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Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

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Adverse events associated with CoronaVac in a university hospital

Lana Naiadhy SILVA-SANTOS[1], Amanda de Jesus SOUZA[1]; Caio de Alcantara CAMPOS[2], Wagner Barbosa ROCHA-SANTOS[3], Carlos Michel SILVA-SANTOS[4], Jeane da Silva SANTOS-ALMEIDA[5], Milena da Motta XAVIER[6]

[1]Universidade Federal de Sergipe, Programa de Residência Multiprofissional em Epidemiologia Hospitalar, Unidade de Gestão de Riscos Assistenciais, Hospital Universitário de Sergipe (HUSE), Aracaju-Sergipe, Brasil; [2]Universidade Federal de Sergipe, Programa de Residência Multiprofissional em Saúde do Adulto e do Idoso, Unidade de Farmácia Clínica, Hospital Universitário de Sergipe (HUSE), Aracaju-Sergipe, Brasil; [3]Universidade Federal de Sergipe, Departamento de Farmácia/Laboratório de Neurociências e Ensaios Farmacológicos, São Cristóvão-Sergipe, Brasil; [4]Universidade Federal de Sergipe, Programa de Residência Multiprofissional em Saúde da Família, Hospital Universitário de Sergipe (HUSE), Aracaju-Sergipe, Brasil; [5]Universidade Federal de Sergipe, Serviço de Vigilância Epidemiológica, Hospital Universitário de Sergipe (HUSE), Aracaju-Sergipe, Brasil; [6]Universidade Federal de Sergipe,Unidade de Gestão de Riscos Assistenciais, Hospital Universitário de Sergipe (HUSE), Aracaju-Sergipe, Brasil

Corresponding author: Silva-Santos LN, lana_pharma@live.com

Submitted: 18-04-2022 Resubmitted: 09-11-2022 Accepted: 23-11-2022

Double blind peer review

Abstract

Objective: The present study aimed to describe suspected adverse events (AEs) reported in employees of a teaching hospital in the state of Sergipe after vaccination with CoronaVac. **Methods:** This is a cross-sectional study based on reports of post-vaccination adverse event notification forms (APVs) from the Hospital Surveillance application (Vigihosp) of the University Hospital of Sergipe, during the months of January to March 2021. analysis included hospital workers aged ≥ 18 years and who received at least one dose of CoronaVac. **Results:** In total, 406 notifications were identified, of which 251 were selected. The nursing technician was the professional category that was not identified the most (38%), followed by the nurse (20%). Women of mixed race and younger age group (<50 years) were more likely to have AEFIs. The most frequent reactions at both doses include pain at the injection site, headache, fatigue and drowsiness. As for severity, most were of mild to moderate intensity. **Conclusion:** The data reinforce the safety of CoronaVac available in Brazil.

Key-words: Adverse Events; CoronaVac; Health Professionals.

Eventos adversos associados a CoronaVac em um hospital universitário

Resumo

Objetivo: O presente estudo objetivou descrever suspeitas de eventos adversos (EAs) relatados por funcionários de um hospital de ensino do estado de Sergipe após a vacinação com a Coronavac. **Métodos:** Trata-se de um estudo transversal baseado em relatórios de fichas de notificação de eventos adversos pós-vacinação (EAPVs) do software de Vigilância Hospitalar (Vigihosp) do Hospital Universitário de Sergipe, durante os meses de janeiro a março de 2021. Esta análise incluiu trabalhadores do hospital com idade ≥ 18 anos e que receberam pelo menos uma dose da CoronaVac. **Resultados:** No total, foram identificadas 406 notificações, das quais 251 foram selecionadas. O técnico de enfermagem foi a categoria profissional que mais notificou (38%), seguido do enfermeiro (20%). Mulheres de cor parda e na faixa etária mais jovem (<50 anos) foram mais propensas as EAPVs. Quanto à intensidade das reações, a maioria foi de intensidade leve a moderada, sendo as mais frequentes em ambas as doses, a dor no local da injeção, cefaleia, fadiga e sonolência. **Conclusão:** Os dados reforçam a segurança da CoronaVac disponível no Brasil.

Palavras-chave: Eventos Adversos; CoronaVac; Profissionais da Saúde.

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Introduction

The COVID-19 pandemic remains the largest public health crisis in modern history. There have been nearly 460 million cases and more than 6.0 million deaths worldwide, including more than 29 million cases and almost 656,000 deaths in Brazil alone[1-3]. Immediately after identifying the virus genetic sequencing, several researchers began to develop vaccines with different types of technologies in historically brief period of time[4,5]. Currently, the World Health Organization (WHO) has approved at least ten vaccines for emergency use[6].

