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Safety and immunogenicity of different booster vaccination schemes for COVID-19 used in El Salvador

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Purpose: The effectiveness of coronavirus disease 2019 (COVID-19) vaccination schemes and the combination of vaccines of various platforms for administering booster doses is still being studied since it will depend on the population's response to vaccines. We aimed to evaluate the safety, protection, and immunogenicity of the Salvadorean population's third dose booster COVID-19 vaccine and the potential benefit of homologous vs. heterologous regimens.

Materials and Methods: This is an analytical observational cohort study in a population aged 18 to 65 years that was primarily vaccinated with AstraZeneca, Sinovac, or Pfizer/BioNTech. Volunteers were recruited (n=223) and followed up for 3 months after receiving the 3rd vaccine (BNT162b2) as a booster. Adverse reactions were monitored, serum anti-spike immunoglobulin G (IgG) was assessed by chemiluminescence, and a polymerase chain reaction was carried out when subjects developed clinical signs.

Results: The cohorts finally included 199 participants, and we observed only mild adverse effects in all cohorts. A significant increase in specific IgG levels was found after the booster dose in all cohorts. The heterologous scheme with Sinovac showed the greatest increase in antibody titer, and a decrease was observed in all participants after 3 months. During the follow-up period, 30 participants showed symptomatology compatible with COVID-19, but only four were laboratory-confirmed and they showed mild clinical signs.

Conclusion: These findings indicate that the booster doses used were safe and promoted an immediate increase in immunogenicity, which decreased over time. The heterologous regimen showed stronger immunogenicity compared to the messenger RNA-based homologous scheme.

Keywords: COVID-19, Vaccine, Reactogenicity, Immunogenicity, Protection

Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in the Hubei province of China and initiated a sanitary and social crisis globally [1]. The highly transmissible virus provokes the coronavirus disease-2019 (COVID-19) with a variable clinical spectrum, ranging from asymptomatic to severe respiratory distress syndrome [2]. The rapid development of highly effective vaccines against SARS-CoV-2 represents one of the most outstanding scientific achievements in the contemporary world [3,4]. Available evidence indicates that eligible COVID-19 vaccines have an acceptable safety profile and are strongly recommended to prevent severe and life-threatening illness. However, the lack of universal and equitable access to COVID-19 vaccines threat-

ens the lives of millions while creating favorable conditions for the emergence of new variants of concern that represent a threat to vaccines [5,6]. The immune response following COVID-19 vaccination may differ individually, and therefore, analysis of the immune response to vaccines may be critical for guidance recommendations to prevent the COVID-19 disease. However, viruses constantly change through mutations that result in a new viral variant that can spread more easily. The Omicron viral variant first emerged by the end of 2021 and were initially detected and described in South Africa. Then, it spread so quickly worldwide that a family of SARS-CoV-2 virus emerged with a high transmission capacity because they overcame some of the immune defenses acquired, mainly neutralizing antibodies and not cellular immunity [7-9]. Different studies demonstrated that the vaccines derived from the ancestral Wuhan viral variant have a reduced neutralizing capacity against Omicron. However, the booster doses incremented the neutralizing titer and since then, the booster administration has been widely recommended to achieve greater protection among vaccinated people.

Since different platforms for COVID-19 vaccines are used, different heterologous vaccination schemes have been recommended for boosting or completing the initial vaccination protocol since safety parameters are accepted and immunogenicity is superior compared to homologous schemes [10,11]. In El Salvador, the non-replicating adenovirus vaccine ChAdOx1-S (Oxford AstraZeneca; AstraZeneca, Cambridge, UK), the messenger RNA (mRNA) vaccine BNT162b2 (Pfizer/BioNtech; Pfizer, New York, NY, USA), and the inactivated SARS-CoV-2 vaccine (Sinovac; Sinovac Biotech Ltd., Beijing, China) were used for primary vaccination. Here, we evaluated the reactogenicity, immunogenicity, and protection of the first booster vaccination, comparing homologous and heterologous regimens using the mRNA-based vaccine Pfizer/BioNtech. Besides, antibody titer was also evaluated during the 3 months following vaccination.

