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Comparison of three different COVID-19 vaccine platforms (CoronaVac, BTN162b2, and Ad5-nCoV) in individuals with and without prior COVID-19: Reactogenicity and neutralizing antibodies

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ABSTRACT

Neutralizing antibodies (NAbs) can be indicators of collective immunity, vaccine efficacy, and the longevity of the humoral response. This study aimed to compare reactogenicity and NAbs generated by three different COVID-19 vaccine platforms in individuals with and without prior COVID-19. 336 individuals vaccinated (112 with CoronaVac [inactivated virus], 112 with BNT162b2 [messenger RNA], and 112 with Ad5-nCoV [non-replicating viral vector]) were included. NAbs were quantified with the cPass SARS-CoV-2 kit. Individuals immunized with the Ad5-nCoV showed higher reactogenicity than those immunized with the other vaccines ($p < 0.001$). The BTN162b2 vaccine-induced NAbs with higher inhibition capacity than the other platforms in the first dose. In individuals without prior COVID-19, the Ad5-nCoV vaccine generated lower NAbs against SARS-CoV-2 than those induced by two doses of the BTN162b2 (Ad5-nCoV 72.10 [55.6-93.4] vs. BTN162b2 98.41 [98.16-98.56], $p < 0.0001$). One individual did not generate NAbs (0.89%) after a complete immunization with CoronaVac; in BTN162b2, all generated these antibodies, and in the Ad5-nCoV group, four individuals (3.57%) did not generate NAbs. Comorbidities, gender, age, and reactogenicity did not significantly influence the generation of NAbs ($p > 0.05$); however, a history of COVID-19 before vaccination was associated with antibodies with greater neutralizing capacity after the first dose ($p < 0.01$). In conclusion, the mRNA vaccine (BTN162b2) had a remarkable better ability to produce NAbs and lower reactogenicity than the other platforms, whereas the Ad5-nCov vaccine induced the lowest NAbs response in individuals without a history of COVID-19; therefore, we suggest that a booster could benefit these individuals.

1. Introduction

SARS-CoV-2 is a new β-coronavirus that can cause a severe acute respiratory syndrome in humans [1]. The World Health Organization (WHO) designated the term "coronavirus disease 2019" (COVID-19) to the disease caused by SARS-CoV-2, declaring it a pandemic in March 2020 [2]. As of May 2022, 525,565,952 cases and 6,277,113 deaths from this disease have been confirmed worldwide [3]. Currently, there are SARS-CoV-2 variants of concern (VOCs) that cause different waves of COVID-19, mainly the Omicron variant; therefore, the successful control of the global COVID-19 pandemic requires the development of vaccines that offer broad protection [4].

In the absence of a 100% efficient therapy to treat COVID-19, the development of vaccines against SARS-CoV-2 was accelerated unprecedentedly. Currently, classic and innovative vaccine platforms are being applied, including those based on inactivated viruses, viral vectors, and

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nucleic acid-based vaccines (mRNA) [5,6].

Mexico has agreements with different pharmaceutical companies for the distribution of vaccines against SARS-CoV-2 with different platforms: Sinovac (CoronaVac) and Covaxin (BBV152) use inactivated virus platforms; Pfizer-BioNTech (BNT162b2) and Moderna (Spikevax) are based on messenger RNA platforms; meanwhile, Cansino (Ad5-nCoV), AstraZeneca (AZD1222), Sputnik V (Gam-COVID-Vac), and Janssen (Ad26.COV2-S) are non-replicating vector platforms. Official reports from May 2022 report that Mexico has 107,031,525 immunized individuals with some of these vaccines [7].

While vaccine authorization requires evidence of safety and efficacy from randomized controlled trials, other questions about vaccine effectiveness can be answered by observational approaches after the vaccine is in use. Based on the above, the measurement of NAbs is essential for evaluating the efficacy of a vaccine [8]. Neutralization is defined as the reduction of viral infectivity when a specific antibody binds to the surface of the viral particles (virion), blocking the cycle of viral replication [9,10].

The identification and quantification of anti-SARS-CoV-2 NAbs are of paramount importance since these antibodies inhibit the binding of the receptor-binding domain (RBD) of protein S with the angiotensin-converting enzyme 2 (ACE2) receptor, which is crucial to preventing viral infection [11] and reduce disease severity [12]; therefore, the determination of NAbs is crucial for identifying people with protective immunity, either by natural infection or by vaccination [13].

The current gold standard for measuring NAbs is the conventional virus neutralization test (cVNT), which requires level 3 biosecurity laboratories (BL3) to manipulate the live pathogen (13). To overcome this barrier, the Duke University School of Medicine in the United States and the National University of Singapore Duke-NUS jointly developed and validated a neutralizing antibody screening test based on a competitive ELISA approved by the FDA (Food and Drug Administration). Its reported sensitivity is from 95% to 100%, and its specificity is 99.93% [14,15]; therefore, sVNT assays can become a tool accessible to clinical laboratories to accurately measure protective immunity without needing the infrastructure of a BL3 laboratory.

There are still many doubts about the behavior of the generation of NAbs induced by vaccination, including which vaccine generates the most significant number of these antibodies and how long they last. Previous reports suggest that age, reactogenicity, gender, a previous natural infection, comorbidities, and some drugs are possible factors associated with differences in NAbs production after immunization [16,17]. However, according to the literature review, few studies on COVID-19 vaccines that on analyzing differences in NAbs percentages after immunization with three different kinds of vaccine platforms. Therefore, this study aimed to compare reactogenicity and NAbs generated by three different COVID-19 vaccine platforms (CoronaVac [inactivated virus], BNT162b2 [messenger RNA], and Ad5-nCoV [non-replicating viral vector]) in individuals with and without prior COVID-19.

2. Material and methods

2.1. Subjects and sample collection

Blood samples were extracted from 336 individuals from Guadalajara, Jalisco, Mexico, vaccinated with one of the following vaccines: CoronaVac (Sinovac), BNT162b2 (Pfizer-BioNTech), or Ad5-nCoV (Cansino Biologics Inc). We perform groups (3) of 112 subjects for each vaccine, matching as much as possible by gender and age. All subjects were recruited at the University Center for Health Sciences (CUCS) of the University of Guadalajara and signed informed consent prior to inclusion. Eligibility criteria included adults 18 years and older, non-pregnant women, and individuals without immunosuppressive drug treatment. Subjects of each group were further subclassified into two subgroups: (1) individuals without a COVID-19 infection before vaccination (n = 75 in the CoronaVac group, n = 58 in the BNT162b2 group, and n = 65 in the Ad5-nCoV group), and (2) individuals with a history of COVID-19 before vaccination (n = 37 in the CoronaVac group, n = 54 in the BNT162b2 group and n = 47 in the Ad5-nCoV group).

