

COMMUNICATION

SARS-CoV-2 semi-quantitative total antibody correlates with symptoms of long COVID in both vaccinated and unvaccinated subjects

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Abstract

Long coronavirus disease (COVID) is defined as an infection-associated chronic condition that occurs after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is present for at least 3 months as a continuous, relapsing, and remitting, or progressive disease state. While COVID-19 vaccines have been credited by public health officials with preventing COVID-associated morbidity and mortality, a portion of the population reports post-vaccination syndrome, often concerning long COVID. To investigate the association between post-vaccination syndrome and long COVID, we performed an observational cohort study at our outpatient clinical practice, evaluating SARS-CoV-2 semi-quantitative spike Ab in 100 consecutive patients (47% female and 53% male) with symptoms of long COVID. A total of 81 participants (46.9% female and 53.1% male) with post-vaccination syndrome and 19 unvaccinated participants (47.4% female and 52.6% male) with symptoms of long COVID were evaluated. SARS-CoV-2 Semi-Quant Spike Ab in the vaccinated cohort showed an average result of 11356.86 U/mL, whereas SARS-CoV-2 Semi-Quant Spike Ab in the unvaccinated cohort showed an average result of 1631.94 U/mL. The findings reveal potential immune differences in both individuals with long COVID and those with post-vaccination syndrome that merit further investigation to better understand these conditions and inform future research into diagnostic and therapeutic approaches.

Keywords: COVID-19; Spike; SARS-CoV-2; Long COVID

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Citation: White JR, Abraham RL, Coleman WT, *et al.* SARS-CoV-2 semi-quantitative total antibody correlates with symptoms of long COVID in both vaccinated and unvaccinated subjects. *Microbes & Immunity*. 2026;3(3):025320077. doi: 10.36922/MI025320077

Received: August 8, 2025

Revised: September 23, 2025

Accepted: October 23, 2025

Published online: November 17, 2025

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1. Introduction

The National Academies of Sciences, Engineering, and Medicine (NASEM) define long coronavirus disease (COVID) as “an infection-associated chronic condition that occurs after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and is present for at least 3 months as a continuous, relapsing, and remitting, or progressive

disease state that affects one or more organ systems.” Long COVID can present with a variety of symptoms, ranging from mild to severe. It can impact one or more systems, including the immune, cardiovascular, gastrointestinal, respiratory, genitourinary, musculoskeletal, endocrine, neurological, and sensory, including taste and smell. Because SARS-CoV-2 continues to mutate, researchers have been unable to accurately predict exactly how many individuals have been or are currently affected by Long COVID, but many online databases estimate that 10–40% of patients who contract SARS-CoV-2 progress to symptoms consistent with a diagnosis of long COVID.

At the onset of COVID-19, given human immunologic naivete to SARS-CoV-2, the innate immune system played a more paramount role than the adaptive immune system in the defense against the virus. Several reports have shown that innate immune status, as conferred by TAS2R (T2R) phenotype, is associated with the severity of illness, including methylation of T2R as a mechanism for gene expression, influencing disease development.^{1–3} If T2R status is associated with the severity of illness with upper respiratory infections, including COVID-19, this is associated with one’s innate immune protection against upper respiratory infections. Severe illness with SARS-CoV-2 infection can be defined in two ways. The first concerns the severity of symptoms, including duration, symptom profile, and hospitalization. The second is increased systemic infection with spike protein circulation, which is increased relative to mild systemic infection. Although these two forms of severity often coincide, they are not invariably linked, especially now that vaccines, monoclonal antibodies, and additional therapies have been rolled out, influencing the adaptive immune response.

COVID-19 vaccines have been credited by public health officials with preventing millions of COVID-19 deaths, but have shown decreasing effectiveness with time.^{4,5} A portion of the population reports a chronic debilitating condition after COVID-19 vaccination, often referred to as post-vaccination syndrome. To explore the potential association between post-vaccination syndrome and long COVID, we evaluated 100 consecutive patients, both vaccinated and unvaccinated, with symptoms of long COVID. While long COVID is defined as an infection-associated chronic condition, we explore the possibility of this condition impacting patients post-vaccination. Reports have shown individuals reporting post-vaccination symptoms resembling long COVID, often referred to as post-vaccination syndrome or post-acute COVID-19 vaccination syndrome.⁶ As expected, vaccinated individuals should exhibit elevated levels of circulating spike protein, but the concern is whether this

ultimately can lead to post-vaccination syndrome with symptoms consistent with long COVID.

