

SPECIAL ARTICLE

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The coronavirus conundrum - Reinfections by COVID-19, long COVID - Bivalent vaccines - The pregnant woman - Human rights & Ethics

El enigma del coronavirus – Reinfecciones por COVID-19, COVID prolongado – Vacunas bivalentes - La gestante – Derechos humanos y Ética

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ABSTRACT

At the end of the second year of the COVID-19 pandemic, it seems that the enigmatic coronavirus is giving us some respite. However, the number of people infected has started to rise in the northern hemisphere, where a strong winter with snowfall is approaching. But this new increase is also observed in the southern hemisphere, as in Peru, when we are in spring. SARS-CoV-2 continues to differentiate into a multitude of variants and subvariants, some of which are more easily able to evade human immunity and that achieved with mRNA vaccines, and also may not respond to monoclonal antibody treatments. Current clinical information is oriented to the expectation that existing vaccines could at least reduce hospitalizations, intensive care admission and deaths. Learning about the clinical effects of SARS-CoV-2 infection, the occurrence of reinfection, and long-term physical and mental harm continues, with prevention of infection, reinfection, and prolonged COVID being sought.

Key words: Novel coronavirus SARS-CoV-2, COVID-19, Viral infection, Mutation, Immunity

RESUMEN

Al finalizar el segundo año de la pandemia COVID-19, da la impresión que el coronavirus enigmático nos estuviera otorgando cierto respiro. Sin embargo, las cifras de infectados han iniciado un ascenso en el hemisferio norte, donde se aproxima un invierno fuerte, ya con nevadas. Pero también se observa este nuevo incremento en el hemisferio sur, como en el Perú, cuando estamos en primavera. El SARS-CoV-2 continúa diferenciándose en multitud de variantes y subvariantes, algunas de las cuales tienen mayor facilidad de evadir la inmunidad humana y aquella alcanzada con las vacunas de ARNm, y también podrían no responder a los tratamientos con anticuerpos monoclonales. La información clínica actual está orientada a la expectativa sobre si las vacunas existentes pudieran al menos minorar las hospitalizaciones, el ingreso a cuidados intensivos y las muertes. Se sigue aprendiendo sobre los efectos clínicos de la infección por el SARS-CoV-2, la ocurrencia de reinfecciones y los daños físicos y mentales a largo plazo, buscándose la prevención de la infección, las reinfecciones y el COVID prolongado.

Palabras clave. Infecciones por coronavirus, SARS-CoV-2, COVID-19, Infección viral, Mutación, Inmunidad

COVID-19 IN PERU

In Peru we are waiting for the fifth wave of COVID-19, in the middle of spring, with a worrying increase in the number of infected people, at a time when the use of masks has been officially declared non-obligatory. Meanwhile, the Nordic countries are already suffering from what they call the fifth, sixth, eighth waves⁽¹⁾. And the question on everyone's mind is when will the Covid pandemic end? In addition, cases of influenza and other viral infections are on the rise, due to less prevention during the pandemic. And despite the fact that Peru had the highest number of deaths per million inhabitants, our healthcare system has not been sufficiently prepared to face new crises. In the world, COVID-19 has caused



nearly 650 million infections and more than 6.6 million deaths⁽²⁾. In Peru, it has occasioned more than 4.2 million cases and more than 217,000 deaths⁽³⁾. A total of 573 doctors and 178 nurses have died in the country by November 2022. The health crisis is minor at the moment, but there is concern about the political, economic, and social problems we face, with unemployment, malnutrition, anemia, restricted and delayed health coverage, which increased during the pandemic. We reached 73% vaccination coverage with the third dose, but only 23% with the fourth dose of the anti-COVID vaccine. There is a threat of the return of polio and measles, among others. Influenza has been unnoticed for a couple of years, but it continues to occur and has increased⁽¹⁾.

The latest Technical Report of the Peruvian Ministry of Health states that, to date, 15,802 cases of the Omicron variant have been reported nationwide, and the circulation of the BA.4 (1,253 cases) and BA.5 (4,388 cases) lineages has been detected, with a tendency to increase since their identification. In addition, the appearance of sublineage BA.2.12.1 in 1,696 persons from week 15-2022 to the present has been noticed, with a higher concentration in Metropolitan Lima. This lineage is characterized by particular mutations in the spike protein, and it is estimated that it can have a 42% higher growth if cases than BA.2. Likewise, the recombinant lineage XE (1), XQ (19) and XT (2), which is a recombination between BA.1 and BA.2, has been detected; initial estimates indicate that it would be 10% more transmissible than BA.2, but it does not appear to have greater severity or different symptomatology⁽⁴⁾. And now MINSA Peru has indicated that the sustained increase in COVID-19 cases since October 2022 is due to a new variant of the virus originating in Peru, which has been named Omicron DJ.1. DJ.1 is one of two mutations of BA.5.1.25 Omicron, which would allow it to be transmitted more easily among vaccinated and recently infected people, with no evidence that it is more lethal⁽⁵⁾.

