

## Adverse events following immunization of elderly with COVID-19 inactivated virus vaccine (CoronaVac) in Southeastern Brazil: an active surveillance study

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### ABSTRACT

Healthcare workers, the elderly and other vulnerable populations were the first to receive COVID-19 vaccines in public health programs. There were few vaccine safety data available on the elderly. This observational study aimed to evaluate the inactivated vaccine (CoronaVac) safety in the elderly, at the beginning of the vaccination program, in Sao Paulo city, Brazil. The elderly people that received CoronaVac at the Reference Center for Special Immunobiologicals (CRIE) or at home, administered by the Interdisciplinary Home Care Team (NADI) of the Hospital das Clinicas were invited to participate in this phase 4 observational study. The vaccination schedule included two CoronaVac doses 28 days apart. The information on solicited and unsolicited adverse events following immunization were collected by phone calls on days 4 and 8 after each vaccine dose. We enrolled 158 adults aged 65 to 101 years (mean of 84.1 years); 63.9% were females and 95.6% had chronic conditions, 21.5% had moderate or severe impairment in daily living activities; 34.2% were pre-frail and 19.6% were frail. We were able to contact 95.6% and 91.6% of the vaccinated people, after the first and second doses, respectively; 31.8% and 23.4% of the contacted participants reported some adverse events (AE) following the first and second doses, respectively. Pain at the injection site, fatigue, myalgia and headaches were the most frequent solicited AE. Most AE were mild to moderate. There were eight severe adverse events, but none of them were considered related to the vaccine. The CoronaVac was safe and well tolerated by these adults of advanced age with frailty and comorbidities.

**Keywords:** COVID-19 vaccine. Inactivated vaccine. Safety. Adverse events. Elderly. Post-marketing product surveillance.

### INTRODUCTION

Brazil was intensely affected by the COVID-19 pandemic with more than 22 million cases and more than 600,000 deaths by the end of 2021<sup>1,2</sup>. In the first semester of 2021, the SARS-CoV-2 gamma variant, initially identified in Manaus, North of Brazil, spread throughout the country, making it the global epicenter of the pandemic<sup>3</sup>. The elderly were seriously affected. Although persons aged 80 years and more represented approximately 2% of the estimated Brazilian population in 2020<sup>4</sup>, deaths in this age group constituted 25 to 30% of all reported COVID-19 deaths in the first six weeks of 2021<sup>5</sup>.

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In December 2020, the phase 3 trials' preliminary results enabled vaccine licensing for emergency use and the introduction of the COVID-19 vaccination in several countries. In Brazil, the vaccination was initiated in late January 2021, with two vaccines: the inactivated vaccine produced by Sinovac/Instituto Butantan (CoronaVac) and the viral vector vaccine produced by Oxford University/AstraZeneca/BioManguinhos (ChAdOx1), both approved by the National Regulatory Agency (ANVISA, Agencia Nacional de Vigilancia Sanitaria). The first months of the Brazilian vaccination program largely relied on the inactivated virus vaccine (CoronaVac). In Sao Paulo state, the COVID-19 vaccination program initially targeted healthcare workers, the elderly, indigenous populations, quilombolas and institutionalized persons. The vaccination for the elderly started in February, for people aged  $\geq 90$  years, followed by people aged 85 to 89 years, and so on, progressively reaching the younger age groups<sup>6</sup>.

The inactivated virus vaccine produced by Sinovac, China, was evaluated in phase 3 trials in several countries, including China, Brazil, Chile<sup>7</sup> and Turkey<sup>8</sup>. In Brazil, the CoronaVac phase 3 trial involved 12,396 healthcare workers aged 18 years or older (only 5.1% were aged  $\geq 60$  years). The most frequent adverse reactions were pain at the injection site, headaches and fatigue<sup>9</sup>. A phase 1 and 2 study in China<sup>10</sup> evaluated 348 people aged  $\geq 60$  years, who received different doses of CoronaVac. In this study, the vaccine was well tolerated and all adverse events were mild to moderate, as well as found in the younger population. Data on specific populations, including the elderly, especially those with comorbidities are scarce which means that phase 4 studies are required to evaluate the vaccine's safety, immunogenicity and effectiveness in those groups. This observational study aimed to evaluate the adverse events following the inactivated virus vaccine (CoronaVac) in the elderly, through active surveillance, in Sao Paulo city.

