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Posted Date: 25 January 2023

doi: 10.20944/preprints202301.0440.v1

Keywords: COVID-19 Vaccines; BNT162 Vaccine; ChAdOx1 nCoV-19; Side Effects and Adverse Reactions; Booster Immunizations; COVID-19; SARS-CoV-2



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Article

Safety Profile of Standard and Booster COVID-19 Vaccines in Physicians in Quito-Ecuador. A Cross-Sectional Study

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Abstract: More than 600 Healthcare workers died due to COVID-19 infection until January 2022 in Ecuador. Even though the COVID-19 vaccines are safe, local, and systemic reactions were reported among physicians. This study aims to analyze the Adverse events (AEs) of COVID-19 vaccines with an emphasis on homologous and heterologous booster doses. An electronic survey was performed in Quito- Ecuador, directed to physicians who were vaccinated with the three doses of COVID-19 vaccines. 210 participants were analyzed after administering any doses of the vaccines. At least one AE was identified in 60.0% (126/210) of the sample after the first dose, 52.40% (110/210) after the second dose, and 75.2% (158/210) after the booster dose. The most frequent AEs were localized pain, myalgia, headache, and fever. At least one drug was used in 44.3% of the population after the first dose, 37.1% after the second dose, and 63.8% in the booster dose. Heterologous booster produces more AEs compared with homologous booster (80.1% vs. 53.8%), and 77.3% of participants reported that interfered with daily activities. Similar studies agree that reactogenicity occurs mainly with heterologous vaccination compared to homologous vaccination. This situation affected physicians' performance in daily activities and led them to use medication for the symptoms.

Keywords: COVID-19 vaccines; BNT162 vaccine; ChAdOx1 nCoV-19; side effects and adverse reactions; booster immunizations; COVID-19; SARS-CoV-2

1. Introduction

The COVID-19 pandemic has produced 568,773,510 cases and 6,381,643 deaths worldwide (1). Healthcare workers (HCWs) are defined as paid or unpaid persons engaged in actions whose primary intent is to enhance health (2). Among the first line HCWs, physicians are one of the most affected groups by COVID-19 infections and the one with the highest mortality (3), for instance, more than 600 physicians died due to COVID-19 infection until January 2022 in Ecuador (4). For this reason, the World Health Organization (WHO) established that physicians were a priority in the administration of vaccines including the booster dose (5).

In Ecuador, 946,487 people were diagnosed with COVID-19(1), the most affected province is Pichincha (6), and Quito, the capital of Ecuador, is the city with the highest number of confirmed cases (7).

A booster dose is the response of the Public Health Systems to the emergence of new SARS-CoV-2 variants (8) and the decay of neutralizing antibodies in people fully vaccinated after 3-6 months (9,10). The National Vaccination Campaign achieved full vaccination of 83.84% of the population and 39.98% got a booster dose(11). The Ministry of Health (MoH) managed the administration of four COVID-19 vaccines: the mRNA Pfizer/BioNTech-Comirnaty, the non-replicating viral vector Oxford/AstraZeneca-Vaxzevria, and CanSino-Convividencia, and the inactivated virus vaccine Sinovac-CoronaVac.

The 56.39% of the total booster doses were primarily administered with Oxford/AstraZeneca-Vaxzevria, 34.78% with Pfizer/BioNTech-Comirnaty, 2.09% with CanSino-Convividencia, and 6.72% with Sinovac-CoronaVac(11).

Even though the COVID-19 vaccines are safe(12), few local and systemic reactions were reported after the first and second doses of vaccination(13) and after the application of a heterologous booster dose among HCWs(14). Regarding the homologous versus heterologous booster, the latter demonstrated a slightly higher rate of adverse events in HCW(15).

This study aims to analyze the adverse events of COVID-19 with an emphasis on homologous and heterologous booster doses in physicians that received three approved vaccines in Ecuador.

2. Materials and Methods

This article was written following the STROBE initiative for the reporting of observational studies (16).

Study Design and Ethical conditions: The present cross-sectional study was approved by the Independent Ethics Committee SOLCA-NUCLEO QUITO with the number OBS.21.202 and during its development, all the norms of Good Clinical Practice and Helsinki principles (17) were compiled to maintain the participant's safety and assure the quality of data obtained.

2.1. Settings, data source, and participants

An open and anonymous electronic survey (27 questions and 6 different screens) was performed in the city of Quito-Ecuador directed to the medical volunteer participants who were vaccinated with the 3 doses of the following vaccines against COVID-19: Oxford/AstraZeneca-Vaxzevria, Pfizer/BioNTech-Comirnaty or Sinovac-CoronaVac (greater than 7 days from the third dose). The instrument was published on different online media and social networks using platforms followed by physicians to delimit the sample; obtaining data from February 15 to April 01 of 2022 through the Google formulary application after individual authorization through the acceptance of electronic Informed Consent. To deal with the risk of duplicated responses, the email address was requested and if duplicated files were identified then the oldest one was eliminated.

