REVISTA BRASILEIRA DE
MEDICINA DO TRABALHO

ORIGINAL ARTICLE / ARTIGO ORIGINAL

Waning immune response with CoronaVac vaccine in different age cohorts among healthcare workers

Declínio da resposta imune com CoronaVac nas diferentes faixas etárias em profissionais de saúde

Monica **Taminato**, Ana Paula **Chaves**, Richarlisson **Morais**, Danielle **Conte**, Maria Cristina **Gabrielloni**, Gabriela **Barbosa**, Eduardo **Medeiros**, Nancy **Bellei**

http://doi.org/10.47626/1679-4435-2022-1048

Recebido/Received: 21/06/2022
Aceito/Accepted: 25/10/2022
Número do comitê de ética: CAE-47617621.6.0000

PRE-PROOF
(as accepted)

This is a preliminary, unedited version of a manuscript that has been accepted for publication in Revista Brasileira de Medicina do Trabalho. As a service to our readers, we are providing this early version of the manuscript, as accepted. The manuscript will still be copyedited, translated, typeset, and approved by the authors before it is published in final form.

Waning immune response with CoronaVac vaccine in different age cohorts among healthcare workers

Monica Taminato[1]
Ana Paula Chaves[1]
Richarlisson Morais[1]
Danielle Conte[1]
Maria Cristina Gabrielloni[1]
Gabriela Barbosa[1]
Eduardo Medeiros[1]
Nancy Bellei[1]

1 – Universidade Federal de São Paulo (UNIFESP), Medicina, São Paulo, SP, Brasil.

Autor correspondente
Gabriela Barbosa
E-mail: gabrielarbarbosa@hotmail.com
https://orcid.org/0000-0002-3386-8581

Abstract

Introduction: The decline in serum antibodies against SARS-CoV-2 observed in several studies raises questions about long-term immunity. Lower antibody levels are associated with new cases of COVID-19 even after vaccination, leading to the administration of booster doses. **Objective:** To evaluate the post vaccination immune humoral response and the relationship between post-vaccination seropositivity rates and demographic data among Healthcare Workers over 6 months after CoronaVac immunization. **Methods:** A cross section study including Healthcare professionals vaccinated with two doses of CoronaVac after six months or more. The study was carried with the analysis of post-vaccination serological test to assess the levels of humoral response (anti-RBD IgG) after vaccination. **Results:** In this study, 325 participants were included, 76% were female and the median age was 42 years (20-85; IQR 31-53). Overall, 18.8% (61) of the participants results were seropositive for anti – RDB IgG; 81.2% did not present sufficient quantitative titles. The IgG titers obtained for female HCWs were not different from those obtained for the male participants with a seropositivity, regardless of age. **Conclusions:** It was possible to identify a group with positive quantitative titles in serological test for IgG antibody against the SARS-CoV-2. Further investigation is required to determine the durability of post-vaccination antibodies and how serological tests can be determine the ideal timing of vaccine booster doses.

Keywords: COVID-19 vaccines; covid-19 serological testing; SARS-CoV-2; antibodies; healthcare workers.

Resumo

Introdução: O declínio dos anticorpos séricos contra o SARS-CoV-2 observado em vários estudos levanta questões sobre a imunidade a longo prazo. Níveis mais baixos de anticorpos estão associados a novos casos de COVID-19 mesmo após a vacinação, levando à administração de doses de reforço. **Objetivos:** Avaliar a resposta imunitária humoral pós-vacinação e a relação entre as taxas de soropositividade pós-vacinação e dados demográficos em trabalhadores da saúde por mais de 6 meses após a imunização com CoronaVac. **Métodos:** Estudo transversal incluindo profissionais de saúde vacinados com duas doses de CoronaVac após seis meses ou mais. O estudo foi realizado com a análise do teste sorológico pós-vacinação para avaliar os níveis de resposta humoral (anti-RBD IgG) após a vacinação. **Resultados:** Neste estudo foram incluídos 325 participantes, 76% do sexo feminino e a idade mediana foi de 42 anos (20-85; IQR 31-53). No geral, 18,8% (61) dos resultados dos participantes foram soropositivos para IgG anti-RDB; 81,2% não apresentaram títulos quantitativos suficientes. Os títulos de IgG obtidos para os profissionais de saúde do sexo feminino não foram diferentes daqueles obtidos para os participantes do sexo masculino com soropositividade, independentemente da idade. **Conclusões:** Foi possível identificar um grupo com títulos quantitativos positivos no teste sorológico para anticorpo IgG contra o SARS-CoV-2. Mais investigações são necessárias para determinar a durabilidade dos anticorpos pós-vacinação e como os testes sorológicos podem determinar o momento ideal das doses de reforço da vacina.