## MATERIALS AND METHODS

This observational retrospective cohort study was conducted at the Reference Center for Special Immunobiologicals (CRIE, Centro de Referencia para Imunobiologicos Especiais) of the Hospital das Clinicas (HC), a tertiary/quaternary care hospital attached to the University of Sao Paulo Medical School (FMUSP, Faculdade de Medicina da Universidade de Sao Paulo), in Sao Paulo city, from February to April 2021. Data were collected in active surveillance of adverse events following the immunization (AEFI). The CoronaVac was administered in a 2-dose schedule, with a 28-day interval between

doses, following the recommendations of the National Immunization Program.

A convenience sample was adopted. The elderly people (EP) who searched for or were referred to CRIE to receive the COVID-19 vaccine were asked for authorization for follow-up calls in order to evaluate the adverse events temporally associated with vaccination. Persons who were vaccinated at home by the HC Interdisciplinary Home Care team (NADI, Nucleo de Assistencia Domiciliar) were also invited to participate. The vaccinated participants were advised to return or make contact with the CRIE staff in case of AEFI.

The following data were collected: age, gender, skin color, comorbidities, functionality (using the Katz Index of Independence in Activities of Daily Living – Katz IADL) and frailty (through the Study of Osteoporotic Fractures – SOF).

The Katz IADL is an instrument to assess functional status as a measurement of the ability to perform activities of daily living independently. The Katz IADL evaluates the performance in the six functions of bathing, dressing, using the toilet, transferring, continence, and feeding, resulting in three classifications: independent, moderate impairment, and severe impairment<sup>11-13</sup>. The Frailty Syndrome is a clinical entity that describes the presence of multisystemic impairment and increasing vulnerability in older adults and can predict adverse health outcomes in this population, such as falls, fractures, severe adverse drug reactions, disabilities and death<sup>14</sup>. The SOF is a simple instrument that provides an operational definition of frailty and determines 3 classifications: frail, prefrail and robust.

The follow-up phone calls were made by healthcare workers and medical students, who made at least three contact attempts for each participant, on days 4 and 8 after both the first and second vaccine doses. If we were not able to talk to the vaccinated participants or his/her caregiver on the scheduled day, we kept trying for 3 to 5 days (at least three attempts). A standardized AEFI form was applied, which was answered by the vaccinated people or, in case of disability, by their caregivers. The solicited local adverse events were pain, erythema, swelling, induration and pruritus at the injection site. Solicited systemic adverse events were fever, chills, fatigue, headaches, myalgia, arthralgia, nausea, vomiting, diarrhea, anorexia and pruritus. The solicited adverse events were based on the most common expected adverse reactions listed in the CoronaVac package insert. The unsolicited adverse events were any other events reported by the vaccinated participants. The data on AEFI intensity, dates of onset and end, medications used and healthcare assistance needed were also collected. We used FDA's toxicity grading scale to classify AEFI

intensity<sup>15</sup>. Accordingly, local and systemic events were classified in: mild (grade 1: does not interfere with daily activity), moderate (grade 2: interferes with activity), severe (grade 3: prevents daily activity or requires outpatient treatment) and potentially life-threatening (grade 4: requires emergency room visit for more than 12 h or hospitalization). We used the WHO-Uppsala Monitoring Centre System for causality assessment<sup>16</sup>, which takes into account expected adverse events, time between vaccination and symptom onset, and the possibility of another cause for the event.

A descriptive analysis was conducted with measures of central tendency for continuous variables and estimation of frequencies for categorical variables. Data were summarized in tables.

This retrospective report was approved by the Research Ethics Committee of the Department of Infectious and Parasitic Diseases (001/22).