All participants provided information by filling out surveys for clinical and demographic characteristics regarding the history of previous SARS-CoV-2 infection and vaccination-associated side effects. The surveys were conducted at the study invitation and 21 days after applying the vaccine. The peripheral blood sample was obtained by venous puncture in vacutainer tubes without anticoagulant for serum collection. Samples were obtained 21 days after vaccinations (first and second doses for immunized with CoronaVac and BNT162b2 and after a single dose for the Ad5-nCov group).

This study was conducted following the Declaration of Helsinki and was approved by the Ethics and Biosafety Committee of CUCS, University of Guadalajara, Mexico (Folio 21-10).

Before vaccination, people with a COVID-19 infection were diagnosed between 3-12 months before with an RT-qPCR test (polymerase chain reaction with real-time reverse transcription); these results were requested for their incorporation into this group. Individuals without a history of COVID-19 were corroborated by evaluating the absence of anti-SARS-CoV-2 IgG/IgM antibodies before vaccination.

2.2. Detection of IgG/IgM

The presence of IgG and IgM against SARS-CoV-2 was determined with the Certum IgG/IgM Rapid Test cassette kit (Certum Diagnostics, Nuevo León, Mexico) according to the manufacturer's instructions.

2.3. Determination of the presence of NAbs and their inhibitory capacity (percentage of neutralization)

The determination of NAbs was performed with the cPass™ SARS-CoV-2 Neutralization Antibody Detection kit (GenScript, Piscataway Township, NJ, USA) according to previously described [17]. The reference value for detecting NAbs against SARS-CoV-2 is an inhibition signal >30%, being 100% the maximum neutralization value. The inhibition rate was calculated with the following formula:

$$Neutralization\ percentage = \left(1 - \frac{OD\ value\ of\ sample}{OD\ value\ of\ negative\ control}\right) x\ 100\%$$

2.4. Statistical analysis

Statistical analysis was conducted on GraphPad Prism software (v.8; San Diego, CA, USA), with a <0.05 p-value considered statistically significant. Data were analyzed using the mean and standard deviation (parametric distribution) or median with interquartile range (nonparametric distribution) according to their normal distribution. Chi-square or exact Fisher tests were used to compare the proportions. For the analysis of variance, the Mann–Whitney U-test was applied for comparing two groups or Kruskal–Wallis for three or more in nonparametric variables, followed by Dunn's multiple comparisons. Spearman correlation coefficients were calculated to test the relationships between the variables.

3. Results

3.1. Description of study groups

The clinical and demographic characteristics of immunized study groups are shown in Table 1. The three groups presented a similar ratio of men/to women. Regarding age, the individuals immunized with CoronaVac were a little younger than the other two groups. Concerning comorbidities, the history of arterial hypertension was more frequent in the Ad5-nCoV-2 group, while the use of some drugs, such as NSAIDs, was

Table 1
Clinic and demographic characteristics of the study groups.

	CoronaVac vaccine n=112		BNT162b2 vaccine n=112		Ad5-nCoV vaccine n=112		
	Without a history of COVID-19 n=75	With a history of COVID-19 n=37	Without a history of COVID-19 n=58	With a history of COVID-19 n=54	Without a history of COVID-19 n=65	With a history of COVID-19 n=47	p-value
Age, mean ± SD	24.60 ± 6.31	23.65 ± 1.93	32.47 ± 5.06	31.61 ± 4.74	29.29 ± 3.86	29.32 ± 4.14	**<0.0001**
Gender, n (%)							
Female	51 (68.00)	23 (62.16)	35 (60.34)	35 (64.81)	46 (70.77)	31 (65.96)	0.8652*
Male	24 (32.00)	14 (37.84)	23 (39.66)	19 (35.19)	19 (29.23)	16 (34.04)	
Comorbidities (≥1), n (%)							
Rhinitis, n (%)	11 (14.67)	3 (8.11)	9 (15.52)	13 (24.07)	10 (15.38)	7 (14.89)	0.9359**
Overweight, n (%)	10 (13.33)	4 (10.81)	11 (18.97)	15 (27.78)	17 (26.15)	15 (31.91)	0.0549*
HAS, n (%)	0 (0.00)	1 (2.70)	3 (5.17)	1 (1.85)	17 (26.15)	15 (31.91)	**<0.0001****
Dermatitis, n (%)	4 (5.33)	3 (8.11)	6 (10.34)	1 (1.85)	1 (1.54)	1 (2.13)	0.1389**
Treatments n (%)							
NSAIDs, n (%)	7 (9.33)	4 (10.81)	1 (1.72)	2 (3.70)	1 (1.54)	0 (0.00)	**0.0301****
Proton pump inhibitors, n (%)	0 (0.00)	1 (2.70)	0 (0.00)	1 (1.85)	0 (0.00)	0 (0.00)	0.1522**
Hypoglycemic agents, n (%)	1 (1.33)	1 (2.70)	2 (3.45)	1 (1.85)	3 (4.62)	2 (4.26)	0.8625**
Antihypertensive agents, n (%)	0 (0.00)	1 (2.70)	3 (5.17)	2 (3.70)	1 (1.54)	1 (2.13)	0.3759**
Supplements, n (%)	0 (0.00)	1 (2.70)	1 (1.72)	3 (5.56)	1 (1.54)	0 (0.00)	0.1916**
Antidepressants, n (%)	10 (13.33)	3 (8.11)	3 (5.17)	7 (12.96)	5 (7.69)	0 (0.00)	0.0660**
Antiasthmatic agents, n (%)	0 (0.00)	1 (2.70)	4 (6.90)	1 (1.85)	0 (0.00)	1 (2.13)	0.0529**
Antiarrhythmic agents, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.70)	0 (0.00)	0 (0.00)	0.0565**
Hormones, n (%)	0 (0.00)	1 (2.70)	4 (6.90)	2 (3.70)	3 (4.62)	2 (4.26)	0.2767**
Hypolipidemic agents, n (%)	0 (0.00)	1 (2.70)	1 (1.72)	0 (0.00)	0 (0.00)	0 (0.00)	0.2273**
Contraceptive, n (%)	2 (2.67)	4 (10.81)	2 (3.45)	0 (0.00)	3 (4.62)	0 (0.00)	0.0680**
Immunosuppressants, n (%)	2 (2.67)	0 (0.00)	0 (0.00)	1 (1.85)	0 (0.00)	0 (0.00)	0.5549**

P values were calculated with Chi-square test (χ^2)* or Fisher's exact test (frequencies <5%) **. SD: standard deviation; NSAIDs: Non-steroidal anti-inflammatory drugs. P values in bold represent statistically significant differences.

more common in the CoronaVac immunized group; these differences showed statistical significance between intergroup comparisons ($p < 0.05$). The rest of the differences regarding comorbidities and treatments were not significant among the three groups ($p > 0.05$).

