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Observational study: does vaccination provide protective effects against long COVID?

Estudo observacional: a vacinação tem efeito protetivo no desenvolvimento da COVID longa?

Estudio observacional: ¿la vacunación tiene efecto protector en el desarrollo de COVID larga?

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ABSTRACT

Objective: To evaluate whether vaccination offers protection against long COVID and its clinical manifestations. **Method:** This observational study included randomly selected patients treated at a university hospital. Participants were individuals aged 18 or older, of both sexes, who had tested positive for SARS-CoV-2 (via RT-PCR or rapid antigen test) between April 2021 and June 2022, with at least four weeks elapsed since their diagnosis at the time of the interview, conducted between April 2022 and May 2023. A researcher-administered questionnaire collected data on vaccination status and Long COVID symptoms (headache, fatigue, chest pain, cough, dyspnea, insomnia, cognitive deficits, oral cavity changes, and others). Participants were divided into two groups—vaccinated and unvaccinated—and the incidence of clinical manifestations was compared. Statistical analyses were conducted using the chi-square and Fisher's exact tests, with a 5% significance level. **Results:** A total of 855 participants were screened, and 120 (14%) met the inclusion criteria: 46 (38.3%) in the unvaccinated group and 74 (61.7%) in the vaccinated group. Vaccinated individuals had a lower incidence of long COVID compared to unvaccinated individuals (p = 0.0128). The incidence of cognitive deficits among those with long COVID was significantly higher in the unvaccinated group than in the vaccinated group (p = 0.0343). **Conclusion:** Vaccination emerged as an effective primary prevention strategy against long COVID, demonstrating efficacy in reducing its incidence, particularly in preventing cognitive deficits.

Descriptors: COVID-19 vaccine; Long COVID; Clinical Manifestations; Cognitive Dysfunction.

RESUMO

Objetivo: *Avaliar se a vacinação tem valor protetor contra o desenvolvimento da COVID longa e de suas manifestações clínicas.* ***Métodos:*** *Trata-se de um estudo observacional, com pacientes selecionados, aleatoriamente, que foram atendidos em um hospital universitário. Os participantes eram indivíduos maiores de 18 anos, de ambos os sexos, com resultado de exame (RT-PCR ou TR-AG) positivo para SARS-CoV-2, dentre abril/2021 e junho/2022, e há, pelo menos, quatro semanas da entrevista, realizada entre abril/2022 e maio/2023. Aplicou-se um questionário por um membro da equipe de pesquisa direcionada para a situação vacinal e as manifestações clínicas da COVID longa (cefaleia, fadiga, dor torácica, tosse, dispneia, insônia, déficit cognitivos, alterações na cavidade oral e outros). Após a coleta de dados, os indivíduos foram divididos em dois grupos—vacinados e não vacinados—e as incidências das manifestações clínicas entre eles foram analisadas. Os resultados foram submetidos ao teste do qui-quadrado e Exato de Fischer, com nível de significância de 5%.* ***Resultados:*** *Foram selecionados 855 participantes, dentre eles, 120 (14%) foram incluídos, 46 (38,3%) são pertencentes do grupo não vacinados e 74 (61,7%) do grupo vacinados. Nos vacinados houve menor incidência da COVID longa, em relação ao grupo de não vacinados (p=0.0128). A incidência de déficit*

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cognitivo na COVID longa foi estatisticamente significante no grupo não vacinados, quando comparado ao grupo vacinados (p=0.0343). ***Conclusão:*** *A vacinação mostrou-se como uma estratégia de prevenção primária para a COVID longa, pois demonstrou eficácia na proteção contra o seu desenvolvimento, reduzindo a incidência de déficits cognitivos.*

Descritores: *Vacina contra o COVID 19; COVID longa; Manifestações Clínicas; Disfunção Cognitiva.*

