In the pre-pandemic period, 2,924 suspected ADEs were reported (44.2% were severe ADEs), especially those involving antineoplastic, antimicrobial, and anticoagulant drugs. In the post-pandemic period, 9,771 suspected ADEs were reported (57.5% severe), especially related to hydroxychloroquine and vaccines against COVID-19. The difference in the proportion of severe suspected ADE reported for the older adults between the periods evaluated was statistically significant ($p < 0.001$). **Conclusions:** ADE notifications and studies that evaluate ADE among older adults are essential to generate information that can support drug therapy optimization and prioritization of harm reduction among them, especially in the pandemic context that considerably affects this population.

KEYWORDS: Aged; Drug-Related Side Effects and Adverse Reactions; Adverse Drug Reaction Reporting Systems; COVID-19

RESUMO

Introdução: Danos decorrentes de eventos adversos relacionados a medicamentos (EAM) estão entre os mais frequentes no mundo. Logo, seu monitoramento é essencial, especialmente entre os idosos que apresentam maior risco de sofrer tais danos. Adicionalmente, a pandemia da COVID-19, a sua elevada incidência entre idosos e o uso frequente de medicamentos *off-label* reforçaram a importância do monitoramento de EAM nessa população. **Objetivo:** Descrever as suspeitas de EAM entre idosos no Brasil antes e após o início da pandemia por COVID-19. **Método:** Foi realizada a descrição das suspeitas de EAM notificadas no sistema VigiMed da Agência Nacional de Vigilância Sanitária envolvendo idosos (idade ≥ 65 anos) no período pré-pandemia (01/2019 a 03/2020) e pós-início da pandemia (04/2020 a 06/2021). A diferença entre a proporção de EAM graves entre os períodos foi avaliada mediante teste qui-quadrado de Pearson. **Resultados:** Foram notificadas 57.167 suspeitas de EAM no período global avaliado; 22,2% envolviam idosos. No período pré-pandemia, 2.924 suspeitas de EAM foram notificadas (44,2% eram EAM graves), destacando-se aquelas envolvendo antineoplásicos, antimicrobianos e anticoagulantes. No período pós-início da pandemia, 9.771 suspeitas de

EAM foram notificadas (57,5% graves), destacando-se a hidroxicloroquina e as vacinas contra a COVID-19. A diferença na proporção de suspeitas de EAM graves notificadas para idosos entre os períodos avaliados foi estatisticamente significativa (p < 0,001). **Conclusões:** Notificações de EAM e estudos que avaliem EAM entre idosos são essenciais para gerar informações que possam subsidiar a otimização da farmacoterapia e a priorização de redução de danos entre eles, sobretudo no contexto pandêmico que afeta consideravelmente essa população.

PALAVRAS-CHAVE: Idoso; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Sistemas de Notificação de Reações Adversas a Medicamentos; COVID-19

INTRODUCTION

Drug-related harm is among the most frequent in the world, both in terms of the product itself and the process of its use[1,2]. Thus, the identification of adverse drug events (ADE) is essential for the adoption of preventive and corrective measures that can avoid damages related to the use of drugs, thus improving the quality of care provided to the patient[3,4].

It is important to define that ADE comprises any damage or injury, resulting from medication, caused by the use or lack of it when necessary. All medication errors that lead to harm are classified as ADE, in addition to all adverse drug reactions (ADRs)[5]. ADEs are a public health problem because they are related to transient or permanent damage to the patient, increased morbidity and mortality, prolonged hospital stays, and increased care costs[6].

In view of the potential harm resulting from their use, continuous monitoring of the safety of drugs throughout their entire life cycle, including the pre- and post-marketing period, is essential[7,3]. In this context, pharmacovigilance activities related to the identification, evaluation, monitoring and reporting of ADEs are essential to ensure that the benefits related to pharmaceutical products outweigh their risks, as verified in the pre-registration period[8,3,9].

In Brazil, as of December 2018, the Brazilian National Health Surveillance Agency (Anvisa) adopted VigiMed as the national system for ADE notifications, replacing Notivisa, which is currently used in the country for monitoring other products subject to health surveillance[10]. VigiMed is a system for reporting adverse events involving drugs or vaccines, carried out voluntarily by citizens, professionals, and health services. It is the adapted version for Brazil of the VigiFlow system, offered by the World Health Organization (WHO) to the national pharmacovigilance centers of the member countries of the Programme for International Drug Monitoring (PIDM). At the initiative of the Pharmacovigilance Management (GFARM), Anvisa signed an agreement with the Uppsala Monitoring Center (UMC), located in Sweden, which receives data sent by Brazil and several countries to compose the global database called VigiBase, allowing the monitoring of medicines worldwide[11]. The information contained in the notifications is made available on Anvisa's Pharmacovigilance Notifications Panel, which presents open data on suspected adverse events, that is, without causality assessment.

In parallel, it is important to highlight that national data indicate a greater number of notifications of incidents related to health care among individuals aged 65 or over[12]. Among other factors, this may be related to the fact that older adults undergo physiological changes associated with aging that alter the pharmacokinetic and pharmacodynamic responses of drugs. These, associated with the high burden of comorbidities, polypharmacy, and inadequate prescription, increase the risk of harm caused by medications among older adults[13]. In March 2020, after the definition of a pandemic context by COVID-19 in Brazil, such pharmacotherapeutic issues and issues related to comorbidities became even more relevant for the monitoring of adverse events in geriatrics[14].

