

## SPECIAL PAPER

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# The coronavirus conundrum – New knowledge on Long COVID – Vaccines

## El enigma del coronavirus – Nuevos conocimientos sobre el COVID prolongado – Vacunas

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### ABSTRACT

By the end of 2023, it appeared that SARS-CoV-2 was being controlled, although its JN.1 variant was infecting more easily, with hospitalizations of older adults and the unvaccinated, but few deaths. Now some light is emerging on Long COVID, how the sequelae affect vital organs and why they persist in a significant number of people. Unfortunately, the brain is one of the most affected organs. Hence, the need for vaccines. We consider this update important as we begin 2024, recognizing the work of Eric Topol as a science communicator who provides a variety of information on what is happening with SARS-CoV-2 and COVID-19. Regarding what we have learned, apart from preparing ourselves for future pandemics, we consider it important to avoid loneliness, seek emotional support, practice virtuality and telemedicine, be creative, wash our hands, use masks to protect us from airborne pathogens and support vaccines.

**Key words:** Coronavirus infections, SARS-CoV-2, COVID-19, SARS-CoV-2 vaccines, Long COVID, Pregnancy, Fetus, Newborn

### RESUMEN

Al finalizar el año 2023, parecía que el SARS-CoV-2 estaba siendo controlado, aunque su variante JN.1 infectaba con mayor facilidad, con hospitalizaciones de adultos mayores y de los no vacunados, pero pocas muertes. Ahora van apareciendo algunas luces sobre el COVID prolongado, el cómo las secuelas afectan los órganos vitales y porqué persisten en un importante número de personas. Desafortunadamente, el cerebro es uno de los órganos más afectados. Por ello, la necesidad de las vacunas. Consideramos importante la presente actualización al empezar el 2024, haciendo un reconocimiento a la labor de Eric Topol como un comunicador científico que proporciona variada información sobre lo que viene ocurriendo con el SARS-CoV-2 y COVID-19. Sobre lo aprendido, aparte de prepararnos para futuras pandemias, consideramos importante evitar la soledad, buscar apoyo emocional, practicar la virtualidad y la telemedicina, seamos creativos, lavémonos las manos, usemos mascarilla que nos protejan de agentes patógenos aéreos y apoyemos las vacunas. **Palabras clave.** Infecciones por coronavirus, SARS-CoV-2, COVID-19, Vacunas, Gestante, Feto, Recién nacido

### INTRODUCTION

In October 2023, HV.1, a variant descendant from EG.5.1 and XBB, was linked to new COVID infections. Then, the hypermutated variant BA.2.86, known as Pirola in Peru, carrying more than 40 new mutations (34 in the spike protein alone) from its ancestor BA.2, with the addition of the L455S mutation, increased and was known as JN.1. JN.1 spread to many European countries, the USA, Israel, the Netherlands, Canada, Singapore, along with JN.2 and JN.3, variants of BA.2.86<sup>(1)</sup>. JN.1 increased hospitalizations mainly in people over 70 years, accounting for a quarter of new coronavirus cases in the USA<sup>(2)</sup>. This variant produced infections almost equivalent to the second major wave of infections in the U.S., but then declined, although it continued to have a significant presence in sewage<sup>(3)</sup>.



## PERINATAL COVID

A major study has quantified COVID-19 pandemic-related changes in obstetric intervention and perinatal outcomes in the U.S. 2015-2021. The study population included 26'604,392 live births and 155,214 stillbirths. The pre-pandemic period was characterized by temporary increases in rates of preterm delivery and induction of preterm labor or cesarean delivery and temporary decreases in macrosomia, post term delivery, and perinatal mortality. The onset of the pandemic was associated with a transient decrease in obstetric interventions (especially induction of preterm labor or cesarean delivery) and a transient increase in perinatal mortality, particularly in at-risk subpopulations. Most of the changes were reversed in the months following the onset of the pandemic<sup>(4)</sup>.

Previous studies suggest that prenatal exposure to COVID-19 may activate an inflammatory cascade in the airways of the newborn. One study examined the relationship between vaccination of mothers who were infected with COVID-19 during gestation and neonatal respiratory distress (RD) using a longitudinal cohort of mother-infant pairs. Two hundred twenty-one mothers with confirmed SARS-CoV-2 during gestation and 277 exposed fetuses entered the study. Unusually high rates of RD were observed in infants not infected with SARS-CoV-2 (17%). The odds ratio of RD was 3.06 in term neonates born to unvaccinated mothers versus those born to women vaccinated prior to infection. Proteomic analysis revealed a strong inflammatory response associated with ciliary dysregulation and increased IgE production among SARS-CoV-2 uninfected neonates with RD. Maternal vaccination against COVID-19 reduces the frequency of neonatal RD<sup>(5)</sup>.

