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Article

A comparative analysis of a self-reported adverse events analysis after receiving one of the available SARS-CoV-2 vaccine schemes in Ecuador.

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Abstract: The COVID-19 pandemic has put a lot of pressure on health systems worldwide. Mass vaccination against SARS-CoV-2 has reduced morbidity and mortality worldwide. Despite their safety profiles, vaccines as any other medical product can cause adverse events. Yet, in countries with poor epidemiological surveillance and monitoring systems, reporting vaccine-related adverse events is scarce.

The objective of this study was to describe self-reported vaccine adverse events after receiving one of the available COVID-19 vaccines schemes in Ecuador. A cross-sectional analysis based on an online self-reporting 32-questionnaire was conducted in Ecuador from April 1st to July 15th, 2021. Participants were invited by social media, radio, and TV to voluntarily participate in our study.

A total of 6,654 participants were included in this study. A 38.2% of the participants reported having at least one comorbidity. Patients received AstraZeneca, Pfizer, and Sinovac vaccines, and these were distributed 38.4%, 31.1% and 30.5%, respectively. Pain, inflammation at the injection site (20,01%) and headache (16,91%) were the most reported adverse events. Women addressed ESAVIs (64%), more often than men (36%). After receiving the first dose of any available COVID-19 vaccine, a total of 19,481 self-reported ESAVIs were informed (86.9% were mild, 11.6% moderate and 1.5% severe). In terms of vaccine's type and brand, the most reactogenic vaccine was AstraZeneca with 57.8%, followed by Pfizer (24.9%) and Sinovac (17, 3 %). After the second dose, 6,757 self-reported ESAVIs were reported (87.0% mild, 10.9% moderate, and 2.1% severe). AstraZeneca vaccine users reported a higher proportion of ESAVIs (72.2%) in comparison to Pfizer/BioNTech (15.9%) and Sinovac Vaccine (11.9%). Swelling at the injection site, headache, muscle pain and fatigue were the most common ESAVIs for the first as well as second dose.

In conclusion, most ESAVIs were mild. AstraZeneca users were more likely to report adverse events. Participants without history of COVID-19 infection, as well as those who receive the first dose were more prone to report ESAVIs.

Keywords: COVID-19; Vaccines; Adverse Events; Self-reporting; Pandemic

1. Introduction

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Vaccination is the most cost-effective public health intervention after water sanitation for the control and management of preventable, contagious, and life-threatening diseases [1]. Vaccines induce artificial immunity to several types of microorganisms, avert the likelihood of acquired infections, and reduce morbidity, disability, and mortality [2]. Vaccines development throughout history has been sluggish; however, in February 2020, as the new SARS-CoV-2 virus started to wreak havoc and increase the rate of deaths globally, science was prompt to create a fast, effective, and safe way to counteract the rapid advance of the SARS-CoV-2 virus [3] . The development of any vaccinal strategies has never been as rapid and promising as the one we experienced with the development of more than 110 COVID-19 candidates, thanks to the global economic effort due to a planetary priority [3,4].

Several companies and a few countries took the lead, investing millions of dollars and putting together several promising vaccine candidates in a record time [4]. In this sense, by December 11th, 2020, the FDA issued the first emergency use authorization for the mRNA-based BNT162b2 vaccine produced by Pfizer/BioNTech [5]. Weeks later, other vaccines came out and by the first trimester of 2021, several countries began to massively vaccinate their population [6,7] (Table 1).

Table 1. The main characteristics of the different mechanisms of action used by different COVID-19 vaccines.

Type of vaccine	Mechanism of action	Vaccine name	Producer	Dose	Storage
mRNA	Protein S extension with proline substitutions	BNT162b2	Pfizer / BioNtech (US)*	30μg 2 doses, interval 21 days	-25 ° to -15 ° C; 2-8 ° C for 30 days. Ambient temperature ≤ 12h
Viral vector	Replication-deficient Chimp adenovirus viral vector and SARS-CoV-2 protein S	ChAdOx1 (AZS1222)	AstraZeneca / Oxford (UK)*	5 * 10^{10} viral particles 2 doses 28 day interval	2-8 ° C for 6 months

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Viral vector	Human adenovirus serotype 26 viral vector with incompetent recombinant replication and stabilized SARS-CoV-2 protein S	Ad26.COV 2.S	Janssen / Johnson & Johnson (US)	5 * 10 ^{10} viral particles 1 dose	-20 ° C; 2-8 ° C for 3 months
mRNA	Spike S protein extension with proline substitutions	mRNA-1273	Modern (US)	100µg 2 doses 28 day intervals	-25 ° C to -15 ° C; 2-8 ° C for 30 days; ambient temperature ≤ 12h
Inactivated virus	SARS-CoV-2 Inactivated HB02 Chain Created from Vero Cells	BBIBP-CorV	Sinopharm ½ (China)	4µg with aluminum hydroxide adjuvant 2 doses 21 day interval	2-8 ° C duration unknown
Inactivated virus	SARS-CoV-2 Inactivated CN02 Chain Created from Vero Cells	CoronaVac	Sinovac Biotech (China)*	3µg with aluminum hydroxide adjuvant 2 doses 14 day interval	2-8 ° C duration unknown
Viral vector	SARS-Cov-2 glycoprotein S full-length loaded adenovirus vector	Gam-COVID-Vac (Sputnik V)	Gamaleya National Research Center for Epidemiology and Microbiology (Russia)	10 ^{11} viral particles per dose for each recombinant adenovirus 2 doses 1st rAd26 2nd rAd5 21-day interval	-18 ° C liquid; 2-8 ° C frozen dry 6 months

Because of the small window of time between the development of new COVID-19 vaccines and their authorization, the identification and reporting of events supposedly

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attributable to vaccination or immunization (ESAVI) became a priority [8]. Although COVID-19 vaccines have shown numerous benefits, some people are still wary of COVID-19 vaccines [9]. Authors suggest that it may be due to the world-record speedy vaccine development and the constant emergence of new adverse events. Therefore, the proper report of COVID-19 vaccine-related adverse events is substantial to ameliorate this problem.

In general, regardless of the immunologic mechanism used by any of the COVID-19 vaccines, serious adverse events are very rare and most of the symptoms associated with the vaccines are mild [10]. For instance, in Poland, according to data on February 18, 2021, approximately 2,131 ESAVIs were reported after the administration of 2,384,794 doses of the Pfizer/BioNTech vaccine (1 ESAVI every 1100 vaccines) [11]. Similarly, Beaty et al. reported that serious ESAVIs were very rare in a cohort of more than 19,000 patients in the U.S. [12].