Despite this, there are few clinical studies that specifically address the effects of drugs in the geriatric population, as well as descriptive studies on the occurrence of ADE in these individuals[15]. Given this scenario, it is imperative to develop studies that provide information about the safety of drug use for the geriatric population, including the pandemic context. Thus, the present study aimed to describe the suspicions of ADE related to older adults notified to Anvisa before and after the beginning of the COVID-19 pandemic in Brazil.

METHOD

This is a descriptive study of suspected ADE reported in the VigiMed system between January 1, 2019, and June 30, 2021, for older adults[16]. Data from the first month of system implementation (December 2018) were excluded, considering the adaptation of the notifiers and possible system instabilities.

In the analysis of the present study, all suspected ADEs presented in Anvisa's Pharmacovigilance Notifications Panel of Vigimed were included, referring to medicines and vaccines, involving older adults, that is, individuals aged 65 years or older, according to the fixed age limit proposed in the filters of the system itself. Data collection was carried out in November 2021.

The total number of reported ADE suspicions involving older adults was described according to categories proposed by VigiMed itself, namely: the gender of the patient (female, male, or uninformed/unknown), the type of notifier (pharmacist, physician, other healthcare professional, consumer, or other non-health professional), and the severity of the ADE (severe or not).

Suspected ADEs were also described according to the reporting period according to the pandemic context: before the pandemic – January 2019 to March 2020 – and after the beginning of the pandemic – April 2020 to June 2021. The difference between the proportion of severe ADE in the pre-pandemic and post-pandemic period was evaluated using Pearson's chi-square test, and a statistically significant difference was considered when the p-value was less than 0.05.

A description of the suspected active ingredients most frequently involved in severe and non-serious ADE was also carried out, up to a cumulative frequency of about 20% of the total ADE. For this description, the ADE data according to the active principles were compiled by quarter of the analyzed period. To describe the suspected active ingredients, classifications were also adopted according to: 1) the list of high-alert medications (HAM) of the Institute For Safe Medication Practices (ISMP) Brazil[17]; and 2) the list of potentially inappropriate medication (PIM) for older adults regardless of the presence of diseases according to the American Geriatric Society Beers criteria in its 2019 version[18].

All data collection was performed manually and in duplicate, due to the impossibility of transferring data from Anvisa's Pharmacovigilance Notifications Panel to the intermediate spreadsheet format automatically. Data were entered into a Microsoft Excel® spreadsheet. For all variables, descriptive analysis was used, with absolute and relative frequency measures being determined as presented in Anvisa's Pharmacovigilance Notifications Panel.

As the present study is based on the descriptions of collective data at the national level presented in Anvisa's blinded and public database, it was not submitted for approval by the research ethics committee.

RESULTS

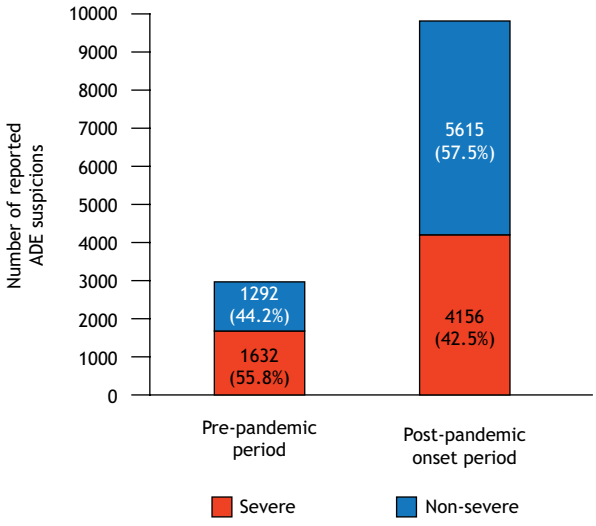
In the period evaluated, a total of 57,167 notifications of suspected ADE were made, of which 12,695 (22.2%) involved older adults and, of these, 6,907 (54.4%) were severe. Among the notifications covering older adults, most involved females (n = 6,986; 55.0%). About half of these notifications were made by pharmacists (n = 6,449; 50.8%); 24.3% (n = 3,080) of them were reported by consumers or other non-health professionals; 5.1% (n = 647) by physicians; and 19.8% (n = 2,520) by another health professional.

In the pre-pandemic period, 2,924 notifications of suspected ADE involving older adults were identified (22.4% of the total notifications in the period), generating an average of 195 notifications per month. In the post-pandemic period, 9,771 ADE notifications for older adults were identified (22.2% of the total notifications for the period), or 651 notifications per month. The proportion of severe ADE was higher in the post-pandemic period (57.5%) than in the pre-pandemic (44.2%) ($p < 0.001$) (Figure).

