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Influence of hybrid immunity and host factors on the concentration of neutralizing antibodies against SARS-CoV-2

Influencia inmunidad híbrida y factores del huésped sobre la concentración de anticuerpos neutralizantes contra SARS-CoV-2

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Abstract

Objective: To analyze the influence of hybrid immunity and host-dependent factors on the baseline concentration of neutralizing antibodies against SARS-CoV-2.

Materials and methods: Observational study of an analytical type, cross-sectional. A sample of 169 participants, over 18 years of age, of both sexes; distributed in two groups. Group A: 84 participants with previous infection + vaccination. Group B: 85 participants without previous infection + vaccination. Baseline concentrations of total anti-RBD antibodies were measured. In all cases, a significance level α 5% was used (p= <0.05).

Results: A positive result was considered from a mean fluorescence index equal to or greater than 1.3 (MIF≥ 1.3). All participants have titles above the cut-off point. Group A: 6.8 ± 2.23 MIF, Group B: 7.39 ± 2.78 MIF. There was no statistically significant difference between them (p= 0.145). Significant differences were evidenced with males (p= 0.049), overweight (p= 0.037) and the Moderna vaccine (mRNA-1273) (p= 0.003). A statistically significant, weak, and direct correlation was evidenced between the number of booster doses and the concentration of antibodies in group A (p= 0.013). The simple linear regression model predicts in group A that a fifth booster dose would generate antibody levels of 8.81 MIF, values much higher than the average (6.80 MIF).

Conclusions: Hybrid immunity influences the humoral response induced by vaccines, favouring increased antibody production with each booster dose received. In our population, overweight is a host-dependent factor that negatively influences the baseline concentration of antibodies in individuals with previous infections.

Keywords: Infection; SARS-CoV-2; COVID-19; Vaccines; Hybrid immunity.

Resumen

Objetivo: Analizar la influencia de la inmunidad híbrida y factores dependientes del huésped sobre la concentración basal de anticuerpos neutralizantes contra el SARS-CoV-2.

Materiales y métodos: Estudio observacional de tipo analítico, transversal. Muestra de 169 participantes, mayores de 18 años, de ambos sexos, distribuidos en dos grupos. Grupo A: 84 participantes con infección previa + vacunación. Grupo B: 85 participantes sin infección previa + vacunación. Se midieron las concentraciones basales de anticuerpos totales anti-RBD. En todos los casos se utilizó un nivel de significación α 5 % (p = <0,05).

Resultados: Se consideró un resultado positivo a partir de un índice de fluorescencia medio igual o superior a 1,3 (MIF ≥ 1,3). Todos los participantes tienen títulos por encima del punto de corte. Grupo A: 6,8 ± 2,23 MIF, Grupo B: 7,39 ± 2,78 MIF. No hubo diferencias estadísticamente significativas entre ellos (p = 0,145). Se evidenciaron diferencias significativas con los hombres (p= 0,049), el sobrepeso (p= 0,037) y la vacuna Moderna (mRNA-1273) (p= 0,003). Se evidenció una correlación estadísticamente significativa, débil y directa entre el número de dosis de refuerzo y la concentración de anticuerpos en el grupo A (p= 0,013). El modelo de regresión lineal simple predice en el grupo A que una quinta dosis de refuerzo generaría niveles de anticuerpos de 8,81 MIF, valores muy superiores a la media (6,80 MIF).

Conclusiones: La inmunidad híbrida influye en la respuesta humoral inducida por las vacunas, favoreciendo el aumento de la producción de anticuerpos con cada dosis de refuerzo recibida. En nuestra población, el sobrepeso es un factor dependiente del huésped que influye negativamente en la concentración basal de anticuerpos en individuos con infecciones previas.

Palabras Claves: Infección; SARS-CoV-2; COVID-19; Vacunas; Inmunidad híbrida.