Materials and Methods

Cohort description and participants

This is an open observational cohort study in the Salvadorean population, with volunteers aged 18 to 65 years old with a complete initial vaccination scheme that attended to the Mega Vaccination Center of Hospital El Salvador to get the updated COVID-19 vaccine booster for additional protection. The time interval for receiving the third dose was accorded to the definition of the vaccination strategic plan in El Salvador with a minimum of 4 months. The study was carried out between June and October 2022 and volunteers received the Pfizer/BioNTech vaccine as the first boost. Of the 223 original participants enrolled, 199 finished the study. They were divided into three cohorts depending on the initial homologous vaccination scheme: Cohort 1 (AstraZeneca–AstraZeneca, n=100), Cohort 2 (Sinovac–Sinovac, n=62), and Cohort 3 (Pfizer/BioNTech–Pfizer/BioNTech, n=37). The inclusion criteria to enroll participants that received the boost vaccine were adults with no symptoms when receiving the booster, regardless if they had suffered from COVID-19 before and whether the last vaccine was received more than 4 months before. Participants were excluded if they were pregnant (when receiving the boost vaccine or during the study), immunocompromised, during breastfeeding or suffered from a moderate to severe adverse reaction in previous COVID-19 vaccination and comorbidities were recorded.

The safety profile of the vaccine booster was recorded in all participants 15 minutes and 48 hours following the administration. We considered a local reaction: pain at the injection site, redness, and swelling. Systemic events included fever, fatigue, headache, chills, vomiting, diarrhea, new or worsening muscle pain, and joint pain. Adverse effects classified as severe were those potentially life-threatening that needed hospitalization.

Participants were contacted during the study if they presented compatible symptoms with COVID-19. In that case, a nasopharyngeal swab was carried out and a reverse transcription-polymerase chain reaction (RT-PCR) test was assessed using Seegene commercial reagent (Seegene Inc., Seoul, Korea).

Ethics statement

The study protocol was approved by the National Ethics Committee, according to the ethical standards of the committee and with the 1964 Helsinki Declaration (CNEIS 2022/08). All volunteers signed informed consent.

SARS-CoV-2 antibody ELISA

Quantitative SARS-CoV-2 spike-specific immunoglobulin G (IgG) antibody titers were measured with the Access SARS-CoV-2 IgG assay (Beckman Coulter C74339; Beckman Coulter Inc., Brea, CA, USA), according to the manufacturer's instructions. The chemiluminescent immunoassay is based on the use of paramagnetic particles coated with recombinant SARS-CoV-2 receptor-binding domain protein. Particles are incubated with the plasma sample containing the specific antibodies;

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materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. A monoclonal anti-human IgG alkaline phosphatase conjugate is added to bind the IgG antibodies captured on the particles. After washing a second separation to remove unbound conjugate is performed. A chemiluminescent substrate is added and light generated by the reaction is measured with a luminometer. The light production is compared to the standard curve build with the cut-off value defined during calibration of the instrument. Access SARS-CoV-2 IgG positive and negative Calibrators are provided by the manufacturer. Plasma concentration of specific IgG was expressed as international units/mL (IU/mL). Blood samples were collected prior to vaccination (Pre-vac), 14 days (T1), and 90 days (T2) following the booster vaccination. Plasma was isolated and stored at -20°C until used.

Data analysis

Statistical significance was determined by the Student t-test test and one-way analysis of variance followed by Bonferroni test. In all cases, $p<0.05$ was considered statistically significant. All data analyses were performed using GraphPad 9.1.2 Prism Software (GraphPad Software, San Diego, CA, USA).