By evaluating immunologic features in patients presenting with symptoms of long COVID, both vaccinated and unvaccinated, we are able to further evaluate and generate hypotheses surrounding the symptom profile and expectations of disease course. As health practitioners continue to manage patients dealing with the short-term effects of COVID-19, long COVID, and post-vaccination syndrome, further evaluation into immunologic features will be essential in helping to manage patient expectations and clinical course.

2. Methods

To investigate the association between post-vaccination syndrome and long COVID, we performed an observational cohort study at our outpatient clinical practice. We evaluated SARS-CoV-2 Semi-Quant Spike Ab (LabCorp; reference interval: negative <0.8 U/mL) results of 100 consecutive patients presenting to Sinus and Nasal Specialists of Louisiana, both vaccinated and unvaccinated, with symptoms of long COVID, including immunological features and symptom profiles in patients presenting for evaluation of persistent symptoms after COVID-19 infection and vaccination. A total of 81 participants with post-vaccination syndrome who reported symptom occurrence within 6 weeks post-vaccination, with no pre-existing comorbidities and with no evidence of recent (3 months) SARS-CoV-2 infection and 19 unvaccinated participants with no history of SARS-CoV-2 vaccination but with evidence of prior SARS-CoV-2 infection, greater than 3 months before inclusion, with symptoms of long COVID, as defined by The NASEM.

2.1. Exclusions

Participants with evidence of active infection with SARS-CoV-2 confirmed through a positive polymerase chain reaction test result at study commencement were excluded. Participants with evidence of prior infection with SARS-CoV-2 or clinical suspicion of infection with SARS-CoV-2 within 3 months at study commencement were excluded. Participants were excluded if their symptoms were not present before inclusion. Participants were excluded from evaluation if they ever received pharmacological immunosuppression treatments or had a diagnosis of immunodeficiency, including agammaglobulinemia, common variable immune deficiency, or hypogammaglobulinemia.

3. Results

The vaccinated cohort consisted of a total of 81 participants (38 [46.9%] female and 43 [53.1%] male) with no pre-existing comorbidities. The unvaccinated cohort consisted

of 19 participants (9 [47.4%] female and 10 [52.6%] male). The vaccinated cohort reported having a history of one or more previous SARS-CoV-2 infections. Even though all post-vaccination syndrome participants developed chronic symptoms following vaccination and not infection, it is important to consider the impact of a subsequent SARS-CoV-2 infection on the results in this study. Individuals in the post-vaccination syndrome cohort completed the primary series of vaccines based on the World Health Organization recommendations, up to 48 months before inclusion. No subjects were included in the analysis if they had pharmacological immunosuppression, immunodeficiency, or a history of SARS-CoV-2 infection within 3 months of evaluation. SARS-CoV-2 vaccination was verified in 81 of the 100 participants.

SARS-CoV-2 Semi-Quant Spike Ab in the vaccinated cohort showed an average result of 11356.86 U/mL (range: 1291 U/mL–>25000 U/mL). SARS-CoV-2 Semi-Quant Spike Ab in the unvaccinated cohort showed an average result of 1631.94 U/mL (range: 1.5 U/mL–4614 U/mL) (Figure 1).

The most frequent symptoms reported by participants, both vaccinated and unvaccinated, were excessive fatigue (81%), brain fog (76%), headaches (75%), muscle and joint aches (71%), anxiety (54%), sleep irregularity (50%), nasopharyngitis/adenoid hypertrophy with associated aural fullness (40%), tinnitus (38%), gastrointestinal discomfort (34%), numbness and tingling (34%), chest pain/tightness (27%), shortness of breath (21%), lymphadenopathy (14%), and diverticulitis (5%).

4. Discussion

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus, which typically presents in infected patients with mild-to-moderate respiratory illness

symptoms. Most patients recover without significant sequelae. However, there is a portion of the population that progresses to develop symptoms of long COVID. Long COVID can present with a variety of symptoms, impacting multiple organ systems, affecting 10–40% of patients previously infected with SARS-CoV-2. Our study findings reveal potential immune differences in both individuals with long COVID and those with post-vaccination syndrome that merit further investigation to better understand these conditions and inform future research into diagnostic and therapeutic approaches.

Based on the results of this study, we propose that long COVID is characterized by elevated levels of circulating spike protein, accompanied by an immune response marked by antibody production, formation of circulating immune complexes, and their subsequent tissue deposition, leading to associated clinical symptoms. Clinically, we initially observed increased levels of inflammation and associated symptoms in addition to recurring upper respiratory infections with increasing prevalence. We have observed a significant increase in the number of patients with deficient pneumococcal antibody titers, often accompanied by lymphoid hypertrophy or inflammation of the nasopharynx or adenoid. This deficiency appears to be more pronounced among individuals who received mRNA-based COVID-19 vaccines, although it is also observed in some unvaccinated individuals with prior SARS-CoV-2 infection.

