

EDITORIAL

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A serial epidemic with no end in sight

Un serial epidémico sin final vislumbrable

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Halfway through the third year of the COVID-19 pandemic, there is a certain relaxation in the attitude of the virus, which seems to be spreading more, but with less severity and death. And what can we expect from its behavior in the future?

The publications of SARS-CoV-2 researchers show that uncertainty continues and there is no easy prognosis.

At present, the number of new weekly cases of COVID-19 worldwide continues to decline from the peak in January 2022. In the week of the end of May and the first days of June, more than three million cases have been reported, a 12% decrease from the previous week, and weekly deaths have also declined by 22%. As of June 5, 2022, more than 529 million confirmed cases and more than six million deaths were reported worldwide⁽¹⁾. In the Americas, new confirmed cases decreased by 1% and deaths by 23%. However, the level of transmission in the United States, Chile, Argentina, Uruguay, and Brazil has remained high, with 100 to 300 positive tests per 100,000 population per week⁽²⁾. The well-known Dr. Anthony Fauci, president of the U.S. National Institutes of Health (NIH) and the foremost expert on infectious diseases in the U.S., has tested positive for the first time for COVID-19. Fauci, 81, fully vaccinated and twice boosted, has experienced mild symptoms. According to Johns Hopkins University, 85 million cases of coronavirus have been confirmed in the United States and more than one million people have died from COVID-related complications. Amid a surge of new cases caused by the Omicron variant, Fauci said in January that 'almost everyone' in the U.S. would be infected⁽³⁾.

In this issue of the Journal, the 10th fascicle of 'The Coronavirus conundrum' reports that millions of variants of SARS-CoV-2 will probably continue to emerge every day. In other words, the virus repeatedly changes its structure and chemistry. Fortunately, most mutations do not improve the virus's ability to survive and reproduce easily and are overtaken by more suitable versions. But the WHO's so-called variants of concern are more transmissible, virulent or able to escape an immune response than the other versions. The latest of the subvariants of the virus that has spread worldwide is the Omicron BA.2.12.1. And there is concern about the BA.4 and BA.5 subvariants that have mutations associated with immune evasion, i.e., they evade the neutralizing antibodies of the original variants and the protection of vaccines⁽⁴⁾. Children under 5 years of age were not infected or hospitalized with COVID-19 until the appearance of the Omicron variant. The Delta variant produced multisystem inflammatory syndrome in children, with deaths. Vaccination has decreased hospitalization in children and adolescents under 18 years of age. However, in one study 4.4% of children and young people infected with SARS-CoV-2 experienced symptoms for more than 4 weeks, and 1.8% experienced symptoms for at least 8 weeks⁽⁵⁾. Rates of



probable mental disorder in children and young people increased between 2017 and 2021 from 11.6% to 17.4% in boys aged 6 to 16 years and from 10.1% to 17.4% among those aged 17 to 19 years⁽⁶⁾.

In this regard, concern remains about long COVID in the adult that persists after the acute presentation and affects with respiratory failure, hypertension, thrombotic conditions, encephalopathy, myocarditis, cardiovascular disease (myocardial infarction and stroke)⁽⁷⁾, hepatic, intestinal, testicular and lymph node involvement⁽⁸⁾. In addition, general debilitation, joint stiffness and pain, myalgia⁽⁹⁾ and disturbing mental health disorders such as anxiety, depression, post-traumatic stress disorder, substance abuse, neurocognitive impairment, sleep disorders⁽¹⁰⁾ are found. A recent study has detected that, within 2 years of infection, 74% reported physical symptoms, 26% mental symptoms, and 16% cognitive symptoms⁽¹¹⁾. That is, the burden of symptomatic sequelae remains quite high at 2 years, about 55%, in COVID-19 survivors, with a health status markedly lower than in the general population⁽⁹⁾.

Recent studies have found SARS-CoV-2 RNA expression in the intestinal mucosa ~7 months after mild acute COVID-19; that is, the viral nucleocapsid protein may persist in the intestinal epithelium and CD8⁺ T cells several months after viral infection⁽¹²⁾ and could be one of the causes of long COVID.

An unusual discovery by virologist Sissy Sonnleitner, who seems to trace almost all cases of COVID-19 in the rugged region of eastern Austrian Tyrol, has prompted this editorial. She found that one vaccinated woman had been testing positive for the coronavirus for months. Before becoming infected with SARS-CoV-2 in late 2020, the woman in her 60s had been taking immunosuppressive drugs to treat a relapse of lymphoma. The COVID-19 infection lingered for more than seven months, causing her relatively mild symptoms, such as fatigue and cough. With more than two dozen viral samples from the woman over time, the researchers discovered through genetic sequencing that she had about 22 coronavirus mutations, half of them Omicron variants that only emerged in the world months later (!). This led researchers to consider that

chronic infections such as this patient's may be the source of Omicron and other variant infections that have led to the rise of COVID-19 worldwide⁽¹³⁾.

Since the new coronavirus emerged in late 2019, scientists have sequenced the genomes of more than 11 million SARS-CoV-2 samples, obtaining an evolutionary tree that shows how the virus has modified during its march around the planet and, through infectivity and immune evasion has on average gained only a couple of stable mutations per month as it moves from person to person. But in chronic infections lasting weeks to months, viruses with advantageous mutations have time to outcompete other viruses. Compared to acute cases, these long-duration infections allow much greater viral diversity to develop over time and, through a process of recombination, beneficial or harmful SARS-CoV-2 mutations could appear in one part of the body. In relation to Omicron, combinations of mutations and several sublineages with many overlapping mutations are observed, with genetic changes related to immune escape and infectivity. Many of these mutations are located in regions of the spike that are targeted by antibodies, such as its receptor binding domain (RBD) and N-terminal domain, which are involved in recognition and infection of host cells. The relative mildness of the Omicron variant could be a result of its preference for infecting cells in the upper respiratory tract, rather than in the lung. The variant probably evolved from a strain that skillfully infected both upper and lower airways⁽¹³⁾.

Individuals with compromised immune systems do not appear to be the only potential source of variants. Researchers have documented SARS-CoV-2 infections lasting several weeks in persons with healthy immune systems. Thus, there is an urgent need to identify effective treatments for chronic infections, particularly in people with immune system deficiencies, who do not always respond strongly to vaccines. Most approved monoclonal antibodies are not effective against Omicron and its variants and subvariants, and researchers are demonstrating that resistance to these therapies can emerge when used to treat chronic infections. Convalescent plasma should create a greater evolutionary barrier than monoclonal antibody therapies⁽¹³⁾.



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