Most ESAVIs are mild and self-limited and can present as systemic or local reactions. A wide spectrum of ESAVIs has been reported being a pain, redness or swelling at the vaccine injection site, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain the most common [13,14]. In very rare cases, vaccines can also cause serious adverse reactions such as anaphylactic shock, vaccine-induced immune thrombotic thrombocytopenia (VITT), or even death, in a disputable rate of less than 0.0025% of deaths according to the CDC [15].

This study aimed to describe the self-reported vaccine adverse events after the application of the available COVID-19 vaccines in Ecuador in addition to the management used to treat reactions.

2. Materials and Methods

2.1. Study design and sample selection

We conducted a cross-sectional study by circulating an independent 32 items- self-reporting online questionnaire through the internet-based survey platform Survey Monkey. We gathered anonymous responses from all over the country using a non-probability sampling method from April 1st to July 15th, 2021.

2.2. Settings and population

Participants were all Ecuadorian residents who have received one of the available COVID-19 vaccines. According to the current government plan, 9 million people were vaccinated by July 2021. In that sense, with a confidence level of 95 % and a margin of error of 1.5 %, our minimum estimated sample was 4,267 responses. The sample size was calculated by using the following formula:

Using the expected population to be vaccinated, the sample size n and margin of error E are given by the following formula:

$$x = Z(c/100)2r(100-r)$$

$$n = N\,x/((N-1)E2 + x)$$

$$E = \mathrm{Sqrt}[(N - n)x/n(N-1)]$$

where N is the population size, r is the fraction of responses, and Z(c/100) is the critical value for the confidence level c.

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All responses that came from respondents who voluntarily agreed to participate in the study and who completed all 32 questions were included. Moreover, only participants that reported they received mRNA vaccine (Pfizer/BioNTech), viral vector (Astra-Zeneca), or inactivated vaccine (Sinovac) were included.

2.3. Survey development and measures

The data was collected using a 32-item online anonymous questionnaire to evaluate self-reported symptoms and adverse events after receiving one or two doses of the available COVID-19 vaccines. Participants' consent was obtained at the beginning of the questionnaire with an explanation of the objective of the study. Participants could proceed with the full questionnaire only after obtaining consent by accepting (electronically marking) a 'Terms and Conditions' and 'Participation Agreement' consent form. A novel questionnaire instrument was developed for this study using items adapted from information about COVID-19 published by the CDC and the WHO alongside items used in previous COVID-19 surveys. The questionnaire was developed and fielded in Spanish and later translated into English for reporting purposes. The full survey instrument is available in the Additional file 1.

The questionnaire was reviewed for validity by three experts in infectious diseases and biostatistics to identify key issues that may be relevant to vaccination and to assess its relevance and accuracy. After incorporating expert feedback, we pilot-tested the survey instrument online with a group of 30 eligible participants. The 30 participants who completed the pilot-testing did not participate in the final survey and the responses collected during pilot-testing were not included in the final analysis.

The questionnaire consisted of four sections: demographic characteristics, comorbidities, past medical history of COVID-19, and vaccination information. The demographic section collected information on age, sex, occupation, and place of residency. The comorbidities section includes questions about respondents' medical history not related to COVID-19 (smoking status, medications, and other diseases). The COVID-19-related medical history was composed of 6 questions that include information related to previous infections. Finally, the vaccination information section was composed of 20 questions that evaluated the type, date, place, and number of doses of the administered vaccine. Moreover, it evaluated the timing and type of vaccine-related symptoms and adverse events.

The questionnaire was sent through national broadcasting news and social media, using snowballing as a sample method. Weekly reminders were sent to participants during the period of the questionnaire.

2.4. Data management

We reviewed case by case to ensure the highest accuracy possible on our results. As such, we identified cases where responses did not match the questions posed. For example, when they answered that they had not received the second dose of the vaccine, but in the section of adverse events attributed to the second dose, they chose a response, that type of cases was automatically eliminated. Moreover, we excluded responses coming from the same IP address to avoid malicious and duplicate answers.

2.5. Statistical analysis

Descriptive and inferential analysis was conducted using the software IBM SPSS Statistics for Windows Version 24.0. The results of each item in the questionnaire were

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reported as men and women in percentage and absolute frequencies with no further intersex variability analysis. The Chi-Square test was used to test the association between nominal qualitative variables. An independent t-test for mean differences was calculated for the ESAVIS quantitative approach. Statistical significance was accepted at $p < 0.05$. Confidence intervals at 95% from means and proportions were also computed.

2.6. Reliability and validation

Reliability was examined using a test-retest questionnaire using the final version of the survey. Since this questionnaire was created only for this project, we tested within the cohort of experts previously selected for the informal interviews.

3. Results

3.1. Demographic information and past medical history

A total of 11,927 responses were collected at the national level, however, after revalidation, 6,654 responses were considered valid for analysis. From the total number of responses, 4,018 (60.4%) were women, 2,631 (39.5%) were men, and 5 (0.1%) defined themselves as others. Most respondents were aged between 21 to 50 years (73.9%) were employed (79.60%); of them 21.2% were healthcare workers. The most frequent comorbidity was hypothyroidism (24.5%) and chronic diseases such as obesity (19.9%) and arterial hypertension (17.0%). Most of the participants did not have COVID-19 at the time of the questionnaire. The three vaccine types available in Ecuador were similarly distributed (Table 2).

Table 2. Demographic characteristics of the study population.

3.2. Self-reported ESAVIs

3.2.1. General characteristics

Overall, women had a higher frequency of self-reported ESAVIs (64%), being the most common pain or inflammation at the injection site (20,01%) and headache (16,91%) . Most symptoms were reported by participants who claimed not to have comorbidities and in those without a personal history of COVID-19 infection (Table 3).

Table 3. Self-reported adverse events after receiving the first and second dose of any of the available COVID-19 vaccines distributed by demographic characteristics

Figure 1 Self-reported ESAVIs among 6,654 patients from Ecuador

After the first vaccine dose, a total of 19,481 self-reported ESAVIs were reported; 86.9% were mild, 11.6% moderate, and 1.5% severe. For the second dose, there were 6,757 self-reported ESAVIs (87.0% mild, 10.9% moderate, and 2.1% severe) (Table 4).