2.2. Measurement of variables

Outcome measures: The results were obtained through the different responses to the questions asked during the development of the survey, keeping as dependent variables the development of any adverse event, the use of 1 or more medications, and the affectation of daily activities 7 days after any dose of vaccination against COVID-19.

The outcome adverse event was evaluated through the closed question "Did you present any subsequent adverse event in the 7 days following the administration of the COVID-19 vaccine?", in each dose administered (3 doses) dichotomizing the answer in Yes/No; in case of an affirmative answer, the type of adverse event was requested through the following non-exclusive question "If yes. Which of the following adverse events occurred during the first 7 days post-vaccination?", awaiting confirmation or denial of the following adverse events: localized pain, localized edema, localized erythema, localized pruritus, thermal elevation, diarrhea, nausea, vomiting, myalgia, arthralgia, headache and the development of other types of adverse events (obtained from the U.S Food and Drug Administration (FDA)(18)).

The use of medication was requested through the closed question "Was any medication administered for these side effects?", at each dose placed obtaining Yes/No answers; in case of an affirmative answer, it was requested to describe which medications were used through the use of the excluding question: Paracetamol, Ibuprofen, Diclofenac, Etoricoxib, and other medications. This qualitative variable was subclassified as the number of drugs used during the 7 days following each dose of the COVID-19 vaccine (None, 1 drug, 2 drugs, 3 or more drugs).

The affectation of daily activities during the 7 days after the administration of each dose of the COVID-19 vaccine was classified as an ordinal qualitative variable and assessed through a Likert-type scale with 4 options requested through the following question "Indicate the relationship between your daily activities and the adverse events present on a scale of 1 to 4", obtaining, as a result, the options: 1) Does not interfere with your daily activities and no treatment is administered; 2) Interferes with daily activities and/or required pharmacological treatment; 3) Impedes the performance of daily activities and required treatment; 4) Was hospitalized.

Individual measures: Participants were asked for sociodemographic information related to their date of birth (for age calculation), sex (male, female), and place of work; this last variable was classified as public, private, or no work. Dates of vaccination and the name of the vaccine applied were also required for each dose; these variables were classified according to the number of doses (first dose, second dose, third dose) and administered vaccine (Oxford/AstraZeneca-Vaxzevria, Pfizer/BioNTech-Comirnaty or Sinovac-CoronaVac). The third dose was subclassified concerning the type of vaccine into homologous (defined as administration of the same vaccine in all three doses) and heterologous (placement of a different vaccine in any dose).

2.3. Biases

As the study requires retrospective data, the risk of memory bias is latent, and it was managed by placing the download link of the vaccination certificate of the MoH of Ecuador and the request based on mixed questions that counted as options for different adverse events that help to remember the events that occurred.

2.4. Statistical analysis

To calculate the sample size, the finite universe formula was used with a sampling error of 5%, a confidence interval of 95%, and an expected proportion of 82.1% for a population of 11,730 physicians of Quito-Ecuador, with a loss of 10%, a sample of 250 participants was obtained. In this project using a non-probabilistic sampling studies snowball.

In case of missing data, the mean of each variable was placed to avoid loss of information. The descriptive analysis for qualitative variables was expressed with frequency tables; for qualitative variables, summary measures such as mean, median, standard deviation, and interquartile range were used and presented according to the type of distribution of each variable. For the bivariate analysis, measures of association were applied with a parametric test (χ^2 and Student's t-tests) and nonparametric test (Mann Whitney U), and risk measures (Odds Ratio) with their respective 95% confidence intervals, using the presence or absence of adverse events as the dependent variable. Statistical analysis was performed with the Statistical Package for the Social Sciences version 26 program® (SPSS; IBM Corp., Armonk, NY).

3. Results

225 participants gave their consent to participate in the study, obtaining a recruitment and completion rate of 100%; 15 research subjects were excluded, 13 for being non-medical professionals, and 2 for receiving another type of vaccine. A total of 210 participants were analyzed with 630 vaccines administered divided into 3 doses (Figure 1). The 65.7% (138/210) are women; the participants present average age of 32 years (RIQ: 11.25) and for the 630 doses administered, 47.3% were Pfizer/BioNTech-Comirnaty, the 39.0% Oxford/AstraZeneca-Vaxzevria and the 13.7% Sinovac-CoronaVac). Table 1 describes the characteristics of the participants; no missing data were identified during the analysis.