RESUMEN

Objetivo: *Evaluar si la vacunación tiene valor protector contra el desarrollo de COVID larga y de sus manifestaciones clínicas.* ***Método****: Se trata de un estudio Observacional, con pacientes seleccionados, aleatoriamente, que fueron atendidos en un hospital universitario. Los participantes eran individuos mayores de 18 años, ambos los sexos, con resultado de prueba (RT-PCR o TR-AG) positivo para SARS-CoV-2, entre abril/2021 y junio/2022, y hay, por lo menos, cuatro semanas de la entrevista, realizada entre abril/2022 y mayo/2023. Fue aplicado un cuestionario por un miembro del equipo de investigación direccionada para la situación vacunal y las manifestaciones clínicas de COVID larga (cefalea, fatiga, dolor torácico, tos, disnea, insomnio, déficits cognitivos, cambios en la cavidad oral y otros). Después de la recogida de datos, los individuos fueron divididos en dos grupos (vacunados y no vacunados), y analizada las incidencias de las manifestaciones clínicas entre ellos. Los resultados fueron sometidos al test Chi-cuadrado y Exacto de Fisher, con nivel de significancia de 5%.* ***Resultados:*** *Fueron seleccionados 855 participantes, entre ellos, 120 (14%) fueron incluidos, (38,3%) son pertenecientes al grupo no vacunado y 74 (61,7%) al grupo vacunado. En los vacunados hubo menor incidencia de COVID larga, con relación al grupo de no vacunados (p=0.0128). La incidencia de déficit cognitivo en la COVID larga fue estadísticamente significante en el grupo de no vacunados (p=0,0343).* ***Conclusión****: La vacunación mostró ser una estrategia de prevención primaria para COVID larga, pues demostró eficacia en la protección contra su desarrollo, reduciendo la incidencia de deficits cognitivos.*

Descriptores: *Vacuna contra la COVID 19; COVID larga; Manifestaciones Clínicas; Disfunción Cognitiva.*

INTRODUCTION

The development and distribution of vaccines against the SARS-CoV-2 virus significantly reduced the risk of severe COVID-19[1,2]. However, post-COVID syndrome, also known as long COVID, continues to be reported despite widespread global vaccination efforts. This condition is characterized by clinical symptoms that persist beyond the acute phase of the disease.

In 2020, the United Kingdom's National Institute for Health and Care Excellence (NICE)[3] published guidelines defining long COVID as the presence of signs and symptoms that persist or arise beyond four weeks after the acute phase, without being explained by an alternative diagnosis. This definition was subsequently adopted by the Brazilian Ministry of Health[4].

As of the 38th epidemiological week of 2024, Brazil has reported approximately 39 million confirmed COVID-19 cases since the pandemic began in 2020[5]. The World Health Organization (WHO) estimates that about 20% of individuals develop long COVID following the acute infection[6]. However, there is a lack of epidemiological data on long COVID within Brazil. Recognizing the significant public health impact of long COVID, the Brazilian Ministry of Health initiated a population-based study in March 2024, named Epicovid 2.0. This study aims to gather data to inform public policies targeting long COVID[7]. A Brazilian study indicated that 80% of individuals with long COVID sought health care services after the acute phase, highlighting the strain on the health care system[8]. Nonetheless, there is a need for studies with larger samples and robust methodologies to provide more reliable insights.

Thus, it is evident that Brazil urgently needs studies that provide data on long COVID within the context of its population. Such research is essential to support efforts and allocate resources to address this pressing public health issue.

The present study aims to expand knowledge about long COVID in Brazil, addressing the gap in the current literature regarding the Brazilian reality. Vaccination has demonstrated significant benefits in protecting against severe cases of the disease and is widely accessible across the country. This study investigates whether vaccination provides any protective effect against the development of long COVID. Additionally, it examines differences in the incidence of clinical manifestations (e.g., headache, fatigue, chest pain, cough, nasal congestion, runny nose, dyspnea, insomnia, cognitive deficits, tachycardia, and oral cavity alterations [including lesions, spots, bleeding, and disturbances in smell and taste]) between vaccinated and unvaccinated groups during long COVID. This analysis could further emphasize the importance of vaccination, providing scientific evidence to support its promotion in public health policies aimed at combating Long COVID in Brazil.