3.2. Side effects associated with CoronaVac, BNT162b2 and Ad5-nCoV vaccination

Table 2 shows the side effects reported by individuals (with and without a history of COVID-19) after the first dose of CoronaVac, BNT162b2, and Ad5-nCoV vaccines. Individuals immunized with Ad5-

Table 2
Self-reported side effects associated with the first dose of CoronaVac, BNT162b2, and Ad5-nCoV vaccines.

	CoronaVac vaccine n=112		BNT162b2 vaccine n=112		Ad5-nCoV vaccine n=112		
n (%)	Without a history of COVID-19 n=75	With a history of COVID-19 n=37	Without a history of COVID-19 n=58	With a history of COVID-19 n=54	Without a history of COVID-19 n=65	With a history of COVID-19 n=47	p-value
At least one symptom (≥1)	28 (37.33)	17 (45.95)	21 (36.20)	19 (35.19)	53 (81.54)	40 (85.11)	**<0.0001***
Fever	3 (4.00)	1 (2.70)	4 (6.90)	3 (5.56)	17 (26.15)	18 (38.30)	**<0.0001****
Cough	2 (2.67)	1 (2.70)	0 (0.00)	1 (1.85)	2 (3.08)	1 (2.13)	0.8826**
Headache	20 (26.67)	11 (29.73)	16 (27.59)	11 (20.37)	38 (58.46)	28 (59.57)	**<0.0001***
Irritability	7 (9.33)	4 (10.81)	4 (6.90)	5 (9.26)	13 (20.00)	7 (14.89)	0.2830**
Chills	4 (5.33)	2 (5.41)	3 (5.17)	3 (5.56)	19 (29.23)	15 (31.91)	**<0.0001****
Myalgia	10 (13.33)	3 (8.11)	0 (0.00)	10 (18.52)	30 (46.15)	25 (53.19)	**<0.0001***
Rhinorrhea	6 (8.00)	3 (8.11)	0 (0.00)	2 (3.70)	4 (6.15)	1 (2.13)	0.1807**
Thoracic pain	1 (1.33)	1 (2.70)	1 (1.72)	1 (1.85)	0 (0.00)	0 (0.00)	0.7872**
Odynophagia	3 (4.00)	1 (2.70)	0 (0.00)	1 (1.85)	3 (4.62)	5 (10.64)	0.1261**
Arthralgia	0 (0.00)	1 (2.70)	1 (1.72)	8 (14.81)	11 (16.92)	14 (29.79)	**<0.0001****
Conjunctivitis	1 (1.33)	1 (2.70)	0 (0.00)	0 (0.00)	1 (1.54)	2 (4.26)	0.4457**
Dyspnea	0 (0.00)	2 (5.41)	0 (0.00)	0 (0.00)	0 (0.00)	3 (6.38)	**0.0024****
Diarrhea	2 (2.67)	1 (2.70)	1 (1.72)	2 (3.70)	0 (0.00)	0 (0.00)	0.5624**
Abdominal pain	3 (4.00)	1 (2.70)	0 (0.00)	1 (1.85)	7 (10.77)	6 (12.77)	**0.0117****
Vomits	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	4 (6.15)	0 (0.00)	**0.0490****
Fatigue	9 (12.00)	4 (10.81)	0 (0.00)	0 (0.00)	26 (40.00)	21 (44.68)	**<0.0001***
Application site pain	4 (5.33)	2 (5.41)	0 (0.00)	0 (0.00)	2 (3.08)	2 (4.26)	0.2228**
Dizziness	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.54)	0 (0.00)	1.0000**
Loss of taste	0 (0.00)	0 (0.00)	1 (1.72)	0 (0.00)	0 (0.00)	2 (4.26)	0.0954**

P-values were calculated with Chi-square test (χ^2)* or Fisher's exact test (frequencies <5%) **. NA: Not applicable. P values in bold represent statistically significant differences.

nCoV vaccine showed a higher prevalence of secondary effects associated with vaccination than those immunized with the other two platforms ($p < 0.05$). Symptoms such as fever ($p < 0.0001$), headache ($p < 0.0001$), chills ($p < 0.0001$), myalgia ($p < 0.0001$), arthralgia ($p < 0.0001$), fatigue ($p < 0.0001$), and abdominal pain ($p = 0.0117$) were more prevalent in the Ad5-nCoV vaccine group than in the other groups. Arthralgia was more prevalent in vaccinated people who had a history of COVID-19 compared to those without prior COVID-19 (Ad5-nCoV: 29.79% vs. 16.92% [$p < 0.05$]; BNT162b2: 14.81% vs. 1.71% [$p < 0.05$]; CoronaVac: 2.70% vs. 0% [$p < 0.05$]). The same was observed for myalgia (Ad5-nCoV: 53.19% vs. 46.15% [$p < 0.05$]; BNT162b2: 18.52% vs. 0% [$p < 0 .05$]). The other side effects did not differ significantly between the three groups ($p > 0.05$).

Table 3 shows the side effects of the second dose of CoronaVac and BNT162b2 vaccines in individuals with and without prior COVID-19. Irritability and fatigue were more frequent in those immunized with CoronaVac than those immunized with BNT162b2 ($p = 0.0367$ and $p < 0.001$). On the contrary, myalgia and rhinorrhea were more frequent in those immunized with the BNT162b2 vaccine than in those immunized with CoronaVac ($p = 0.0071$ and $p = 0.0273$). The second dose of Ad5-nCoV was not evaluated because it is a single-dose vaccine. On the other hand, myalgias were more frequent in individuals with a history of COVID-19 (15.82% vs. 27.78%, $p < 0.05$) in the group immunized with BNT162b2. The other side effects were not significant between groups ($p > 0.05$).

3.3. Generation of NAbs against SARS-CoV-2 in response to CoronaVac, BNT162b2, and Ad5-nCoV vaccines

Fig. 1 shows that after the first vaccine dose, individuals with a history of COVID-19 before immunization produce antibodies with greater neutralizing capacity than those without a COVID-19 history (CoronaVac [95.9% vs. 45.63%, p<0.01], BNT162b2 [98.06% vs. 88.83%, p<0.0001], or Ad5-nCoV [97.95% vs. 72.10%, p<0.0001]). Overall, the CoronaVac vaccine-induced fewer NAbs in the first dose compared to BTN162b2 and Ad5-nCoV vaccines.