## RESULTS

From February 8<sup>th</sup> to March 3<sup>rd</sup>, 2021, 158 elderly people who received the first dose of the COVID-19 inactivated virus vaccine (CoronaVac) agreed to be contacted by phone for AEFI assessment; 126 of them were vaccinated at CRIE-HC and 32 persons received the vaccine at home, administered by the NADI-HC team. Their demographic characteristics, underlying diseases and functional status are presented in [Table 1](#). Their ages ranged from 65 to 101 years old, with a median of 83 years. And 74.7% of participants were aged ≥80 years. Most participants (95.6%) had at least one underlying disease; the most frequent morbidity was arterial hypertension (60.1% of participants), followed by heart disease (32.9%), dyslipidemia (25.3%) and diabetes (22.8%).

The Katz IADL showed that 7.6% and 13.9% of participants had, respectively, moderate and severe impairment in activities of daily living. The SOF showed that 34.2% of participants were pre-frail and 19.6% were frail ([Table 1](#)).

Of the 158 vaccinated people, 151 participants (95.6%) were successfully contacted at least once for the AEFI assessment after the first vaccine dose and 48 (31.8%) of the contacted vaccinated participants reported at least one AEFI; 154 (97.5%) subjects received the second vaccine dose within the follow-up period (up to April 8<sup>th</sup>, 2021), of whom 141 (91.6%) were successfully contacted at least once for the AEFI assessment after the second vaccine dose and 33 (23.4%) of the latter reported at least one AEFI ([Table 2](#)). The numbers of AEFI ranged from one to six (mean of 1.8) per person after the first vaccine dose and from one to five (mean of 2.2) per person after the second vaccine dose.

**Table 1** - Characteristics of 158 elderly participants included in the active surveillance of adverse events following the COVID-19 inactivated vaccine (CoronaVac). Sao Paulo, February to April 2021.

Characteristic	
Age (years)	
Min.-Max.	65 – 101
Median	83.00
Mean ± Std. Dev.	84.09 ± 5.75
Gender (n=158)	
Female	101 (63.92)
Skin color (n=155)	
White	114 (73.55)
Black / Mixed ethnicity	35 (22.58)
Asian	5 (3.23)
Indigenous	1 (0.65)
Not informed	3 (1.94)
Comorbidity	
At least one	151 (95.57)
None	3 (1.90)
Not informed	4 (2.53)
Arterial hypertension	95 (60.13)
Cardiopathy	52 (32.91)
Dyslipidemia	40 (25.32)
Diabetes mellitus	36 (22.79)
Hypothyroidism	26 (16.46)
Neoplasms	21 (13.29)
Alzheimer's disease / Other dementia	14 (9.43)
Immune-mediated inflammatory diseases	15 (9.43)
Chronic lung disease	12 (8.86)
Chronic kidney disease	13 (8.23)
Osteoporosis	9 (5.70)
Neurologic / Psychiatric disease	9 (5.70)
Obesity	7 (4.43)
Other*	22 (13.92)
Immunosuppressive therapy	8 (5.03)
Katz IADL**	
Independent	117 (74.05)
Moderate impairment	12 (7.59)
Severe Impairment	22 (13.92)
Not evaluated	7 (0.44)
SOF*** Frailty Index	
Robust	66 (41.77)
Prefrail	54 (34.18)
Frail	31 (19.62)
Not evaluated	7 (0.44)

\*HIV/AIDS (3), depression (3), adrenal insufficiency (2), labyrinthitis (2), macular degenerative disease (2), aorta aneurysm (2), Chagas disease (2), pulmonary tuberculosis (1), sickle cell anemia (1), hyperthyroidism (1), thyroid nodule (1), pemphigus (1), liver transplantation (1); \*\*Katz IADL – Katz Index of Independence in Activities of Daily Living; \*\*\*SOF – Study of Osteoporotic Fractures.

[Table 2](#) presents the reported solicited local and systemic AEFI, as well as the unsolicited adverse events according to the vaccine dose. The most common solicited adverse event after the first vaccine dose was pain at the injection site (13 reports, 8.7% of contacted participants), followed by fatigue (9, 6%) and headaches, diarrhea and pruritus (6,

**Table 2** - Numbers of reported adverse events (AE) following the COVID-19 inactivated vaccine (CoronaVac) in the elderly and proportions of events per contacted participants, according to dose. Sao Paulo, 2021.