Therefore, this study aimed to evaluate whether vaccination offers protective effects against the development of long COVID as well as its clinical manifestations.

METHOD

This was an observational study that assessed the general clinical manifestations of long COVID, including headache, fatigue, chest pain, cough, nasal congestion, runny nose, dyspnea, insomnia, cognitive deficits (such as issues with concentration and memory), tachycardia, and oral cavity alterations (e.g., lesions, spots, bleeding, and disturbances in smell or taste). The incidence of these manifestations was compared between two groups: vaccinated and unvaccinated individuals. The aim was to evaluate the influence of vaccination on the development of long COVID.

Individuals treated at the hospital of our university, aged 18 or older, of both sexes, who had previously tested positive for SARS-CoV-2 via RT-PCR and/or rapid antigen test conducted at the hospital were included in the study. The test must have been performed at least four weeks (28 days) before the research team contacted the participant by phone. This time frame aligns with the Brazilian Ministry of Health's definition of long COVID, characterized by the presence of signs, symptoms, and/or conditions persisting or developing four weeks or more after the initial SARS-CoV-2 infection, without an alternative diagnosis[4]. To be included in the study, participants had to meet all the criteria simultaneously; failure to meet any one of them resulted in exclusion.

The exclusion criteria for the study were as follows: individuals who did not respond to the phone contact, those who declined to participate in the study, and/or those who did not agree to the Free and Informed Consent Form (FICF). The presence of any of these conditions resulted in exclusion from the study.

A total of 855 individuals were randomly selected from the clinical laboratory database (MV 2000) at the Pontifical Catholic University of Campinas (PUC-Campinas) hospital, all of whom met the inclusion criteria. These individuals had undergone SARS-CoV-2 testing between April 2021 and June 2022. Telephone contacts were initiated in April 2022 and concluded in May 2023. Of these, 120 individuals (14%) were included in the study, while the remaining 735 individuals (86%) were excluded for not meeting all the inclusion criteria.

Participants were contacted by phone by a trained health care worker from the research team, who administered the questions from an online questionnaire created by the authors. The questionnaire included the FICF and a phone-based anamnesis focused on the clinical history of long COVID symptoms and COVID-19 vaccination status[9-11]. The information collected from participants included: the date of questionnaire completion, gender, age, preexisting comorbidities prior to COVID-19, vaccination status at the time of their positive SARS-CoV-2 test, and a list of clinical manifestations. Participants were asked to select symptoms that developed during the acute infection, persisted for at least four weeks after diagnosis, and were still present at the time of the phone interview. Examples of symptoms included headache, chest pain, cough, nasal congestion, runny nose, fatigue, insomnia, cognitive deficits, tachycardia, diarrhea, vomiting, anxiety, depression, anosmia, ageusia, and oral cavity lesions or bleeding. Additionally, participants were given space to report any other symptoms not previously listed if they were present. A member of the research team recorded all responses.

Data were collected and organized in Excel and divided into two groups: the vaccinated group (VG) and the unvaccinated group (UVG). A statistical comparison was conducted to evaluate the incidence of Long COVID and its clinical manifestations between the two groups. Results were analyzed by using the BioEstat 5.3 software and subjected to the chi-square and Fisher's exact tests, with a significance level of 5%.

This study was approved by the human research ethics committee at PUC-Campinas under opinion no. 4.946.660 and CAAE no. 50740821.4.0000.5481. It complies with Resolution 466/2012 of the National Health Council.