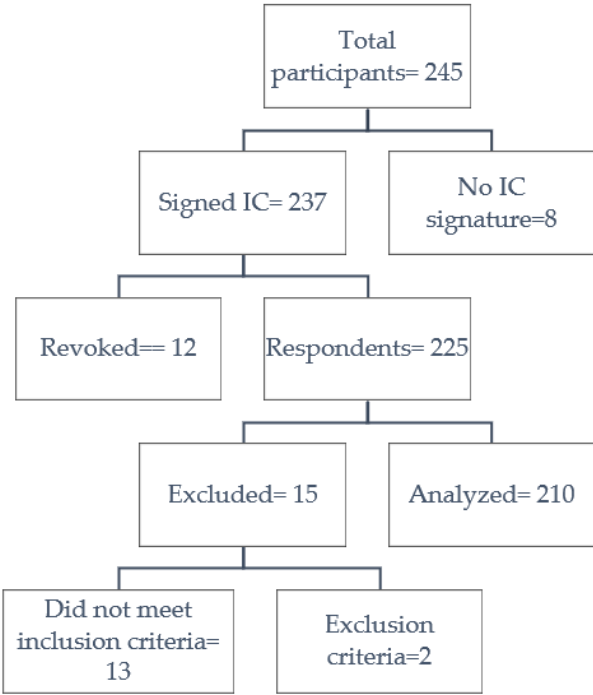


Figure 1. Summary of participants.

Table 1. Sociodemographic characteristics and vaccine administered to participants.

		n (%)
General		210 (100.0)
Sex	Female	138 (65.7)
	Male	72 (34.3)
Age (Years)	Under 30 years of age	88 (41.9)
	30 to 39 years old	70 (33.3)
	40 to 49 years old	25 (11.9)
	50 to 59 years old	15 (7.1)
	Over 60 years old	12 (5.7)
Vaccine	Total	630 (100.0)
	Pfizer/BioNTech-Comirnaty	298 (47.3)
	Oxford/AstraZeneca-Vaxzevria	246 (39.0)
	Sinovac-CoronaVac	86 (13.7)

3.1. Doses administered

It has been identified that 62.5% (394/630) of the doses administered presented at least one adverse event during the 7 days after the administration of any dose of the vaccine, with a frequency of 60.0% (126/210) after the first dose, 52.40% (110/210) and in the second dose 75.2% (158/210) after the third dose. The most frequent adverse event reported was localized pain in 49.5% (312/630) followed by myalgia in 28.3% (178/630), headache in 24.9% (157/630), and thermal elevation with a frequency of 21.6% (136/630). Concerning the use of medications, 48.4% (305/630) of the participants reported having used at least one medication for the management of adverse events, 44.3% (93/210) after the first dose, 37.1% (78/210) after the second dose and 63.8% (134/210) in the third dose applied; of the participants who reported at least one adverse event, the 44.7% (176/391) reported that their daily activities were affected and/or required pharmacological treatment. The characteristics of each dose are described in Table 2.

Table 2. Descriptive characteristics of adverse events, medication, and relationship with daily activities.

	Total n (%)	First Dose n (%)	Second Dose n (%)	Third Dose n (%)
General	630 (100.0)	210 (33.3)	210 (33.3)	210 (33.4)
Adverse Events	394 (62.5)	126 (60.0)	110 (52.4)	158 (75.2)
Pain	312 (49.5)	107 (51.0)	91 (43.3)	114 (54.3)
Myalgia	178 (28.3)	45 (21.4)	36 (17.1)	97 (46.2)
Headache	157 (24.9)	43 (20.5)	30 (14.3)	84 (40.0)
Thermal elevation	136 (21.6)	30 (14.3)	19 (9.0)	87 (41.4)
Arthralgia	111 (17.6)	29 (13.8)	17 (8.1)	65 (31.0)
Edema	40 (6.3)	11 (5.2)	5 (2.4)	24 (11.4)
Pruritus	39 (6.2)	11 (5.2)	11 (5.2)	17 (8.1)
Erythema	36 (5.7)	14 (6.7)	6 (2.9)	16 (7.6)
Other types of adverse events	100 (15.9)	30 (3.6)	16 (7.3)	54 (25.8)
Use of medication	305 (48.4)	93 (44.3)	78 (37.1)	134 (63.8)
1 drug	243 (79.7)	84 (90.3)	68 (87.2)	91 (67.9)
2 drugs	54 (17.7)	6 (6.5)	8 (10.3)	40 (29.9)
3 or more drugs	8 (2.6)	3 (3.2)	2 (2.6)	3 (2.2)
Daily Activities	394 (100.0)	126 (100.0)	110 (100.0)	158 (100.0)
Do not interfere with your daily activities and no treatment is administered	158 (40.1)	64 (50.8)	56 (50.9)	38 (24.1)
Interferes with daily activities and/or required pharmacological treatment.	176 (44.7)	55 (43.7)	46 (41.8)	75 (47.5)
Impedes the performance of daily activities and required treatment	57 (14.5)	7 (5.6)	8 (7.3)	42 (26.6)
Was hospitalized	3(0.8)	0 (0.0)	0 (0.0)	86 (1.9)