The Table shows the characterization of the suspected active ingredients involved in ADE and severe ADE reported for older adults. Among the therapeutic classes, antineoplastics, antimicrobials, and anticoagulants were among the most frequently involved in reports of severe and non-severe ADE in the pre-pandemic period. Paclitaxel was present as the suspected active ingredient most frequently involved in non-severe ADE in all quarters evaluated before the pandemic, and carboplatin, piperacillin with tazobactam, and oxaliplatin were present in four of the five quarters evaluated before the pandemic. When evaluating suspected severe ADE reported in the pre-pandemic period, it was possible to observe that the active ingredients most frequently involved in the events were: piperacillin with tazobactam, and carboplatin (present in four of the five trimesters evaluated); paclitaxel, warfarin, and oxaliplatin (present in three of the five trimesters evaluated).

In the post-pandemic period, antineoplastics, antimicrobials, and anticoagulants continued to be among the therapeutic classes most involved in suspected serious and non-severe ADE in older adults. Additionally, it was observed that hydroxychloroquine was the suspected active ingredient most frequently involved in ADE (n = 115; 11.7%) and severe ADE (n = 50; 12.7%) in the second quarter of 2020, a period that comprises the first three months of the pandemic. It is also important to highlight that, in the last two quarters evaluated (first and second quarters of 2021), the active ingredients most frequently involved in severe and non-severe ADE were CoronaVac and AstraZeneca vaccines.

Furthermore, most of the suspected active ingredients most frequently involved in both severe and non-serious ADE were



Source: Elaborated by the authors, 2021.

Figure. Notifications of suspected adverse drug-related events for older adults made on VigiMed and their severity according to the pre-pandemic period (January/2019 to March/2020) and post-pandemic onset (April/2020 to June/2021). Brazilian National Health Surveillance Agency (Anvisa).

Table. Active ingredients most frequently involved in suspected drug-related adverse events (ADE) and reported serious ADE (cumulative frequency of about 20% of total ADE) involving older adults per quarter. Brazil, 2019-2021.

Frequency of suspected active ingredients involved in ADE n (%)										
Period	**Before the pandemic**						**After pandemic onset**			
Quarter	**1/2019**	**2/2019**	**3/2019**	**4/2019**	**1/2020**	**2/2020**	**3/2020**	**4/2020**	**1/2021**	**2/2021**
Most frequent active ingredients	• Paclitaxel* 12 (6.7) • Carboplatin* 7 (3.9) • Not encoded 6 (3.4) • Piperacillin + Tazobactam 6 (3.4) • Vancomycin 5 (2.8)	• Warfarin* 20 (6.9) • Fluorouracil* 11 (3.7) • Morphine* 10 (3.5) • Oxaliplatin* 10 (3.5) • Paclitaxel* 10 (3.5) • Piperacillin + Tazobactam 10 (3.5)	• Piperacillin + Tazobactam 32 (5.0) • Oxaliplatin* 22 (3.4) • Carboplatin* 21 (3.3) • Paclitaxel* 21 (3.3) • Warfarin* 18 (2.7) • Docetaxel* 16 (2.5) • Pembrolizumab* 16 (2.5)	• Piperacillin + Tazobactam 48 (5.9) • Paclitaxel* 35 (4.3) • Carboplatin* 24 (2.9) • Oxaliplatin* 24 (2.9) • Docetaxel* 22 (2.7) • Ceftriaxone 21 (2.6)	• Oxaliplatin* 54 (5.4) • Paclitaxel* 37 (3.7) • Docetaxel* 31 (3.1) • Metamizole 29 (2.9) • Rituximab* 28 (2.8) • Carboplatin* 27 (2.7)	• Hydroxychloroquine 115 (11.7) • Paclitaxel* 57 (5.8) • Carboplatin* 38 (3.9)	• Oxaliplatin* 63 (5.7) • Paclitaxel* 50 (4.5) • Enoxaparin* 38 (3.4) • Carboplatin* 33 (3.0) • Piperacillin + Tazobactam 32 (2.9) • Warfarin* 31 (2.8)	• Piperacillin + Tazobactam 57 (3.7) • Warfarin* 51 (3.3) • Cetuximab* 48 (3.0) • Paclitaxel* 46 (2.9) • Enoxaparin* 42 (2.7) • Oxaliplatin* 39 (2.5) • Rituximab* 36 (2.3)	• CoronaVac vaccine 144 (5.1) • AstraZeneca vaccine 126 (4.5) • Cetuximab* 87 (3.1) • Secukinumab 65 (2.3) • Dutasteride + Tamsulosin 54 (1.9) • Oxaliplatin* 53 (1.9) • Paclitaxel* 50 (1.8)	• AstraZeneca vaccine 359 (10.8) • CoronaVac vaccine 358 (10.8)
Others	143 (79.8)	218 (75.4)	498 (77.3)	643 (78.7)	789 (79.4)	773 (78.6)	859 (77.7)	1.244 (79.6)	2.230 (79.4)	2.603 (78.4)
Total	179 (100.0)	289 (100.0)	644 (100.0)	817 (100.0)	995 (100.0)	983 (100.0)	1,106 (100.0)	1,563 (100.0)	2,809 (100.0)	3,320 (100.0)
Frequency of suspected active ingredients involved in severe ADE n (%)										
Period	**Before the pandemic**						**After pandemic onset**			
Quarter	**1/2019**	**2/2019**	**3/2019**	**4/2019**	**1/2020**	**2/2020**	**3/2020**	**4/2020**	**1/2021**	**2/2021**
Most frequent active ingredients	• Paclitaxel* 7 (5.1) • Carboplatin* 5 (3.7) • Not encoded 5 (3.7) • Piperacillin + Tazobactam 5 (3.7) • Vancomycin 5 (3.7) • Rituximab* 4 (2.9)	• Warfarin* 16 (8.5) • Piperacillin + Tazobactam 10 (5.3) • Carboplatin* 9 (4.8) • Oxaliplatin* 8 (4.3)	• Piperacillin + Tazobactam 17 (5.8) • Oxaliplatin* 11 (3.7) • Warfarin* 11 (3.7) • Metamizole 8 (2.7) • Amiodarone** 7 (2.4)	• Piperacilin + Tazobactam 19 (5.6) • Carboplatin* 15 (4.4) • Paclitaxel* 14 (4.1) • Docetaxel* 12 (3.5) • Warfarin* 12 (3.5)	• Oxaliplatin* 22 (6.6) • Carboplatin* 17 (5.1) • Cyclophosphamide* 13 (3.9) • Docetaxel* 13 (3.9) • Paclitaxel* 12 (3.6)	• Hydroxychloroquine 50 (12.7) • Carboplatin* 24 (6.1) • Paclitaxel* 23 (5.9)	• Oxaliplatin* 30 (7.0) • Enoxaparin* 19 (4.4) • Warfarin* 18 (4.2) • Paclitaxel* 17 (3.9)	• Cetuximab* 45 (7.1) • Enoxaparin* 24 (3.8) • Warfarin* 24 (3.8) • Rituximab* 21 (3.3) • Fluorouracil* 18 (2.8) • Oxaliplatin* 18 (2.8)	• CoronaVac vaccine 124 (6.5) • AstraZeneca vaccine 94 (4.9) • Cetuximab* 84 (4.4) • Secukinumab 64 (3.4) • Dutasteride + Tamsulosin 53 (2.8)	• CoronaVac vaccine 292 (12.9) • AstraZeneca vaccine 223 (9.9)
Others	105 (77.2)	145 (77.1)	241 (81.7)	269 (78.9)	255 (76.9)	296 (75.3)	346 (80.5)	485 (76.4)	1,485 (78.0)	1,748 (77.2)
Total	136 (100.0)	188 (100.0)	295 (100.0)	341 (100.0)	332 (100.0)	393 (100.0)	430 (100.0)	635 (100.0)	1,904 (100.0)	2,263 (100.0)