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Introduction

Hybrid immunity (HI) is defined as the robust immune response developed by vaccinated individuals who have previously experienced natural infection by the wild pathogen (contagion + vaccination)[1]. This scenario has been shown to favor a greater immune response, with a significant increase in the production of neutralizing antibodies (25x – 100x), with broader cross-protection against virus variants; compared to vaccinated individuals with a complete immunization schedule without previous infection[2,3].

The World Health Organization (WHO) recognizes the immunological benefits of HI, however, no public health policies have been developed based on this potential vaccination strategy[4]. It is argued that HI is still under investigation and it is not known with certainty how effective it is compared to natural or artificial immunity, since its effectiveness may be influenced by host determinants factors (age, sex, comorbidities, habits), the number of doses received, interval between doses, immunisation strategy (Homologous vs Heterologous), among other variables. Therefore, it is an active field of research today[5].

Two years after the end of the COVID-19 pandemic, SARS-CoV-2 remains one of the most worrying pathogens with high pandemic potential[6]. Therefore, population-level serological surveillance is the indicated public health tool to evaluate the duration of immunity, the efficacy of vaccines and the effectiveness of the immunization strategy used. The objective of our study is to analyze the influence of hybrid immunity and host-dependent factors on the baseline concentration of anti-RBD antibodies to SARS-CoV-2 in a city in the Colombian Caribbean. An analysis of serological status in a post-pandemic context.

Materials and methods

The research work methodologically corresponds to an observational study of an analytical type, cross-sectional; following the ethical principles for medical research on human beings, the Declaration of Helsinki of the World Medical Association (WMA) and Colombian legislation (Ministry of Health through resolution 008430 of 1993)[7,8]. The research proposal was evaluated and endorsed by the research ethics committee of the Universidad Libre Seccional Pereira – Colombia (Ethics committee approval code 2022-11-04-001) and the ethics committee of the Universidad Internacional Iberoamericana de México. Informed consent was applied to the participants in the study. A structured questionnaire on anthropometric variables, comorbidities, habits, and sociodemographic characteristics was used as a data collection instrument.

The study was carried out with a sample of 169 individuals, over 18 years of age, of both sexes, belonging to the National Immunization Plan against COVID-19 in the city of Barranquilla, Colombia. The sample was selected in a simple random manner (probabilistic sampling). The participants were

recruited between March and June 2024, taking into account selection, exclusion and elimination criteria. They were organized into two groups (A and B). Group A: 84 participants with previous or natural SARS-CoV-2 infection + partial or complete vaccination against COVID-19. All with a clinical diagnosis confirmed by molecular biology or serological tests. Group B: 85 participants without previous or natural SARS-CoV-2 infection + partial or complete vaccination against COVID-19. All without respiratory symptoms suggestive of COVID-19, at least one month prior to vaccination.

Prior to signing informed consent, voluntary approval and compliance with the selection criteria; biological samples were taken to measure the antibodies of interest. Plasma from a venipuncture was used following biosafety techniques and protocols for both the patient and the health professional responsible for sampling. With the corresponding specifications.

The quantification of total anti-RBD antibodies of SARS-CoV-2 was performed from the commercial ProcartaPlex™ Human Coronavirus Ig Total kit, Invitrogen ThermoFisher Scientific9. Measurements from serum and plasma samples using Luminex™ magnetic bead technology. The MAGPIX MILLIPLEX® MAP equipment from the Center for Dental Research, of the Pontificia Universidad Javeriana, Bogotá - Colombia, was used. Following the manufacturer's specifications. Test results are reported as positive or negative based on the mean fluorescence index (MFI). MFI = <1, the target Ig is absent. MFI = 1–1.3, the result is indeterminate. MFI = >1.3, the target Ig is present.

A database was designed using Microsoft Excel spreadsheet software. Descriptive and inferential statistical analysis was performed based on the data obtained from the population studied. The IBM SPSS Statistics® version 20 (Statistical Package for the Social Sciences) statistical software was used. The descriptive statistics of the data were carried out using the indicators of measures of central tendency (mean, median, mode), measures of dispersion (standard deviation, interquartile ranges, minimum and maximum), measures of position (quartiles, deciles, percentiles) and measures of shape (asymmetry, kurtosis). For numerical (quantitative) variables, the mean or average was used, and for categorical (qualitative) variables, proportion or percentage was used. Data normality was analyzed using the Shapiro-Wilk test when the comparison groups had an $n<50$; otherwise ($n\geq 50$) the Kolmogorov-Smirnov test was used. To determine the homoscedasticity (equality of variances) between the samples, the Levene test was used. In all cases, a significance level α 5% was used (p value = <0.05).