Table 4 Self-reported ESAVIs after receiving the first and second dose of any of the available COVID-19 vaccines in Ecuador (n=6,645)

Self-reported ESAVIs were higher among young adults (55.8%) and adults (34.5%) compared to older adults (7.6%), however, there are no significant differences in terms of the occurrence of adverse events after performing the corresponding statistical tests (Figure 2).

Figure 2 Self-reported ESAVIs between men and women by age

The behavior of the reported effects shows a common trend when analyzed among all different age groups (9 groups) in favor of pain or swelling at the injection site in all age groups as the most reported, beside, tiredness or fatigue is presented as the second most frequent in age strata of subjects under 30 years of age and between 70 and 90 years,

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while this place is occupied by headache in participants of age strata of subjects over 30 years of age (40 to 70 years of age) (Figure 3).

Figure 3 Age-specific self-reported adverse event among 6654 patients

Figure 4 shows the effect of the comparison of the number of adverse events between the different age ranges, it was found that the effects due to vaccination differ only between the age ranges up to 70 years ($p < 0.05$). In participants older than 70 years, the number of adverse effects is very similar ($p > 0.05$) (Figure 4). Along the same lines, when addressing the influence of age between only two age groups, taking 50 years as the cut-off point, it was shown that the group under 50 years of age presents various symptoms more frequently ($p < 0.05$) (Table 3).

Figure 4 T-Test analysis among age groups

3.2.2. Self-reported ESAVIs after the first vaccine dose

The proportion of ESAVIs after the first vaccine dose was higher in users of AstraZeneca (57.8%), followed by Pfizer (24.9%), and Sinovac (17.3%). In the same way, the most common self-reported ESAVIs with AstraZeneca vaccine were headache (9.1%), muscle pain (8.9%), and discomfort (8.6%). For the Pfizer/BioNTech vaccine, the most common self-reported ESAVIs were pain or swelling at the injection site (16.5%), headache (7.7%), and fatigue or tiredness (7.6%). Finally, for the Sinovac inactivated virus vaccine, pain or swelling at the injection site (11.3%) fatigue or tiredness (9.8%), and headache (9.7%) were the most common self-report ESAVIs (Table 5).

Table 5 Self-reported ESAVIs after the first dose of any of the available vaccine

3.2.3. Self-reported ESAVIs after the second vaccine dose

Second dose AstraZeneca vaccine users reported a higher proportion of ESAVIs (72,21%) compared to Pfizer/BioNTech (15,85%) and Sinovac (11,93%) vaccine. For AstraZeneca vaccine, headache (8.7%), pain or swelling at the injection site (7.7%), and fatigue or tiredness (7.2%) were the more common self-reported ESAVIs. After Pfizer/BioNTech vaccine the more common self-reported ESAVIs were pain or swelling at the injection site (10.3%), headache (7.2%), and muscle pain (6.7%). Finally, with the Sinovac vaccine, participants self-reported they had pain or swelling at the injection site (9.5%), headache (7.6%), and fatigue or tiredness (6.8%) more frequent

Table 6 Self-reported ESAVIs after receiving the second dose of any of the available vaccine

In general, the effect of the available vaccines in Ecuador showed that the most common adverse event was pain at the injection site, followed by headache (Figure 5).

Figure 5 Symptoms depending on the vaccine administered

3.2. Figures, Tables and Schemes

Table 2. Demographic characteristics of the study population.

Demographic characteristics			
		n	**(%)**
Gender	Female	4,018	60.4%
	Male	2,631	39.5%
	Other	5	0.1%
	Total	**6,654**	**100%**

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Age (years)	10 to 20	204	3.1%
	21 to 30	1,553	23.3%
	31 to 40	1,895	28.5%
	41 to 50	1,471	22.1%
	51 to 60	997	15.0%
	61 to 70	428	6.4%
	71 to 80	82	1.2%
	81 to 90	19	0.3%
	91 to 100	5	0.1%
	Total	**6,654**	**100%**
Occupation	Health care workers	1,405	21.1%
	Outside health care area workers	3,892	58.5%
	Unemployed	1,357	20.4%
	Total	**6,654**	**100%**
Live in Ecuador	Yes	6,634	99.7%
	No	20	0.3%
	Total	**6,654**	**100%**
Comorbidities	Asthma	188	7.4%
	Cardiovascular disease	164	6.4%
	Arterial hypertension	432	17.0%
	Obesity	506	19.9%
	Hypothyroidism	624	24.5%
	Cancer	25	1.0%
	Chronic liver disease	25	1.0%
	Type 1 Diabetes	49	1.9%
	Type 2 Diabetes Mellitus	135	5.3%
	Hyperthyroidism	49	1.5%
	Psoriasis	95	3.7%
	Chronic kidney disease	17	0.7%
	Respiratory disease	61	2.4%
	Stroke (ischemic or hemorrhagic)	16	0.6%
	Chronic neurological disorders	30	1.2%
	Coagulation disorders	59	2.3%
	Tuberculosis	2	0.1%
	Peptic ulcers	57	2.2%
	HIV/AIDS	13	0.5%
	Total	**2,547**	**100%**
History of COVID-19 infection	I think yes, but did not take the test	264	4.0%

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	Yes/confirmed	1,450	21.8%
	No	4,940	74.2%
	Total	**6,654**	**100%**
Vaccine type	Pfizer	2,069	31.1%
	AstraZeneca	2,553	38.4%
	Sinovac	2,032	30.5%
	Total	**6,654**	**100%**

Table 3. Self-reported adverse events after receiving the first and second dose of any of the available COVID-19 vaccines distributed by demographic characteristics

