

SPECIAL PAPER

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The coronavirus conundrum – BA.2.86 variant of SARS-CoV-2 – What's new about long COVID – Vaccines – Nobel Prizes

El enigma del coronavirus – La variante BA.2.86 del SARS-CoV-2 – Lo nuevo sobre el COVID prolongado – Vacunas – Premios Nobel

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ABSTRACT

The coronavirus has continued to move around the world with new variants, some of which are of concern. Hospitalizations increased in some places with the BA.2.86 variant, especially in obese or morbid elderly people, but have decreased, as have deaths. Women who gestated by assisted reproductive techniques had similar morbidity as those who gestated spontaneously, but with more adverse maternal-perinatal outcomes in those older, with multiple pregnancies, nulliparity, body mass index >30. Children born at the beginning of the pandemic showed a different microbiome composition than those born before the pandemic, which could affect their health later in life. Among people with long COVID, a quarter of them suffer organ and system sequelae, with limitation and lost years of activity, as well as the possibility of premature death. Long COVID occurs more in women between 35-49 years of age and in those with lower income. They could develop type 2 diabetes. There would be direct interactions between SARS-CoV-2 and mitochondrial proteins essential in energy production. Viral RNA has been detected in coronary atherosclerotic lesions and the spike has been found in skull bones, meninges and brain. Coronavirus vaccines protect pregnant women and their newborns through placental transfer and lactation. In the population, protective immunity from infection and vaccines declines over time and new vaccination will be required at an as yet undetermined regularity.

Key words: Coronavirus infections, SARS-CoV-2, COVID-19, SARS-CoV-2 vaccines, Pregnant woman, Fetus, Newborn

RESUMEN

El coronavirus ha continuado paseándose por el mundo con nuevas variantes, algunas consideradas de preocupación. Las hospitalizaciones aumentaron en algunas partes con la variante BA.2.86, especialmente en personas mayores obesas o con morbilidad, pero han disminuido, así como los fallecimientos. Las mujeres que gestaron mediante técnicas de reproducción asistida tuvieron similar morbilidad que quienes gestaron espontáneamente, pero con más resultados maternoperinatales adversos en aquellas de mayor edad, con embarazos múltiples, nuliparidad, índice de masa corporal >30. Los niños que nacieron al inicio de la pandemia mostraron un microbioma de diferente composición que quienes nacieron antes de la pandemia, lo que pudiera afectar su salud más adelante en la vida. Las personas que presentan COVID prolongado, un cuarto de ellas sufre secuelas en órganos y sistemas, con limitación y años perdidos de actividades, así como posibilidad de muerte prematura. El COVID prolongado ocurre más en mujeres entre 35 y 49 años y en quienes tienen menos ingresos económicos. Podrían desarrollar diabetes tipo 2. Habría interacciones directas entre el SARS-CoV-2 y proteínas mitocondriales esenciales en la producción de energía. El ARN viral ha sido detectado en lesiones ateroscleróticas coronarias y la espiga ha sido hallada en huesos del cráneo, meninges y cerebro. Las vacunas contra el coronavirus protegen a las gestantes y sus recién nacidos a través de transferencia placentaria y la lactancia. En la población, la inmunidad protectora de la infección y de las vacunas declina con el tiempo y se requerirá nueva vacunación con una regularidad aún no determinada.

Palabras clave. Infecciones por coronavirus, SARS-CoV-2, COVID-19, Vacunas SARS-CoV-2, Gestante, Feto, Recién nacido



SARS-CoV-2 AND VARIANTS

SARS-CoV-2 Omicron infection has been associated with increased risk of reinfection in nursing home and long-term care residents. Reinfected participants have lower serum neutralizing antibodies to ancestral SARS-CoV-2 and to Omicron BA.1, as well as lower anti-receptor-binding domain (RBD) IgG and IgA antibodies after initial Omicron infection. In older adults, a less robust hybrid humoral immune response would contribute to the risk of Omicron reinfection⁽¹⁾.

The hypermutated BA.2.86 variant has appeared in many parts of the world at a time when genomic and sewage surveillance has declined. Its new mutational burden is known to be considerable and not limited to the spike, with more difficulty for immune response. Neutralizing antibody levels will be much lower against BA.2.86 than against the versions of the virus against which we have been vaccinated or immunized⁽²⁾.