In mid-June 2021, Brazil launched its national vaccination plan against COVID-19 to reach its population comprised by 211.8 million inhabitants. Initially, only two vaccines were approved for emergency use, Covishield (Oxford-AstraZeneca/Fiocruz) and CoronaVac – produced in Brazil by the Butantan Institute in partnership with Chinese biopharmaceutical company Sinovac[7]. In the first phase, the campaign focused mainly on health professionals and on the indigenous and aged population groups. Coverage was subsequently expanded to other groups and is currently ongoing[8]. Up to June 2021, 153,284,824 Brazilians had been completely immunized; however, more than 21 million had not concluded the vaccination cycle[9]. According to Bartsch et al. (2020), coverage rates above 70% to 80% are necessary to control the COVID-19 pandemic[10].

A total of 952 individuals were interviewed in a study that evaluated trust in the vaccines and hesitation towards being vaccinated in Brazil. Of them, 16.5% showed hesitation towards being vaccinated. Three out of the five reasons mentioned by the interviewees for such hesitation are related to doubts about safety and effectiveness of the vaccines[11]. According to the literature, factors related to sociodemographic conditions, such as schooling level, age or professional occupation, can also affect adherence to vaccination [12-14]. Despite the assessment conducted during the pre-clinical trials and phase I, II and II studies, there are still a series of questions to which we will only find answers after their use at a large scale in the population[7,15]. The most commonly reported PVAEs related to CoronaVac are pain in the injection site and fatigue[16]. However, rare cases of Guillain-Barré syndrome, Bell's palsy, infadenopathy, myocarditis, thromboembolic events, sensorineural hearing loss and appendicitis after vaccination have been reported in several countries[17-21].

In this context, it becomes fundamental to implement pharmacovigilance systems that allow for the notification, investigation and registration of the numerous PVAEs reported by health professionals and users[22]. These systems can detect AEs that went unnoticed in clinical trials, as well as assist in better understanding the cause-effect relationship between the different PVAEs[23,24]. This study aims at describing the incidence of PVAEs reported by employees of a University Hospital in the state of Sergipe after receiving the first and second CoronaVac doses, from January to March 2021.

Methods

This is a descriptive and cross-sectional study with a quantitative approach conducted from January to March 2021 in a university hospital from northeastern Brazil. This hospital is of medium-size, accredited to the Network of Sentinel Hospitals of the National Health Surveillance Agency (*Agência Nacional de Vigiância Sanitária*, ANVISA), has 125 active beds and is a reference in medium and high complexity in the state of Sergipe, being one of the main in the region in the treatment of COVID-19[24].

The data were collected from the Vigihosp app reports, from voluntary notifications made by employees who reported suspicion of PVAEs and through an active search carried out by clinical nurses previously trained by the multiprofessional team of the hospital's Care Risk Management Unit (*Unidade de Gestão de Riscos Assistenciais*, UGRA). The active search was made via telephone contacts on the first and third days after vaccination, guided by a semi-structured questionnaire, standardized by the National Epidemiological Surveillance System[23].

The suspected AEs were analyzed, totaling 406 cases. The notifications that met the following criteria were included: (i) employees aged ≥ 18 years old; and (ii) having received at least one CoronaVac dose up to the moment when the study was conducted. Employees with incomplete data were excluded.

The local PVAEs included pain, edema, erythema, heat and hardening. In turn, all those that were not local reactions were included among the systemic ones. The intensity of the reactions was classified under three categories: mild, does not require medication or does not interfere with daily routine activities; moderate, requires medications and causes some difficulty in the daily activities; and severe, requires hospitalization and evolves to death[25,26]. Onset and duration of the AEs were also evaluated[25,26]. The variables analyzed were presented as absolute frequency, percentage (%) or mean. Pearson's chi-square test was used to compare characteristics of the categorical variables between the groups. The data were analyzed using the *GraphPad Prism* software, version 7.0, adopting $p<0.05$ as significance level.

This article is an integral part of the project entitled "Analysis of Public Health Events, Complications and Compulsory Notification Diseases in a University Hospital'', which was submitted to and approved by the Committee of Ethics in Research involving Human Beings under opinion No. 2,944,215 (CAAE No. 99423418.9.0000.5546).

Results

A total of 406 notifications were evaluated in Vigihosp, about suspected PVAEs associated with CoronaVac from January to March 2021. Of these, 113 were excluded for receiving another immunobiological or for providing incomplete answers. We had at least 170 employees, mostly female (98%) and brown-skinned (54%). The mean age was 41 years old, with a minimum of 25 and a maximum of 65. Most of the notifications were made by nursing technicians (38%), followed by nurses (20%), physicians (9%) and multiprofessional residents (9%). The demographic characteristics are detailed in Table 1.