Source: Elaborated by the authors, 2021.
Not encoded: drug or vaccine not identified in the notification; CoronaVac vaccine: COVID-19 *vaccineinact* (Vero) CZ02; AstraZeneca vaccine: COVID-19 *vaccine* NRVV Ad (ChAdOx1 nCoV-19); *HAM: high-alert medications; **PIM: potentially inappropriate medication for older adults; ADE: adverse drug event.

antineoplastic and anticoagulant drugs, which are classified as HAM. On the other hand, among the PIM for older adults, only amiodarone (n = 7; 2.4%) was involved in severe ADE in the third quarter of 2019.

DISCUSSION

Of the notifications of suspected ADE, a considerable percentage involved older adults, regardless of the period evaluated. This data is in line with the findings of Mota et al.[19], who indicated that 19.6% of ADE reports analyzed in the old Brazilian pharmacovigilance system (Notivisa) involved people aged 65 years or older. Suspicions of ADE involving older adults may be associated with physiological changes that can alter the pharmacokinetic and pharmacodynamic parameters of the drugs, in addition to the presence of comorbidities that require the use of several drugs[13].

Regarding the majority of reports for older female patients, this factor was also reported as the most important predictor of patient-related ADE in different studies[20,21,22,23]. Among the issues that contribute to the increase in this risk among women are: greater demand for health services, greater use of medications, and pharmacokinetic and pharmacodynamic differences (e.g. differences in body weight, hormonal factors, reduced hepatic clearance)[21].

As for the significant participation of pharmacists in ADE notifications, this finding is consistent with the study by Melo et al.[24], which showed that pharmacists were the main notifiers in Brazil, according to the assessment of notifications made in Notivisa, from 2009 to 2018. This data is due to the greater knowledge of this professional about pharmacovigilance issues, as well as the fact that ADE notifications in the hospital environment are generally under the responsibility of pharmacists[25]. On the other hand, only a quarter of the notifications were registered by other health professionals. This demonstrates the need to expand training in pharmacovigilance and encourage notifications to all other health professionals, aiming at interdisciplinary work in promoting patient safety.