Palavras-chave: vacinas contra COVID-19; teste sorológico para COVID-19; SARS-CoV-2; anticorpos; trabalhadores da saúde.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people around the world. Brazil is among the countries with the highest numbers of confirmed cases and deaths from SARS-CoV-2[1-3].

The CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine, was approved for emergency use by ANVISA, Brazil Ministry of Health in January 2021, and was first distributed soon after authorization on January 18, 2021[4]. As one of the most affected groups in the COVID-19 pandemic, the Heal care workers (HCW) was one of the prioritized groups to receive the vaccine. Thus, two doses of the CoronaVac vaccine with the recommended dosing interval of 28 days between the first and second doses were administered. This interval was considered to induce the highest efficacy against the more severe outcomes of hospitalization, ICU admission, and death[5].

The decline in serum antibodies against SARS-CoV-2 observed in several studies raises questions about long-term immunity. Lower antibody levels are associated with new cases of Covid-19 even after vaccination, leading to the administration of booster doses[6-8]. The SARS-CoV-2 antibodies seropositivity over time might be associated with the risk of future infection since studies have shown that neutralizing and binding antibodies show a strong correlation with efficacy[6].

The Brazilian vaccination plan was implemented in October 2021, so that a third dose for HCWs and people aged 60 years and over was administered. However, the persistence of CoronaVac, vaccine-induced immunity is unknown, and immunogenicity according to age cohorts may differ among individuals. This study aimed to evaluate the post-vaccination immune humoral response, and the relationship between post-vaccination seropositivity rates and demographic data, (age and sex) among HCW after six months of two doses of CoronaVac.

METHODS

We performed a cross section study including healthcare professionals from São Paulo Hospital (São Paulo, Brazil), vaccinated with CoronaVac with at least six months after the administration of the second dose. The study was carried out in October 2021 with an analysis of post-vaccination IgG antibodies.

Subjects

São Paulo Hospital healthcare workers were invited to have their blood samples collected for serological tests to determine the quantitative anti-RDB IgG to assess the levels of humoral response after at least six months of vaccination by the whole-virion CoronaVac (Sinovac Life Sciences). All professionals who had received the second dose of the CoronaVac vaccine in a period of six months or more were eligible. Exclusion criteria were a previous infection with COVID-19, immunosuppression or use of immunosuppressive drugs. The study was approved by the Ethics Committee of the Federal University of São Paulo (CAE-47617621.6.0000.5505). All participants signed an informed consent form and participated in the study.

Laboratory study

The study was carried out in October 2021 in the Virology Laboratory. Briefly, three to five mL of venous blood was taken from the volunteers participating in the study. Sera were separated and stored in a −20°C freezer until the antibody studies were performed. IgG antibody assays against SARS-CoV-2 RBD protein were performed using the Access SARS-CoV-2 IgG antibody (1°IS) (Beckman Coulter, Inc.). The antibodies against the RBD of the spike protein were quantitatively analysed and were interpreted as positive (signal for test sample/signal at cut-off value if ≥ 30 UI/mL or BAU/mL) or negative (if ≥ 30 UI/mL) in accordance with the Access SARS-CoV-2 IgG Antibody Test.

Statistical analysis

Data are presented as counts, percentages, and 95% confidence intervals (CIs). Comparisons were obtained between positive and negative groups according to the detection of IgG anti-RBD. The Shapiro-Wilk normality test was performed to verify normality, and the significance level was set at 5%. The Kruskal–Wallis test, also with a 5% significant level, was used for variables that did not follow normality. When there was significance, the Dunn test was used to check for multiple comparisons.

RESULTS

A total of 325 HCW were recruited aged 20-86 years. Among the 325 participants, 248 (76%) were female and the median age was 42 years (20-85; IQR 31-53). Overall, 18.8% (61) of the participants results were positive with a 64.47 BAU/mL anti –RDB IgG median quantitative titer (IQR 42.87-125.5) obtained for the whole study group. The minimum and maximum titers obtained for the positive samples were 30.16 – 1094 BAU/mL. The seropositivity was 18.1% for females and 20.7% for male HCWs. Three participants presented a titer above 506 BAU/mL, a titer previously considered as a correlate of 80% vaccine efficacy against symptomatic SARS-CoV-2 infections. The negative group included 81.2% (264) of the participants with a 8.55 anti –RDB IgG median quantitative titer (IQR 5.5-13.92) and the maximum titer was 29.92 BAU/mL ($p < 0.001$).