Results

Study cohort and reactogenicity of the booster vaccine

To define the impact of the first booster of the COVID-19 vaccine on the Salvadorean population, participants from the San Salvador Department (n=145), La Libertad (n=45), and La Paz, Santa Ana, Ahuachapán, Cuscatlán, Sonsonate, and La Unión (n=33) were offered the Pfizer/BioNtech vaccine. A total of 233 individuals expressed their initial intention to participate in the study, and 199 were finally enrolled and met the inclusion and exclusion criteria. Subjects were grouped in three cohorts according to the primary vaccination (homologous schemes) regardless of previous infection. Cohort 1 was composed of individuals vaccinated with the ChAdOx1nCoV-19 Corona (n=110), Cohort 2 consisted of subjects who received the Sinovac-Coronavac vaccine (n=70), and the Cohort 3 encompassed individual that were vaccinated with the Pfizer/BioNtech vaccine (n=43). Table 1 describes the baseline characteristics of subjects. Participants received the booster vaccine and were on-site observed for the next 15 minutes and followed up for 48 hours for adverse reactions by telephone contact. The most frequent adverse effects reported were pain at the injection site following the boost administration.

Regarding systemic reactions, fever was frequently reported. All subjects had local and systemic mild reactions following 15 minutes (n=7) and 48 hours (n=173) vaccination. No significant differences in the frequency and severity of the vaccine reactogenicities were observed among the cohorts. Total mild adverse reactions were observed in 90%, 88.7%, and 94.5% of participants of Cohorts 1, 2, and 3, respectively (Table 2).

Table 1. Baseline characteristics of participants of the study

Characteristic	Cohort 1	Cohort 2	Cohort 3
No. of participants	100	62	37
Age (yr)	40±8.2	38.3±11.9	35.6±9.9
Gender			
Female	69 (69)	44 (70)	25 (67)
Male	41 (41)	26 (42)	18 (49)
Comorbidities			
Diabetes	7 (7)	5 (8)	5 (13.5)
Asthma	1 (1)	1 (1.6)	0
Cancer	1 (1)	0	0
Hypertension	12 (12)	6 (10)	4 (11)
Obesity	0	0	0
Cardiovascular disease	0	0	0

Values are presented as mean±standard deviation or number (%).

Immunogenicity induced by the booster vaccine

The concentration of SARS-CoV-2 anti-spike IgG antibodies was evaluated prior to vaccination (Pre-vac), 14 days (T1), and 90 days (T2) following the boost administration. Fig. 1A shows the specific antibody level at the vaccination time and compares the immunity elicited among cohorts by the primary homologous vaccination schemes. All participants received the last dose at least 4 months before and subjects that were vaccinated with the homologous primary scheme with BNT162b2 (Cohort 3) showed a significant higher titer of specific antibodies than participants from Cohorts 1 and 2. The

Table 2. Adverse local and systemic events following the boost administration

Variable	Cohort 1	Cohort 2	Cohort 3
Local reactions			
Pain	62 (62)	49 (79)	21 (57)
Erythema	1 (1)	0	0
Swelling	6 (6)	7 (11)	5 (13.5)
Systemic reactions			
Fever	25 (25)	10 (16)	13 (35)
Headache	0	0	0
Diarrhea	0	0	0

Values are presented as number (%).