It was also found that the number of notifications involving older adults in the post-pandemic period more than tripled when compared to those recorded in the pre-pandemic period, which can be explained by the greater interest of the population in health issues since the declaration of emergency for public health by COVID-19. Despite this increase, underreporting in Brazil is still a limitation, which compromises the identification of safety signs and the implementation of measures for the safe use of medicines[19,26]. According to the literature, the main causes of underreporting are: misinformation about the notification process (ignorance), insecurity in notifying suspected cases of ADE (insecurity), indifference or lack of interest (indifference), the belief that only safe drugs are released for commercialization (complacency), and the lack of training in pharmacovigilance[26]. In addition, the participation of drug consumers and other professionals who do not work in the health area in the notification of ADE is still historically low, despite having increased in the context of the pandemic: in the pre-pandemic period, these social actors contributed with only 2.8% of the notifications and in the post-pandemic period, with 29.8% (results not previously presented). These data are relevant and demonstrate greater empowerment of the population about their health and the occurrence of ADE in the pandemic context. On the other hand, the need for a careful analysis of national ADE databases is reinforced, which now has a considerable proportion of notifications made by laypeople.

Most suspicions of ADE involving older adults were classified as severe, which can be explained by the increased risk that these individuals have of suffering harm as a result of the use of drugs and other pharmaceutical products[27]. However, it is important to highlight that a statistically significant increase was observed in the proportion of ADE classified as severe in the post-pandemic period, when compared to the pre-pandemic period. This raises special concern in view of the high morbidity and mortality, already expected by COVID-19 in this population, which can be aggravated by the occurrence of an ADE[28]. On the other hand, a study that evaluated the factors associated with the occurrence of severe ADR among patients with COVID-19 identified that older patients with COVID-19 were more likely to have severe ADR[29]. Finally, it is important to highlight that Brazilian legislation defines the notification of suspected serious ADE as mandatory, with defined deadlines for the pharmaceutical industry and health services, which can interfere in the proportion of serious events in relation to others reported in VigiMed[30,31,32].

In the pre-pandemic period, data showed that three pharmacological classes were predominant in reports of severe and non-severe ADE (antineoplastic, antimicrobial, and anticoagulant). Similar results were found in the study by Mota et al.[19] and Silva et al.[33]. These drug classes are part of the acronym "A PINCH", proposed by the WHO, which refers to drugs frequently involved in serious medication errors in the world[34] and includes, in addition to antimicrobials, antineoplastics, and anticoagulants, the following groups of HAM: potassium chloride, insulin, and narcotics. Such drugs are a priority target of the third Global Patient Safety Challenge with the theme "Medications without harm", which aims to reduce serious and preventable drug-related harm by 50% by 2022[17,34].

The use of HAM is often related to the occurrence of ADE, especially in the hospital environment, according to a study by Bohomol[35]. This profile of drugs involved in ADE results from the majority participation of hospitals, especially those that make up the sentinel network, in ADE notifications[35]. Thus, the present study corroborated the findings in the literature, evidencing the participation of this group of drugs in severe and non-severe ADE among older adults, especially with the involvement of anticancer drugs.

Regarding the ADE reported in the post-pandemic period, the three pharmacological classes (antineoplastic, antimicrobial, anticoagulant) remained among the main suspects of involvement in ADE. However, with the COVID-19 pandemic, several

multicenter studies were carried out to evaluate potential treatments for the infection. Among these, the Solidarity study, coordinated by the WHO, which proposed the evaluation of the efficacy in adult patients hospitalized with COVID-19 of one of the four proposed treatments with potential effects in *in vitro* studies (rendesivir, lopinavir+ritonavir, interferon β_{1A}, chloroquine/hydroxychloroquine)[36]. International studies ended up not demonstrating the effectiveness of these treatments, but despite this, the population was exposed to the prescription and use of drugs without evidence of established efficacy, such as hydroxychloroquine/chloroquine[37,38].

In this context, in the second quarter of 2020, hydroxychloroquine appeared with an important percentage of severe and non-severe ADE. Another Brazilian study also identified an increase in the number of adverse events involving hydroxychloroquine (59.5%) in hospitalized patients with COVID-19, according to Anvisa's notification data between March and August 2020. In addition, chloroquine and hydroxychloroquine were also the only drugs associated with the occurrence of a severe adverse event in this study[29]. These findings underscore that the off-label use of drugs for COVID-19 involves considerable risks, especially among older adults. The stimulation of the use of drugs, without proven efficacy, in a population with frequent practice of self-medication may have contributed to the increase in ADE involving these drugs[24].

In the third and fourth quarters of 2020, enoxaparin appears as a suspect drug in both severe and non-serious ADE reports, possibly because of the implementation of anticoagulation and prophylaxis in patients with COVID-19, due to the hypercoagulable state and hematological changes caused by the disease[39].

In 2021, with the start of vaccination against COVID-19 in Brazil, which prioritized older adults, the CoronaVac and AstraZeneca vaccines, the first vaccines approved in the country, prevailed among suspected ADEs, especially in the second trimester. The CoronaVac vaccine was more involved in suspected severe ADE in both periods. With the pandemic, there was an increase in the attention of the world population to the occurrence of adverse events involving vaccines, including the attention from professionals and non-health professionals, causing the number of ADE reported for these products to increase regardless of their plausible causality[40].