Symptoms	**Gender n (%)**				**Comorbidities n (%)**			**History of COVID-19 infection n (%)**			**Age n (%)**		
	Female	**Male**	**Other**	**P value***	**No**	**Yes**	**P value***	**No**	**Yes**	**P value***	**< 50 years**	**> 50 years**	**P value***
Tachycardia	191 (74.3)	66 (25.7)	0 (0.0)	0.830	112 (43.6)	145 (56.4)	**0.003**	189 (73.5)	68 (26.5)	0.702	193 (75.1)	64 (24.9)	0.398
Diarrhea	287 (71.0)	117 (29.0)	0 (0.0)	1	213 (52.7)	191 (47.3)	**<0.001**	305 (75.5)	99 (24.5)	**0.004**	308 (76.2)	96 (23.8)	**0.004**
Joint pain	1,083 (66.9)	535 (33.0)	1 (0.1)	0.200	890 (55.0)	729 (45.0)	**<0.001**	1,151 (71.1)	468 (28.9)	0.799	1,292 (79.2)	327 (20.2)	**<0.001**
Headache	2,355 (67.2)	1,143 (32.6)	4 (0.1)	0.593	2,021 (57.7)	1,481 (42.3)	**<0.001**	2,565 (73.2)	937 (26.8)	**<0.001**	2,785 (79.5)	717 (20.5)	**<0.001**
Muscle pain	1,865 (64.4)	1,028 (35.5)	4 (0.1)	**<0.001**	1,683 (58.1)	1,214 (41.9)	**<0.001**	2,086 (72.0)	811 (28.0)	0.708	2,308 (79.7)	589 (20.3)	**<0.001**
Pain or swelling at the injection site	2,969 (66.0)	1,528 (34.0)	3 (0.1)	**0.045**	2,570 (57.1)	1,930 (42.9)	**<0.001**	3,337 (74.2)	1,163 (25.8)	**<0.001**	3,609 (80.2)	891 (19.8)	**<0.001**
Skin rash	116 (73.0)	43 (27.0)	0 (0.0)	0.776	82 (51.6)	77 (48.4)	**0.0166**	119 (74.8)	40 (25.2)	**0.019**	124 (78.0)	35 (22.0)	**<0.001**
Shaking chills	1,375 (65.5)	723 (34.4)	2 (0.1)	0.071	1,302 (62.0)	798 (38.0)	**<0.001**	1,506 (71.7)	594 (28.3)	0.582	1,760 (83.8)	340 (16.2)	**<0.001**
Fatigue or tiredness	220 (66.9)	1,088 (32.9)	5 (0.2)	0.192	1,931 (58.5)	1,371 (41.5)	**<0.001**	2,480 (75.1)	822 (24.9)	0.056	2,739 (82.9)	563 (17.1)	**<0.001**
Mild/low grade fever (37.1 C°- 38 C°)	941 (64.1)	527 (35.9)	1 (0.1)	0.385	889 (60.5)	580 (39.5)	**<0.001**	1,005 (68.4)	464 (31.6)	0.374	1,245 (84.8)	224 (15.2)	**<0.001**
Fever (>38C°)	536 (64.7)	291 (35.1)	2 (0.2)	0.857	523 (63.1)	306 (36.9)	**<0.001**	578 (69.7)	251 (30.3)	**0.006**	686 (82.8)	143 (17.2)	**<0.001**
Guillain Barre sd.	4 (40.0)	6 (60.0)	0 (0.0)	1	9 (90.0)	1 (10.0)	1	9 (90.0)	1 (10.0)	1	8 (80.0)	2 (20.0)	1
Facial swelling	17 (65.4)	9 (34.6)	0 (0.0)	1	12 (46.2)	14 (53.8)	0.254	18 (69.2)	8 (30.8)	1	18 (69.2)	8 (30.8)	0.279
High Blood Pressure	62 (71.3)	25 (28.7)	0 (0.0)	0.227	21 (24.1)	66 (75.9)	**0.002**	66 (75.9)	21 (24.1)	0.529	50 (57.5)	37 (42.5)	0.922
Swollen Glands	315 (74.3)	108 (25.5)	1 (0.2)	**0.048**	235 (55.4)	189 (44.6)	**<0.001**	308 (72.6)	116 (27.4)	0.844	351 (82.8)	73 (17.2)	**0.045**
General Discomfort	1,801 (64.5)	988 (35.4)	5 (0.2)	0.691	1,692 (60.6)	1,102 (39.4)	**<0.001**	2,005 (71.8)	789 (28.2)	0.283	2,300 (82.3)	494 (17.7)	**<0.001**
Transverse Myelitis	1 (50.0)	1 (50.0)	0 (0.0)	N/D	1 (50.0)	1 (50.0)	N/D	1 (50.0)	1 (50.0)	#N/D	2 (100.0)	0 (0.0)	N/D
Gastrointestinal Discomfort	367 (69.4)	162 (30.6)	0 (0.0)	0.328	286 (54.1)	243 (45.9)	**<0.001**	405 (76.6)	124 (23.4)	**0.023**	419 (79.2)	110 (20.8)	0.075
Urinary Discomfort	71 (69.6)	31 (30.4)	0 (0.0)	0.288	67 (65.7)	35 (34.3)	0.086	68 (66.7)	34 (33.3)	0.225	85 (83.3)	17 (16.7)	0.297
Nausea	564 (77.2)	166 (22.7)	1 (0.1)	0.389	406 (55.5)	325 (44.5)	**<0.001**	545 (74.6)	186 (25.4)	0.843	606 (82.9)	125 (17.1)	0.544
Facial Paralysis	7 (63.6)	4 (36.4)	0 (0.0)	0.206	6 (54.5)	5 (45.5)	0.206	8 (72.7)	3 (27.3)	1	8 (72.7)	3 (27.3)	0.513
Pruritus (Itching)	239 (79.4)	62 (20.6)	0 (0.0)	0.833	158 (52.5)	143 (47.5)	**0.019**	206 (68.4)	95 (31.6)	1	249 (82.7)	52 (17.3)	**<0.001**
Coagulation Disorders	18 (56.3)	14 (43.8)	0 (0.0)	0.355	17 (53.1)	15 (46.9)	1	17 (53.1)	15 (46.9)	1	26 (81.3)	6 (18.8)	**0.039**

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Vomit	110 (79.1)	29 (20.9)	0 (0.0)	0.808	75 (54.0)	64 (46.0)	**<0.001**	99 (71.2)	40 (28.8)	**0.022**	115 (82.7)	24 (17.3)	0.056
Anaphylaxis	4 (44.4)	5 (55.6)	0 (0.0)	1	5 (55.6)	4 (44.4)	0.906	5 (55.6)	4 (44.4)	0.906	8 (88.9)	1 (11.1)	0.495

*The p-value was obtained by Chi-Square test

Table 4 Self-reported ESAVIs after receiving the first and second dose of any of the available COVID-19 vaccines in Ecuador (n=6,645)

