Post-Coronavirus Disease 2019 Effects in an Active University Population: A Within-Campus Cross-Sectional Study at a Major Educational Institution

Marcelo Hernández-Mora, MD; René Arredondo-Hernández, PhD;
Carmen A. Castañeda-Camacho, MD; Pamela X. Cervantes-Gutierrez, MD;
Gonzalo Castillo-Rojas, PhD; Samuel Ponce de León, MD;
and Yolanda López-Vidal, PhD

Abstract

Objective: To evaluate the associations among post-coronavirus disease 2019 (COVID-19) prevalence; risk factors and comorbidities have not been firmly established within a university outpatient population.

Patients and Methods: Records from 881 COVID-19 outpatient patients (504 females [57.9%] and 366 males [42.07%]), most of whom were between 30 and 40 years of age (mean=37.3 years old; 95% CI, 36.5-38.2), with initial infection data from February 2020 to August 2022 were reviewed once, whereas the survey took place during 2 different moments during the pandemic. The first period (April 20, 2021, to June 21, 2021) yielded 279 responses, whereas in the second period (June 23, 2021, to October 4, 2021), 602 responses were recorded. The instrument used contained 20 questions across 3 main domains: general information, data related to infection and adverse effects, and service satisfaction experience.

Results: All the patients were positive for immunoglobulin G antibodies against nucleocapsid by the third week. Post-COVID-19 symptoms arose at least 2 weeks after recovery from the initial illness; 654 individuals reported at least one symptom after the acute COVID-19 period, for a post-COVID-19 prevalence of 74.96%. The most frequent symptoms were fatigue (84%), headache (71%), and difficulty concentrating (71%). More than 60% of participants reported at least one comorbidity, among which the most common ones were obesity (35.9%), smoking (17.5%), and hypertension (12.2%).

Conclusion: In this study, we assessed post-COVID-19 prevalence among outpatients and found that comorbidities were strongly related to consequences impacting quality of life and mental health burden.

Acute manifestations caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vary widely among individuals, ranging from asymptomatic to atypical pneumonia and acute respiratory distress syndrome, leading to death by multiple organ failure.[1-3] However, soon after the commencement of the SARS-CoV-2 (coronavirus disease 2019 [COVID-19]) pandemic, a substantial proportion of patients who recovered from the disease experienced postacute manifestations of unknown cause, varying in intensity and duration.[4-11]

As homeostasis is reset, postacute conditions after several infections take place in the form of specific syndromes, such as fatigue syndrome after Q fever from *Coxiella burnetii* or chronic fatigue or myalgic encephalomyelitis associated with viral infections such as AH1N1 influenza, chickenpox or herpes zoster, and some enteroviruses. In addition, nonspecific manifestations have been described in multiple postinfections of microorganisms, such as dengue virus, Ebola virus, Epstein-Barr virus, and *Giardia lamblia*.[12] In particular, Epstein-Barr virus (and, to a lesser extent, herpesvirus type and cytomegalovirus)

From the MD, Center for SARS-CoV-2 Diagnosis for the University Community, National Autonomous University of Mexico (M.H.-M., C.A.C., P.X.C.-G., Y.L.-V.), Microbiome Laboratory, Research Division (R.A.-H., S.P.d.L.), Microbial Molecular Immunology Program, Department of Microbiology and Parasitology (G.C.-R., Y.L.-V.),

Affiliations continued at the end of this article.

is universally latent worldwide, although seroconversion age[13] and sex differences,[14] and geographic hotspots have been acknowledged for some time. Of coincidence, in several highly endemic countries in Africa[15] and Latin America,[16] its detection rate in lymphoblastic tumors seems to be greater than that in Europe.[17] Whereas it is also active in tonsillitis in the Mexican population,[18] recent evidence has suggested that Epstein-Barr virus is associated with multiple sclerosis (anti-EBNA1 immunoglobulinG titer-mediated risk)[19] and myalgic encephalomyelitis,[20] both of which share demographic and clinical features with post-COVID-19, which might result from reactivation and cross-talk,[21] leading to an unbalanced immune response, worsening the symptoms of acute COVID-19 disease (and vice versa) or increasing the risk of developing post-COVID-19, especially in its early stages.[22-24] Further research is needed to determine the utility of joint analysis for the presence of herpes viruses in the identification of patients at risk of developing post-COVID-19.