In individuals without a history of COVID-19, ten individuals immunized with CoronaVac did not generate NAbs (8.92%) at the first vaccine dose (inhibition signal <30%); whereas this finding was observed in a single individual (0.89%) immunized with BTN162b2 and 4 (3.57%) immunized with Ad5-nCoV. On the other hand, in individuals with a history of COVID-19, CoronaVac was the only vaccine where three individuals with a previous history of COVID-19 did not generate NAbs.

After the second immunization (Fig. 2), there were no significant differences in NAbs percentages between individuals with and without a history of COVID-19 ($p > 0.05$) immunized with CoronaVac or BTN162b2 vaccines.

In individuals with a history of COVID-19, we observed that CoronaVac generates fewer NAbs compared to BTN162b2 and Ad5-nCoV vaccines (CoronaVac 96.6 [92.54-98.30], BTN162b2 98.46 [98.41-98.5] and Ad5-nCoV 97.95 [97.6-98.17], p<0.0001). Ad5-nCoV and BTN162b2 induced similar neutralizing levels, $p > 0.05$. Regarding groups without prior COVID-19, CoronaVac also generates fewer NAbs compared to BTN162b2 (CoronaVac 92.2 [72.9-96.7] vs. BTN162b2 98.41 [98.16-98.56], $p < 0.0001$). In this same group, the levels of NAbs generated by the single dose of Ad5-nCoV vaccine (72.10 [55.6-93.4]) were lower than those induced by the full regimen (two doses) of BTN162b2 ($p < 0.0001$) but were similar to those observed in the CoronaVac vaccine (p>0.05).

After the complete schema, in CoronaVac (2 doses), one individual did not generate NAbs (0.89%); in BTN162b2, all generated these antibodies; and in the Ad5-nCoV group, four individuals (3.57%) did not generate NAbs. For CoronaVac, the individual who did not generate NAbs was from the subgroup with a history of COVID-19, and in the Ad5-nCoV group, the four individuals were from the subgroup without prior COVID-19.

Table 3
Self-reported side effects associated with the second dose of the CoronaVac and BNT162b2 vaccines.

	CoronaVac vaccine n=112		BNT162b2 vaccine n=112		
n (%)	Without a history of COVID-19 n=75	With a history of COVID-19 n=37	Without a history of COVID-19 n=58	With a history of COVID-19 n=54	p-value
At least one symptom (≥1)	27 (36.00)	11 (29.72)	18 (31.03)	22 (40.74)	0.6439*
Fever	2 (2.67)	2 (5.41)	4 (6.90)	7 (12.96)	0.1460**
Cough	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	1.0000**
Headache	15 (20.00)	5 (13.51)	12 (20.69)	12 (22.22)	0.7639*
Irritability	5 (6.67)	1 (2.70)	0 (0.00)	0 (0.00)	**0.0367****
Chills	3 (4.00)	2 (5.41)	5 (8.62)	6 (11.11)	0.4054**
Myalgia	6 (8.00)	2 (5.41)	9 (15.52)	15 (27.78)	**0.0071****
Rhinorrhea	0 (0.00)	0 (0.00)	3 (5.17)	4 (7.41)	**0.0273****
Thoracic pain	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	1.0000**
Odynophagia	1 (1.33)	0 (0.00)	2 (3.45)	2 (3.70)	0.6686**
Arthralgia	2 (2.67)	2 (5.41)	4 (6.90)	7 (12.96)	0.1460**
Conjunctivitis	1 (1.33)	0 (0.00)	1 (1.72)	0 (0.00)	1.0000**
Dyspnea	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	1.0000**
Diarrhea	3 (4.00)	1 (2.70)	0 (0.00)	0 (0.00)	0.2318**
Abdominal pain	2 (2.67)	0 (0.00)	0 (0.00)	1 (1.85)	0.6987**
Vomits	2 (2.67)	0 (0.00)	0 (0.00)	0 (0.00)	0.5383**
Fatigue	15 (20.00)	9 (24.32)	0 (0.00)	3 (5.56)	**<0.0001****
Application site pain	1 (1.33)	0 (0.00)	0 (0.00)	0 (0.00)	1.0000**
Dizziness	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.85)	0.4063**
Loss of taste	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	NA

P-values were calculated with Chi-square test (χ^2)* or Fisher's exact test (frequencies <5%) **. NA: Not applicable. P values in bold represent statistically significant differences.

3.4. Factors associated with the percentage of neutralization in CoronaVac, BNT162b2, and Ad5-nCoV vaccines

We analyzed possible intervenient factors over neutralizing antibody generation in subjects vaccinated with CoronaVac, BNT162b2 y Ad5-nCoV. Comorbidities, gender, and reactogenicity (shown in Tables 1–3), were not associated with the generation of NAbs in any type of vaccine (Table 4). Fig. 3 also shows that age was not significantly correlated with the percentage of neutralization after vaccination with any evaluated vaccine (CoronaVac, $p = 0.6014$; BTN162b2, $p = 0.3605$; Ad5-nCoV, $p = 0.3449$).

4. Discussion

NAbs are indicators of the protective immunity of different vaccines against COVID-19 and could be a valuable tool to guide vaccination strategies and reassess the distribution of available vaccines [18,19]. The present study compared the differences between three vaccines against SARS-CoV-2 to generate NAbs. In addition, the possible relationship of some factors that could be associated with greater or lesser production of antibodies in response to the vaccines was analyzed.

In some communities, there is a collective belief that the presence of reactions to a vaccine is a predictive sign of a favorable immunological response; however, a predictive association between reactogenicity and the adaptive response has not been demonstrated, suggesting that the concept of "No pain, no gain" may not be valid, at least at the individual level [20]. This is consistent with our results since side effects (reactogenicity) did not influence the generation of NAbs.