	1 <sup>st</sup> dose		2 <sup>nd</sup> dose	
	Number of reported AE / Number of contacted participants	%	Number of reported AE / Number of contacted participants	%
<b>Solicited local AE</b>	21/151	13.91	6/141	4.26
Pain	13/150	8.67	5/141	3.55
Erythema	2/151	1.33	0/141	0
Swelling	2/151	1.33	0/141	0
Induration	1/151	0.66	1/141	0.71
Pruritus	3/151	1.99	0/140	0
<b>Solicited systemic AE</b>	48/151	31.79	49/141	34.75
Fever	0/151	0	2/141	1.42
Chills	4/151	2.65	2/141	1.42
Fatigue	9/150	6.00	8/138	5.80
Headache	6/150	4.00	6/138	4.34
Myalgia	5/150	3.33	10/138	7.24
Arthralgia	2/151	1.33	0/138	0
Nausea	5/150	3.33	6/138	4.34
Diarrhea	6/151	3.97	3/141	2.13
Vomiting	2/151	1.33	2/141	1.42
Anorexia	3/150	2.00	7/139	5.04
Pruritus	6/151	3.97	3/139	2.16
<b>Solicited AE</b>	69	-	55	-
<b>Unsolicited AE</b>	n	% of contacted	N	% of contacted
<b>Unsolicited AE</b>	18	-	19	-
Drowsiness	3	1.99	3	2.13
Dizziness	1	0.66	2	1.42
Sweating	0	0	2	1.42
Pallor	0	0	1	0.71
Cough	2	1.33	2	1.42
Hoarseness	0	0	1	0.71
Flu-like symptoms	0	0	1	0.71
Arm pain	1	0.66	0	0
Bruise	1	0.66	0	0
Injection site bleeding	0	0	1	0.71
Painful adenomegaly	1	0.66	0	0
Abdominal pain	0	0	1	0.71
Seizures	1	0.66	1	0.71
Syncope	1	0.66	0	0
Anemia	1	0.66	0	0
Pneumonia	1	0.66	0	0
Urinary infection	2	1.33	0	0
Stroke	2	1.33	3	2.13
Death	2	1.33	0	0
Total reported AE	88	-	73	-
Severe AE	5*		3**	
COVID-19	1		1	

\*Severe AE following the 1<sup>st</sup> dose: Emergency Room visit (2), hospitalization (1), deaths (2); \*\*Severe AE following the 2<sup>nd</sup> dose: hospitalization (3)

4% each). After the second dose, the most common solicited adverse event was myalgia (10 reports, 7.2%), followed by fatigue (8, 5.8%), anorexia (7, 5%), and headaches and nausea (6, 4.3% each).

There were 37 unsolicited AEFI, 18 after the first vaccine dose and 19 after the second dose (Table 2). Drowsiness was the most frequent unsolicited AE (6 reports, 3 after each dose), followed by stroke (5 events, two after the first dose and three after the second dose). Seven people presented eight severe adverse events (two deaths, four hospitalizations and two Emergency Room visits), five after the first vaccine dose and three after the second dose (Table 2). None of these severe AEFIs were considered related to the vaccine. A detailed description of the severe AEFI is presented in Supplementary Material S1.

There were two COVID-19 cases among those vaccinated, one case diagnosed 25 days after the first vaccine dose and another diagnosed two days after the second vaccine dose. They did not require hospitalization.

Most solicited local AE were mild and did not interfere with daily activities (80.95% of local AE after the first dose and 5/6 AE after the second dose). The systemic solicited AE were mild (63.8% and 62.2% of systemic AE after the first and second dose, respectively) or moderate / had little interference in daily activities (27.6% and 31.1% of systemic AE after the first and second dose, respectively). Few solicited systemic adverse events (8.5% and 6.7% AE after the first and second dose, respectively) were intense, preventing daily activities (Table 3).