3.2. Vaccine administered

About the vaccine administered it becomes evident that 74.8% (184/246) of the participants that were given Oxford/AstraZeneca-Vaxzevria presented adverse events, with a mean of 3.4 (SD=2.0) adverse events. In the group of participants administered with Pfizer/BioNTech-Comirnaty, a frequency of 59.1% (176/298) with a mean of 2.4 (SD=1.6) adverse events were identified, and in the Sinovac-CoronaVac group, 39.5% (34/86) presented at least one adverse event with a mean of 1.8 (SD=1.2) (Figure 2). Concerning the use of medication, 63.0% (155/246) of the Oxford/AstraZeneca-Vaxzevria group reported using a medication, compared to 42.3% (126/298) of the Pfizer/BioNTech-Comirnaty group and 27.9% (24/86) of the participants inoculated with Sinovac-CoronaVac. The characteristics of adverse events, the use of medication, and the relationship with daily activities are described in Table 3. In Appendix A Table A1 descriptive characteristics of adverse events with the doses and the vaccine.

Table 3. Descriptive characteristics of adverse events, medication, and relationship to daily activities in relation to the vaccine.

	Oxford/AstraZeneca- Vaxzevria n (%)	Pfizer/BioNTech- Comirnaty n (%)	Sinovac- CoronaVac n (%)
General	246 (100.0)	298 (100.0)	86 (100.0)
Adverse Events	184 (74.8)	176 (59.1)	34 (39.5)
Pain	129 (52.4)	152 (51.0)	31 (36.0)
Myalgia	111 (45.1)	62 (20.8)	5 (5.8)

Headache	94 (38.2)	53 (17.8)	10 (11.6)
Thermal elevation	91 (37.0)	41 (13.8)	4 (4.7)
Arthralgia	78 (31.7)	32 (10.7)	1 (1.2)
Edema	23 (9.30)	13 (4.4)	4 (4.7)
Pruritus	18 (7.3)	18 (6.0)	3 (3.5)
Erythema	16 (6.5)	16 (5.4)	4 (4.7)
Other types of adverse events	62 (22.3)	38 (12.7)	0 (0.0)
Use of medication	155 (63.0)	126 (42.3)	24 (27.9)
1 drug	111 (71.6)	110 (87.3)	22 (91.7)
2 drugs	40 (25.8)	12 (9.5)	2 (8.3)
3 or more drugs	4 (2.6)	4 (3.2)	0 (0.0)
Daily Activities	184 (100.0)	176 (100.0)	34 (100.0)
Do not interfere with your daily activities and no treatment is administered	54 (77.0)	79 (44.9)	25 (73.5)
Interferes with daily activities and/or required pharmacological treatment.	88 (79.0)	79 (44.9)	9 (26.5)
Impedes the performance of daily activities and required treatment	39 (18.0)	18 (10.2)	0 (0.0)
Was hospitalized	3 (1.6)	0 (0.0)	0 (0.0)

3.3. Group vaccine

In the group of participants with heterologous reinforcement, it is evident that 80.1% (137/171) presented at least 1 adverse event, compared to 53.8% (21/39) of the homologous group; they also report that 70.2% (120/171) report the use of medication for the control of adverse events in the heterologous group compared to 35.9% (14/39) of the homologous group. The characteristics of adverse events, medication use, and their relationship with daily activities are described in Table 4.

Table 4. Adverse events after vaccination medication, and relationship to daily activities: Heterologous vs Homologous.

	Heterologous n (%)	Homologous n (%)
General	171 (100.0)	39 (100.0)
Adverse Events	137 (80.1)	21 (53.8)
Pain	97 (56.7)	17 (43.6)
Myalgia	89 (52.0)	8 (20.5)
Thermal elevation	80 (46.8)	7 (17.9)
Headache	78 (45.6)	6 (15.4)
Arthralgia	61 (35.7)	4 (10.3)
Edema	23 (13.5)	1 (2.6)
Pruritus	15 (8.80)	2 (5.1)
Erythema	14 (8.20)	2 (5.1)
Other types of adverse events	51 (29.9)	3 (7.7)
Use of medication	120 (70.2)	14 (35.9)
1 drug	82 (68.3)	9 (64.3)
2 drugs	35 (29.2)	5 (35.7)
3 or more drugs	3 (2.5)	0 (0.0)
Daily Activities	137 (100.0)	21 (100.0)
Do not interfere with your daily activities and no treatment is administered	28 (20.4)	10 (47.6)
Interferes with daily activities and/or required pharmacological treatment.	68 (49.6)	7 (33.3)
Impedes the performance of daily activities and required treatment	38 (27.7)	4 (19.0)

Was hospitalized 3 (2.2) 0 (0.0)

3.4. Factors related to the occurrence of adverse events.

In the bivariate analysis, it was identified that 62.5% (394/630) of the participants developed some adverse event, where being female (OR: 1.76 (1.25 -2.46)), receiving the third dose (OR: 2.36 (1.64-3.42)), the Oxford/AstraZeneca vaccine (OR: 2.45 (1.79-3.49)) and a heterologous vaccine (OR: 3.63 (2.31-5.69)) increased the probability of presenting an adverse event, Table 5 describes these results.