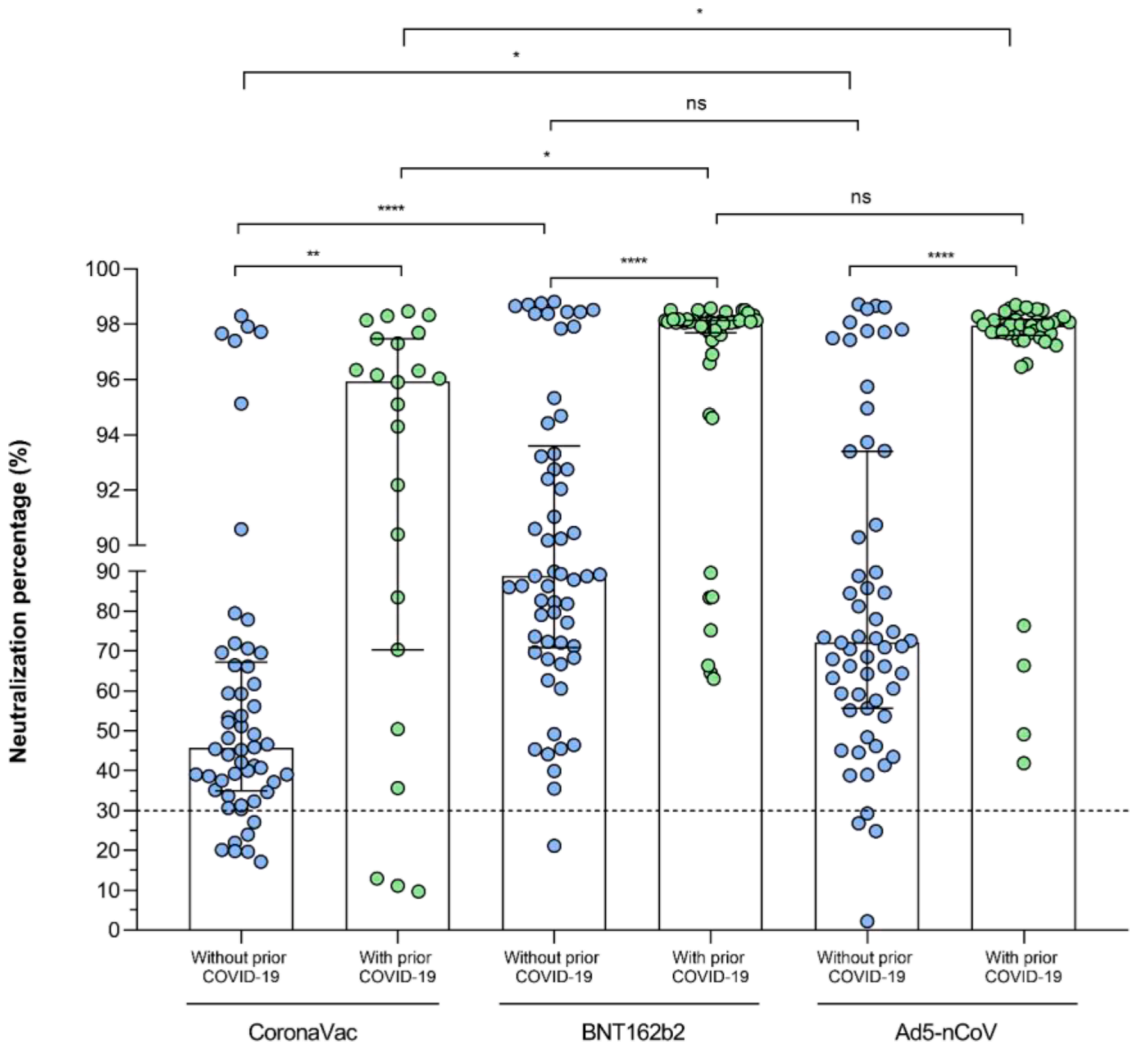

Fig. 1. Neutralization percentages of antibodies generated in response to the first dose of three different vaccines (CoronaVac, BNT162b2, and Ad5-nCoV). The difference between groups was determined using the Kruskal-Wallis and Dunn's multiple comparison tests. Results are presented as median and interquartile ranges. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$; ns, non-significant ($p>0.05$). NAbs against SARS-CoV-2 were determined 21 days after immunization.

Klugar et al. reported that mRNA-based vaccines were associated with a higher prevalence of local side effects (pain at the injection site). In comparison, viral vector-based vaccines were associated with a higher prevalence of systemic side effects (headache, myalgia, arthralgia, chills, and fatigue) [21]. In the present study, individuals immunized with the vector vaccine Ad5-nCoV reported more reactogenicity than those immunized with vaccines based on mRNA (BTN162b2) or inactivated virus (CoronaVac). This finding agrees with that reported by Zhang et al., as they observed that unlike viral vector or mRNA vaccines, the onset of fever after immunization is relatively low for inactivated virus-based vaccines such as CoronaVac [22]. In this same way, Niyomnaitham et al. made a comparison between heterologous and homologous mixtures of different platforms, where the homologous dose group with CoronaVac was the one that presented less reactogenicity systemic [23]. The greater reactogenicity of vaccines based on viral vectors may be due to the combined immune response that they induce, that is, to the vector and the antigen they carry.

Currently, there are some studies showing that vaccinated individuals with a prior SARS-CoV-2 infection had a significantly higher antibody response than those without a prior infection [24,25]. Bates et al. even show that infection with SARS-CoV-2 before or after vaccination (post-vaccination infection) gives a significantly greater boost to the neutralizing antibody response compared to people vaccinated without any natural infection [26]. Hall et al. in a longitudinal study, reported considerable protection of 6 months for people without previous infection vaccinated against SARS-CoV-2, while one year for those with a pre-vaccination infection [27]. However, this association has not been explored simultaneously on different SARS-CoV-2 vaccine platforms.

In three different vaccine platforms against COVID-19, we show that individuals with a history of SARS-CoV-2 infection before immunization generated more NAbs after the first vaccine dose than those without prior SARS-CoV-2 infection. However, these differences disappeared after applying the second vaccine dose to those immunized with the BTN162b2 or CoronaVac vaccines since both groups reached optimal neutralization levels (close to 100%). This highlights the importance of the population obtaining complete vaccine schemes (2 doses) for the BTN162b2 and CoronaVac vaccines. Moreover, it supports the proposal that a second dose of the Ad5-nCoV vaccine may be necessary as this vaccine-induced similar NAbs to those immunized with the first dose of the BTN162b2 vaccine. In fact, Li et al. recently reported that the combination of Ad5-nCoV with CoronaVac has good results in producing antibodies and protection even against the delta variant [28].