**Table 3** - Intensity of solicited adverse events (AE) following the COVID-19 inactivated vaccine (CoronaVac) in the elderly, according to dose. Sao Paulo, 2021.

	Grade 1 / Mild	Grade 2 / Moderate	Grade 3 / Intense	Grade 4 / Serious
	Does not interfere with daily activities	Interferes little with daily activities	Prevents daily activities; requires medical assistance	Potentially life-threatening; requires hospitalization or emergency room visit
<b>1<sup>st</sup> dose (n)</b>				
Local pain (13)	9	4	0	0
Erythema (2)	2	0	0	0
Swelling (2)	2	0	0	0
Induration (1)	1	0	0	0
Pruritus (3)	3	0	0	0
<b>All local AE after 1<sup>st</sup> dose (21)</b>	<b>17 (80.95%)</b>	<b>4 (19.05%)</b>	0	0
Headache (6)	2	3	1	0
Fatigue (9)	5	3	1	0
Myalgia (5)	3	1	1	0
Arthralgia (2)	0	2	0	0
Chills (4)	4	0	0	0
Nausea (5)	3	2	0	0
Vomiting (2)	1	0	1	0
Diarrhea (6, 1 NI)	4	1	0	0
Anorexia (3)	3	0	0	0
Pruritus (6)	5	1	0	0
<b>All systemic AE after 1<sup>st</sup> dose (48, 1 NI)</b>	<b>30/47 (63.83%)</b>	<b>13/47 (27.66%)</b>	<b>4/45 (8.51%)</b>	0
<b>2<sup>nd</sup> dose (n)</b>				
Pain (5)	4	1	0	0
Induration (1)	1	0	0	0
<b>All local AE after 2<sup>nd</sup> dose (6)</b>	<b>5/6</b>	<b>1/6</b>	0	0
Fever (2; 1 NI)	1	0	0	0
Headache (6)	2	3	1	0
Fatigue (8)	5	3	0	0
Myalgia (10)	5	5	0	0
Chills (2)	2	0	0	0
Nausea (6)	3	2	1	0
Vomiting (2)	0	1	1	0
Diarrhea (3; 2 NI)	1	0	0	0
Anorexia (7; 1 NI)	6	0	0	0
Pruritus (3)	3	0	0	0
<b>All systemic AE after 2<sup>nd</sup> dose (49, 4 NI)</b>	<b>28/45 (62.22%)</b>	<b>14/45 (31,11%)</b>	<b>3/45 (6.67%)</b>	0

NI = not informed.

Most of the solicited AE started soon after or in the first days following the vaccination (local AE, 0-6 days, mean=1.4; systemic AE, 0-7, mean=1.9 days) and the last few days (local AE, 1-5 days, mean=1.9; systemic AE, 1-9 days, mean=2.4) (Table 4).

## DISCUSSION

This study evaluated the safety of CoronaVac, an inactivated SARS-COV-2 vaccine, in adults of advanced age (mean age of 83 years); 53.8% were pre-frail or frail; 21.5% had moderate to severe impairment in ADL; and most of them (95.6%) had a chronic condition. We were able to make contact with most of the vaccinated participants,

and 31.8% and 23.4% of participants reported at least one adverse reaction following the first and second vaccine doses, respectively. Most common adverse events reported, such as pain at injection site, fatigue, headaches, diarrhea, pruritus and myalgia, were expected and are listed in the vaccine package insert. Most adverse reactions were mild to moderate. There were eight serious adverse events, but none of them were considered related to the vaccine. The severe AE occurred mainly in frail or pre-frail individuals of advanced age (>80 years), with comorbidities, who were at high risk of negative health outcomes independent of the vaccination<sup>17</sup>.

Few studies evaluated CoronaVac safety in the elderly, particularly in those very old and with comorbidities. In

**Table 4** - Interval from elderly vaccination with the COVID-19 inactivated vaccine (CoronaVac) to adverse events (AE) and duration of AE, according to event and dose. Sao Paulo, 2021.