Table 5. Factors related to the development of adverse events.

	Total (n/%)	Adverse Event No (n/%)	Adverse Event Yes (n/%)	p Value	OR (CI 95%)
General	630(100.0)	236 (37.5)	394 (62.5)	-	-
Sex					
Female	414 (65.7)	136 (57.6)	278 (70.6)	0.001	1.76 (1.25 – 2.46)
Age					
Over 32 years old	522 (82.9)	193 (81.8)	329 (83.5)	0.579	1.12 (0.73 - 1.72)
Doses administered					
First Dose	210 (33.3)	84 (35.6)	126 (32.0)	0.353	0.85 (0.60 - 1.19)
Second Dose	210 (33.3)	100 (42.4)	110 (27.9)	< 0.001	0.52 (0.37 - 0.74)
Third Dose	210 (33.3)	52 (22.0)	158 (40.1)	< 0.001	2.36 (1.64 - 3.42)
Vaccine					
Pfizer/BioNTech-Comirnaty	298 (47.3)	122 (51.7)	176 (44.7)	0.087	1.32 (0.95 – 1.83)
Oxford/AstraZeneca-Vaxzevria	246 (39.0)	62 (26.3)	184 (46.7)	< 0.001	2.45 (1.73 - 3.49)
Sinovac-CoronaVac	86 (13.7)	52 (22.0)	34 (8.6)	< 0.001	0.33 (0.20 - 0.53)
General	420(100.0)	152 (36.2)	268 (63.8)	-	-
Group Vaccine					
Heterologous	171 (40.7)	34 (22.4)	137 (51.1)	< 0.001	3.63 (2.31 – 5.69)
Homologous	249 (59.3)	118 (77.6)	131 (48.9)		

CI: Confidence Interval.

4. Discussion

During the first year of the pandemic, scientists worldwide developed safe and effective vaccines to reduce hospitalization and deaths associated with COVID-19. However, due to the limited availability of vaccine doses, vaccination was prioritized for HCWs and was the best strategy to control deaths and diseases in this population(19). It is essential to describe the characteristics of the local and systemic AEs presented by the HCW and to analyze their relationship with the degree of affectation in the performance of daily activities after full or booster immunization and thus improve vaccination plans in the future.

Our study shows a high prevalence of local and systemic adverse events (62.5%), in medical personnel after 7 days of administration of the approved vaccines in Ecuador, describing a higher frequency after administration of the third dose (75.2%), compared to the first and second doses (60.0% and 52.4%, respectively). Of these adverse events, the great majority did not interfere or slightly interfered with daily activities, showing that they were mild to moderate, despite this, 48.4% of the participants administered some medication to control the side effects. Regarding the most frequent side effects, localized pain at the injection site (local event), myalgia, and headache (systemic events) were reported. Likewise, it was identified that being a woman, receiving an mRNA vaccine, Oxford/AstraZeneca-Vaxzevria, the third dose of any vaccine, and the heterologous vaccine as a booster increased the risk of presenting adverse events.

Naito T. et al.(20) conducted a study with HCWs in Japan with a population that received Pfizer/BioNTech-Comirnaty and Moderna vaccines. They reported similar frequencies of adverse reactions during the first eight days after the second and third vaccination. Also, they found that the incidence of adverse reactions was significantly higher in heterologous vaccination compared to homologous vaccination (20), which is consistent with our results.

In a German study performed by Nachtigall et al. (21), in health workers, the most reported local adverse event during the first eight days, at any vaccination dose, was pain at the injection site (50.2%), followed by malaise (30.1%). Homologous vaccination produced fewer adverse events (49.4%) than heterologous vaccination (81.4%) (21), similar to our results.

In Thailand, a prospective study was performed in HCWs, where the most common systemic adverse events after the Sinovac-CoronaVac / Oxford/AstraZeneca-Vaxzevria booster dose included myalgia, headache, and fever (37%, 34%, and 34%). The AE prevalence was significantly lower for individuals in the Oxford/AstraZeneca-Vaxzevria group after the CoronaVac booster. The most common symptoms observed in this group were headache, myalgia, and fatigue (13%, 11%, and 9%, respectively), and the local reaction was 14%, in comparison with 17% of the other group (22), similar our results showed previously.