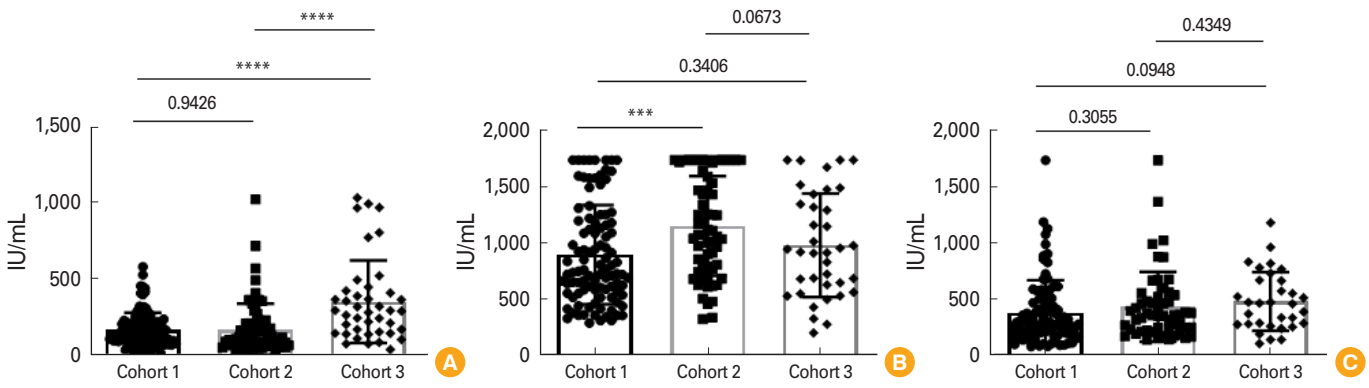

Fig. 1. Concentration of spike-specific immunoglobulin G in plasma at different timepoints in all cohorts. **(A)** Prior to booster vaccination; **(B)** 14 days following the booster administration; and **(C)** 90 days following the booster administration. Values are presented as mean±standard error of mean. p-value was determined by Student t-test and one-way analysis of variance, followed by Bonferroni post-test. $p<0.05$ was considered as significant. $^{***}p<0.001$, $^{****}p<0.0001$.

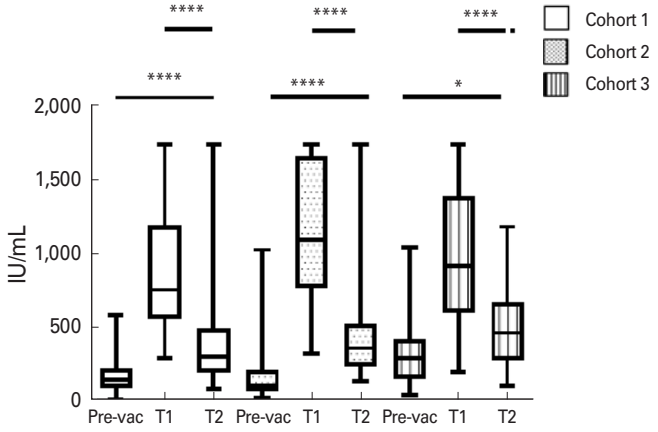

Fig. 2. Peripheral concentration of specific immunoglobulin G in all cohorts at different timepoints: Pre-vac, 14 days (T1) and 90 days following the booster administration (T2). Values are presented as mean standard error of mean. p-value was determined by Student t-test and one-way analysis of variance, followed by Bonferroni post-test. $p<0.05$ was considered as significant. $^{*}p<0.05$, $^{****}p<0.0001$.

same analysis was done for plasma-specific IgG levels at T1 and T2 (Fig. 1B, C). Following the boost with Pfizer/BioNtech, we observed that samples from Cohort 1 showed the lowest level of specific antibodies (864.5 IU/mL, 1,150 IU/mL, and 976.8 IU/mL for Cohorts 1, 2, and 3, respectively). In contrast, at T2, all cohorts exhibited no statistical difference in the residual anti-spike antibody levels (441.8 IU/mL, 444.8 IU/mL, and 460.5 IU/mL for Cohorts 1, 2, and 3, respectively). These findings show that all participants significantly increased the titer of anti-spike IgG antibodies after the booster administration (T1) (Supplement 1), indicating that all volunteers, regardless of the initial vaccination scheme, responded to the mRNA booster. Likewise, at 3 months after the boost (T2), all participants showed decreased IgG levels ($p<0.0001$) compared with T1 (Fig. 1, Supplement 1). Nevertheless, samples of individuals from Cohorts 1 and 2 (heterologous boost schemes) showed residual antibody levels at T2 higher than those prior to boost vaccine administration ($p<0.001$) (Fig. 2). Additionally, the analysis of the specific IgG levels at T1 showed that samples from subjects of Cohort 2 had the highest concentration of anti-spike antibodies (Fig. 2).

The combination of the adenoviral vaccine or the complete virus vaccine with the mRNA vaccine showed to promote higher specific antibody titers than the homologous regimen, and the heterologous combination with Sinovac resulted in being significantly superior to the other combination schemes at T1.