In the second quarter of 2021, the most frequent drugs in the other notifications, after vaccines, were anticancer drugs, dutasteride+tamsulosin, warfarin, and teriparatide; and among the reports of suspected severe ADE were antineoplastic drugs, dutasteride + tamsulosin, teriparatide, and tumor necrosis factor (TNF) inhibitors (result not described in the Table). No studies were found that described ADE involving vaccines against COVID-19 specifically among older adults, but the analysis of the WHO database indicates that this age group was more frequently related to severe ADE, especially over 75 years[41].

Regarding PIM for older adults, in this study only amiodarone was involved in suspected ADEs in the pre-pandemic period, and all the events reported for this were serious. PIM are those with the potential to cause risks that outweigh the benefits when used by older patients, and correspond to one of the main drug-related risk factors that predict ADE in this population[42,43,27]. However, it is believed that, due to the historical profile of notifiers in Brazil being composed mostly of professionals linked to sentinel hospitals, notifications involving drugs used in the hospital environment are more frequent, causing the number of notifications of suspected PIM to be reduced[44,24].

The present study has as limitations the analysis of data from aggregated values from the VigiMed database. This prevents the analysis of more detailed description of the profile of the notified ADEs or the evaluation of associated factors.

However, to our knowledge, this is the first study to describe notifications of suspected ADE for Brazilian older adults after the implementation of the notification by VigiMed, as well as the profile of notifications in the post-pandemic context.

CONCLUSIONS

The present study described the main ADE suspicions that were reported in Anvisa's pharmacovigilance system involving older patients before and after the onset of the COVID-19 pandemic, demonstrating a statistically significant increase in the proportion of severe ADE in the post-pandemic context. The products most involved in notifications in the pre-pandemic period were antineoplastics, antimicrobials, and anticoagulants; and, after the beginning of the pandemic, hydroxychloroquine and vaccines against COVID-19 were the most frequent. These results highlight how the off-label use of medicines during the COVID-19 pandemic was relevant and reinforce the importance of ADE notifications to pharmacovigilance systems, aiming at the implementation of practices that promote the rational use of medicines and, above all, reduce the occurrence of severe ADE. In addition, studies that assess ADE in the geriatric population are essential to provide information regarding pharmacotherapy, risks and prioritization of harm reduction among older patients, considering the incipience of clinical studies that encompass this population.

REFERENCES

1. World Health Organization – WHO. Patient Safety. Geneva: World Health Organization; 2019[acesso 18 abr 2021]. Disponível em: https://www.who.int/news-room/fact-sheets/detail/patient-safety

2. Chui MA, Pojanoska-Mantyla M, Snyder ME. Improving medication safety in varied health systems. Res Social Adm Pharm. 2019;15(7):811-2. https://doi.org/10.1016/j.sapharm.2019.04.012