## LONG COVID

Science has published a major multinational, prospective study of people with Long Covid and controls, conducted to systematically evaluate at 6 and 12 months nearly 6,600 proteins in 268 blood samples to determine which were associated with Long Covid. It found lower levels of antithrombin III, higher levels of thrombospondin-1 and von Willebrand factor, factors known to be associated with blood clot formation. The predictors of Long Covid were activation of the

complement system, which causes C-terminal (lower) factors (C5b, C6, C7, C8, C9) to bind to the endothelium of the blood vessels, help propagate tissue injury, and promote both inflammation and microcoagulation. Self-amplification of local complement activation and endothelial damage is triggered, further and persistently driving complement activation and tissue injury. The finding of monocyte and platelet aggregates in Long Covid participants is consistent with this discovery. In addition to complement system activation, other incitement was observed with specific antibodies against cytomegalovirus (CMV) and Epstein-Barr virus (EBV), the former correlated with symptom severity. The new report offers hope that complement markers in the blood can be used as biomarkers to confirm the diagnosis, objectify the goodness of treatment, and help develop effective treatments. In addition, there are complement inhibitor drugs, such as pegcetacoplan, iptacopan and vericoplan, which are used for rare immune diseases and could be considered for testing in Long Covid<sup>(6)</sup>.

Cognitive symptoms after Covid-19 disease are well known. It is unclear whether objectively measurable cognitive deficits exist and how long they persist. In a study in England, 800,000 adults were invited to complete an online assessment of cognitive function. Participants with persistent symptoms resolved after Covid-19 had objectively similar cognitive function to participants with shorter-duration symptoms, although short-duration Covid-19 remained associated with small cognitive deficits after recovery. The long-term persistence of cognitive deficits and their potential clinical implications remain uncertain<sup>(7)</sup>.

A nationwide, 1-year, long-term British Covid study evaluated 351 patients requiring hospitalization and more than 2,900 matched healthy controls. Cognitive deficits were marked and equivalent to the impact of 20 years of aging. In addition, biomarkers of brain injury indicated that the process of tissue damage was persistent, and the loss of gray matter raises concern about the magnitude of the problem. A different way of assessing brain injury by SARS-CoV-2 has been to use human induced pluripotent stem cells in culture and verify the findings in autopsy specimens from patients. It turned out that dopaminergic neurons were selective-



ly targeted by SARS-CoV-2 infection, and this induced accelerated aging, which was also observed in autopsies. The effects were attenuated by 3 drugs: metformin, imatinib and riluzole. The authors postulated that there is a need to closely monitor patients with COVID-19 for an increased risk of developing symptoms related to Parkinson's disease, in light of the marked increase in Parkinson's disease decades after the 1918 influenza pandemic<sup>(8)</sup>.

In another study from England, nearly 113,000 participants, with or without Covid infections, completed a cognitive and memory assessment and another after 12 weeks, with or without resolution of symptoms. The 8-domain cognitive assessment showed that the impact of Covid was seen primarily in memory, executive function, and reasoning. The adverse cognitive impact was worse with the original (ancestral) virus and the Alpha variant, compared with the later Delta and Omicron variants, and there was some protective effect of vaccination<sup>(7)</sup>. In Norway, more than 134,000 participants in a nationwide study with Covid testing completed a 13-question memory questionnaire prior to Covid testing and at various points thereafter until 3 years were completed. Approximately half of the nearly 112,000 participants with Covid tests were either positive or negative. Prior to having Covid, their baseline scores were the same, but there was a significant decline in participants at each time point assessed in those who tested positive for Covid during extended follow-up<sup>(9)</sup>.

A systematic study of individuals with Long Covid and controls, using MRI, brain-specific S100 $\beta$  protein, white blood cells RNA-seq, cultured endothelial cell response, provided new insights into blood-brain barrier (BBB) disruption in individuals with Long Covid and brain fog symptoms. Beyond the BBB, notable findings were dysregulation of the coagulation system and pro-inflammatory effects of endothelial cells<sup>(10)</sup>.

Whether menopausal status influences the risk of having Long COVID has been studied in 347 women in Latin America. Women with Long COVID had poor lifestyle, severe menopausal symptoms, hypertension, insomnia, depression, anxiety, chronic diseases/conditions, risk of hospitalization, sleep disorder, and low menopause-related quality of life, compared to women without the disease. Anxiety was the only fac-

tor that was significantly associated with Long COVID, while other covariates were confounders<sup>(11)</sup>.

## TREATMENTS

Many treatments have been used for COVID with varying degrees of success for patients, such as dexamethasone, hydroxychloroquine, remdesivir, or a combination of lopinavir and ritonavir, based on their efficacy against other pathogens with similar structure or mechanism of action to SARS-CoV-2. During the first wave of COVID-19, hydroxychloroquine was used off-label despite the absence of evidence documenting its clinical benefits. A meta-analysis of randomized trials showed that the use of hydroxychloroquine was associated with 11% increase in mortality rate<sup>(12)</sup>.