Self-reported ESAVIs after COVID-19 vaccination		**First Dose**		**Second Dose**		**P value***
		n	**(%)**	**n**	**(%)**	
Time of ESAVIs onset	Minutes	490	7.4%	210	3.2%	**<0.001**
	Hours	3,317	49.8%	1,325	19.9%	
	Days	921	13.8%	463	7.0%	
	Weeks	69	1.0%	0,0	0.0%	
	No side effects	1,857	27.9%	4,656	70.0%	
	Total	**6,654**	**100%**	**6,654**	**100%**	
Mild self-reported ESAVIs	Joint pain	1,185	7.0%	434	7.4%	0
	Headache	2,567	15.2%	935	15.9%	
	Muscle pain	2,139	12.6%	758	12.9%	
	Pain or swelling at the injection site	3,283	19.4%	1,217	20.7%	
	Chill	1,656	9.8%	444	7.5%	
	Fatigue or tiredness	2,458	14.5%	844	14.4%	
	Low-grade fever (37.1 °-38 °)	1,124	6.6%	345	5.9%	
	Discomfort	2,026	12.0%	768	13.1%	
	Gastrointestinal discomfort	413	2.4%	116	2.0%	
	Urinary discomfort	82	0.5%	20	0.3%	
	Total reports	**16,933**	**100%**	**5,881**	**100%**	
Moderate self-reported ESAVIs	Diarrhea	296	13.1%	108	14.7%	0
	Skin rash	119	5.3%	40	5.4%	
	Fever (>38°)	654	29.1%	175	23.8%	
	Swollen glands	279	12.4%	145	19.7%	
	Nausea	566	25.1%	165	22.4%	
	Pruritus	237	10.5%	64	8.7%	
	Vomit	100	4.4%	39	5.3%	
	Total reports	**2,251**	**100%**	**736**	**100%**	
Severe self-reported ESAVIs	Anaphylaxis	8	2.7%	1	0.7	0
	Changes in heart rhythm	176	59.9%	81	57.9%	
	Guillain Barre sd.	7	2.4%	3	2.1%	
	Facial swelling	20	6.8%	6	4.3%	
	High blood pressure	55	18.7%	32	22.9%	
	Transverse myelitis	2	0.7%	0	0.0%	
	Facial paralysis	6	2.0%	5	3.6%	

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	Coagulation disorders	20	6.8%	12	8.6%	
	Total reports	**294**	**100%**	**140**	**100%**	
Measures to mitigate self-reported ESAVIs	Only wait	2,295	41.2%	883	40.7%	**<0.001**
	Taking medication	2,929	52.6%	1,151	53.1%	
	Visiting a physician	319	5.7%	126	5.8%	
	Hospitalization	23	0.4%	10	0.5%	
	Total	**5,566**	**100%**	**2,170**	**100%**	

*The p-value was obtained by Chi-Square test

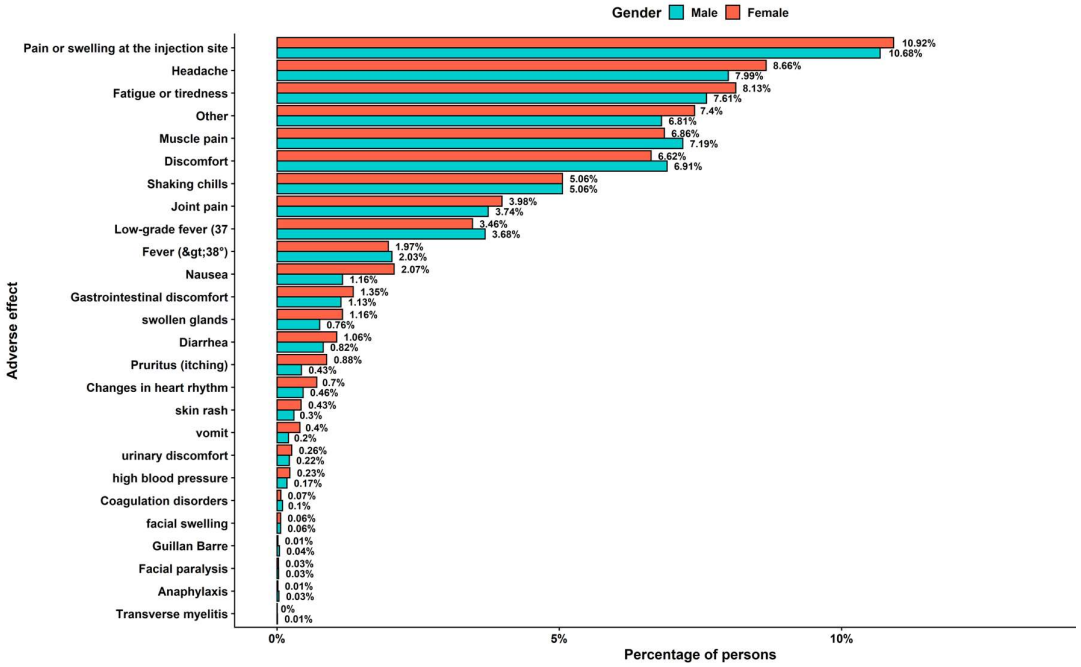

Figure 1 Self-reported ESAVIs among 6,654 patients from Ecuador

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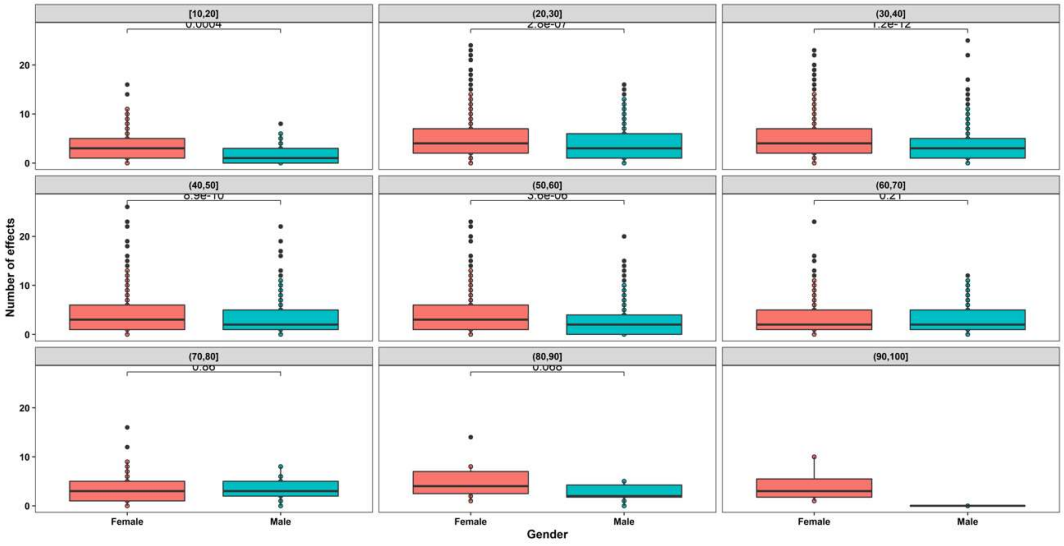