IgG titers obtained for female HCWs were not different from those obtained for the male participants with a seropositivity test of 62.93; IQR 42.33-110.0 and 73.02 IQR 49.79 - 154.0 BAU/mL respectively ($p > 0.296$).

The testing volumes, number of positive results, and IgG titers in each age group are shown in the Table 1 and Figure 1.

Table 1. IgG anti-RBD seropositivity and antibody titers detection after 6 months of immunization with 2 doses of CoronaVac vaccine in HCW

Age (years)	No.[a]	Positive – No. (%)	IgG titers med.[b] – BAU/ml[c] (IQR[d])	OR[e] (95% CI)	p value[*]	ANOVA[*] [*]
20-30	76	10 (13.15)	74.06 (46.80-94.37)	Ref. [f]	Ref.	Ref.
31-40	74	18 (24.32)	62.85 (44.9-102.00)	0.47 (0.20-1.10)	0.09	0.99
41-50	72	13 (18.06)	105.80 (47.00-503.30)	0.68 (0.28-1.68)	0.4	0.0145
>51	103	20 (19.42)	51.73 (40.67-137.10)	0.62 (0.27-1.43)	0.32	0.99
TOTAL	325	61 (18.26)	64.47 (42.87-125.5)	-	-	-

[a] Number of cases; [b] Median [+-c] Biding Antibodies Units per milliliter[2] [d] Interquartile range [e] Odds ratio
[f]Reference * Fisher's exact test ** Multiple comparison ANOVA/ Tukey's test and Dunn test.

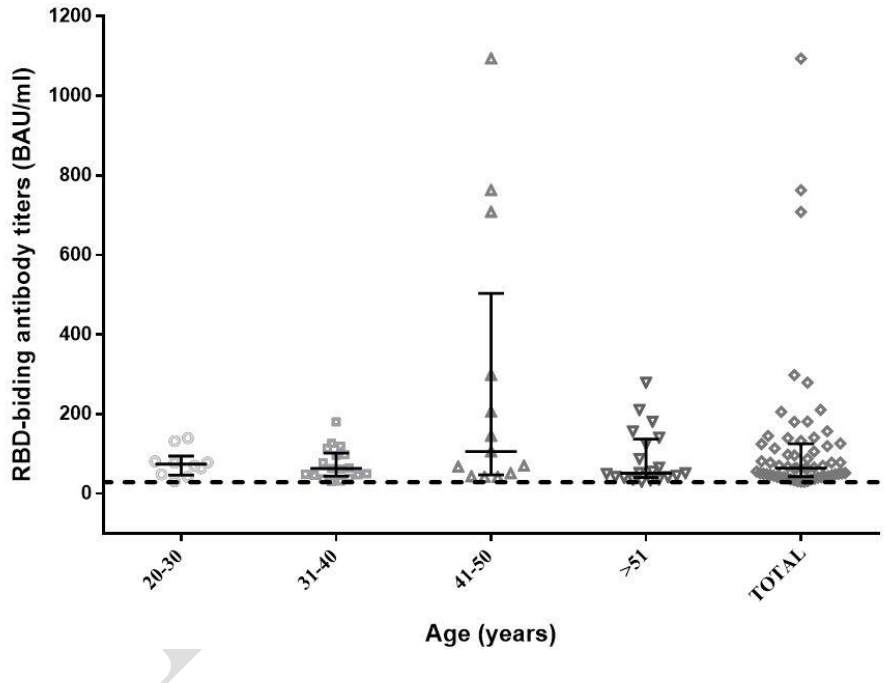

Figure 1. Comparison of Severe Acute Respiratory Virus 2 anti-RBD antibodies titers in HCW according to age groups.

Dashed line indicates cut-off for seropositivity (³30 BAU/ml). Vertical solid lines indicate the distance between the interquartile ranges. The middle horizontal solid lines indicate the median of antibodies titers, meanwhile the upper and lower horizontal edges represent the 25% and 75% percentiles of antibodies levels.

DISCUSSION

The major challenge, at present, is to develop predictive models of immunological protection for COVID-19 and to define the correlates of protection to establish vaccination programs[7-9]. Data from previous studies have suggested that a 28 days dosage interval reaches a more robust antibody response and a longer persistence, compared to an interval of 14 days between the two doses[10]. Our study found that less than 20% of the evaluated healthcare professionals without previous SARS-CoV-2 infection vaccinated with two doses were seropositive after six months or more.

Recent research has suggested that a high level of neutralizing titers is required to protect against severity and death from circulating SAR-CoV-2 variants[11]. We have observed a decrease in the antibody detection without significant differences among different age groups. Indeed, there were no statistical differences between age and sex regarding IgG levels. Only three participants obtained a high level of antibody titer that was considered to be correlated with protection, according to a recently published study[9].