One hypothesis for long COVID is that increased levels of circulating spike protein, with deposition, either isolated or with immune complex deposition, deposit in various organ systems, leading to two consequences. The first is associated with problems related to deposition into organ systems, including pericarditis, myocarditis, headaches, endocrine dysfunction, inflammatory bowel disease, diverticulitis, and Bell's palsy, to name a few. Second, elevated levels of circulating spike protein also cause an immune response with the production of antibodies. This is typically an appropriate immune response. The potential problem lies in the long-term increased levels of the circulating spike proteins due to chronic antibody production, thereby leading to immune fatigue, including pneumococcal antibody deficiencies.

Post-vaccination syndrome could cause long-term symptoms by several mechanisms. Vaccine components could lead to chronic inflammation through stimulation of innate immune response through pattern recognition receptors by mRNA, adenoviral vectors, and/or nanoparticles.^{7,8} This vaccine-induced immune response could trigger autoreactive lymphocytes.^{6,9} Spike protein expression following vaccination is detectable in the plasma

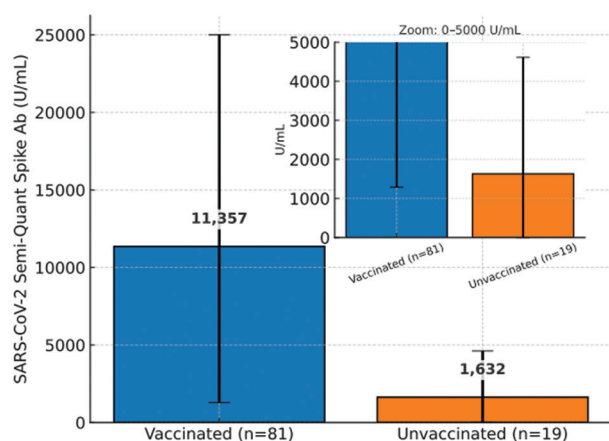


Figure 1. SARS-CoV-2 Semi-Quant Spike Ab in vaccinated versus unvaccinated cohorts

within one day, and host interaction with full-length spike protein, subunits, or peptide fragments could result in prolonged symptoms.^{6,10,11} The potential ability of the spike proteins to cross the blood–brain barrier could result in neural or cognitive symptoms, based on biodistribution models of lipid nanoparticles for mRNA.^{6,12} Another concern is that chronically increased circulating levels of spike protein, along with an immune response, may lead not only to immune fatigue but could also promote the oncogenic potential of the virus through altered function of neutrophils, memory cells, T cells, and antibodies.

In response to managing this problem, further investigation is needed to better understand these conditions and inform future research into diagnostic and therapeutic approaches. There is limited and conflicting data related to systemically binding the spike protein involving nattokinase, bromelain, and curcumin.^{13,14} Another interesting possibility is the interaction between nicotine receptors and viral cell entry. Nicotine binds to nicotinic acetylcholine receptors, which are distributed throughout the body, including the respiratory tract, and exhibit similarities to angiotensin-converting enzyme 2 receptors, the entry point for SARS-CoV-2 into host cells.

There is selection bias in this study, as all patients were referred to an otolaryngology practice for symptoms of sinonasal origin with concerns for long COVID, and they did not typically represent all symptoms associated with long COVID. The results of testing were a snapshot in time of the population and not followed on a set time period following known COVID infection, though all testing occurred at a minimum of three months after SARS-CoV-2 infection. An additional possibility is that post-vaccination syndrome could result from an asymptomatic COVID-19 immediately following the vaccination, as up to 40% of the infections are reported as asymptomatic,¹⁵ leading to inappropriately presumed post-vaccination syndrome.

5. Conclusions

Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least three months as a continuous, relapsing, and remitting, or progressive disease. While COVID-19 vaccines have been credited by public health officials with preventing COVID-19-associated morbidity and mortality, a portion of the population reports post-vaccination syndrome, often concerning long COVID, based on symptom profile. Our study findings reveal potential immune involvement in both individuals with long COVID and those with post-vaccination syndrome that merit further investigation to better understand these conditions and inform future research into diagnostic and management approaches.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

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Writing-review & editing: All authors

Ethics approval and consent to participate

Consent was obtained from the participants before their participation.

Consent for publication

Participants gave consent for publication of their data in this study.

Availability of data

Data are available from the corresponding author upon reasonable request.

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