The results regarding the AEs reported by the employees after the first and second CoronaVac doses are described in Table 2. Pain in the injection site was the most commonly reported PVAE after the first and second doses (35% and 20%, respectively). Cephalea (19%), fatigue (9%) and somnolence (6%) were the most frequently notified systemic reactions after the first application. Other symptoms that were reported less frequently included myalgia, runny nose/rhinorrhea, nasal congestion, cough, sneezing, nausea/vomiting, abdominal pain, joint pain, other pain, fever, vertigo and sore throat. Only three reports were classified as with a hypersensitivity reaction; one of them with a previous history of sensitivity to the timerosal compound – used in the production of some vaccines. More rare or unusual conditions (5%) such as

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lymphadenomegaly, hypotension, dry mouth, hyperemia and eye pruritus, flatulence, urinary infection, tachycardia, pharyngitis, dyspnea on exertion, pain in the hemithorax and lumbar, cervical pain and paresthesia in the foot region were also recorded, being more common among the participants with a recent history of COVID-19 infections and in those with comorbidities. We only had one case of a moderate event, in which at least one day away from work was necessary due to diarrhea. No severe AEs were identified in this initial stage

Table 1. Demographic characteristics of employees at the university hospital in Sergipe (Brazil) vaccinated with CoronaVac, from January to March 2021.

Variables	N*	Percentage	Median	Range
Reported PVAEs	251			
Feminine	246	98%		
Age (years)			41	25 - 65
Color				
Whites	41	16%		
Black	17	7%		
Brown	135	54%		
Yellow	6	2%		
Profession Doctors	23	9%		
Nurses	51	20%		
Physiotherapists	2	1%		
Receptionist	4	2%		
Lab Technicians	5	2%		
Nursing Technicians	95	38%		
Multiprofessional Residents	23	9%		
Pharmacists	2	1%		
Other Professions	44	18%		

(*) Absolute values

Among those who reported any PVAE after the first dose, 48% also notified after the second application. Comparing both doses, local and systemic AEs (Adverse Events) were reported more frequently after the initial dose than after the second, except for cough (2%) and nausea/vomiting (4%), which were more commonly identified at the second dose applied. Nine cases (4%) were classified as rare or uncommon, such as alopecia, amigdalitis, tachycardia, insomnia, dyspnea and pain in the eyes. Most of them affected people with chronic diseases, history of positive PCR for SARS-CoV-2 and for allergy to medications, such as non-steroidal anti-inflammatories (NSAIDs) and dipyrone. Only one reaction with suspected hypersensitivity was recorded. No severe adverse events were notified.

In general, the systemic and local reactions were of mild and moderate nature, with a tendency to occur on the same day or one day after vaccination, lasting a mean of 1-2 days. Late reactions were reported by 2% of the participants after the first and second doses. In both applications, these AEs were more common in brown-skinned (24% vs. 16% and 26% vs. 12%, respectively) women (36% vs. 20% and 38% vs. 23%, respectively) (Table 3). In addition to that, PVAES were more frequently reported in the youngest age group (<50 group) than in older individuals (≥50 years old) (33% vs 19% and 36% vs 20%, respectively). However, the incidence of these AEs did not differ significantly in relation to the variables analyzed in both applications, except for the notifications made by brown-skinned people after the second dose (p=0.02).

Considering the monitoring phase on the third day after vaccination (Table 4), 44% reported that the symptoms disappeared three days after the first dose while 29% reported so after the second application. The persistence of a worsening in the symptoms was limited in both doses (18% vs. 8%). Among the persistent symptoms, cephalea was the systemic reaction with the highest

Table 2. PVAEs reported by employees of the university hospital in Sergipe (Brazil) after the first and second doses of CoronaVac, from January to March 2021.

	After first dose		After second dose	
PVAEs	**n***	**%**	**n***	**%**
Local pain/swelling	87	35%	51	20%
local erythema	4	2%	4	2%
Local heat/hardening	4	2%	3	1%
headache	48	19%	28	11%
Somnolence	15	6%	10	4%
Fatigue	22	9%	12	5%
Myalgia	7	3%	8	3%
runny nose/rhinorrhea	13	5%	9	3%
Nasal congestion	2	1%	2	1%
Cough	1		5	2%
sneeze	6	2%	3	1%
Nausea/vomiting	8	3%	9	4%
Abdominal pain	4	2%	4	2%
Diarrhea	8	3%	5	2%
another pain	4	2%	6	2%
Allergy	3	1%	1	
Fever	2	1%	1	
Vertigo	2	1%	S.R	
Sore throat	9	4%	10	4%
Others	12	5%	9	4%
Overall mean onset and duration of symptoms	(1, 2)		(1,2)	

(*) Absolute values

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number of records. In relation to the local reactions, we only had four notifications on local pain with or without presence of hematoma after the first dose, and six notifications after the second dose. All PVAEs were self-limiting, only requiring medication or non-pharmacological management in moderate cases for reversing the condition. Among the most used therapeutic classes, analgesics such as dipyrone stand out, followed by NSAIDs and antihistamines. Only seven individuals required medical care and performance of the RT-PCR test, although there was no severe case reported without any need for hospitalization Most of the notifiers (83%) had no course of action. During this phase of the study, pregnant women were still not included in the vaccination schedules; however, an employee reported being pregnant and not knowing her condition at the moment of the second dose. We received no information about her outcomes.