The effect of a prior infection before vaccination has been studied more in individuals immunized with the BTN162b2 vaccine. Abu-Raddad et al. reported in more than one and a half million individuals

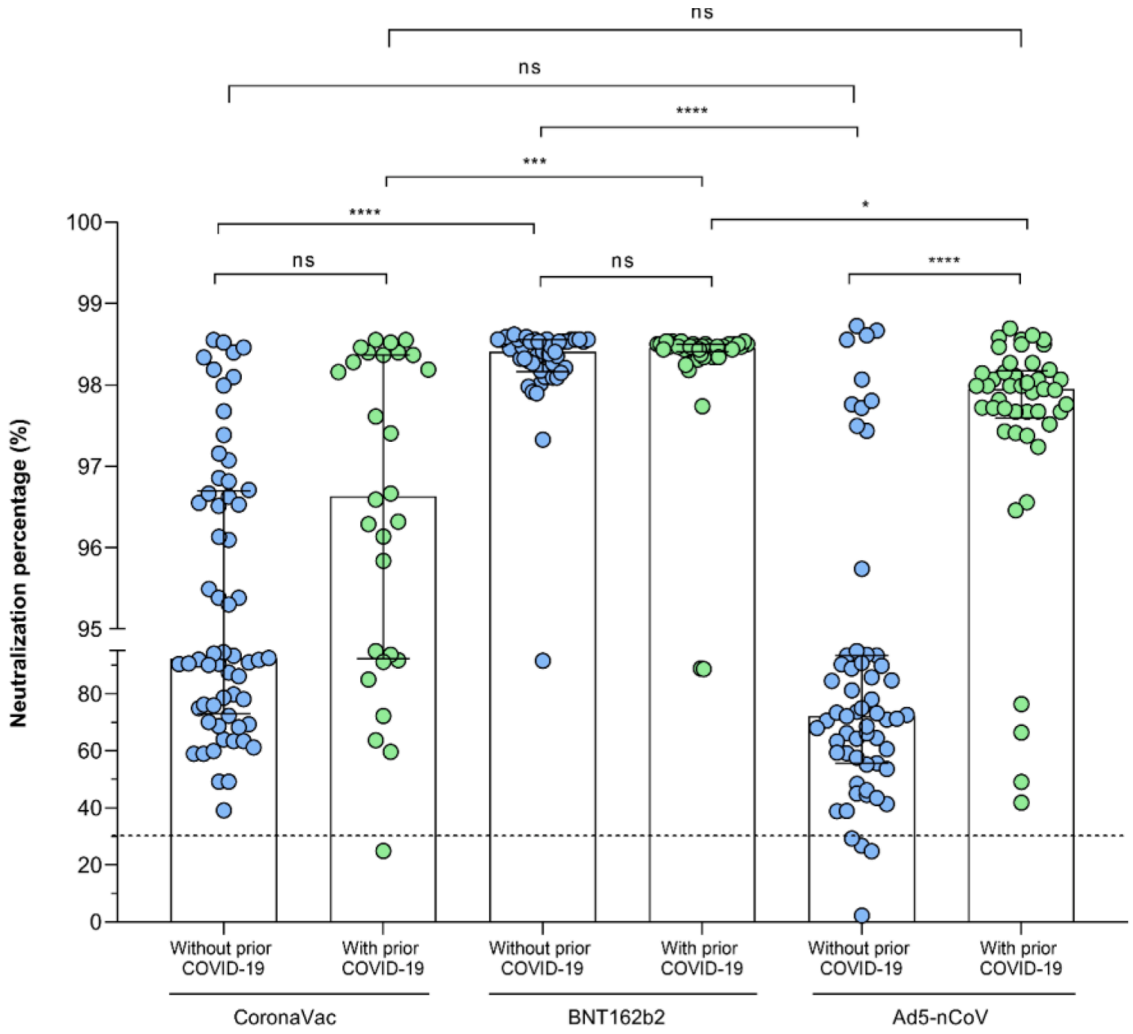

Fig. 2. Neutralization percentages of antibodies generated in response to a complete vaccination schedule of three different vaccines (CoronaVac, BNT162b2, and Ad5-nCoV. The difference between groups was determined using the Kruskal-Wallis test and Dunn's multiple comparison test. Results are presented as median and interquartile ranges. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; ****, $p<0.0001$; ns, non-significant ($p>0.05$). For this analysis, antibodies neutralizing the percentage of individuals immunized with Ad5-nCoV are those generated after the single dose.

that prior SARS-CoV-2 infection was associated with a statistically significant reduction in the risk of irruptive infection [29]. Furthermore, Ontañon et al. reported that at least ten months after SARS-CoV-2 infection, the immune system can produce a rapid and robust secondary antibody response after a single dose of vaccine and found no further improvement in antibody response to the second dose [30]. Before the appearance of variants of concern, that finding has led several authors to suggest that people with previous SARS-CoV-2 infection can be vaccinated with a single dose [31,32,33] and reach optimal NAbs titers. However, Elliott et al. recorded a subset of individuals previously infected with SARS-CoV-2 (25% of 345 individuals) required both doses to reach maximum antibody titers, where the biological significance of differences between previously infected individuals remains uncertain [34].

For CoronaVac, Cucunawangsih et al. concluded in a group of health workers that those immunized with prior SARS-CoV-2 infection had stable and significantly higher levels of anti-antibodies S compared with those vaccinated without prior SARS-CoV-2 infection [35]; another study has supported the same result for this vaccine [36].

A novel aspect of the present study is the analysis of three different types of vaccination platforms to compare their ability to induce NAbs. Rogliani et al. performed a comparison of different platforms against SARS-CoV-2 using a SUCRA analysis (surface under the cumulative ranking curve) which allows for interpretation and choosing the best treatments in a network meta-analysis [37]; they placed the BTN162b2 vaccine as one of the most effective to produce NAbs (first quartile), then CoronaVac (third quartile), and finally Ad5-nCoV (third quartile) [38].

Our results also showed a higher neutralizing capacity of the antibodies induced by the BTN162b2 vaccine both in individuals with a history of the previous infection and those without a COVID-19 history. Regarding the CoronaVac and Ad5-nCoV vaccines, they showed a less potent effect in those individuals without a history of COVID-19 since they induced antibodies with a significantly lower neutralizing capacity than in those with a history of COVID-19. Importantly, the smaller effect was more notable for the Ad5-nCOv vaccine, suggesting again that the second dose of this vaccine may be important to optimize neutralization levels without neglecting the surveillance of adenoviral antibodies that could be generated by being an adenoviral vector to which a humoral response can be generated after the first immunization [39,40].

Khoury et al. compared levels of NAbs as predictors of immune protection against symptomatic infections by SARS-CoV-2. For this purpose, they took the mean neutralization level of phase I and II trials and the protective efficacy of phase III trials of seven vaccines, as well as the protection observed in a cohort of convalescent individuals. Similar to us, they reported that the BTN162b2 vaccine showed a higher percentage of protection compared to CoronaVac [41], which could be

Table 4
Identification of possible intervenient factors over NAbs generation in subjects vaccinated with CoronaVac, BTN162b2, and Ad5-nCoV.