The inferential statistical analysis used to compare the mean difference (baseline levels of anti-RBD antibodies) between the two groups was the student t test when the assumption of normality and homoscedasticity of the data was met, otherwise, the Mann-Whitney U test was used. For the mean difference in k samples (≥ 3), the unifactorial ANOVA test was used when the assumption of normality and homoscedasticity of the data was met, otherwise the Kruskal-Wallis test was used. The correlation analysis between the quantitative variables was performed with Pearson's R test, when the assumption of normality and homoscedasticity of the data was met, otherwise Spearman's Rho test was used. Bivariate linear regression analyses were also performed in the tests with positive correlation. A significance level α 5% was used in all statistical tests (p value = <0.05). The interpretation of results was carried out through graphs such as tables for the description and presentation of the data.

Results

Table 1 summarizes the characterization of the participants in the study, distributed by groups. Qualitative variables are represented as a function of absolute frequencies (#) and relative (%). Quantitative variables are represented as a function of the mean or average ($\bar{x}$) and standard deviation (s).

Table 1. Characterization of the participants in the study

Variables	Group A	Group B	Total
Sex			
Male (# - %)	20 (23.8%)	16 (18.8%)	36 (21.3%)
Female (# - %)	64 (76.2%)	69 (81.2%)	133 (78.7%)
Age (y/o) ($\bar{x}$ - s)	46 (±14.6)	46 (±15.46)	46 (± 15.03)
Weight (kg) ($\bar{x}$ - s)	72.9 (± 14.8)	69.59 (± 12.91)	71.24 (± 13.85)
Size (m) ($\bar{x}$ - s)	1.65 (± 0.07)	1.62 (± 0.07)	1.63 (± 0.07)
BMI (kg/m²) ($\bar{x}$ - s)	26.78 (± 5.19)	26.32 (± 4.51)	26.55 (± 4.85)
Comorbidities			
AHT (# - %)	16 (19.04%)	14 (16.47%)	30 (17.75%)
DM (# - %)	10 (11.9%)	6 (7.05%)	16 (9.46%)
Overweight (# - %)	27 (32.14%)	39 (45.88%)	66 (39%)
Obesity (# - %)	23 (27.38%)	12 (14.11%)	35 (20.71%)
Habits			
Tobacco (# - %)	3 (3.57%)	1 (1.17%)	4 (2.36%)
Alcohol (# - %)	11 (13.09%)	10 (11.76%)	21 (12.42%)
Social Stratum			
1 (# - %)	22 (26.19%)	34 (40%)	56 (33.13%)
2 (# - %)	19 (22.61%)	29 (34.11%)	48 (28.4%)
3 (# - %)	20 (23.8%)	17 (20%)	37 (21.89%)
4 (# - %)	14 (16.66%)	3 (3.52%)	17 (10%)
5 (# - %)	6 (7.14%)	0 (0.0%)	6 (3.55%)
6 (# - %)	3 (3.57%)	2 (2.35%)	5 (2.95%)
COVID-19			
Mild (# - %)	59 (70.23%)	0 (0.0%)	59 (34.91%)
Moderate (# - %)	21 (25%)	0 (0.0%)	21 (12.42%)
Severe (# - %)	4 (4.76%)	0 (0.0%)	4 (2.36%)
Immunisation			
Pfizer (mRNA BNT162b2) (# - %)	31 (36.9%)	30 (35.29%)	61 (36.09%)

To be continued...