A randomized trial of a gut microbiome intervention in 463 Long Covid participants with a 'symbiotic' preparation of combined prebiotics and probiotics containing 20 billion colony-forming units of three bacterial strains, *B adolescentis*, *Bifidobacterium bifidum* and *Bifidobacterium longum*, with three prebiotic compounds, galactooligosaccharides, xylooligosaccharides and resistant dextrin, has been published in Hong Kong. This preparation provided at 6 months improvement in most of the important symptoms of Long Covid, but no improvement in quality of life. The probable down-modulation of the immune response by the intestinal microbiome needs to be tested<sup>(13)</sup>.

## NEW VACCINES

An update from the Netherlands Center for Infectious Disease Control provided strong evidence for the efficacy of the monovalent booster XBB.1.5. The prevention of hospital admissions to the ICU for age groups 60 years and older was quite high. This good news correlates with multiple laboratory studies that provided unexpected data for cross-reactivity of the immune response between XBB.1.5 and current circulating variants such as JN.1<sup>(14)</sup>.

Given the above and the doubts of the population, the National Academy of Medicine of Peru published a statement indicating that in 2021 the Lambda variant predominated and in 2022 and 2023 the highly contagious Omicron variant prevailed. In the Northern Hemisphere, the



low lethality of Omicron has been increasing from sublineages BA.2/BA.4, BA.5, to sublineage XBB.1.5. The WHO indicates that the Omicron sublineage XBB.1.5 could lead to an increase in cases globally and therefore suggests the need to search for new vaccines with effectiveness for the new variants. The bivalent vaccine currently in Peru has activity for the original SARS-COV-2. The second fraction of the bivalent is for Omicron BA.4-5 and may have action on the known sublineages of this viral strain, but probably minimal or no action on the new sublineages. It is essential that the population be confident that the vaccines are safe<sup>(15)</sup>.

There is inadequate recognition of the risk of Long Covid, or the protection offered by vaccination. If we think that as many as 2 million Americans become infected in a day, even if only 1% go on to get chronic Covid which can be profoundly debilitating, that represents 20,000 eventual new Long Covid added to the millions already affected. The recent wave has been going on for weeks and it is estimated that 4%-5% of Americans will have been infected<sup>(3)</sup>.

A recent meta-analysis of 24 studies on whether Covid vaccines protect against Long Covid provides encouraging evidence that the risk is reduced by 70% (at least, 30% to 50%<sup>(16)</sup>). This is exceeded only by not getting Covid which, of course, provides 100% protection against Long Covid<sup>(17)</sup>.

Promising new vaccines are being tested for upper respiratory mucosal immunity to help block SARS-CoV-2 virus infections and their spread. One of these is a nasal spray that was tested during the Omicron surge in China. These vaccines significantly amplify the neutralizing antibodies and T-cell response and would be expected to help prevent severe COVID<sup>(18)</sup>.

## THE MAJOR ERRORS

Peru's macroeconomic success and moderate health security index were paradoxically combined with one of the highest levels of COVID-19 mortality in the world and significant inequality in health outcomes of the pandemic. The paradox was related to the concentration of risk and vulnerability in low-income urban households, differences in social conditions, and the failure to address deficits in primary care systems and

social protection for vulnerable households. Responses to the pandemic must articulate with these realities, invest in social conditions and local health systems, connect the population to public services and social protection, and regenerate public trust<sup>(19)</sup>.

## WHAT HAVE WE LEARNED?

Four years ago, in March, the COVID-19 pandemic began, producing lethality that included family and friends and a number of hospitalizations. Now, we are beginning to learn about the complexity of Long Covid, which includes fatigue, joint or muscle pain, chest pain, dizziness, changes in taste, smell and, most complex, immune dysregulation and difficulty in thinking or concentrating, the 'brain fog'. On the other hand, there have been some new habits, such as e-learning, disinfection of food premises. A recent article refers to 6 lessons learned from this pandemic: 1) Loneliness is detrimental to health; hence the need to rely on family, friends, and new friendships. 2) We talk more fluently about our emotional well-being and seek support; psychologists and psychiatrists have more work to do. 3) Telemedicine works and stayed. A survey conducted by the American Medical Association in 2023 found that more than 74% of physicians used telemedicine with their patients; it is another form of doctor-patient rapprochement. 4) Face masks are effective in reducing the spread of airborne pathogens. 5) We now have more hobbies involving creativity, sensory engagement, self-expression, relaxation, and cognitive stimulation. 6) We practice better hygiene, such as frequent hand washing<sup>(20)</sup>. We will remain attentive.

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