RESULTS

A total of 120 participants were included in the study, with 74 (62%) belonging to the vaccinated group (VG) and 46 (38%) to the unvaccinated group (UVG). Regarding gender distribution, 45 (61%) participants in the VG were women, and 29 (39%) were men. In the UVG, 30 (65%) were female, and 16 (35%) were male. Gender distribution was homogeneous between the groups, showing no statistically significant differences ($p = 0.7711$). Overall mean age was also similar between the two groups, with 42 years in the UVG and 40 years in the VG.

By using data from the clinical laboratory at PUC-Campinas hospital, it was possible to compare the date of the SARS-CoV-2 test with the date participants responded to the questionnaire. This process ensured that participants with clinical manifestations were indeed within the timeframe of long COVID. This conclusion was based on the reliable confirmation of SARS-CoV-2 infection through positive test results conducted at the hospital. Consequently,

it was possible to confirm that participants met the Brazilian Ministry of Health's definition of long COVID[4], which is characterized by signs and/or symptoms persisting for at least four weeks (28 days) after the acute infection.

The average number of days post-positive SARS-CoV-2 test differed significantly between the two groups. The vaccinated group (VG) had an average of 114 days, while the unvaccinated group (UVG) averaged 780 days. The UVG showed a post-acute infection timeframe nearly seven times longer than the VG.

Regarding the vaccination status within the VG (Table I), all participants had completed at least the full primary vaccination series (1st and 2nd doses) at the time of their acute SARS-CoV-2 infection diagnosis (38%), with the majority having also received the first booster dose (61%).

Table I. Vaccination status among the vaccinated group at the time of acute SARS-CoV-2 infection diagnosis. Campinas, São Paulo, Brazil, 2023.

Vaccination status	Participants	%
Incomplete schedule (only 1 dose)	0	0%
Full primary series (2 doses or single dose)	28	38%
Full primary series + 1st booster dose	45	61%
Full primary series + 1st and 2nd booster doses	1	1%

Source: Authors' own data.

Regarding the prevalence of pre-existing comorbidities before SARS-CoV-2 infection between the groups (Table II), it was observed that approximately 55% of the vaccinated group (VG) and 52% of the unvaccinated group (UVG) reported no comorbidities. Among the comorbidities reported, there were no statistically significant differences in prevalence between the groups. The four most prevalent comorbidities were similar in both groups: systemic arterial hypertension (16% VG; 17% UVG), diabetes (11% VG; 13% UVG), hypercholesterolemia (11% VG; 13% UVG), and allergic rhinitis (11% VG; 11% UVG).

Table II. Prevalence of comorbidities before SARS-CoV-2 infection among vaccinated and unvaccinated groups. Campinas, São Paulo, Brazil, 2023.

Comorbidities	Vaccinated		Unvaccinated		p-value
	Participants	%	Participants	%	
No comorbidities	41	55%	24	52%	0.8752
Systemic arterial hypertension	12	16%	8	17%	0.9331
Diabetes	8	11%	6	13%	0.9378
Allergic rhinitis	8	11%	5	11%	0.9996
Hypercholesterolemia	8	11%	6	13%	0.9378
Thyroid diseases (hypothyroidism/hyperthyroidism)	4	5%	4	9%	0.7090
Asthma	3	4%	2	4%	0.9928
Anxiety	1	1%	0	0%	1.0000
Cancer	2	3%	0	0%	0.5232
Depression	1	1%	1	2%	1.0000
Muscular dystrophy	1	1%	0	0%	1.0000
Fibromyalgia	1	1%	0	0%	1.0000
Bipolar disorder	1	1%	0	0%	1.0000
Osteoarthritis	0	0%	1	2%	0.3833
Hepatitis B	0	0%	1	2%	0.3833
Charcot-Marie-Tooth neuropathy	0	0%	1	2%	0.3833
Tuberculosis	1	1%	0	0%	1.0000

Source: Authors' own data.

Regarding the incidence of long COVID clinical manifestations reported in each group (Table III), the absence of symptoms was significantly higher in the VG at 66%, compared to the UVG at 41% (p = 0.0128). Among all symptoms evaluated, cognitive deficits (memory loss/forgetfulness) were observed in both groups but were significantly more prevalent in the UVG (35%, p = 0.0343). Other reported symptoms did not show statistically significant differences between the groups.