After hospitalisation for COVID-19, people are at risk of multiorgan abnormalities in the medium term. 259 C-MORE patients (mean age 57 years; 158 [61%] male and 101 [39%] female) were assessed at a median of 5.0 months after hospital discharge. Compared with non-COVID-19 controls, patients were older, living with more obesity, and had more comorbidities. Multiorgan abnormalities on MRI were more frequent in patients than in controls (157 [61%] of 259 vs 14 [27%] of 52; $p < 0.0001$) and independently associated with COVID-19 status (OR 2.9; $p_{\text{adjusted}} = 0.0023$). Compared with controls, patients were more likely to have MRI evidence of lung abnormalities ($p = 0.0001$; parenchymal abnormalities), brain abnormalities ($p < 0.0001$; more white matter hyperintensities and regional brain volume reduction), and kidney abnormalities ($p = 0.014$; lower medullary T1 and loss of cortico-medullary differentiation), whereas cardiac and liver MRI abnormalities were similar between patients and controls. Patients with multiorgan abnormalities were older (difference in mean age 7 years, mean age of 59.8 years, with multiorgan abnormalities vs mean age of 52.8 years [11.9] without multiorgan abnormalities; $p < 0.0001$), more likely to have three or more comorbidities (OR 2.47; $p_{\text{adjusted}} = 0.0059$), and more likely to have a more severe acute infection (acute CRP > 5 mg/L, OR 3.55; $p_{\text{adjusted}} = 0.025$) than those

without multiorgan abnormalities. Presence of lung MRI abnormalities was associated with a two-fold higher risk of chest tightness, and multiorgan MRI abnormalities were associated with severe and very severe persistent physical and mental health impairment⁽³⁾.

The coronavirus that caused more than 750 million human infections and nearly 7 million deaths. But it has also spread to other creatures large and small, with coronavirus infections confirmed in 39 countries in lions, tigers, dogs, cats, armadillos, anteaters, otters and manatees, among others. In most cases, the animals do not become seriously ill, but are capable of transmitting the virus to other members of their species, as are asymptomatic humans who have become 'silent spreaders'. As SARS-CoV-2 spreads in animals, the virus has the opportunity to acquire new mutations that could make it more dangerous to humans⁽⁴⁾.

The COVID-19 pandemic is considered to have helped clarify the fair and equitable allocation of scarce medical resources, i.e., maximizing benefits and minimizing harms, mitigating unfair disadvantages and equalizing moral concern and reciprocity. Priority attention has been agreed to be given to health care workers, people living in group housing, and those at greatest risk of death, such as older adults and people with medical conditions. And the allocation of the new vaccine will be to minimize severe disease and death, especially among infants and children⁽⁵⁾.

PREGNANCY, COVID-19 AND ADVERSE OUTCOMES

The incidence of adverse outcomes associated with COVID-19 such as pneumonia, admission to intensive care, and death has not been different in women who conceived while on COVID-19 than in women following medically assisted reproduction pregnancies. However, the risk of obstetric and neonatal complications was higher in pregnancies achieved by medically assisted reproduction in women with COVID-19. Maternal age, multiple pregnancies, nulliparity, and body mass index > 30 before pregnancy contributed to the increased risk of adverse pregnancy outcomes (hypertensive disorders, gestational diabetes mellitus, cervical insufficiency, peripartum



hemorrhage, cesarean delivery, preterm delivery, or admission to neonatal intensive care), independent of medically assisted reproduction⁽⁶⁾.

Infants born during the first few months of the COVID-19 pandemic have a different gut microbiome composition compared to those born before the March 2020 lockdowns. Gut microbiome imbalance has been linked to psychiatric disorders, skin conditions, and gastrointestinal problems. Babies acquire many gut microbes from their environment, and evidence is emerging to suggest that being born into the unique situation of confinement can have a lasting effect on the microbiome that may affect other aspects of babies' development. The first 1,000 days are critical for forming a healthy microbiome. Without adequate establishment of beneficial bacteria during this period, babies are at an increased risk for future health problems⁽⁷⁾.

WHAT'S NEW ABOUT LONG COVID?

Survey data indicate that the prevalence of long COVID among U.S. adults aged > 18 years decreased from 7.5% during June 2022 to 6.0% during June 2023, regardless of having had prior COVID-19, and from 18.9% to 11.0% in adults reporting prior COVID-19. After an initial decline, prevalence has remained unchanged as of January 2023. Approximately one-quarter of adults with long COVID report significant limitations in their activity⁽⁸⁾.

Data from the CDC's National Health Interview Survey revealed that, in 2022, 6.9% of adults had ever had long COVID and 3.4% had it at the time of interview. Women were more likely than men to have long COVID and it varied by race and Hispanic origin. Adults ages 35–49 represented the age group most likely to have had (8.9%) or currently have (4.7%) long COVID. Adults with family incomes at or above 400% of the federal poverty level were less likely to have had or have long COVID than those with family incomes between 200%–399%. Current long COVID is less prevalent in large central metropolitan areas⁽⁹⁾.