In this study, two doses of an adenovirus vector vaccine were evaluated with 28 days after the second dose and an antibody level to obtain an 80% efficacy against symptoms needed to present a mean of 506 (95% BAU / ml10.) Another report evaluated an immune correlate analysis of the mRNA-1273 COVID-19 vaccine trial estimated a 90% vaccine efficacy of RBD IgG level of 775 BAU/ml at the time[12]. In our study, even the seropositive HCW would not be protected against symptomatic infection after the time period we analyzed.

One limitation of this study is the use of an immunochemiluminescence test as a surrogate marker of the immune humoral response and not a plaque reduction neutralization test. Nonetheless, the assay detected the total immunodominant neutralizing antibodies that targeted the spike protein receptor binding domain (RBD).

Other immunological markers present in the cellular immunity not tested in our study may contribute to the protection of previously immunized patients, even in the absence of antibody persistence. A non-peer-reviewed study with Brazilian HCW reported a 50.7% efficacy of CoronaVac in the prevention of severe forms of SARS-CoV-2 infections in a

phase 3 clinical trial[13]. Another study published in China showed that HCW maintained their B cells and T cells specific for SARS-CoV-2 detection five months after two doses of the Sinopharm vaccine[14].

CONCLUSION

Further investigation is required to determine the durability of post-vaccination antibodies in individuals, including other immunologic markers, and to elucidate how serological tests can be predictive of effectiveness and determine the ideal timing of vaccine booster doses for population protection. Inactived vaccines are safe, but the immunogenicity according to age cohorts may differ among individuals, especially when it has been considered to be administered in children.

Acknowledgments

This work was supported by Beckman Coulter® through materials and supplies.

REFERENCES

1. World Health Organization (WHO). WHO Coronavirus (COVID-19) Dashboard. Geneva: WHO; 2021 [Accessed 2021 Nov 15]. Available from: https://covid19.who.int

2. de Souza WM, Buss LF, Candido DS, Carrera JP, Li S, Zarebeski AE, et al. Epidemiological and clinical characteristics of the COVID-19 epidemic in Brazil. Nat Hum Behav. 2020;4:856-65.

3. Sant'Ana G, Imoto AM, Amorim FF, Taminato M, Peccin MS, Santana LA, et al. Infection and death in healthcare workers due to COVID-19: a systematic review. Acta Paul Enferm. 2020.33:eAPE20200107.

4. COVAX Global Supply Forecast. July 12, 2021 [Acessed 2021 Nov 20]. Available from: https://www.gavi.org/sites/default/files/covid/covax/COVAX-Supply-Forecast.pdf

5. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. N Engl J Med. 2021;385(10):875-84. DOI: 10.1056/NEJMoa2107715

6. Ranzani O, Hitchings M, Dorion M, D'Agostini TL, de Paula RC, de Paula OFP, et al. Effectiveness of the CoronaVac vaccine in the elderly population during a P.1 variant associated epidemic of COVID-19 in Brazil: A test-negative case control study. medRxiv 2021.05.19.21257472 [preprint]. 2021. Available from: https://www.medrxiv.org/node/383881.external-links.html. DOI: https://doi.org/10.1101/2021.05.19.21257472

7. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27(7):1205-11.

8. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. N Engl J Med. 2021;385(16):1474-84. DOI: 10.1056/NEJMoa2109072

9. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al.; Oxford COVID Vaccine Trial Group. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. Nat Med. 2021;27:2032-40. DOI: https://doi.org/10.1038/s41591-021-01540-1

10. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181-92. DOI: 10.1016/S1473-3099(20)30843-4

11. Cromer D, Steain M, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants and the impact of boosting: a meta-analysis. Lancet Microbe. 2022;3(1):e52-e61. DOI: 10.1016/S2666-5247(21)00267-6

12. Gilbert PB, Montefiori CD, Mcdermontt AB, Fong Y, Benkeser D, Deng W, et al. ; Immune Assays Team§; Moderna, Inc. Team§; Coronavirus Vaccine Prevention Network (CoVPN)/Coronavirus Efficacy (COVE) Team§; United States Government (USG)/CoVPN Biostatistics Team§. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science. 2022;375(6576):43-50. DOI: 10.1126/science.abm3425

13. Palacios R, Batista AP, Albuquerque CSN, Patiño EG, Santos JP, Conde MTRP, et al. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study. SSRN J. 2021. Available from: https://ssrn.com/abstract=3822780. DOI: 10.2139/ssrn.3822780

14. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. Lancet Infect Dis. 2022;22(4):483-95. DOI: 10.1016/S1473-3099(21)00681-2