Efficiency for protection against COVID-19

During the study, 30 participants reported clinical signs compatible with COVID-19: fever (n=8), rhinitis (n=6), nasal congestion (n=11), cough (n=8), odynophagia (n=10), and headache (n=7). Ten out of the 30 participants were from Cohort 1, 11 participants were from Cohort 2, and three were from Cohort 3. A healthcare professional collected a nasopharyngeal swab, and RT-PCR was performed to diagnose COVID-19. We found four positive samples: two from Cohort 1 and two from Cohort 2. All participants who tested positive for COVID-19 in the laboratory had elevated specific IgG antibodies, with values ranging from 212 to 1,370 IU/mL.

Discussion

El Salvador and other countries face the challenge of achieving a

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sustained immunity to SARS-CoV-2 through vaccine coverage using different platforms available for booster vaccination. The mRNA-based Pfizer/BioNtech vaccine was used as a booster in this study. This vaccine has shown to be safe, immunogenic, and highly effective to prevent severe COVID-19 in combination with other platforms [10,11]. Since different vaccines were employed to prime the Salvadorean population, heterologous or homologous regimes were the options. Adenoviral-(AstraZeneca), mRNA-(Pfizer/BioNtech), or complete virus-based vaccines were used for the initial two-dose regimen. The use of heterologous or homologous strategy has proved to protect different populations, but in some countries, it has been demonstrated that the heterologous scheme, using an mRNA-based schemes was superior to the homologous one [10,11]. This point has been relevant when the priority objective was to accelerate the rate of vaccination. The outbreak produced by Omicron since September 2022 accelerated the administration of the booster vaccines to increase the efficiency for protection of Wuhan-based monovalent COVID-10 vaccines.

In this study, Salvadorean volunteers were randomly grouped into three cohorts according to the different primary vaccination schemes to evaluate the local and systemic reactogenicity, immunogenicity, and protective efficacy for symptomatic disease of the booster dose in heterologous (Cohorts 1 and 2) or homologous regimens (Cohort 3).

Regarding reactogenicity, no recipient showed moderate to severe reactions. Mild reactions, such as pain at the site of inoculation and fever, were mainly observed during the 48 hours following the booster administration. Various studies similar to our investigation have reported that severe and potentially life-threatening reactions are very rare and that the most common adverse reactions are local pain and fever [1,12-14]. The ZOE COVID 2021 study by Menni et al. [15] reports that the reactogenicity of the booster doses with AstraZeneca, Pfizer-BioNTech, and Moderna vaccines was similar to that of the second dose of the initial vaccination scheme and that homologous booster promoted fewer systemic side effects than heterologous boost. Moreover, according to our results, vaccination with the Pfizer/BioNtech booster had a similar frequency of local and systemic reactions in heterologous (Cohorts 1 and 2, 79% and 74%, respectively) and homologous boosters (Cohort 3 with 79%).

When we analyzed the immunogenicity of the different booster schemes, we found that 2 weeks following the booster application, a significant elevation of plasma anti-spike IgG titer was observed in all cohorts, regardless of the basal level of specific antibodies and prior infection. Similar results were found by Alvear Cardona et al. [16] and Munive-Lima et al. [17] after assessing specific IgG antibodies following the third dose of the vaccine in different schemes (mRNA vaccines, replicant viral vectors, and inactivated viruses). In all of them, a high rate of seroconversion was observed. When comparing the baseline or pre-vaccination values with those determined at 14 days after vaccination (T1), Cohort 1 showed an increase in the average antibody titration levels of 5.4 times, while Cohort 2 showed the most pronounced seroconversion (6.9×) and the Cohort 3 showed an increase of 2.8 times. This indicates that the use of a dead virus vaccine in the initial complete scheme and a mRNA vaccine as a booster dose was more effective in inducing an increase in humoral immunity. As it has been demonstrated in other studies, the heterologous schemes, and the use of mRNA vaccines as a booster dose, generates the highest titer of antibodies [10,11,18]. When applying a dead virus vaccine, such as Sinovac, in the initial scheme, the effectiveness in the induction of antibodies is superior with an mRNA vaccine booster compared to the use of this vaccine in the initial vaccination. Similar results were recently reported in Argentina by the study of Nuñez et al. [11], where the inactivated virus-based Sinopharm vaccine was used and 16 combinations of vaccines were investigated. Humoral and cellular immune responses were superior when this platform was used in the initial scheme and the mRNA vaccine was used as a booster [11]. In our study, we also observed that the use of a heterologous booster scheme such as in the cohort 1 and 2, with an adenoviral or complete dead virus vaccine, respectively, as the initial scheme, generated a greater increase in anti-spike antibody titer compared to a homologous scheme (Cohort 3). The results found here endorse the combination of vaccine platforms to enhance the humoral immune.