Table III. Incidence of clinical manifestations in vaccinated and unvaccinated long COVID groups. Campinas, São Paulo, Brazil, 2023.

Symptoms	Vaccinated		Unvaccinated		p-value
	Participantes	%	Participantes	%	
No symptoms	49	66%	19	41%	0.0128*
Headache	13	18%	6	13%	0.6870
Cognitive deficit (memory loss/forgetfulness)	12	16%	16	35%	0.0343*
Fatigue	10	14%	5	11%	0.8871
Dyspnea	9	12%	9	20%	0.4002
Palpitation	8	11%	1	2%	0.1507
Body aches	6	8%	3	7%	1.0000
Insomnia	5	7%	5	11%	0.5041
Reduced concentration	5	7%	3	7%	1.0000
Anxiety	5	7%	2	4%	0.7085
Recurrent tonsillitis or throat scraping sensation	4	5%	0	0%	0.1599
Dysgeusia	5	7%	6	13%	0.3311
Runny nose	3	4%	0	0%	0.2849
Cough	3	4%	1	2%	1.0000
Anosmia	2	3%	5	11%	0.1050
Precordial pain	3	4%	0	0%	0.2849
Nasal congestion	1	1%	0	0%	1.0000
Depression	2	3%	1	2%	1.0000
Hair loss	2	3%	0	0%	0.5232
Arthralgia	0	0%	1	2%	0.3833
Recurrent oral cavity sores	1	1%	1	2%	1.0000

*Statistically significant differences.
Source: Authors' own data.

DISCUSSION

This study found a higher incidence of long COVID in the UVG compared to the VG. This finding supports the association of vaccination as a protective factor against the development of long COVID. It aligns with a Brazilian study that, through online interviews, found a lower incidence of long COVID among vaccinated individuals (59%) compared to unvaccinated individuals (72.5%, p < 0.001)[8].

According to Al-Aly et al.[12], the protective mechanism of vaccines against Long COVID is suggested to be immune-mediated. Vaccinated individuals with compromised immune systems were observed to have a higher risk of developing long COVID compared to immunocompetent individuals. Current reports indicate that vaccination provides a dual benefit: it acts as a protective factor against the development of long COVID when administered before infection[12] and improves outcomes for individuals vaccinated during the acute phase of infection[13].

These findings underscore vaccination as a primary prevention strategy—not only against acute COVID-19 infection but also against its long-term sequelae, such as long COVID. Health care workers should be aware of this fact and actively promote awareness of the benefits of vaccination. Promoting vaccination in the community can help combat misinformation and contribute to better public health outcomes.

The average time of evaluation after acute COVID-19 infection differed significantly between the groups: 114 days for VG and 780 days for UVG. A potential hypothesis is that the persistence of long COVID symptoms in the UVG, even after such an extended period, could be linked to the likelihood of participants experiencing more severe cases and hospitalizations during the acute phase. These factors are known to increase the risk of developing Long COVID[14-17].

Although this study did not evaluate hospitalization rates or disease severity during the acute phase, vaccination is known to reduce disease morbidity, thereby reducing hospitalization rates[18]. This supports the idea that by reducing the severity of acute infection, vaccination also offers protection against the development of long COVID. This, in turn, leads to lower public spending on treatments and hospitalizations. Investing in public policies focused on health promotion and primary prevention is essential for ensuring adequate health conditions for the population. Such initiatives also enable the intelligent management of public resources, providing significant societal and economic benefits.

According to Al-Aly et al.[12], individuals who develop long COVID tend to experience similar symptoms regardless of their vaccination status. In the current study, symptoms were observed in both groups; however, cognitive deficits were significantly more prevalent in the UVG ($p = 0.0343$).