The aforementioned coronaviruses that cause severe disease in humans, SARS-CoV-1[6] and MERS,[10] are also related to persistent postinfection symptoms, mainly neuromuscular and neuropsychiatric manifestations partially explained by major disease severity;[6] however, in a major number of post-COVID-19 cases, symptoms appear regardless of the severity of the acute infection. Mainly a new and neglected condition, in low-income and middle-income countries,[25] the lack of treatment precludes worse symptoms and sequelae,[26] whereas valuable information regarding the prevalence, sex ratio, and risk factors for developing remission or death in different genetic backgrounds has not been reported.[12]

In that respect, post-COVID-19 identification of previous risk conditions among ambulatory patients is highly relevant to health systems to address burdens and allocate resources to cope with disability, because at least 1.5% of COVID-19 survivors worldwide (estimated to be 669,728,000 as of April 2024),[27] will experience long-lasting symptoms.

As of July 25, 2023, in Mexico, 6,885,378 recovered COVID-19 cases had been recorded by Consejo Nacional de Humanidades,

Ciencia y Tecnología through data from the General Office of Epidemiology.[28]

Various definitions and terms have been proposed for post-COVID-19, but they are all in agreement regarding the presence of symptoms unexplained by other causes after COVID-19.[10,29-32]

Owing to the heterogeneity of the various definitions, in this study, we used the conservative post-COVID-19 definition provided by the Centers for Disease Control to refer to the syndrome or conditions starting 4 weeks from the start of the initial infection (Table 1).

In Mexico, the National Survey of Health and Nutrition 2021 (ENSANUT 2021) is conducted each year to assess national public health, covering more than 12,619 homes; therefore, we obtained ENSANUT data on men and women aged 20 to 60 years or older with diabetes or hypertension, among whom 35% declared that their parents suffered diabetes or hypertension. The risk factors and comorbidities observed in our study population at the time of SARS-CoV-2 infection diagnosis are shown in Supplemental Figure (available online at http://www.mcpiqo journal.org).

The aim of this study was to evaluate the associations among post-COVID-19 prevalence, risk factors, and comorbidities within a university outpatient population.

TABLE 1. Demographic Characteristics of the Population				
Total 870	N	%	Mean	95% CI
Sex				
Female	504	57.9		
Male	366	42.1		
Type				
Student	365	43.6		
Worker	472	56.3		
Age (y)			37.6	36.5-38.2
<18	7	0.8		
18-29	297	34.1		
30-39	179	20.6		
40-49	221	25.4		
50-59	137	15.8		
>60	29	3.3		
Hospitalization				
Yes	24	2.8		
No	846	97.3		

PATIENTS AND METHODS

From March 2020 to June 23, 2022 (the last cutoff date was completely recorded), the Center for the Diagnosis of SARS-CoV-2 for the UNAM community evaluated 11,464 patients; within the evaluation was a survey concerning medical history, such as previous infection with SARS-CoV-2. As a result of the increasing number of reports of the lingering effects of the disease beyond acute infection,[4,5,7-11] a tool was implemented to evaluate these continued effects in our population. For this purpose, a 20-question instrument was designed for the collection of information along 3 main domains: general information (name, student or worker profile, age, and address), information about the infection, and secondary effects (date of initial infection, predominant symptoms, type of ambulatory or hospitalization care, medications used, whether oxygen was applied, postrelease symptoms, time to recovery from symptoms, taste or smell alterations, and postinfection rehabilitation), and third, experience in the clinic. Finally, once the national vaccination program against SARS-CoV-2 began in Mexico (December 24, 2020), 3 more questions regarding adverse reactions to the live attenuated vaccine were added. The instrument was made accessible through a QR code, which was distributed through invitation mail or telephone calls or posters located in the evaluation offices for patients, to address patients who, at least 1 month before, had a SARS-CoV-2 infection confirmed by reverse transcription—polymerase chain reaction in the university clinic. From this population, patients who agreed to complete the survey were recruited. The data were collected through the Survey Monkey platform, and analysis was performed by Microsoft Excel. Because the survey collected retrospective information at a single moment after a previous infection, this study is considered retrospective cross-sectional; therefore, the analysis of risk factors by the odds ratio (OR) as a measurement of association was justified, whereas score matching analysis identified relative weights over clinical evolution and addressed confounding variable effects by XLSTAT premium, version 2024.2.2, 1422. Finally, all the patients underwent rapid serologic testing 30 days after the onset of infection. The above research was approved by the IEC (Research and Ethics Committees at the Faculty of Medicine, UNAM [FMED/CEI/MHU/012/2020]). All participants gave their written informed consent before sample collection.