Adverse events	Interval from vaccination to AE onset (days)		Duration (days)	
	Min.-Max. (Mean)		Min.-Max. (Mean)	
<b>1<sup>st</sup> dose</b>				
Pain (13)	0 – 5	(1.54)	1 – 4	(1.08)
Erythema (2)	0	(1 NI)	1 – 5	(3.0)
Swelling (2)	0		2 – 3	(2.5)
Induration (1)	NI		NI	
Pruritus (3; 1 NI)	2 – 6	(4.0)	2 – 4	(3.0)
<b>All local AE after 1<sup>st</sup> dose</b>	<b>0-6</b>	<b>(1.42)</b>	<b>1-5</b>	<b>(2.05)</b>
Headache (6)	0 – 7	(2.67)	1 – 4	(1.67)
Fatigue (9; 1 NI)	0 – 6	(1.88)	1 – 6	(2.63)
Myalgia (5; 1 NI)	0 – 4	(1.0)	1 – 4	(1.75)
Arthralgia (2)	1 – 2	(1.5)	2	
Chills (4)	0 – 2	(1.0)	1 – 2	(1.25)
Nausea (5)	2 – 7	(5.0)	1 – 2	(1.4)
Vomiting (2)	1 – 6	(3.5)	2	
Diarrhea (6; 1 NI)	0 – 7	(3.80)	1 – 4	(1.60)
Anorexia (3)	0 – 7	(2.67)	1	
Pruritus (6; 1 NI)	1 – 5	(2.4)	1 – 4	(3.0)
<b>All systemic AE after 1<sup>st</sup> dose</b>	<b>0 – 7</b>	<b>(2.69)</b>	<b>1-6</b>	<b>(1.98)</b>
<b>2<sup>nd</sup> dose</b>				
Pain (5)	0 – 1	(0.8)	1 – 2	(1.6)
Induration (1)	3		2	
<b>All local AE after 2<sup>nd</sup> dose</b>	<b>0 – 3</b>	<b>(1.17)</b>	<b>1 – 2</b>	<b>(1.50)</b>
Fever (2)	0 – 3	(1.50)	4 – 7	(5.50)
Headache (6)	0 – 3	(1.0)	1 – 4	(2.17)
Fatigue (8)	0 – 2	(0.88)	1 – 7	(2.75)
Myalgia (10)	0 – 4	(1.20)	1 – 7	(2.90)
Chills (2)	0 – 5	(2.50)	1 – 3	(2.0)
Nausea (6)	0 – 5	(1.83)	1 – 9	(2.83)
Vomiting (2; 1 NI)	2		3	
Diarrhea (3; 1 NI)	1 – 2	(1.5)	3 – 5	(4.0)
Anorexia (7; 1 NI)	0 – 7	(1.67)	1 – 3	(2.0)
Pruritus (3)	0 – 1	(0.67)	3 – 8	(5.0)
<b>All systemic AE after 2<sup>nd</sup> dose</b>	<b>0 – 7</b>	<b>(1.33)</b>	<b>1 – 9</b>	<b>(2.91)</b>

NI = Not Informed.

China, phase 1 and 2 clinical trials evaluated CoronaVac safety in healthy adults aged  $\geq 60$  years<sup>10</sup>. It is important to emphasize that their population was healthier and younger (mean age = 65.8 and 66.6 years, respectively, in phase 1 and phase 2 trials) than those included in our study. They reported lower adverse reaction rates (21% or 84/421 participants reported at least one adverse reaction) as compared to our study (31.8% and 23.4% of those vaccinated reported adverse reactions after the first and second doses, respectively). Pain at the injection site was the most common local solicited adverse reaction in both studies. In the Chinese study, fever (3%) was the most frequent systemic reaction whereas fatigue, myalgia and headaches were more common in our study.