3. Agência Nacional de Vigilância Sanitária – Anvisa. Alertas de farmacovigilância a partir da detecção de sinais. Boletim de Farmacovigilância n. 13. set 2020[acesso 14 abr 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/fiscalizacao-e-monitoramento/farmacovigilancia/boletins-de-farmacovigilancia/boletim-de-farmacovigilancia-no-13.pdf/view
4. Oliveira JR, Xavier RMF, Júnior AFS. Eventos adversos notificados ao Sistema Nacional de Notificações para a Vigilância Sanitária (Notivisa): Brasil, estudo descritivo no período 2006 a 2011. Epidemiol Serv Saúde. 2013;22(4):671-8. https://doi.org/10.5123/S1679-49742013000400013
5. ASHP Reports. Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events, and adverse drug reactions. Am J Health Syst Pharm. 1998;55(2):165-6. https://doi.org/10.1093/ajhp/55.2.165.
6. Souza TT, Godoy RR, Rotta I, Pontarolo R, Fernandez-Llimos F, Correr CJ. Morbidade e mortalidade relacionadas a medicamentos no Brasil: revisão sistemática de estudos observacionais. Rev Cienc Farm Básica Apl. 2014;35(4):519-32.
7. US Food and Drug Administration – FDA. Drugs safety priorities 2015-2016. Silver Spring: US Food and Drug Administration; 2015[acesso 10 maio 2021]. Disponível em: https://www.fda.gov/files/drugs/published/CDER-Drug-Safety-Priorities-2015-2016.pdf
8. Pan American Health Organization – PAHO. Boas práticas de farmacovigilância para as Américas. Washington: Pan American Health Organization; 2011[acesso 12 abr 2021]. Disponível em: https://www.paho.org/hq/dmdocuments/2011/Red-PARF-5-Port.pdf
9. Agência Nacional de Vigilância Sanitária – Anvisa. Farmacovigilância. Brasília: Agência Nacional de Vigilância Sanitária; 2021[acesso 14 abr 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/fiscalizacao-e-monitoramento/farmacovigilancia
10. Agência Nacional de Vigilância Sanitária – Anvisa. Eventos adversos: Anvisa lançará VigiMed em dezembro. Medicamentos Inovação. 26 nov 2018[acesso 14 abr 2021]. Disponível em: http://antigo.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=5136066&_101_type=content&_101_groupId=219201&_101_urlTitle=eventos-adversos-anvisa-lancara-vigimed-em-dezembro&inheritRedirect=true.
11. Agência Nacional de Vigilância Sanitária – Anvisa. Boletim de atendimento n. 5. Brasília: Agência Nacional de Vigilância Sanitária; 2018[acesso 13 abr 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/educacao-e-pesquisa/publicacoes-sobre-educacao-e-pesquisa/boletim-de-atendimento-anvisa-ndeg-05-de-2018.pdf/view
12. Agência Nacional de Vigilância Sanitária – Anvisa. Boletim segurança do paciente e qualidade em serviços de saúde n. 20: incidentes relacionados à assistência à saúde - 2018. Brasília: Agência Nacional de Vigilância Sanitária; 2018[acesso 10 maio 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/servicosdesaude/boletim-seguranca-do-paciente/boletim-seguranca-do-paciente-e-qualidade-em-servicos-de-saude-n-20-incidentes-relacionados-a-assistencia-a-saude-2018.pdf/view
13. Lavan PH, Gallangher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7(1):11-22. https://doi.org/10.1177/ 2042098615615472
14. World Health Organization – WHO. WHO announces COVID-19 outbreack a pandemic. Geneva: World Health Organization; 2020[acesso 25 out 2021]. Disponível em: http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic
15. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. Am Fam Physician. 2013;87(5):331-6.
16. Agência Nacional de Vigilância Sanitária – Anvisa. Notificações de farmacovigilância. Brasília: Agência Nacional de Vigilância Sanitária; 2021[acesso 5 abr 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas/notificacoes-de-farmacovigilancia.
17. Instituto para Práticas Seguras no Uso de Medicamentos – ISMP. Medicamentos potencialmente perigosos de uso hospitalar: lista atualizada 2019. Brasília: Instituto para Práticas Seguras no Uso de Medicamentos; 2019[acesso 10 maio 2021] Disponível em: https://www.ismp-brasil.org/site/wp-content/uploads/2019/02/BOLETIM-ISMP-FEVEREIRO-2019.pdf
18. American Geriatrics Society – AGS. American Geriatrics Society 2019 Updated AGS Beers criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-94. https://doi.org/10.1111/jgs.15767
19. Mota DM, Vigo A, Kuchenbecker RS. Reações adversas a medicamentos no sistema de farmacovigilância do Brasil, 2008 a 2013: estudo descritivo. Cad Saúde Pública. 2019;35(8):1-14. https://doi.org/10.1590/0102-311X00148818
20. Mahony D, Connor MN, Eustace J, Byrne S, Petrovic M, Gallagher P. The adverse drug reaction risk in older persons (ADRROP) prediction scale: derivation and prospective validation of an ADR risk assessment tool in older multi-morbid patients. Eur Geriatr Med. 2018;9(2):191-9. https://doi.org/10.1007/s41999-018-0030-x
21. Mudigubba MK, Murthy MK, Swaroop AM, Nayantara M, Dahiya S. A systematic review of risk factors of adverse drug reactions in hospitalized patients. Asian J Pharm Clin Res. 2018;11(10):25-9. https://doi.org/10.22159/ajpcr.2018.v11i10.27759

22. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;1(9):2079-86. https://doi.org/10.2147/CIA.S71178

23. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol. 2001;2(6):349-51. https://doi.org/10.2165/00128071-200102060-00001

24. Melo JRR, Duarte EC, Arrais PSD. Notificação de eventos adversos de medicamentos no Brasil: perfil dos profissionais que notificam ao sistema de farmacovigilância brasileiro. Cad Saúde Pública. 2021;37(11):1-3. https://doi.org/10.1590/0102-311X00237221

25. Modesto ACF, Ferreira TXAM, Provin MP, Amaral RG, Lima DM. Reações adversas a medicamentos e farmacovigilância: conhecimentos e condutas de profissionais de saúde de um hospital da rede sentinela. Rev Bras Educ Med. 2016;40(3):401-10. https://doi.org/10.1590/1981-52712015v40n3e01502015

26. Agência Nacional de Vigilância Sanitária - Anvisa. Boletim de farmacovigilância n. 7. Brasília: Agência Nacional de Vigilância Sanitária; 2019[acesso 15 nov 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/fiscalizacao-e-monitoramento/farmacovigilancia/boletins-de-farmacovigilancia/boletim-de-farmacovigilancia-no-07.pdf

27. Agência Nacional de Vigilância Sanitária - Anvisa. Boletim de farmacovigilância n. 7. Brasília: Agência Nacional de Vigilância Sanitária; 2019[acesso 15 nov 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/fiscalizacaoe-monitoramento/farmacovigilancia/boletins-defarmacovigilancia/boletim-de-farmacovigilancia-no-07.pdf

28. Instituto para Práticas Seguras no Uso de Medicamentos - ISMP. Medicamentos potencialmente inadequados para idosos. Brasília: Instituto para Práticas Seguras no Uso de Medicamentos; 2017[acesso 15 nov 2021]. Disponível em: https://www.ismp-brasil.org/site/wp-content/uploads/2017/09/is_0006_17a_boletim_agosto_ismp_210x276mm_v2.pdf

29. Centers for Disease Control and Prevention - CDC. COVID-19 risks and vaccine information for older adults. Atlanta: Centers for Disease Control and Prevention; 2021[acesso 5 abr 2021]. Disponível em: https://www.cdc.gov/aging/covid19/covid19-older-adults.html

30. Melo JRR, Duarte EC, Moraes MV, Fleck K, Silva ASN, Arrais PSD. Reações adversas a medicamentos em pacientes com COVID-19 no Brasil: análise das notificações espontâneas do sistema de farmacovigilância brasileiro. Cad Saúde Pública. 2021;37(1):1-17. https://doi.org/10.1590/0102-311X00245820

31. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 36, de 25 de julho de 2013. Institui ações para a segurança do paciente em serviços de saúde e dá outras providências. Diário Oficial União. 26 jul 2013.

32. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 406, de 22 de julho de 2020. Dispõe sobre as boas práticas de farmacovigilância para detentores de registro de medicamento de uso humano, e dá outras providências. Diário Oficial União. 23 jul 2020.

33. Agência Nacional de Vigilância Sanitária - Anvisa. Resolução RDC Nº 475, de 10 de março de 2021. Estabelece os procedimentos e requisitos para submissão de pedido de autorização temporária de uso emergencial (AUE), em caráter experimental, de medicamentos e vacinas para COVID-19 para o enfrentamento da emergência de saúde pública de importância nacional decorrente do surto do novo coronavírus (SARS-CoV-2). Diário Oficial União. 11 mar 2021.

34. Silva AEBC, Reis AMM, Miasso AI, Santos JO, Cassiani SHB. Eventos adversos a medicamentos em um hospital sentinela do estado de Goiás, Brasil. Rev Lat Am Enfermagem. 2011;19(2):1-9. https://doi.org/10.1590/S0104-11692011000200021

35. World Health Organization - WHO. Medication safety in high-risk situations. Geneva: World Health Organization; 2019[acesso 1 fev 2022]. Disponível em: https://apps.who.int/iris/handle/10665/325131

36. Bohomol E. Erros de medicação: estudo descritivo das classes dos medicamentos e medicamentos de alta vigilância. Esc Anna Nery Rev Enferm. 2014;18(2):311-6. https://doi.org/10.5935/1414-8145.20140045

37. World Health Organization - WHO. "Solidarity" clinical trial for COVID-19 treatments. Geneva: World Health Organization; 2020[acesso 2 fev 2022]. Disponível em: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

38. Instituto para Práticas Seguras no Uso de Medicamentos - ISMP. Tratamentos potenciais para COVID-19: promoção do uso seguro durante a pandemia. Brasília: Instituto para Práticas Seguras no Uso de Medicamentos; 2020[acesso 15 nov 2021]. Disponível em: https://www.ismp-brasil.org/site/wp-content/uploads/2020/04/BOLETIM-ISMP-BRASIL_COVID-19.pdf

39. Agência Nacional de Vigilância Sanitária - Anvisa. Boletim de farmacovigilância n. 14. Brasília: Agência Nacional de Vigilância Sanitária; 2021[acesso 15 nov 2021]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/fiscalizacao-e-monitoramento/farmacovigilancia/boletins-de-farmacovigilancia/boletim-de-farmacovigilancia-no-14.pdf

40. Ramos RP, Ota-Arakaki JS. Trombose e anticoagulação na COVID-19. J Bras Pneumol. 2020;46(4):1-2.

41. Haas JW, Bender FL, Ballou S, Kelley JM, Wilhelm M, Miller FG et al. Frequency of adverse events in the placebo arms of COVID-19 vaccine trials a systematic review and meta-analysis. JAMA Netw Open. 2022;5(1):1-15. https://doi.org/10.1001/jamanetworkopen.2021.43955

42. Kaur RJ, Dutta S, Charan J, Bhardwaj P, Tandon A, Yadav D et al. Cardiovascular adverse events reported from COVID-19 vaccines: a study based on who database. Int J Gen Med. 2021;14:3909-27. https://doi.org/10.2147/IJGM.S324349.

43. Yadesa TM, Kitutu FE, Deyno S, Ogwang PE, Tamukong R, Alele PE. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: a systematic review and meta-analysis. SAGE Open Med. 2021;9:1-14. https://doi.org/10.1177/20503121211039099

44. Oliveira MG, Amorim WW, Oliveira CRB, Coqueiro HL, Gusmão LC, Passos LC. Consenso brasileiro de medicamentos potencialmente inapropriados para idosos. Geriatr Gerontol Aging. 2016;10(4):1-14. https://doi.org/10.5327/Z2447-211520161600054

45. Agência Nacional de Vigilância Sanitária – Anvisa. Boletim de farmacovigilância n. 1. Brasília: Agência Nacional de Vigilância Sanitária; 2012[acesso 2 fev 2022]. Disponível em: https://www.gov.br/anvisa/pt-br/centraisdeconteudo/publicacoes/fiscalizacao-e-monitoramento/farmacovigilancia/boletins-de-farmacovigilancia/boletim-de-farmacovigilancia-no-01.pdf

Author's Contributions

Souza BG, Rezende CP, Nascimento MMG – Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Detoni KB, Capucho HC, Rosa MB, Carmo Júnior NM – Writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.