Concerning the vaccine type, Oxford/AstraZeneca-Vaxzevria vaccine showed the highest risk of adverse events (OR 2.45, CI 95% 1.73 - 3.49, $p < 0.001$) with similar results in several other studies (27,28). On the other hand, a systematic review and meta-analysis performed by Kouhpayeh and Ansari reported that inactivated vaccines such as Sinovac-CoronaVac have no relationship with systemic adverse events (RR 1.13, CI 95% 0.79 – 1.61) (29) as in our study where Sinovac-CoronaVac showed the least risk for AE (OR 0.33, 95% CI 0.20 - 0.53, $p < 0.001$).

Our study cohort consisted of physicians, and therefore in terms of age distribution, most participants were of working age; this may constrain the generalizability of our results, especially for the elder age groups. Further analysis including nurses, paramedics, and laboratory staff, should be performed to generalize our results to the Healthcare workers group.

5. Conclusion

This study presents the descriptive characteristics of local and systemic adverse events in medical personnel from Quito who were immunized with Oxford/AstraZeneca-Vaxzevria, Pfizer/BioNTech-Comirnaty, and Sinovac-CoronaVac during the National Vaccination Campaign in Ecuador. This study compares the symptoms described most frequently by the participants in the different doses and in the group that received homologous and heterologous vaccination. In addition, the relationship between vaccination and daily activities performance is analyzed, with the requirement of pharmacological treatment to alleviate the reported symptoms. People who received the Vaxzevria vaccine had more adverse events (74.8%) compared to those who received Comirnaty (59.1%) and CoronaVac (39.5%). The highest degree of adverse events occurs with heterologous vaccination compared to homologous immunization (80.1% vs. 53.8%), coinciding with other international results. All the vaccines used by medical personnel produced local and systemic adverse events from the first dose to the booster dose during the first seven days, and the booster dose presented a higher prevalence of adverse events. This situation led to the use of medication for the symptoms presented and affected the performance of physicians' daily activities during the pandemic.

Supplementary Materials: Not applicable.

Author Contributions: Conceptualization, J.R., L.F., and N.F.; methodology, J.R., L.F. and N.F.; software, J.R., L.F. and N.F.; validation, J.R., L.F., M.J. and N.F.; formal analysis, J.R., T.O. and C.M.; investigation, J.R., L.F., and G.G.; resources, J.R., L.F., G.G. and M.J.; data curation, J.R. and M.J.; writing—original draft preparation, J.R., L.F., and N.F.; writing—review and editing, J.R., L.F., T.O., C.M., M.J., G.G., and N.F.; supervision, J.R., and L.F.; project administration, J.R., L.F., and N.F.; funding acquisition, G.G.

Funding: Not applicable.

Institutional Review Board Statement: This study was approved by the Independent Ethics Committee SOLCA-NUCLEO QUITO with the number OBS.21.202 and during its development, all the norms of Good Clinical Practice and Helsinki principles were compiled to maintain the participant's safety and assure the quality of data obtained.

Informed Consent Statement: Electronic informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to maintaining privacy data of the participants such as e-mail addresses.

Acknowledgments: ANID - MILENIO - NCS2021_013.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1 descriptive characteristics of adverse events in relation to the dose and vaccine.

Table A1. Descriptive characteristics of adverse events in relation to the dose and vaccine.

	First Dose (n=210)			Second Dose (n=210)			Third Dose (n=210)	
	Oxford/AstraZe-neca-Vaxzevria n (%)	Pfizer/BioNTech-Comirnaty n (%)	Sinovac-CoronaVac n (%)	Oxford/AstraZe-neca-Vaxzevria n (%)	Pfizer/BioNTech-Comirnaty n (%)	Sinovac-CoronaVac n (%)	Oxford/AstraZe-neca-Vaxzevria n (%)	Pfizer/BioNTech-Comirnaty n (%)
N	32 (100.0)	135 (100.0)	43 (100.0)	32 (100.0)	135 (100.0)	43 (100.0)	182 (100.0)	28 (100.0)
Adverse Events	25 (78.1)	84 (62.2)	17 (39.5)	17 (53.1)	76 (56.3)	17 (39.5)	142 (78.0)	16 (57.1)
Pain	18 (56.3)	74 (54.8)	15 (34.9)	11 (34.4)	64 (47.4)	16 (37.2)	100 (54.9)	14 (50.0)
Edema	2 (6.3)	7 (5.2)	2 (4.7)	0 (0.0)	3 (2.2)	2 (4.7)	21 (11.5)	3 (10.7)
Erythema	2 (6.3)	11 (8.1)	1 (2.3)	0 (0.0)	3 (2.2)	3 (7.0)	14 (7.7)	2 (7.1)
Pruritus	1 (3.1)	9 (6.7)	1 (2.3)	3 (9.4)	6 (4.4)	2 (4.7)	14 (7.7)	3 (10.7)
Thermal elevation	9 (28.1)	19 (14.1)	2 (4.7)	1 (3.1)	16 (11.9)	2 (4.7)	81 (44.5)	6 (21.4)
Diarrhea	2 (6.3)	2 (1.5)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	12 (6.6)	2 (7.1)
Nausea	2 (6.3)	2 (1.5)	0 (0.0)	1 (3.1)	5 (3.7)	0 (0.0)	15 (8.2)	0 (0.0)
Vomiting	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.1)	0 (0.0)
Myalgia	14 (43.8)	29 (21.5)	2 (4.7)	7 (21.9)	26 (19.3)	3 (7.0)	90 (49.5)	7 (25.0)
Arthralgia	12 (37.5)	17 (12.6)	0 (0.0)	5 (15.6)	11 (8.1)	1 (2.3)	61 (33.5)	4 (14.3)
Headache	12 (37.5)	24 (17.8)	7 (16.3)	5 (15.6)	22 (16.3)	3 (7.0)	77 (42.3)	7 (25.0)
Other types of adverse events	5 (15.6)	16 (11.9)	0 (0.0)	2 (6.3)	5 (3.7)	0 (0.0)	20 (11.0)	3 (10.7)