	CoronaVac vaccine, n=112		BNT162b2 vaccines, n=112		Ad5-nCoV, n=112	
Median (IQR)	Without a history of COVID-19 n=75	With a history of COVID-19 n=37	Without a history of COVID-19 n=58	With a history of COVID-19 n=54	Without a history of COVID-19 n=65	With a history of COVID-19 n=47
Comorbidities						
Presence	91.98 (79.76-96.86)	97.41 (93.71-98.37)	98.36 (98.09-98.53)	98.47 (98.36-98.50)	70.98 (53.67-93.43)	97.94 (97.67-98.33)
Absence	93.33 (69.74-96.52)	96.14 (93.66-98.28)	98.50 (98.33-98.56)	98.44 (98.42-98.47)	72.64 (61.25-88.10)	97.99 (97.56-98.14)
p-value	0.3363	0.6783	0.1271	0.8035	0.5783	0.9366
Rhinitis	94.34 (91.25-96.80)	98.19 (97.25-98.37)	98.10 (98.04-98.42)	98.49 (98.42-98.50)	55.69 (48.39-90.74)	98.03 (97.94-98.53)
No rhinitis	91.25 (70.66-96.64)	96.59 (91.74-98.37)	98.47 (98.27-98.56)	98.44 (98.41-98.47)	72.37 (59.67-92.62)	97.86 (97.45-98.14)
p-value	0.3563	0.2494	0.0528	0.2636	0.5202	0.0877
Overweight	90.44 (81.35-96.29)	97.48 (96.52-98.39)	98.44 (98.14-98.55)	98.44 (98.34-98.50)	70.98 (56.65-94.34)	97.76 (97.67-98.13)
No overweight	92.94 (71.33-96.70)	96.49 (91.59-98.30)	98.40 (98.18-98.55)	98.47 (98.41-98.50)	72.64 (58.13-90.41)	97.99 (97.56-98.15)
p-value	0.9131	0.3578	0.9123	0.6930	0.9264	0.7450
HAS	NA	98.16 (NA)	98.44 (98.31-98.49)	NA	70.98 (56.65-94.34)	97.76 (97.67-98.13)
No HAS	92.26 (74.30-96.68)	96.59 (92.70-98.37)	98.40 (98.18-98.55)	98.46 (98.41-98.50)	72.64 (58.13-90.41)	97.99 (97.56-98.15)
p-value	NA	0.7102	0.9635	NA	0.9264	0.7450
Dermatitis	62.29 (61.75-62.83)	81.15 (72.45-89.85)	98.46 (98.17-98.51)	88.66 (NA)	2.24 (NA)	41.89 (NA)
No dermatitis	92.94 (75.98-96.70)	96.63 (93.98-98.35)	98.39 (98.18-98.56)	98.47 (98.41-98.50)	72.37 (57.99-92.73)	97.97 (97.67-98.16)
p-value	0.0609	0.9289	0.2496	0.0937	0.0942	0.0976
Gender						
Male	90.57 (71.77-95.32)	96.37 (94.16-97.60)	98.40 (98.12-98.53)	98.44 (98.34-98.47)	73.40 (64.47-88.87)	97.72 (97.07-98.15)
Female	94.36 (77.66-96.90)	97.89 (93.02-98.42)	98.41 (98.25-98.56)	98.47 (98.42-98.50)	70.77 (54.05-92.74)	97.99 (97.67-98.19)
p-value	0.2396	0.2960	0.5448	0.1180	0.5559	0.3190
Symptoms ^{first} dose						
Presence (≥1)	87.45 (70.11-96.67)	94.97 (81.79-98.30)	98.38 (98.22-98.55)	98.47 (98.44-98.48)	73.18 (60.56-93.43)	97.99 (97.67-98.15)
Absence	93.33 (77.41-96.69)	93.33 (77.41-96.69)	98.46 (98.13-98.55)	98.44 (98.38-98.50)	57.40 (46.72-77.01)	97.55 (96.69-98.13)
p-value	0.6036	0.2960	0.8559	0.4414	0.0959	0.3582
Symptoms ^{second} dose						
Presence (≥1)	90.50 (68.82-96.33)	90.50 (68.82-96.33)	98.39 (98.21-98.56)	98.47 (98.39-98.50)	NA	NA
Absence	95.34 (87.50-96.74)	97.04 (92.47-98.21)	98.27 (98.09-98.53)	98.47 (98.41-98.50)	NA	NA
p-value	0.3082	0.9213	0.2544	0.6510	NA	NA

P-values were calculated using Mann–Whitney U-test. IQR: Interquartile range; NA, not applicable.

associated with the degree of neutralization of the antibodies generated by the mentioned vaccines.

Lim et al. also reported significantly lower levels of NAbs after a single dose of the CoronaVac vaccine compared with a single dose of the BTN162b2 vaccine; the level of NAbs increased after the second dose but remained lower than that observed with the BTN162b2 vaccine [42].

Considering only the production of NAbs between the three platforms studied, we could suggest that BTN162b2 is the one that generates the highest efficiency. However, the efficacy of immunization also depends on the cellular immune response; it is pertinent to note that the three platforms analyzed may have advantages or weaknesses in this context. Moreover, there are other factors to evaluate the immune response to vaccines and their advantages; for example, mRNA-based vaccines have the indisputable advantage that they can be rapidly redesigned to mimic new SARS-CoV-2 mutations and thus be ready for use quickly [43]. Meanwhile, inactivated virus vaccines generate antibodies against different antigens, which neither of the other two platforms does [44]. The latter confers a great advantage to inactivated vaccines against SARS-CoV-2 variants such as Omicron because specific CD4+ T cells are required to evoke powerful B-cell responses that lead to the maturation of antibody affinity. Zhang et al. studied inactivated vaccines and reported that T cells recognize peptides derived from S protein, nucleoprotein, and matrix, as well as other viral proteins [45].

In the case of vector vaccines such as adenovirus-based vaccines, it is known that their extensive tissue tropism and their ability to promote strong expression of the target antigen allows for increased immunogenicity [46].

In the present study, we also evaluated whether other factors such as comorbidities, drugs, gender, and age can influence the outcomes of NAbs after immunization; however, no association was observed with these variables. Zimmermann and Curtis describe that only kidney and liver diseases have been associated with a lower humoral response, being malnutrition, uremia, and a generalized immunosuppressive state the factors responsible for a lower response to vaccination [47]. Those variables were exclusion criteria in the present study; thus, we can not corroborate those findings.

Gils et al. also report that comorbidities did not affect the generation of NAbs after the immunization with the BTN162b2 vaccine [48]. In contrast, Muena et al. analyzed the generation of antibodies to the BTN162b2 and CoronaVac vaccines in naïve and previously infected groups, where three patients did not seroconvert, and multivariate analyzes confirmed that obesity is an underlying comorbidity that affects the response to vaccination [24]. Another study identified that dermatitis could be a factor associated with a low synthesis of NAbs, which could be related to the use of some topical treatments for the disease [49].