Figure 2 Self-reported ESAVIs between men and women by age

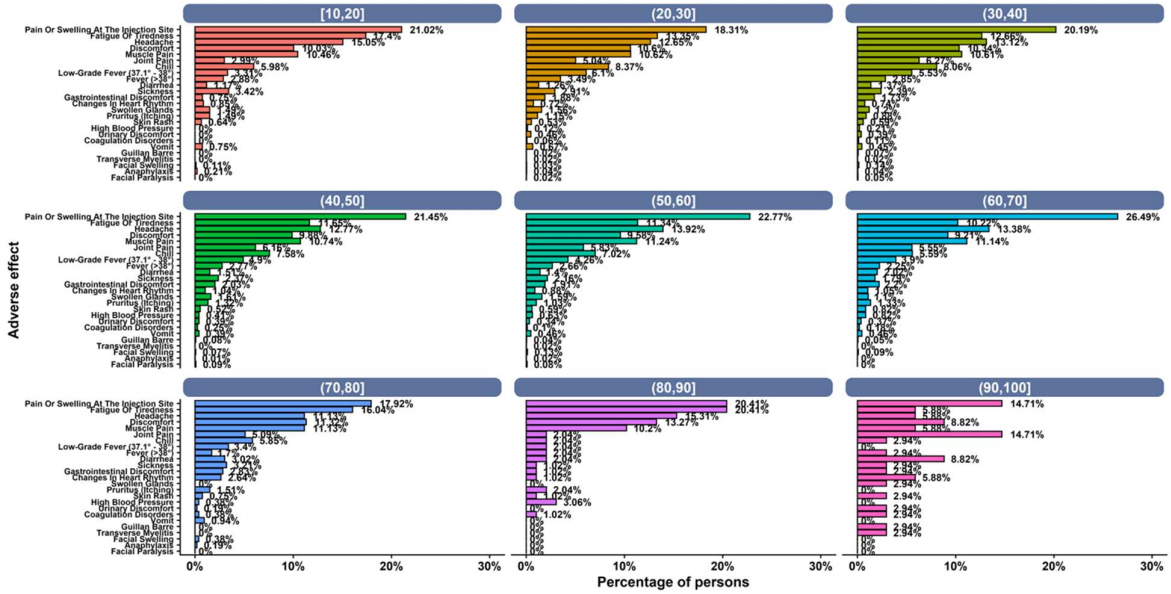

Figure 3 Age-specific self-reported adverse event among 6654 patients

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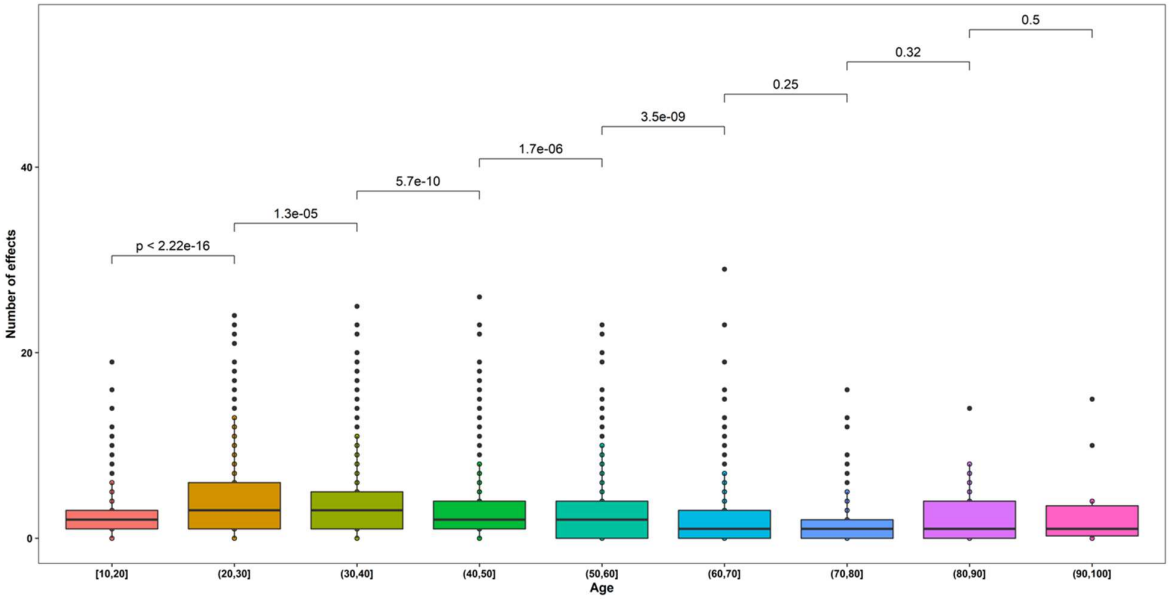

Figure 4 Number of effects among age groups

Table 5 Self-reported ESAVIs after the first dose of any of the available vaccine

	AstraZeneca		Pfizer/BioNTech		Sinovac		P
Symptoms	**(n)**	**(%)**	**(n)**	**(%)**	**(n)**	**(%)**	**value***
Tachycardia	97	0.6%	40	0.5%	39	0.7%	**<0.001**
Diarrhea	147	1.0%	62	0.8%	87	1.5%	**<0.001**
Joint Pain	862	5.7%	216	2.6%	109	1.9%	**<0.001**
Headache	1372	9.1%	627	7.7%	571	9.7%	**<0.001**
Muscle Pain	1338	8.9%	507	6.2%	298	5.1%	**<0.001**
Pain Or Swelling at The Injection Site	1273	8.5%	1348	16.5%	665	11.3%	**<0.001**
Skin Rash	56	0.4%	38	0.5%	25	0.4%	**0.002**
Shaking chills	1236	8.2%	250	3.1%	173	2.9%	**<0.001**
Fatigue Or Tiredness	1266	8.4%	620	7.6%	575	9.8%	**<0.001**
Mild/low grade fever (37.1 C°-38 C°)	857	5.7%	194	2.4%	75	1.3%	**<0.001**
Fever (>38C°)	525	3.5%	88	1.1%	41	0.7%	**<0.001**
Guillain Barre sd.	4	0.0%	3	0.0%	0	0.0%	0.705
Facial Swelling	9	0.1%	8	0.1%	3	0.1%	0.212
High Blood Pressure	25	0.2%	23	0.3%	7	0.1%	**0.004**
Swollen Glands	115	0.8%	105	1.3%	59	1.0%	**<0.001**
General Discomfort	1297	8.6%	427	5.2%	305	5.2%	**<0.001**
Transverse Myelitis	1	0.0%	1	0.0%	0	0.0%	1
Gastrointestinal Discomfort	231	1.5%	81	1.0%	101	1.7%	**<0.001**
Urinary Discomfort	58	0.4%	13	0.2%	11	0.2%	**<0.001**
Nausea	317	2.1%	116	1.4%	133	2.3%	**<0.001**
Facial Paralysis	2	0.0%	1	0.0%	3	0.1%	0.606
Pruritus (Itching)	109	0.7%	74	0.9%	54	0.9%	**<0.001**