RESULTS

In the first data collection period (April 20, 2021, to June 21, 2021), 279 individual subject responses were recorded, whereas in the second period (June 23, 2021, to October 4, 2021), which included a vaccination question, we observed an increase in responsiveness, resulting in 602 responses recorded, for a total of 881 completed surveys. Desegregated data revealed that 57.9% of the respondents were women (504), whereas men contributed 42.07% (366) of the survey information (Figure 1); the mean age was 37.3 years (95% CI, 36.5-38.2), with 80% of the survey participants in their 30s and 40s (Table 1).

Among the patients surveyed, 97% (846) were treated as outpatients, whereas only 3% required hospitalization. All patients were positive for immunoglobulinG antibodies against nucleocapsid from the rapid serologic test. With respect to the presence of post-COVID-19 symptoms at least 2 weeks after recovery from the initial disease, 654 people reported at least 1 symptom after the acute COVID-19 period, for a 74.96% prevalence of post-COVID-19 symptoms.

In terms of complaints, the most frequent symptom was fatigue (84%), followed by headache (61.4%), and difficulty maintaining focus or brain fog (71%), among 16 other symptoms (anxiety-depression > insomnia, > myalgia, > arthralgia with a reported prevalence greater than 50%, whereas chest pain > cough > palpitations, and anosmia occurred in 35%-20% of the cases). Importantly, the post-COVID-19 symptom pattern in our population differed from that reported during acute infection. Although fever, anosmia or ageusia, and headache were the most prevalent symptoms during acute infection, insomnia and palpitations were the hallmark post-COVID-19 symptoms. However, the prevalence of anxiety, depression, and fatigue, followed by arthralgia, myalgia, and thoracic