The CoronaVac phase 3 trial in Brazil included 632 persons aged  $\geq 60$  years (316 in the vaccine group)<sup>18</sup>. Considering only the vaccinated group, 24.7% of participants reported any solicited local adverse reaction after the first dose and 31.7% after the second dose, both higher than in our study (13.9% and 4%, respectively). The Brazilian trial reported lower solicited systemic adverse reactions (24% of the vaccinated participants with any systemic AE after the first dose and 25.6% after the second one) as compared to our study (31.8% and 34.8%, respectively, [Table 2](#)). In both studies, most adverse reactions were mild to moderate.

An interim analysis of CoronaVac in healthy adults, in Chile, included 37 volunteers aged  $\geq 60$  years (25 in the vaccine group), with a mean age of 64 years<sup>7</sup>. Considering only the vaccine group, pain at the injection site was the most frequent solicited local reaction (55.6%). Headaches were the most frequent systemic reaction (37.5%), followed by fatigue (25%)<sup>7</sup>. Both frequencies were higher than the ones found in our study, even though the sample size of the Chilean study was very small, which may have biased the results.

The comparison of adverse events following immunization with distinct vaccine platforms, in different countries, is very difficult, but local reactions were less common after CoronaVac, in our study, than reported for BNT162b2 and ChAdOx1 in phase 4 studies. A phase 4 active surveillance study of the BNT162b2 vaccine in people aged  $\geq 75$  years, in South Korea, used methods similar to ours (phone calls 7 days after each vaccine dose to assess adverse events)<sup>19</sup>. Local reactions were reported by 50.3% of 638 vaccinated participants after the first dose and 45.2% of 560 vaccinated participants after the second dose. Systemic reactions were reported by 15.2% and 26% of participants, after the first and second dose, respectively. Pain at the injection site, muscle pain, fatigue, chills and fever were the most frequently reported

adverse reactions<sup>19</sup>. A large phase 4 observational study in the UK assessed BNT162b2 and ChAdOx1 safety through self-report<sup>20</sup>. Systemic adverse events were reported by 13.5% and 22% of recipients of BNT162b2, after the first and second doses, respectively, and by 33.7% of persons after the first ChAdOx1 dose (none of the participants had received the second ChAdOx1 dose at the time of study analysis). Headaches and fatigue were the most frequent systemic AE after both vaccines. Local adverse events were reported by 71.9% and 68.5% of vaccinated participants after the first and second dose of BNT162b2, respectively, and by 58.7% after the first dose of ChAdOx1. Tenderness and pain at the injection site were the most frequent local AE for both vaccines<sup>20</sup>.

A strength of our research is the active surveillance of adverse events after immunization by follow-up phone calls after each dose. This makes it possible to capture mild and moderate events, which are not usually reported in passive surveillance systems. Limitations of our study include the small sample size and the lack of a control unvaccinated group. However, this is the first research to evaluate CoronaVac in adults of advanced age, with frailty and comorbidities in a real-world study, and we were able to contact the vast majority of participants.

## CONCLUSION

Our results are similar to those found in other studies involving the inactivated COVID-19 vaccines among the elderly. Most reported adverse events were mild to moderate as expected, suggesting that the COVID-19 inactivated virus vaccine (CoronaVac) is safe in very old adults, even with multiple comorbidities. Other pharmacovigilance studies with larger samples are needed to determine the real frequency of AEFI and if there are prognostic factors for AEFI in the elderly.

## AUTHORS' CONTRIBUTIONS

All authors have reviewed and approved the final version of the article. KTM was responsible for developing the study design, analyzing, discussing results and writing the manuscript. LYUI and LCJ were responsible for collecting data, making a database and analyzing results; ACRS, CMP, ANL and CCMR were responsible for collecting data and making a database. MH was responsible for analyzing and discussing results. FCL and KTH were responsible for discussing results; MHL participated in the study design and discussion of results and AMCS coordinated the study, analyzed results and wrote the manuscript.

## CONFLICT OF INTERESTS

KTM is an employee of Instituto Butantan since March 22, 2021, after the inclusion of participants and data collection. The following authors received grants from Instituto Butantan to develop some more research with the COVID Vaccine, not related to this study: ACRS, ANL, CMP, MHL and AMCS. All grants were received after the inclusion of participants and data collection. The other authors declared no conflict of interests.

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