Fatigue and cognitive deficits are often reported together [19]. A Brazilian ambidirectional cohort study that followed individuals six and 12 months after hospital discharge for COVID-19 found that the most common symptoms at both time points were fatigue (55.3% and 40.6%, respectively) and cognitive deficits (36.8% and 20%)[20]. According to a systematic review by Ceban et al.[19], an analysis of multiple studies revealed that fatigue affects approximately 33% of individuals, while over 20% experience cognitive deficits 12 weeks or more after infection. In the present study, fatigue ranked as the fourth most common symptom in both groups, with 14% for VG and 11% for UVG. However, no statistically significant difference was found between the groups ($p = 0.8871$).

On the other hand, cognitive deficits—characterized by recurring forgetfulness and difficulty recalling information—were significantly more prevalent in the UVG (35%) compared to the VG (16%), with a statistically significant difference ($p = 0.0343$). Reports suggest that cognitive deficits may be associated with hypometabolism in the cerebellum, triggered by SARS-CoV-2 infection[21]. One potential contributing factor is that, unlike other symptoms that are often self-limiting, fatigue and cognitive deficits may worsen over time[22,23]. This could explain their higher prevalence in the UVG.

Sharing this information with health services, particularly primary care, is critical. There is also an urgent need for trained health care workers to monitor and manage persistent cognitive impairment using an integrated approach. This should include health education and effective recovery strategies for patients. Such measures are vital for ensuring comprehensive care, a cornerstone of Primary Health Care, and addressing the long-term impacts of COVID-19 on affected individuals.

Lopez-Leon et al.[24] reported that most symptoms of Long COVID are like those observed during the acute phase, with ageusia being the only oral cavity-related symptom, occurring in 23% of cases. Similarly, Santos et al.[25] identified a significant incidence of oral manifestations during acute COVID-19, including 38% experiencing taste disorders, 43% xerostomia, and 20.5% oral mucosal lesions. In the present study, ageusia did not show statistically significant prevalence during long COVID in either group. Regarding dysgeusia and anosmia, these symptoms were present in both groups (VG: 7% and 3%; UVG: 13% and 11%, respectively), but no significant differences were found between them. These symptoms are known to be self-limiting and typically occur during the acute phase, even in fully vaccinated individuals[26].

A major strength of this study was the reliability of the diagnosis of COVID-19 and long COVID, ensured by both the hospital database and the refined data collection process conducted by a trained member of the research team. This approach minimized the risk of including individuals who had not previously had COVID-19 and reduced the potential for bias in the interpretation of questionnaire responses.

CONCLUSION

Vaccination proved effective in protecting against the development of long COVID and reducing the incidence of cognitive deficits, with a lower prevalence observed among vaccinated individuals. Based on the findings of this study, vaccination can be recommended as a primary prevention strategy for long COVID.

However, further studies involving a larger number of individuals within the Brazilian population are needed to generate robust scientific evidence on this issue. Such evidence could inform the development of health policies and ensure the intelligent allocation of public resources based on the specific needs of the Brazilian reality. These

policies should prioritize health promotion initiatives, including the training of health care workers, community health education projects, and the use of vaccines as a primary prevention strategy to effectively prevent long COVID.

In our study, achieving a larger sample size proved to be a significant challenge. While telephone contact facilitated data collection by eliminating the need for participants to travel, it also posed a barrier. The high incidence of scams and prank calls in Brazil via phone created distrust among individuals, leading to the loss of potential participants.

Despite the challenges and limitations of this study, the importance of vaccination in ensuring better public health outcomes was evident as well as its impact on reducing health care costs associated with the long-term sequelae of COVID-19.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

CONTRIBUTIONS

Maria Luiza Ricarte Ruggeri and **Sérgio Luiz Pinheiro** contributed to the elaboration and design of the study; data acquisition, analysis and interpretation; writing and revision of the manuscript. **Carlos Eduardo Fontana** and **Elisa Donalisio Teixeira Mendes** contributed to the writing and revision of the manuscript.

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