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Coagulation Disorders	14	0.1%	4	0.0%	2	0.0%	**0.002**
Vomit	56	0.4%	20	0.2%	24	0.4%	**<0.001**
Anaphylaxis	2	0.0%	2	0.0%	4	0.1%	0.607
Total	**11269**	**100%**	**4868**	**100%**	**3364**	**100%**	

*The p-value was obtained by Chi-Square test

Table 6 Self-reported ESAVIs after receiving the second dose of any of the available vaccine

Symptoms	**AstraZeneca**		**Pfizer/BioNTech**		**Sinovac**		**P**
	n	**%**	**n**	**%**	**n**	**%**	**value**
Tachycardia	9	0.4%	61	0.7%	11	0.6%	**<0.001**
Diarrhea	27	1.3%	58	0.7%	23	1.3%	**<0.001**
Joint Pain	58	2.7%	336	3.9%	43	2.4%	**<0.001**
Headache	185	8.7%	620	7.2%	134	7.6%	**<0.001**
Muscle Pain	101	4.8%	577	6.7%	83	4.7%	**<0.001**
Pain Or Swelling at The Injection Site	164	7.7%	887	10.3%	168	9.5%	**<0.001**
Skin Rash	6	0.3%	27	0.3%	7	0.4%	**0.003**
Shaking chills	74	3.5%	342	4.0%	30	1.7%	**<0.001**
Fatigue Or Tiredness	152	7.2%	575	6.7%	120	6.8%	**<0.001**
Mild/low grade fever (37.1 C°- 38 C°)	48	2.3%	283	3.3%	14	0.8%	**<0.001**
Fever (>38C°)	27	1.3%	142	1.6%	6	0.3%	**<0.001**
Guillain Barre sd.	0	0.0%	2	0.0%	1	0.1%	0.563
Facial Swelling	1	0.0%	4	0.0%	1	0.1%	0.368
High Blood Pressure	8	0.4%	22	0.3%	2	0.1%	**<0.001**
Swollen Glands	7	0.3%	124	1.4%	14	0.8%	**<0.001**
General Discomfort	123	5.8%	562	6.5%	85	4.8%	**<0.001**
Transverse Myelitis	0	0.0%	0	0.0%	0	0.0%	N/D
Gastrointestinal Discomfort	21	1.0%	69	0.8%	26	1.5%	**<0.001**
Urinary Discomfort	4	0.2%	15	0.2%	1	0.1%	0.472
Nausea	35	1.7%	105	1.2%	25	1.4%	**<0.001**
Facial Paralysis	1	0.0%	2	0.0%	2	0.1%	1
Pruritus (Itching)	10	0.5%	43	0.5%	11	0.6%	**<0.001**
Coagulation Disorders	7	0.3%	5	0.1%	0	0.0%	0.779
Vomit	5	0.2%	32	0.4%	2	0.1%	**0.003**
Anaphylaxis	1	0.0%	0	0.0%	0	0.0%	0.607
Total	**1074**	**100%**	**4893**	**100%**	**809**	**100%**	

*The p-value was obtained by Chi-Square test

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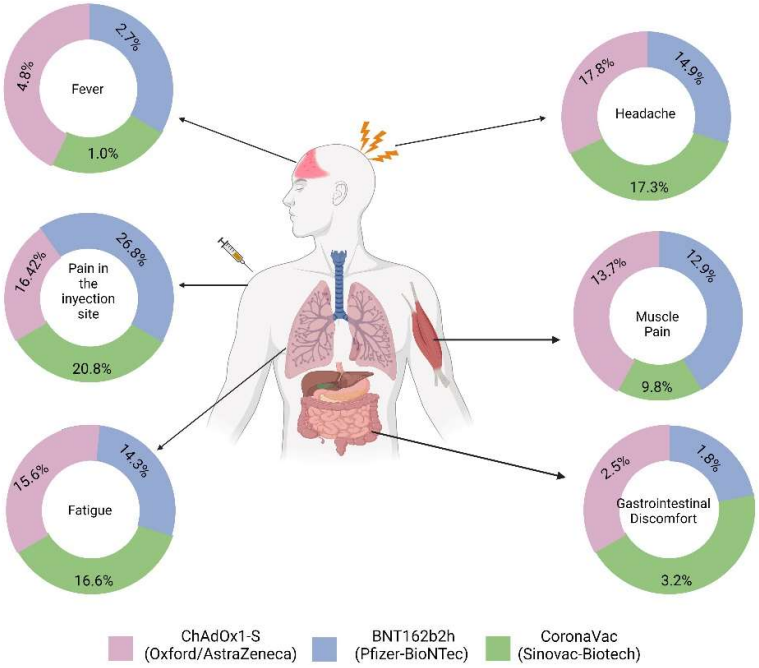

Figure 5 Symptoms depending on the vaccine administered (two doses)

4. Discussion

To the best of our knowledge, this is the first study in Latin America examining self-reported ESAVIs after one or two COVID-19 vaccine doses. This analysis revealed that women, young adults, participants without COVID-19 infection history, participants after the first vaccine dose, and AstraZeneca users developed ESAVIs more frequently. Most self-reported ESAVIs were mild and moderate.

Although this sample only represents a small subset of all vaccinated people in Ecuador, our results are like the ones described in other reports. Regarding sex, we found that women developed more ESAVIs than men. These results are similar to those seen in several studies **[16–18]**. The distribution of self-reported ESAVIs according to age showed that participants under 50 years of age had more ESAVIs compared to older participants. This is in line with data reported by Zare et. al who exposed a greater presence of adverse events in those under 40 years of age. Moreover, Cuschieri et al. and Menni et. al found more reports of ESAVIs in people under 45 years of age and 55 years of age, respectively **[19–21]**.