FIGURE 1. Post-COVID-19 risk factors. COVID-19, coronavirus disease 2019.
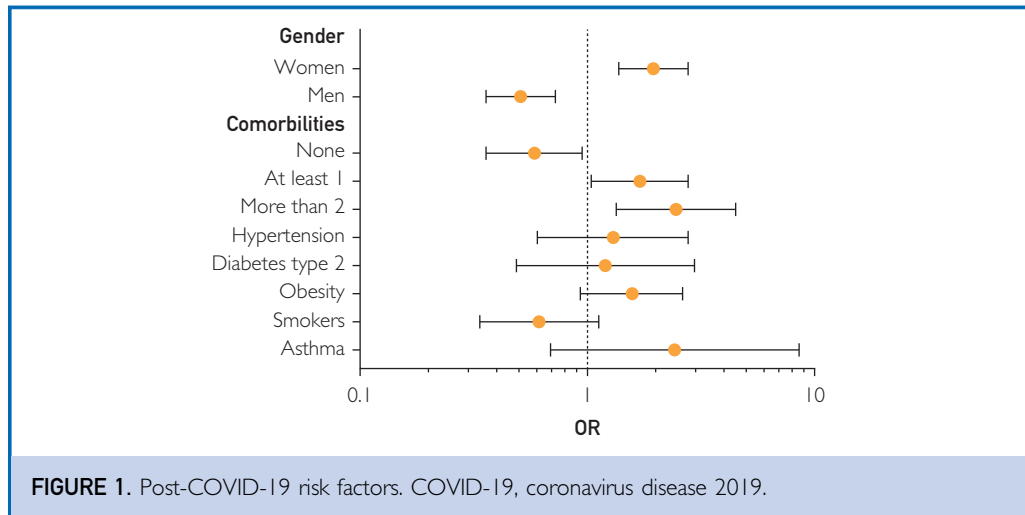
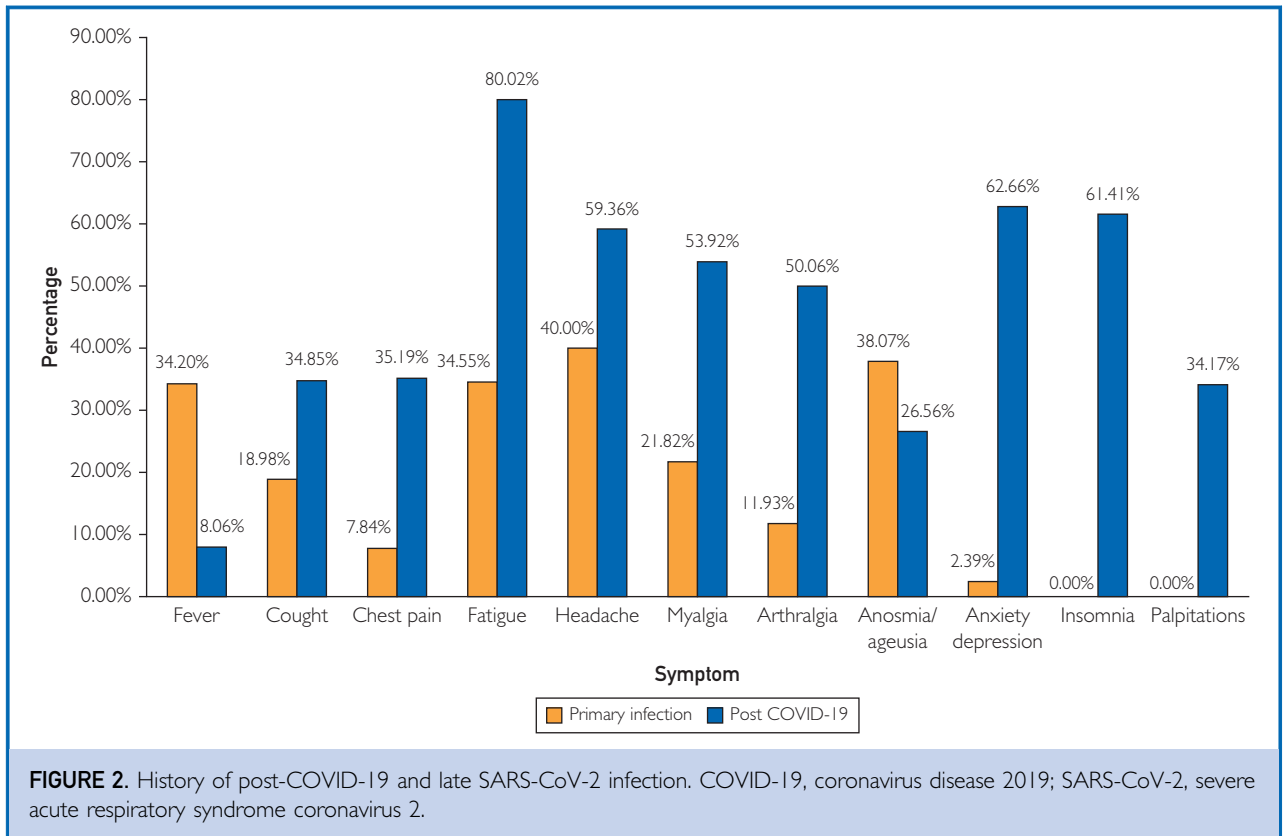pain increased the most from preintervention to postintervention (Figure 2).

The incidence of previous infection (within a month prior) varied slightly during the pandemic. Although the incidence from 2021-2022 was 73.1%, the maximum incidence (76.1%) occurred in the first wave, whereas the prevalence rates during the second and third waves were 63.2% (α) and 70.7% (Δ), respectively . Even when only cases in which the variant became dominant (Consejo Nacional de Humanidades, Ciencia y Tecnología Vigilance Committee of SARS-CoV-2 variants[33] and from the Global Initiative on Sharing All Influenza Data variant database)[34] were considered, a χ^2 test revealed no significant difference in terms of the proportions with respect to the study total (Figure 3 and Supplemental Figure [available online at http://www.mcpiqojournal.org]).

Finally, to identify which risk factors took prominence over the occurrence of post-COVID-19, comorbidities and their possible influence on the development of post-COVID-19 conditions, such as ORs, are presented in Table 2, which shows the most frequent comorbidities assessed in this study. Over 60% of the participants reported at least 1 comorbidity, whereas the most common comorbidities were obesity (35.9%), smoking (17.5%), and hypertension (12.2%). Regarding the analysis of proportions, the OR was calculated for the prevalence of post-COVID-19 and revealed that male sex (OR,