Moderna (mRNA-1273) (# - %)	14 (16.66%)	17 (20%)	31 (18.34%)
AstraZeneca (ChAdOx1) (# - %)	7 (8.33%)	14 (16.47%)	21 (12.42%)
Sinovac (CoronaVac) (# - %)	21 (25%)	15 (17.64%)	36 (21.3%)
Janssen (Ad26.COV2.S) (# - %)	11 (13.09%)	9 (10.58%)	20 (11.83%)
Full scheme (# - %)	74 (88.09%)	71 (83.52%)	145 (85.79%)
Booster dose			
1 (# - %)	42 (50%)	37 (44.52%)	79 (46.74%)
2 (# - %)	26 (30.95%)	26 (30.58%)	52 (30.76%)
3 (# - %)	6 (7.14%)	6 (7.05%)	12 (7.1%)
4 (# - %)	0 (0.0%)	2 (2.35%)	2 (1.18%)

Note: y/o: years old, kg: kilograms, m: metres, BMI (Body Mass Index): kg/m^2, AHT: Arterial Hypertension, DM: Diabetes Mellitus.
Source: Own elaboration.

In relation to comorbidities, it was evidenced that overweight and obesity were the most prevalent comorbidity in the study participants, 39% of the total participants had a BMI equal to or greater than 25 kg/m^2 (66/169), of which 27 belonged to group A (32.14%) and 39 to group B (45.88%). 20.71% of the participants were obese (BMI ≥ 30 Kg/m^2), 23 in group A (27.38%) and 12 in group B (14.11%). 17.75% of the participants had a clinical diagnosis of AHT (30/169), of which 16 belong to group A (19.04%) and 14 to group B (16.47%). The total number of DM patients corresponded to 9.46% (16/169), of which 10 belong to group A (11.9%) and 6 to group B (7.05%), respectively.

Regarding the habits variable, it was evidenced that alcohol consumption was more prevalent than smoking, 12.42% of the total participants versus 2.36%. The absolute and relative frequency of alcohol habit by groups was 11/64 - 13.09% for A and 10/85 - 11.76% for B. Tobacco was more prevalent in group A (3.57%) than in group B (1.17%). In relation to the social stratum variable, it was evidenced that 33.13% of the participants belong to level 1; 28.4% to level 2; 21.89% at level 3; 10% at level 4; 3.55% at level 5 and 2.95% at level 6.

The clinical history of COVID-19 in group A shows that 70.23% had a mild case, 25% moderate, and 4.76% severe, according to WHO criteria[10]. The analysis of the immunization schedule against SARS-CoV-2/COVID-19 in the study participants showed that the most prevalent vaccine was Pfizer (mRNA BNT162b2) with 36.09%, followed by Sinovac (CoronaVac) with 21.3%, Moderna (mRNA-1273) 18.34%, AstraZeneca (ChAdOx1) 12.42% and Janssen (Ad26.COV2.S) 11.83%. 85.79% (145/169) have a complete immunization schedule, with a frequency of booster doses of 46.74% (1 dose), 30.76% (2 doses), 7.1% (3 doses) and 1.18% (4 doses).

A positive result, presence of antibodies against RBD, was considered from a mean fluorescence index equal to or greater than 1.3 (MIF≥ 1.3). Table 2 shows the anti-RBD anti-SARS-CoV-2 antibody titers, groups A and B. It was evidenced that all participants in the study have baseline antibody concentrations above the established cut-off point.

Table 2. Results descriptive and inferential statistics as a function of MIF [anti-RBD], groups A and B.

Participants	SARS-CoV-2 RBD Ig MIF			*p*-value
	$\bar{x}$	s	Min - Max	
Group A (n=84)	6.80	2.23	2.7 - 12.4	0,145*
Group B (n=85)	7.39	2.78	1.7 - 13.7	

Source: Own elaboration.

The analysis of results by group shows that the participants in group A, on average, have antibody levels that multiply up to 5.2X the reference value, with a range ranging from 2.7 – 12.4 MIF, a mean of 6.8 MIF, and a standard deviation of ± 2.23. In the participants of group B, an average of antibodies multiplying up to 5.6X the reference value was also evidenced; with a range ranging from 1.7 – 13.7 MIF, a mean of 7.39 MIF, and a standard deviation of ± 2.78. When statistically contrasting the antibody titers, there was no statistically significant difference between them (p=0.145).