A new paper on mitochondrial biology has shown the existence of direct interactions between SARS-CoV-2 and essential mitochondrial proteins as a possible basis for long COVID, at least in some individuals. The main function of mitochondria is energy production, which ex-

plains why mitochondria are the powerhouse of cells. The virus binds directly to essential mitochondrial proteins, suppressing mitochondrial gene expression (both nuclear-encoded and mitochondrial) and inducing dysfunction of mitochondrial energy production and activation of the innate immune response. Virus suppression of mitochondrial genes inhibits or inactivates the entire OXPHOS complex, forcing an alternative pathway for energy production and essentially sequestering the cells to produce more virus. Autopsy samples indicate that this alteration occurs in many organs, especially the heart, liver, kidneys, and lymph nodes. Potential therapies that could restore intact mitochondrial function would be the mTOR inhibitor rapamycin and metformin⁽¹⁰⁾.

Several articles have been published on COVID outcomes from Veteran Affairs data during the pandemic. An article in *Nature Medicine* addresses what has happened 2 years later to nearly 140,000 people who had COVID, compared to nearly 6 million uninfected control persons. Of the people with COVID, 188,238 were not hospitalized and 20,580 were hospitalized. Eighty sequelae classified into 10 organ systems were prespecified at 2 years after COVID. When studying disability-adjusted life years (DALYs, number of years lost due to illness, disability, or premature death), hospitalized severe COVID persons had worse outcomes and DALYs compared with nonhospitalized mild-to-moderate COVID persons. However, in the nonhospitalized group, about 30% of the 80 sequelae, including gastrointestinal and neurologic sequelae, remained significantly elevated, with death 1.39 times and (repeat) hospitalization 2.57 times. Another publication in *JAMA Internal Medicine* reports on more than 208,000 veterans with COVID who were compared to uninfected individuals. Mortality was 8.7% among veterans who had had COVID and 4.1% in the uninfected, with persistent risk of death among those hospitalized. On the other hand, a meta-analysis has shown increased risk of type 2 diabetes in more than 60% of cases with COVID, or an excess of 3-5% in the population. The impact of vaccination in reducing diabetes (vs. unvaccinated) has been substantial. Another study showed that SARS-COV-2 viral RNA was detectable and able to replicate in atherosclerotic coronary lesions at autopsy in 8 individuals. In addition, the SARS-CoV-2 spike has been found in the skull bones, meninges and



brain at autopsy of individuals with COVID who died for other reasons. There would be brain neuroinflammation. In summary, two years after the onset of COVID, a substantial burden of symptoms and multisystem organ involvement persists in a significant subgroup of people. It is unpredictable who will suffer from these prolonged symptoms. It will be many years before the sequelae of COVID are fully understood, as they have been after influenza or poliomyelitis⁽¹¹⁾.

More than 3 years after worldwide exposure to SARS-CoV-2 it is beginning to be understood why some people escape COVID disease after being infected by the virus, while others develop a prolonged, often quite debilitating illness. A smartphone app (Citizen Science) tracked the COVID symptoms and results of nearly 30,000 participants (more than 1,400 asymptomatic with a positive test). A human leukocyte antigen (HLA) locus with immune function (HLA-B*15:01) was found to be strongly associated with the absence of symptoms. The odds ratio of asymptomatic to symptomatic was ~2.5-fold for this allele. Individuals with 2 copies of the HLA-B*15:01 allele were more than 8-fold more likely to remain asymptomatic, reinforcing the importance of this finding with a gene-dose relationship. In contrast, the transcription factor gene FOXP4 is widely expressed in the body, in almost all tissues, and the variant of interest has been associated with increased expression in the lung and hypothalamus. In the results of Genome-Wide Association Studies (GWAS) in more than 6,400 people with long COVID and more than one million control cases derived from 24 studies in 16 countries, only the FOXP4 gene locus on chromosome 6 reached statistical significance of association, as it was previously with COVID, lung function and cancer. The risk of having this variant, with an allele frequency of 4.2%, was overall 1.6 times higher with long COVID (up to 36% in East Asians). Thus, in addition to preventive measures for long COVID (vaccination, Paxlovid, and metformin), the GWAS finding helps to get to the root of this condition and may lead to better treatments and vaccine. In contrast to this article on FOXP4, another genomic study of long COVID from the UK company Precision Life notes that there are no loci that reach a high level of statistical significance of association with severe COVID and long COVID. However, it has

suggested that 73 variants could be associated with long COVID, most of which have previously been linked to neurological or cardiometabolic conditions, and 9 of the variants have been linked to myalgia-encephalomyelitis/chronic fatigue syndrome⁽¹²⁾.