0.51; 95% CI, 0.35-0.72) and not having comorbidities (OR, 0.58; 95% CI, 0.36-0.95) were post-COVID-19 syndrome protective factors, whereas female sex (OR, 1.95; 95% CI, 1.37-2.78) and suffering from at least 1 comorbidity (regardless of which comorbidity) resulted in an increased risk of developing post-COVID-19 conditions (OR, 1.70; 95% CI, 1.05-2.77), which further increased with 2 or more additional comorbidities (OR, 2.46; 95% CI, 1.34-4.51) (Figure 1). However, no comorbidity was significantly associated with an increased risk of developing post-COVID-19 when analyzed individually. In addition, to evaluate the antecedents and comorbidities (explicative variables) of COVID-19 in our cohort, a propensity score matching analysis was performed with recovery of smell as the independent variable. The model was considered good (area under the curve=0.7), indicating that age and obesity were the most important contributing factors, followed by the need for oxygen during active infection and hypertension, heart disease, or asthma status. Chronic obstructive pulmonary disease, chronic kidney disease, and immunosuppression also made minor contributions to the risk of developing post-COVID-19.

DISCUSSION

Postacute syndrome following SARS-CoV-2 infection manifests predominantly among women, a finding replicated in various studies,[11,35-37] with females currently having

FIGURE 2. History of post-COVID-19 and late SARS-CoV-2 infection. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

almost double the number of cases as males near the median age of the population, and among the youngest individuals (>18 years of age), an alarming trend toward a wider health gender gap has been reported among women with fatigue, anxiety-depression, insomnia, and extremely debilitating conditions,[35] with a growing prevalence that causes the highest post-COVID-19 burden, at least with regard to years living with disability.[38,39] Fatigue has emerged as the most important factor in post-COVID-19.[1,7-9,11,40] A systematic review of 74 studies performed at the end of 2021 on individuals with fatigue and cognitive disability reported a 32% prevalence, which is surprisingly lower than that reported in most previous studies (intervals between 30% and 80%),[1,8,9,40] including ours; however, other systematic reviews reported a prevalence of fatigue between 58%[7] and 64%,[11] indicating high variability in studies post-COVID-19, even in meta-analyses. The prevalence of anxiety and depression might have been overestimated; if the symptom prevalence is much higher than that reported in

any other study (11%-28%),[36] close follow-up is recommended. However, by using the Centers for Disease Control definition, our study allowed us to identify symptoms at an early phase and endow clinicians with a post-COVID-19 symptomatic pattern, differentiating it from acute infection in ambulatory patients. Because the continued secretion of inflammatory factors, particularly those in

TABLE 2. Prevalence of Previous Comorbidities

Variable	Prevalence (%)
None	37.5
At least 1	62.5
≥2	27.8
Hypertension	12.2
Type 2 diabetes mellitus	8.1
Obesity	35.9
Smoking	17.5
Asthma	5.9
Others	18.4

Others: Comorbidities with less than 5% prevalence.

FIGURE 3. Post-COVID-19 according to the dominant variant at the time of diagnosis.
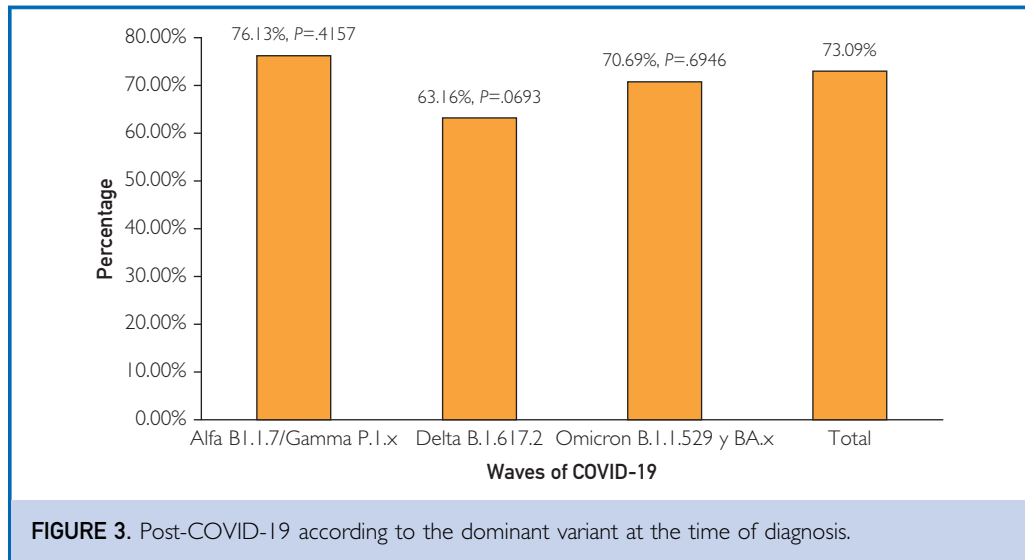
brain areas, underlies senescence and neurologic sequelae,[41] interventions as early as possible may be indicated. Pathophysiologically, a shared mechanism, kynurenine pathway dysregulation, may be involved in long-lasting inflammation and Epstein-Barr virus reactivation after COVID-19. This pathway is responsible for processing tryptophan into aryl hydrocarbon receptor ligands and is a major source of nicotinamide-adenine dinucleotide, mitochondrial oxidative stress and inflammatory regulation. Moreover, limited serotonin production, the last metabolite in the pathway, and/or accumulation of neurotoxic quinolinic acid might be the underlying causes of depression and persistent headache in post-COVID-19 patients.[42] We previously reported significant activation of IDO1 (a limiting step in the pathway) in the saliva of severe, but not moderate, mild, or control individuals.[43] Because IL6 stimulates IDO1 and a correlation exists between the kynurenine or tryptophan ratio and the worst outcomes, which occur in obese, diabetic, male, and elderly individuals, this relationship should be further investigated in the context of post-COVID-19.