References

1. WHO. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2022 Apr 20]. Available from: <https://covid19.who.int/>
2. WHO. The World Health Report. 2006: Working Together for Health. World Health Organization. 2006;
3. Bandyopadhyay S, Baticulon RE, Kadhum M, Alser M, Ojuka DK, Badereddin Y, et al. Infection and mortality of healthcare workers worldwide from COVID-19: a systematic review. *BMJ Glob Health* [Internet]. 2020 [cited 2022 Apr 20];5:3097. Available from: <http://dx.doi.org/10.1136/bmjgh-2020-003097>
4. La Federación Médica reporta decesos de profesionales de la salud por ómicron [Internet]. Ecuavisa. 2022 [cited 2022 Jul 28]. Available from: <https://www.ecuavisa.com/noticias/ecuador/la-federacion-medica-reporta-decesos-de-profesionales-de-la-salud-por-omicron-DJ1281757>
5. WHO. Access and allocation: how will there be fair and equitable allocation of limited supplies? [Internet]. 2021 [cited 2022 Jul 26]. Available from: <https://www.who.int/news-room/feature-stories/detail/access-and-allocation-how-will-there-be-fair-and-equitable-allocation-of-limited-supplies>
6. Ministerio de Salud Pública. Situación Epidemiológica Nacional COVID-19, Ecuador [Internet]. 2022. [cited 2022 Jul 28]. Available from: <https://www.salud.gob.ec/wp-content/uploads/2022/01/10.1.2022-epi.pdf>

7. COE provincial de Pichincha. Situación cantonal por COVID-19. Distrito Metropolitano de Quito [Internet]. 2021. [cited 2022 Jul 28]. Available from: <https://coe-pichincha.senescyt.gob.ec/situacion-cantones-pichincha/>
8. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 2021 593:7857 [Internet]. 2021 Mar 8 [cited 2022 Apr 21];593(7857):130–5. Available from: <https://www.nature.com/articles/s41586-021-03398-2>
9. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. *The Lancet* [Internet]. 2021 [cited 2022 Apr 21];397:2331–3. Available from: <http://ees.elsevier.com/thelancet/www.thelancet.com>
10. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nature Medicine* 2021 27:7 [Internet]. 2021 May 17 [cited 2022 Apr 21];27(7):1205–11. Available from: <https://www.nature.com/articles/s41591-021-01377-8>
11. Ministerio de Salud Pública. Vacunómetro COVID-19 [Internet]. 2022 [cited 2022 Jul 26]. Available from: <https://app.powerbi.com/view?r=eyJrIjoieYkzNTFkMmUtZmUzNi00NDcwLTg0MDEtNjFkNzhkZTg5ZWYyIiwidCI6IjcwNjIyMGRiLTliMjktNGU5MS1hODI1LTl1NmIwNmQyNjlmMyJ9&pageName=ReportSection>
12. CDC. Selected Adverse Events Reported after COVID-19 Vaccination | CDC [Internet]. *Vaccines*. 2022 [cited 2022 Apr 21]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html>
13. Nohl A, Brune B, Weichert V, Standl F, Stang A, Dudda M. COVID-19: Vaccination Side Effects and Sick Leave in Frontline Healthcare-Workers-A Web-Based Survey in Germany. 2022 [cited 2022 Apr 21]; Available from: <https://doi.org/10.3390/vaccines10030411>
14. Kitro A, Sirikul W, Thongkum W, Soponpong S, Yasamut U, Kiratipaisarl W, et al. Dynamic of anti-spike receptor binding domain (RBD) levels and short-term adverse events following a heterologous booster dose of BNT162b2 after two doses of CoronaVac in Thai health care workers. [cited 2022 Apr 21]; Available from: <https://doi.org/10.1016/j.vaccine.2022.04.020>
15. Hillus D, Schwarz T, Tober-Lau P, Vanshylla K, Hastor H, Thibeault C, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. *Lancet Respir Med* [Internet]. 2021 Nov 1 [cited 2022 Apr 21];9(11):1255–65. Available from: <http://www.thelancet.com/article/S221326002100357X/fulltext>
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* [Internet]. 2008 Apr 1 [cited 2022 Dec 27];61(4):344–9. Available from: <http://www.jclinepi.com/article/S0895435607004362/fulltext>
17. Helsinki Statement. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Internet]. 64th WMA General Assembly. Fortaleza, Brazil; 2013 Oct [cited 2022 Dec 15]. Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
18. Food and Drug Administration. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials | FDA [Internet]. Center for Biologics Evaluation and Research, editor. 2007 [cited 2022 Apr 19]. 1–10 p. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical>
19. Organización Panamericana de la Salud. Introducción de la vacuna contra la COVID-19: Orientaciones para determinar los grupos prioritarios y elaborar la microplanificación [Internet]. 2021 Jan [cited 2022 Dec 27]. (1). Report No.: 1. Available from: <https://www.campusvirtualsp.org/es>
20. Naito T, Tsuchida N, Kusunoki S, Kaneko Y, Tobita M, Hori S, et al. Reactogenicity and immunogenicity of BNT162b2 or mRNA-1273 COVID-19 booster vaccinations after two doses of BNT162b2 among healthcare workers in Japan: a prospective observational study. *Expert Rev Vaccines* [Internet]. 2022 [cited 2022 Dec 27];21(9):1319–29. Available from: <https://www.tandfonline.com/doi/abs/10.1080/14760584.2022.2093722>