Table 3. Local and systemic events reported by employees of the university hospital in Sergipe (Brazil) according to gender, age and color after the first and second dose, from January to March 2021.

	Female n (%)**	Male n (%)**	p#	< 50 n (%)**	≥50 year n (%)**	p#	Brown n (%)**	Orthers n (%)**	p#
EA Local									
dose 1	91 (36)	1 (0)	0,12	82 (33)	9 (2)	0,22	61 (24)	28 (11)	0,30
dose 2	49 (20)	3 (1)	0,13	47 (19)	5 (1)	0,30	41 (16)	11 (4)	0,02
Systemic AE									
dose 1	94 (38)	2 (1)	0,49	89 (36)	15 (6)	0,80	64 (26)	37 (15)	0,17
dose 2	57 (23)	1 (0)	0, 48	50 (20)	10 (4)	0,26	29 (12)	22 (9)	0,26

(**) percentage and (#) Pearson's chi-square test

Table 4. PVAEs and procedures performed by employees of the Sergipe University Hospital (Brazil) three days after the first and second doses, from January to March 2021.

	Three days after first dose n*	%	Three days after first dose n*	%
absence of symptoms	110	44%	73	29%
Persistence of symptoms	45	18%	20	8%
Conducts				
Medicines	23	9%	18	7%
cold compress	1		S.R	
Medical consultation	2	1%	5	2%
Hospitalization	S.R		N.A	
No ducts	98	39%	73	29%

(*) Absolute values

Discussion

The results suggest that CoronaVac was safe and well tolerated among the professionals at the Sergipe University Hospital. For both doses, we verified that local and systemic PVAEs were more frequent in women of mixed race and in the younger age group (<50 years old)[27,28]. Pain in the injection site, headache and fatigue were the most commonly reported reactions by approximately more than 50% of the notifiers, similarly to the result found in the studies by Demirbakan et al. (2022) and Palacios et al. (2021) with health professionals[29,30]. In relation to the most observed systemic reactions, our data are in agreement with the report issued by the Butantan Institute, which showed participants who received CoronaVac and reported headache and fatigue more frequently within 7 days. This same document also describes that PVAEs tend to be less frequent with the second dose[31]. Allergic reactions were of low frequency, most of them related to individuals with a previous history of hypersensitivity to medications, excipients or food products. Other events, such as tachycardia, dyspnea, infections, alopecia, and ophthalmologic and otological reactions, were considered rare or uncommon[31,32]. It is noteworthy that, according to the literature, some of these symptoms do not seem to be correlated with vaccination. However, according to international pharmacovigilance databases, they are more frequently associated with other vaccines, such as Pfizer, AstraZeneca and Moderna manufacturers[33]. As the vaccination criteria expand, more information will be acquired and shared.

Our study presented some limitations. In the first place, given the self-report research nature, the frequency of PAVEs may have been over- or underestimated. In addition to that, we did not fully investigate the previous history of COVID-19 infections, comorbidities or allergies. We only evaluated the short-term adverse effects and long-term surveillance in the general population necessary to investigate duration of the symptoms, as well as onset of new adverse reactions and, finally, we did not perform a causality analysis of these events and the data refer exclusively to a hospital from Sergipe.

Conclusion

This study shows that, in a two-dose regimen, CoronaVac presented a good safety and tolerability profile among the health professionals at the University Hospital of the state of Sergipe. In addition to that, we provided relevant information on the incidence of PVAEs, especially in women and younger individuals, which may contribute to larger studies and, consequently, to confidence in and acceptance of the currently available vaccines.

Funding resources

Own financing.

Collaborators

LNSS - Article writing and data analysis and interpretation; AJS - Writing of the articleCAC - Writing and critical review WBRS - Writing and translating the article CMSS - Interpretation of data JSSA- Preparation and execution of the MMX project- Preparation and execution of the project.

Acknowledgments

To the employees of the Sergipe University Hospital for their participation in the study. To UGRA and the Epidemiological Surveillance Service (*Serviço de Vigilância Epidemiológica*, SVE) of the Sergipe University Hospital for their support in carrying out this study.

Conflict of interest statement

The authors declare that they have no conflict of interest with this research.

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