However, and as expected, 3 months after the booster all participants showed significant decreased specific IgG levels, which does not mean that immunity is lost. However, comparing T2 and Pre-vac titers, the heterologous boosters (Cohorts 1 and 2) induced a higher increase in antibody titers than the homologous booster scheme (Cohort 3) (2.67×, 2.65×, and 1.3× for Cohorts 1, 2, and 3, respectively).

The fact that the booster dose promotes an increase in antibody titers (T1) indirectly indicates that immune memory is being promoted by the induction of antibody secreting plasma cells and memory B and T lymphocytes. Although the serum levels of specific antibodies decline, memory cells are the ones that maintain immune memory. Israel et al. [19] demonstrated that with BNT 162b2 the levels of anti-spike IgG de-

creased by up to 40% after the complete scheme a month after the administration and that at 6 months only 16.1% showed positive values. However, infected individuals showed a decrease of 5% a month later and 120% had values below the detection threshold [19]. The same has been observed in other vaccines, with variable percentages of decay in antibodies depending on the vaccine [20]. This reinforces the idea of boost vaccines to expand central memory lymphocytes that have the ability to re-enter the lymph nodes, target the T or B zone, interact with dendritic cells and induce new cycles of immune maturing of T-dependent B cells. This improves the efficiency of antigen recognition and expands the spectrum of diversity of specificities, so a booster can induce a recognition pattern that includes epitopes that were not present in the original immunogen. This takes place with booster doses of COVID-19 vaccines, which despite being targeted at the eradicated Wuhan viral variant, the elicited immune response generates neutralizing antibodies against the new variants and subvariants of Omicron in preclinical studies and in clinical trials [21]. Nevertheless, no vaccine or natural infection generates long-lasting or lifelong immunity.

Finally, the effectiveness of the booster schemes against symptomatic infection was analyzed during the 3-month follow-up and we found that 30 participants showed compatible symptoms with COVID-19. The quantitative RT-PCR test performed in nasal swabs indicated that four cases were positive: two from the Cohort 1 and two from Cohort 2. In all cases, the symptoms were mild. Similar results were reported by Fowlkes et al. [22] in their study on the effectiveness of COVID-19 vaccines. They found that the number of infections in fully vaccinated individuals was reduced, even at times when the Delta variant predominated and that most hospitalizations were observed in individuals who were not completely vaccinated [22].

Despite the fact that in this study the vaccinated volunteers who developed COVID-19 had mild symptoms and all showed elevated titers of anti-spike-specific antibodies, the reduced number of subjects in the cohorts does not allow to conclude on the effectiveness of the different vaccination schemes in preventing transmission and symptomatic disease. The main limiting factor in this cohort study was the reduced number of participants in the individual cohorts.

In conclusion, we found that using homologous and heterologous booster vaccination schemes did not induce local or systemic severe reactogenicity, and that the heterologous schemes generated significantly higher levels of specific IgG antibodies compared with the homologous booster. Nevertheless, no differences in antibody titers were found at 3 months when comparing the three cohorts. The low number of symptomatic infected participants could reflect acceptable parameters of effectiveness in the protection from symptomatic and severe disease.

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Supplementary Materials

Supplementary material is available at Clinical and Experimental Vaccine Research website (http://www.ecevr.org).

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