21. Nachtigall I, Bonsignore M, Hohenstein S, Bollmann A, Günther R, Kodde C, et al. Effect of gender, age and vaccine on reactogenicity and incapacity to work after COVID-19 vaccination: a survey among health care workers. *BMC Infect Dis* [Internet]. 2022 Dec 1 [cited 2022 Dec 27];22(1):1–13. Available from: <https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-022-07284-8>
22. Cohen G, Jungsomsri P, Sangwongwanich J, Tawinprai K, Siripongboonsitti T, Porntharukchareon T, et al. Immunogenicity and reactogenicity after heterologous prime-boost vaccination with CoronaVac and ChAdox1 nCov-19 (AZD1222) vaccines. <https://doi.org/10.1080/2164551520222052525> [Internet]. 2022 [cited 2022 Dec 27];18(5). Available from: <https://www.tandfonline.com/doi/abs/10.1080/21645515.2022.2052525>
23. Kadali RAK, Janagama R, Peruru S, Malayala S v. Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. *International Journal of Infectious Diseases* [Internet]. 2021 May 1 [cited 2022 Dec 27];106:376–81. Available from: <http://www.ijidonline.com/article/S1201971221003581/fulltext>
24. Bae S, Lee YW, Lim SY, Lee JH, Lim JS, Lee S, et al. Adverse Reactions Following the First Dose of ChAdOx1 nCoV-19 Vaccine and BNT162b2 Vaccine for Healthcare Workers in South Korea. *J Korean Med Sci* [Internet]. 2021 Apr 1 [cited 2022 Dec 27];36(17):1–9. Available from: <https://doi.org/10.3346/jkms.2021.36.e115>
25. Beatty AL, Peyser ND, Butcher XE, Cocohoba JM, Lin F, Olgin JE, et al. Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination. *JAMA Netw Open*. 2021 Dec 22;4(12).
26. Nguyen DC, Dao TL, Truong TMD, Nguyen TH, Phan TN, Nguyen HM, et al. Short-Term Adverse Effects Immediately after the Start of COVID-19 Booster Vaccination in Vietnam. *Vaccines (Basel)*. 2022 Aug 1;10(8).
27. Alqahtani S, Jokhdar H, Al-Tawfiq JA, Al-Otaibi S, Assiri A, Almudarra S, et al. Adverse events following administration of COVID-19 vaccines in Saudi Arabia. *Sci Rep*. 2022 Dec 1;12(1).
28. Montano D. Frequency and Associations of Adverse Reactions of COVID-19 Vaccines Reported to Pharmacovigilance Systems in the European Union and the United States. *Front Public Health*. 2022 Feb 3;9.
29. Kouhpayeh H, Ansari H. Adverse events following COVID-19 vaccination: A systematic review and meta-analysis. *Int Immunopharmacol*. 2022 Aug 1;109.

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