The analysis of the influence of host determinants on the baseline concentration of anti-RBD antibodies by group (Table 3) showed that there are statistically significant differences between them, in relation to the sex variable. A p value of 0.049 was evidenced for men. It was observed that males with prior SARS-CoV-2 infection have lower levels of anti-RBD antibodies compared to males who were not infected. There were no statistically significant differences for women (p = 0.575). There was no evidence of statistically significant differences between the two genders (men vs. women) (p = 0.368, data not shown). With respect to age, there were no statistically significant differences between participants with a higher or lower age than average (46 years), with a p value of 0.447 and 0.206 respectively. The analysis of comorbidities showed statistically significant differences between the levels of anti-RBD antibodies and the overweight variable in both groups (p value = 0.037); it was evidenced that overweight participants with previous infection produce fewer anti-RBD antibodies than overweight participants without previous infection. No statistically significant differences were observed with respect to the obesity variable (p value = 0.369 – 0.194); AHT (p value = 0.637 – 0.100), DM (p value = 0.966 – 0.095) and alcohol habit (p value = 0.881 – 0.114).

The analysis of the social stratum variable did not show statistically significant differences between the participants of group A and B, with a p value of 0.609 for stratum 1; 0.158 for stratum 2 and 0.313 for stratum 3.

The analysis of the influence of COVID-19 severity on baseline antibody concentration showed that there are no statistically significant differences between participants in group A who presented a mild, moderate, or severe clinical picture (p value = 0.244), according to WHO criteria[10].

In relation to the type of vaccine applied and its influence on baseline antibody levels, it was evidenced that there are no statistically significant differences between the concentration of antibodies and the type of biological received. Pfizer (mRNA BNT162b2) (p value = 0.341), AstraZeneca

Table 3. Inferential statistical results between anti-RBD antibody levels according to history of COVID-19 (Group A and B) and host determinants.

Variables		SARS-CoV-2 RBD Ig MIF			*p*-value
		COVID-19	$\bar{x}$	s	
Sex	Male	A (n=20)	6.17	2.33	**0,049***
		B (n=16)	8.1	3.25	
	Female	A (n=64)	7.0	2.17	0,575*
		B (n=69)	7.22	2.65	
Age	> 46	A (n=39)	7.35	2.36	0,447*
		B (n=41)	7.79	3.01	
	< 46	A (n=44)	6.32	2.03	0,206*
		B (n=44)	7.01	2.51	
Overweight	Yes	A (n=27)	6.53	2.24	**0,037****
		B (n=39)	7.84	2.59	
	No	A (n=34)	6.97	2.32	0,995*
		B (n=34)	6.76	2.83	
Obesity	Yes	A (n=23)	6.87	2.13	0,369**
		B (n=12)	7.68	3.08	
	No	A (n=61)	6.78	2.28	0,194*
		B (n=73)	7.34	2.74	
AHT	Yes	A (n=16)	8.05	2.22	0,637*
		B (n=14)	8.49	3.37	
	No	A (n=68)	6.51	2.14	0,100*
		B (n=71)	7.17	2.61	
DM	Yes	A (n=10)	7.54	2.72	0,966**
		B (n=6)	7.46	3.99	
	No	A (n=74)	6.70	2.15	0,095*
		B (n=79)	7.38	2.69	
Alcohol	Yes	A (n=11)	7.03	2.19	0,881**
		B (n=10)	6.87	2.81	
	No	A (n=73)	6.77	2.24	0,114*
		B (n=75)	7.46	2.78	

Note: *Mann-Whitney U test, **Student's t-test.
Source: Own elaboration.

(ChAdOx1) (p value = 0.584), Sinovac (CoronaVac) (p value = 0.238), Janssen (Ad26.COV2.S) (p value = 0.592). Statistically significant differences were observed between the concentration of anti-RBD antibodies (Groups A and B) depending on the Moderna vaccine (mRNA-1273) (p value = 0.003). Higher antibody production was evidenced in participants without prior infection compared to participants with HI. Table 4 summarizes the inferential statistical results between anti-RBD antibody levels and the type of vaccine received.