Some other symptoms, such as hair loss and dyspnea, were not as common in our population (0% and 13%, respectively) when compared with other studies (24% and 8%-50%, respectively).[7,11] A plausible explanation in the case of dyspnea is that the patients in our study did not develop critical disease,

given that, as mentioned, most patients did not require hospitalization during active infection.

The survey revealed a post-COVID-19 prevalence close to 75%, indicating that the results of this study are within the higher tier of the expected range (varying between 40% and 85% in the literature)[1,7,35,44] despite being a single-center survey study, which recruited almost entirely (97%) outpatient patients. Mexico is at an advanced epidemiological transition, and the 2022 National Survey of Health and Nutrition (ENSANUT-2022), which is representative of a state scale, revealed a 23.7% prevalence of diabetes and a 28.4% prevalence of hypertension, whereas 19.1% of respondents were smokers (one to more than 20 cigarettes a day),[45] all behaviors or conditions constituting risk factors for post-COVID-19 conditions.[46] Another contribution from our cohort, in addition to confirming the increased risk associated with female sex, is the additive probability from each comorbidity to post-COVID-19 risk among Mexican outpatients. The diamond forest plot shows an increased risk of asthma, 2 or more comorbidities, >female sex, >obesity, >HAS, and type II diabetes mellitus. With respect to smoking, the results agree with those of Ploubidis et al,[47] who did not report effects of tobacco use,[48] heart rate, or years of disability caused by type II diabetes mellitus among men and 7.2% among women over the past 27 years in Mexico City.

Finally, despite the suspected weight of spike protein mutations over time (March 2020-July 2022), the possible effects of predominant circulating SARS-CoV-2 variants were insignificant, despite common knowledge of omicron causing post-COVID-19. An important limitation of our study is that correlations with variants (or lack thereof) cannot be determined by sequencing RNA from cohort isolates but rather by national epidemiologic follow-up of variants of interest. Among the possible explanations for our results are the circulation of less virulent variants, previous exposure, and a high rate of vaccination among patients.

CONCLUSION

Long-term symptoms and sequelae from COVID-19 appear at the border of active infection, as a new addition to the chronic disease burden; a clear relationship between the number of COVID-19 cases and disease risk means that an opportunity gap widens with respect to women and the disadvantaged.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

ETHICS STATEMENT

This study was evaluated and approved by the local IRB FMED/CEI/MHU/012/2020 from Faculty of Medicine, UNAM.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Affiliations (Continued from the first page of this article.): and University Research Programme on Emerging and Epidemiological Risks (PUIREE) (S.P.d.L.), National Autonomous University of Mexico, Mexico City, Mexico.

Correspondence: Address to Yolanda López-Vidal, PhD, Microbial Molecular Immunology Program, Department of Microbiology and Parasitology, National Autonomous University of Mexico, UNAM, 3000 University Av., H Building, 4th Floor, Coyacan, Mexico City, Mexico, 04510 (lvidal@unam.mx).

ORCID
Yolanda López-Vidal: https://orcid.org/0000-0001-7111-8813

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