Ward et al. analyzed two different platforms, mRNA (BTN162b2) and vectorial (ChAdOx1), where older age was associated with a decreased response to vaccines [50]. In the present study, the generation of NAbs was not correlated with age in any of the three platforms studied. However, our three groups were composed of individuals from 18 to 38 years, and it has been reported that age only seems to influence the antibodies synthesis in older adults, possibly due to the phenomenon of immunosenescence [51, 52].

Based on the above discrepancies, there is a growing need to corroborate whether the factors described above are factors that can modify the immunogenicity of COVID-19 vaccines or whether they can be mainly affected by genetic factors.

As perspectives of the study, it would be important to analyze in a long-term way the importance of a previous infection as well as the effect of a post-vaccination infection on the production of NAbs, the impact that heterologous vaccination schemes against SARS-CoV-2 and its relationship to the production of broadly neutralizing antibodies (bNAbs) that could address VOCs. In the same way, carry out studies that have a wide range of ages and with the presence of more comorbidities to evaluate the impact of these variables on the generation of NAbs.

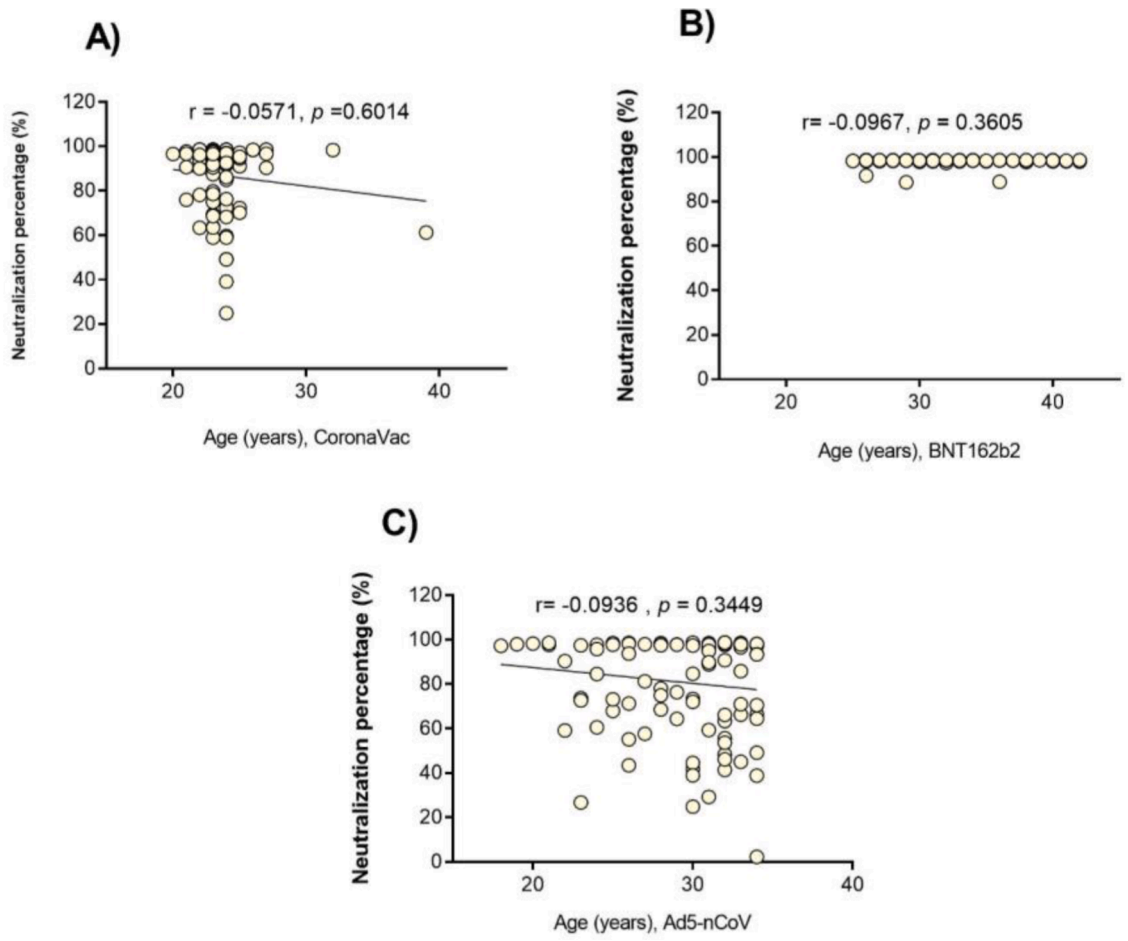

Fig. 3. Correlation between age and neutralization percentage in subjects vaccinated with CoronaVac, BNT162b2, and Ad5-nCoV. (a) Complete vaccination schedule with CoronaVac, (b) complete vaccination schedule with BNT162b2, and (c) complete vaccination schedule with Ad5-nCoV. Correlations were evaluated with the Spearman correlation coefficient test.

5. Conclusion

The mRNA vaccine (BTN162b2) had a remarkable better ability to produce NAbs than the other platforms (inactivated virus or non-replicating viral vector)—also, this mRNA vaccine-induced less reactogenicity. The Ad5-nCov vaccine induced the lower NAbs response in individuals without a history of COVID-19; therefore, we suggest that a booster could benefit these individuals.

Finally, reactogenicity and the evaluated comorbidities are not associated with the generation of NAbs. However, a SARS-CoV-2 infection before vaccination potentiates the generation of NAbs; therefore, this factor could help at the time of health strategies for vaccination to prioritize the doses of available vaccines.

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Institutional review board statement

The Ethics Committee of the University Center of Health Sciences of the University of Guadalajara (protocol code 21-10) approved this study conducted according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all the patients to publish this paper.

CRediT authorship contribution statement

José Javier Morales-Núñez: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **José Francisco Muñoz-Valle:** Conceptualization, Methodology, Resources, Visualization, Supervision, Funding acquisition. **Andrea Carolina Machado-Sulbarán:** Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Visualization. **Saúl Alberto Díaz-Pérez:** Software, Formal analysis, Data curation, Writing – original draft. **Paola Carolina Torres-Hernández:** Validation, Investigation, Writing – original draft. **Beatriz Verónica Panduro-Espinoza:** Investigation. **Jonathan Adrián Gallegos-Díaz de Leon:** Validation, Investigation. **Carlos David Munguía-Ramirez:** Investigation. **Jorge Hernández-Bello:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

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