Table 4. Inferential statistical results between anti-RBD antibody levels according to history of COVID-19 (Group A and B) and type of vaccine received.

Vaccine Type	SARS-CoV-2 RBD Ig MIF			*p*-value
	COVID-19	$\bar{x}$	s	
Pfizer (mRNA BNT162b2)	A (n=31)	6.80	2.44	0,341*
	B (n=30)	7.25	2.62	
Moderna (mRNA-1273)	A (n=14)	6.52	2.15	**0,003****
	B (n=17)	9.48	2.73	
AstraZeneca (ChAdOx1)	A (n=7)	6.58	1.51	0,584**
	B (n=14)	7.22	2.79	
Sinovac (CoronaVac)	A (n=21)	7.09	2.10	0,238**
	B (n=15)	6.14	2.62	
Janssen (Ad26.COV2.S)	A (n=11)	6.76	2.59	0,592**
	B (n=9)	6.22	1.59	

Note: *Mann-Whitney U test, **Student's t-test.
Source: Own elaboration.

The results of inferential statistics between the type of vaccination strategy received (homologous immunity vs. heterologous immunity) and its influence on baseline antibody levels showed that there are no statistically significant differences between the two groups (p value = 0.196 and p value = 0.486).

Regarding the influence of the number of booster doses received, it was evidenced that there is a statistically significant weak and direct (positive) degree of correlation between the number of booster doses and the baseline concentration of antibodies in group A participants (p value = 0.013). There was no statistically significant correlation between the participants in group B (p value = 0.224). Table 5 summarizes the results of inferential statistics.

The mathematical analysis of the simple linear regression model, y = a + bx, where y is the dependent variable [anti-RBD], a the constant (5.055), b the intercept (0.751) and x the independent variable (# booster dose), predicts in the participants of group A, that the application of a fifth booster dose would generate baseline antibody levels of 8.81 MIF, securities much higher than the baseline average (6.80 MIF). The application of a sixth and seventh booster doses would generate titers of 9.56 MIF and 10.31 MIF, respectively. When contrasting the concentrations of antibodies, statistically significant differences were evidenced between them (p = 0.001).

Table 5. Results of simple linear correlation analysis between antibody levels and number of booster doses (Group A and Group B)

SARS-CoV-2 RBD Ig MIF vs Booster dose	COVID-19	
	Group A	Group B
Spearman's Rho correlation	0,269	0,133
p-value	**0,013**	0,224
Degree of correlation	weak	N.A

Source: Own elaboration.

Discussion

The RBD region, Receptor Binding Domain, is part of the S1 subunit of the SARS-CoV-2 S protein. It plays a key role in the entry of the virus into host cells[11]. RBD is the main target of neutralizing antibodies (NA) observed in convalescent individuals who have overcome natural infection, therefore, it has become the antigenic target to which the antibodies induced through vaccination point[12]. In the context of public health, the serological status of NA in the community is essential to limit viral replication, minimize morbidity and mortality from COVID-19, and decrease the emergence of new variants of interest or concern[13]. Therefore, two years after the end of the pandemic, quantification of anti-RBD antibodies remains a valid tool to assess and monitor the efficacy of natural or acquired immunisation against SARS-CoV-2[14].

Our study is the first nationwide research to analyze the influence of HI and host-dependent factors on baseline NA concentration in a post-pandemic context (serological surveillance). Early studies of HI in the immune response against COVID-19 vaccines documented a higher production of neutralising antibodies (25x – 100x) in previously infected individuals compared to individuals without pre-existing infection[15].