VACCINES

Thirty-two studies support the safety of the COVID-19 vaccine and its protective effects in pregnant women and their newborns. Most studies (n=24) reported the use of Pfizer and Moderna COVID-19 vaccines in pregnant women; only 6 reported on the Janssen vaccine. After vaccination, pregnant women had a robust immune response and the vaccines conferred protective immunity to the infants through placental transfer and breast milk⁽¹³⁾.

The development of safe and effective vaccines and treatments against SARS-CoV-2 within one year of its identification represents one of the great successes of modern science. Most of the world's population has received the vaccine, but not in sufficient percentages⁽¹⁴⁾. While the number of deaths and hospitalizations from COVID-19 has declined, the virus has continued to evolve to infect rapidly, with a resurgence of hospitalization and death⁽¹⁵⁾. Immunity from infections and vaccines wanes over time, so we will need to be vaccinated with some as yet unspecified regularity⁽¹⁴⁾.

In relation to the new vaccines, the large number of mutations in the BA.2.86 strain compared to BA.2, the ancestral strain (Wuhan-1) and XBB.1.5, with possible increased immune evasion, is noted. Early human data from Moderna's new monovalent vaccine XBB.1.5 show very good levels of neutralizing antibodies induced against BA.2.86, in line with the response to the XBB.1.5 target and to 2 of the major current circulating variants EG.5.1 and FL.1.5.1. But the FLip variants are gaining strength and exhibit greater immune evasion capacity than the current circulating variants. The double mutation in the spike (F456L and L455F) seems to be appearing in higher proportions. Thus, the value of the XBB.1.5 booster, which will not provide long-lasting additional protection, will be of benefit to those at higher risk, such as those over 65 years of age or immunocompromised⁽¹⁶⁾.



SARS-CoV-2-specific antibody-secreting plasma cells (PCs) that mediate specific humoral immunity have been identified in human bone marrow (BM) after having COVID-19 or SARS-CoV-2 vaccination. In one study, SARS-CoV-2 spike-S1-specific PCs were detectable in all bone marrow samples analyzed from previously vaccinated individuals, representing 0.22% of total bone marrow plasma cells (BMPCs). Most of the SARS-CoV-2-specific BMPCs expressed IgG and their specificity for the spike S1 protein indicated the appearance of a response to systemic vaccination. One-fifth of the SARS-CoV-2-specific BMPCs showed the phenotype of memory plasma cells, i.e., down-regulated CD19 and present or absent CD45 expression. These results suggest the induction of long-lasting humoral immunity after basic mRNA vaccination against SARS-CoV-2⁽¹⁷⁾.

Infants younger than 6 months are ineligible for COVID-19 vaccination and are at risk for COVID-19-associated complications. During the period of recent SARS-CoV-2 Omicron predominance, maternal receipt of an mRNA COVID-19 vaccine during pregnancy reduced the likelihood of COVID-19-related hospitalizations and serious complications among infants aged <6 months and especially among infants <3 months. Therefore, expectant mothers should keep up to date with COVID-19 vaccination to protect themselves and their infants from hospitalization and severe outcomes associated with COVID-19⁽¹⁸⁾.

The Nobel Prize in Physiology or Medicine has been awarded to biochemist Katalin Karikó of the University of Szeged (Hungary) and immunologist Drew Weissman of the University of Pennsylvania in Philadelphia (UPenn), for discoveries that led to the development of messenger RNA (mRNA) vaccines against COVID-19. The vaccines have saved millions of lives and prevented serious diseases in millions of people. The laureates discovered a way to introduce the mRNA into cells without triggering an unwanted immune response by exchanging one type of molecule, uridine, in the genetic material for a similar one called pseudouridine⁽¹⁹⁾.

A third COVID-19 vaccine, manufactured by Novavax, will soon be available to the public. The Food and Drug Administration (FDA) cleared Novavax's vaccine for use as a booster dose in people 12 years of age and older. The Pfizer-Bi-

oNTech and Moderna vaccines use messenger RNA technology to identify and target the spike protein found on the surface of the SARS-CoV-2 virus, while the Novavax vaccine directly delivers large amounts of the spike protein to the body to do the same. Both types of vaccines train the immune system⁽²⁰⁾. mRNA-vaccine developers are now setting their sights on mpox (monkeypox), influenza and cancer.

Meanwhile, throughout multiple pandemics global health governance institutions have struggled to secure State compliance with international legal and political commitments, ranging from data sharing to adherence to WHO guidelines for vaccines sharing. In response, governments are negotiating a new pandemic treaty and revising the International Health Regulations⁽²¹⁾.

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