One interesting and controversial point is the relationship between COVID-19 history and ESAVIs. In our study, participants without a history of infection at the time of the questionnaire had higher reported adverse events. Our findings contrast with several studies **[19,21]**. Regarding these differences, an increase in reactogenicity related to an increase in antibody titers conditioned by the previous infection in vaccinated individuals has been proposed. However, to date this causal relationship has not been fully demonstrated, assuring us that the role of the history of the previous infection does not cause an increased the number of ESAVIs in patients receiving vaccines against the SARS-CoV-2 virus **[22,23]**.

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The most common reported ESAVIs were pain or swelling at the injection site, headache, and fatigue, as observed by several authors in other investigations based on their own reports, such as Menni et al. in the UK, Elgendy et. al in the Egyptian population, as well as in the clinical trial by Polack et al. **[16,21,24]**. When comparing the frequency of ESAVIs according to the number of doses, no important differences were found between the ESAVIs reported after the first and the second dose, even though the absolute number of ESAVIs was reported in greater quantity after the first dose, a finding that is similar to recent reports **[24]**. However, previous studies showed opposite data since the effects caused by the AstraZeneca and Pfizer vaccines had the highest prevalence when receiving the second dose compared to the first in populations larger than our study **[16,25]**. In the same context, it is interesting that the most frequent moderate ESAVIs reported, in general were fever and nausea, while within the severe ESAVIs, changes in heart rhythm (tachycardia) occurred in more than half of the reports, in addition, within the study of infrequent severe adverse events (rare n < 30) such as Guillain Barre Syndrome, transverse myelitis, anaphylaxis, and coagulation disorders, we found that these were reported in users of the three vaccines (AstraZeneca, Pfizer, Sinovac). In addition, twice the frequency or more was observed after receiving the first dose of vaccination, however, throughout the self-reported studies available at the moment, only one showed data on the presence of anaphylaxis in its participants, these differences could be due to the difficulty of the participants to define and know with certainty these diagnoses **[26]**. The nature of these findings is difficult to elucidate, in the case of the relationship between vaccines against COVID-19 and the development of Guillain Barre syndrome, an analysis developed by Keh et. al in databases from the United Kingdom stated that there are no demographic or phenotypic differences that can ensure the development of Guillain Barre syndrome due to vaccines against COVID-19, however, most of the population studied was UK ethnic white (90.3%) with a minimal presence of Latin Americans **[17]**. Otherwise, in the case of anaphylaxis, an extensive meta-analysis managed to show that although reports of anaphylaxis due to the possible cause of SARS-CoV-2 virus vaccines are higher than with other rare adverse effects, these are not can be attributed to receiving these vaccines, since they occur with a wide range of vaccines and are related to the components of the vaccines mainly **[18]**.

Regarding the ESAVIs reported by users who received the CoronaVac vaccine (Sinovac) in our study, the most frequently recorded were pain or inflammation at the injection site, headache, and fatigue for the first and second doses, these data are consistent with what was found in the Chinese population by Zhang et. As with fatigue, muscle pain, and headache for both doses **[27]**, while in the Turkish population Riad et. Al found pain at the injection site, fatigue, headache, and muscle pain as the most frequent adverse events **[28]**.

Our findings show differences in the frequency of reporting of ESAVIs when comparing the type of vaccine, the data showed that the greatest number of ESAVIs was attributed to the ChAdOx1 viral vector vaccine, the same as that presented by Menni et. al, Klugar et. al, Omeish et. to the. and Alhazmi et. al **[21,29,30]**. Besides, when addressing these differences about the number of doses, the reported distribution shows different patterns, in the case of the first dose, the ChAdOx1 vaccine was responsible for the majority of adverse events, while among the participants they received the second dose of vaccination the BioNTech vaccine was the one that was attributed more than half of ESAVIs, this trend is similar to that found in Egypt **[24]**.

In the analysis of the time of ESAVIs onset, we found that the majority of ESAVIs significantly occurred after within the first day after receiving the vaccine. Other authors observed the same behavior in their participants, although they did not find statistically significant differences **[24,30,31]**. On the other hand, the measures that the adverse

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events caused our participants to take were characterized by taking medication to correct the symptoms in most cases and in a very small proportion to visit a doctor, these behaviors have been previously observed in proportions similar in the population of Saudi Arabia **[30]**, and in almost zero proportion to require hospitalization due to adverse events, likewise, this trend was similarly evidenced in studies that evaluated adverse effects due to AstraZeneca, Pfizer vaccines and Sinopharm **[30,31]**.

5. Limitations

Our study has several limitations inherent to the cross-sectional self-reported design; such that, some observations should be interpreted with caution. Because the questionnaire was distributed through social networks, the information belonging to the population that did not have the resources to access the questionnaire was relegated from the study. Similarly, most older adults handle electronic devices and the Internet with difficulty. This may cause selection bias; however, we consider that our sample calculation provided a considerable sample size to reduce this bias. Social desire bias is another potential limitation that could have affected responses due to the self-report nature of the questionnaire. In other words, negative or positive self-reported symptoms may be underreported or overreported because respondents want to mark what they consider "socially acceptable" responses. However, the use of an anonymous online questionnaire should have somewhat mitigated the risk of this bias. Despite these limitations, we managed to obtain a large amount of information provided by many participants based on official data on the number of vaccinated in Ecuador. Likewise, our data was subjected to extensive filtering to provide valid results. For the aforementioned reasons, we consider this study to be a reliable approximation of the self-reported ESAVIs of Ecuadorians and that can help to inform their symptoms and somehow decrease COVID-19 hesitancy

6. Conclusion

This is the first report in Ecuador and in the region on adverse events attributed to COVID-19 vaccines. In general, it can be observed that the adverse events reported are mostly mild and transitory, which further supports the fact that COVID-19 vaccines are safe. Mild ESAVI's were the most self-reported events described in Ecuador. We found that first doses were associated with a higher proportion of ESAVI's compared to subjects who received a subsequent dose. We also found that participants without COVID-19 past-medical history, AstraZeneca users and younger populations are more likely to develop ESAVIs.

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Ethical Approval: The analysis included anonymized, un-identifiable information and received an exemption letter from the Universidad de las Americas Ethics Committee CEISH on March 10th, 2020. All methods were carried out in accordance with local guidelines and regulations and the National Review Board within the Minister of Public Health.

Availability of supporting data: The dataset with the total responses can be obtained from the authors upon reasonable request. The questionnaire summary and its results are included in this article.

Competing interests: The authors have no conflict of interest to declare

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