The study by Reynolds et al, showed that infected individuals, after a single dose of the BNT162b2 vaccine (Pfizer/BioNTech), confer a greater humoral response against the S protein, with cross-immunity against the B.1.1.7 and B.1.351 variants, compared to vaccinated individuals with the same dose who had no previous infection[16]. Krammer et al, showed that pre-existing immunity generates a greater antibody response compared to immunologically naive participants against the new coronavirus[17]. Anti-RBD IgG levels were found to be 25 times higher compared to the control group with a complete vaccination schedule using mRNA platforms (Vaccines BNT162b2 [Pfizer] and mRNA-1273 [Moderna]).

Our results differ from those of the studies mentioned above. We believe that the epidemiological period in which the research was conducted influences the results observed. The first studies were conducted during the pandemic, in late 2020 and early 2021, when a large part of the world's population had not completed the immunization schedule and had not even received the initial “priming” dose, in addition to the epidemiological behavior of the circulating strains. In other words, most of the individuals evaluated immunologically were still virgins, and the virus was not yet endemic. In our research, participant recruitment began between March and June 2024, in a post-pandemic context (May 5, 2023 according to WHO), with a highly immunized population, both naturally and artificially, and SARS-CoV-2 embedded in the population virome.

Our hypothesis is consistent with the concept of HI accepted by the WHO, "*Hybrid immunity is defined as immune protection in people who have received one or more doses of a COVID-19 vaccine and have experienced at least one SARS-CoV-2 infection before or after the start of vaccination*"[4].

This would explain that group B participants, even if they had not had infection prior to vaccination, were able to be in contact with the dominant strain of SARS-CoV-2 during the period of time between their last booster dose and recruitment into the study. Scientific argument that allows us to understand the results of inferential statistics between both groups (p= 0.145). Consequently, we can infer that HI would be involved in the maintenance of immunity against SARS-CoV-2 in our population, taking into account serostatus, high reactivity against the RBD region and a significant decrease in the number of COVID-19 cases[18].

We believe that further studies are needed to fill the knowledge gap on this topic in modern vaccinology.

The influence of host-dependent factors on the immune response induced by vaccines has a scientific basis in the psycho-neuro-immuno-endocrine (PNIE) axis, which explains the synchronous relationship between the four organ systems and their impact on the pathophysiology of human diseases[19]. In the context of vaccinology, it has been shown that certain host conditions such as gender, age, comorbidities, habits, stress, and sociocultural environment can modulate the immune response induced by vaccines and affect their effectiveness[20].

In our study we evaluated the influence of host determinants on baseline anti-RBD antibody concentration among participants in group A and B. We demonstrated that anthropometric characteristics such as gender (sex) can influence baseline antibody concentration. It was observed that males with previous infection have lower antibody concentrations compared to males without a history of infection. In the literature review, no references were found that documented the reproducibility of our findings, therefore, we consider that the results could be due to a type I error (α), taking into account the small sample of male participants in the study (n= 36, 20 in group A and 16 in group B). For future research, we plan to expand the number of male participants and evaluate the association between the variables mentioned.

In relation to comorbidities, it was shown that overweight participants with previous infection have fewer antibody titers relative to overweight participants without pre-existing infection. Scientifically, it has been shown that being overweight is associated with a progressive chronic proinflammatory state and dysregulation of the immune response, favoring a scenario of immunoparesis or immune fatigue[21,22]. Excessive adiposity can lead to T cell dysfunction, altered cytokine production, and a suboptimal immune response. These changes can compromise the efficacy of vaccines[23,24].

Regarding the type of vaccine applied, it was evidenced that there are no statistically significant differences with the BNT162b2, ChAdOx1, CoronaVac and Ad26.COV2.S vaccines. Statistically significant differences were evidenced with the Moderna vaccine (mRNA-1273). Participants with prior infection were observed to have lower anti-RBD antibody titers compared to participants without pre-existing infection. However, the detailed analysis of the data manages to show that the titles are still above the established cut-off point.

All vaccines showed a 100% seropositivity against the RBD region in each immunized individual, with a serostatus dating from 21 – 23 months since the last booster dose. Consequently, it can be inferred that all vaccines approved in the national territory offer long-term immunity, regardless of the type of biological and previous SARS-CoV-2 infections.

The results of inferential statistics between the type of vaccination strategy received (homologous immunity vs. heterologous immunity) and its influence on baseline antibody levels showed that there are no statistically significant differences between the two groups. Participants with prior infection and who received a homologous immunization schedule have the same reactivity against the RBD region, compared to participants who received a heterologous immunization schedule. Therefore, both strategies are effective in generating immunity against SARS-CoV-2 in the long term.

Regarding the influence of the number of booster doses received, it was evidenced that there is a statistically significant weak and direct (positive) degree of correlation between the number of booster doses and the baseline concentration of antibodies in group A participants. Mathematical analysis of the simple linear regression model predicts that the application of booster doses would generate antibody levels well above the baseline mean (6.80 MIF).

An immunological explanation for the observed results could be due to the fact that participants with HI have had recognition of the entire antigenic load of the infecting strain, which promotes a synchronous stimulation of all the effector mechanisms of the innate and acquired immune response, both in its cellular and humoral branches. Therefore, receiving booster doses stimulates the trained immunity of the innate component and the immunological memory of the acquired component, resulting in greater production of antibodies[25,26,27].

These results allow us to generate the following hypotheses:

1. In a biological scenario, where instead of a booster dose, it is an antigenic encounter with the circulating strain; individuals with HI will have the ability to synthesize more antibodies to each stimulus, thus guaranteeing long-term immunity against SARS-CoV-2.

2. Each antigenic stimulus will generate in patients with HI the activation of memory B lymphocytes, which experience somatic hypermutation and consequently greater diversity of antibodies with greater neutralizing capacity. Important for the recognition of new variants of SARS-CoV-2.

3. With the advent of SARS-CoV-2 to the population virome (endemic virus), annual or seasonal vaccination could be contemplated at the national level in individuals at high risk of developing severe COVID-19.

Conclusions

In our population, HI has a positive influence on the humoral response induced by COVID-19 vaccines, promoting greater antibody production with each booster dose received. The serological status of our population shows long-term immunity, 21–23 months, with high reactivity against the RBD region of SARS-CoV-2. All vaccines approved in the country are effective and offer prolonged immunity, regardless of the type of strategy and previous SARS-CoV-2 infections. Our study showed that being overweight negatively affects the baseline antibody concentration in people with previous infections..

Conflict of interest

All researchers declare that they have no conflict of interest with regard to the design and execution of this research project

Ethical considerations

This study was approved by the research ethics committee of the Universidad Libre Seccional Pereira, Colombia, and the ethics committee of the Universidad Internacional Iberoamericana, Mexico, with the following approval code: 2022-11-04-001.

Use of artificial intelligence

The authors declare that they have not used any applications, software, or generative artificial intelligence websites in the writing of the manuscript, in the design of tables and figures, or in the analysis and interpretation of the data.

Authors' contributions

Conceptualisation: F.E.T.J., E.M.T., M.F.T.F.; Data curation: F.E.T.J., A.E.A.O., N.S.R.M., J.C.V.P.; Formal analysis: F.E.T.J., A.E.A.O., N.S.R.M., J.C.V.P.; Fundraising: F.E.T.J., E.M.T., M.F.T.F.; Research: F.E.T.J., E.M.T., M.F.T.F., A.E.A.O., N.S.R.M., J.C.V.P.; Methodology: F.E.T.J., E.M.T., M.F.T.F., A.E.A.O.; Project management: F.E.T.J., E.M.T., M.F.T.F.; Resources: F.E.T.J., A.E.A.O., N.S.R.M., J.C.V.P.; Software: F.E.T.J., M.F.T.F., A.E.A.O.; Supervision: F.E.T.J., E.M.T.; Validation: F.E.T.J., N.S.R.M., J.C.V.P.; Visualisation: F.E.T.J., E.M.T., M.F.T.F.; Drafting of the original manuscript: F.E.T.J., E.M.T., M.F.T.F.; Writing, revision and editing: F.E.T.J., E.M.T., M.F.T.F., A.E.A.O., N.S.R.M., J.C.V.P.

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