COVID-19 INFECTION AND REINFECTIONS

Most adults have IgG antibodies after SARS-CoV-2 infection for longer than 12 months (low strength of evidence [SoE]). Prior infection provides substantial and sustained protection against symptomatic reinfection with the Delta variant (high SoE) and reduces the risk of severe

disease from the Omicron variants (moderate SoE). Prior infection is less protective against reinfection with Omicron overall (moderate SoE), but protection from earlier variants declines rapidly (low SoE)⁽⁶⁾.

The safeguard of prior SARS-CoV-2 infection against reinfection by variants of concern BA.4 or BA.5 has been modest when the previous infection was caused by a pre-Omicron variant, but strong when it was caused by a post-Omicron subvariant (including BA.1 or BA.2). The protection of a previous infection against reinfection with a BA.4 or BA.5 subvariant is less than that against reinfection with a BA.1 or BA.2.3-5 subvariant, due to a greater decline in immune protection over time and a greater evasiveness of the immune system with BA.4 and BA.5 subvariants⁽⁷⁾.

Contracting COVID-19 multiple times is more dangerous than previously thought. The health records of 443,000 people from the U.S. Department of Veterans Affairs who tested positive for COVID-19 once have been analyzed and compared with the records of 41,000 people who tested positive two or more times and with 5.3 million people with no COVID-19 infection at all. Compared with people who were infected only once, those with multiple infections were three times more likely to be hospitalized for COVID-19 and twice as likely to die from the disease. They were also 3.5 times more likely to develop lung problems, 3 times more likely to have heart conditions, and 1.6 times more likely to have brain disorders⁽⁸⁾.

It is considered that, to avoid a first, second or third infection, it is necessary to be vaccinated and reinforced, to wear a mask in closed public places and to avoid meetings if one is sick. Now, in many countries such as ours, there is no longer an obligation to wear masks, at a time when COVID-19 infections and reinfections are on the rise. The Massachusetts Department of Elementary and Secondary Education decided in February 2022 to allow school districts to suspend universal masking during the 2021-2022 school year. 72 school districts in the Boston metropolitan area that discontinued masking at varying times were studied: 46 districts stopped masking in the first week after the announcement, 17 in the second week, 7 in the third week, and two never discontinued masking. One week later, COVID-19



rates differed significantly between districts that continued and those that did not continue masking. The differences ranged from 1.4 to 9.7 additional cases of COVID-19 per 1,000 students and staff per week and accounted for 29% of all cases during the study period. The results clearly support the benefits of incorporating universal masking into public policy approaches to control COVID-19 in congregate settings⁽⁹⁾.

HEALTH CONSEQUENCES OF COVID AND LONG COVID

Most people who develop COVID-19 recover completely, but some people experience a variety of medium and long-term effects after recovering from their initial illness. These effects are known as post-COVID-19 syndrome or long or prolonged COVID, which we have already referred to in previous issues of the *Peruvian Journal of Gynecology and Obstetrics*. Researchers are working with patients who develop post-COVID-19 to better understand its cause, symptoms, and effects. The World Health Organization states that it will update information and materials as we learn more⁽¹⁰⁾. In children, COVID-19 is a relatively mild and short-lived disease, but some have symptoms for at least four weeks and, among those hospitalized, about a quarter have symptoms up to four months later, such as fatigue, chronic pain and brain fog, seizures, limited mobility, and fatigue. Many children with long COVID gradually recover even without treatment, but in others, medical professionals' lack of knowledge about the disease has made treatment difficult⁽¹¹⁾.

MENTAL PROBLEMS CAUSED BY COVID-19

The World Health Organization has noted that anxiety and depression increased by 25% worldwide in the first year of the COVID-19 pandemic, with risk of developing these and other mental disorders up to a year after recovery. Others may suffer strokes, anxiety, memory disorders, and sensory disturbances. It is believed that the immune system would react with inflammation throughout the body and even in the brain. Also, the endothelial cells of the cerebral blood vessels are altered during COVID-19 infection and thus would affect mental function. Microglia cells can attack neurons and damage synapses. In addition, it is possible that COVID-19 may

compromise the diversity of bacteria and microbes in the gut. Since gut microbes produce neurotransmitters such as serotonin and dopamine that regulate mood, their modification could be at the root of some neuropsychiatric problems. Risk factors for these complications are having a diagnosed mental disorder before becoming ill with COVID, having severe COVID-19 symptoms, and a long hospital stay. Young people may exhibit suicidal and self-injurious behaviors after COVID-19 infection. Women are more likely than men to report mental health effects. Finally, people with problems such as asthma, cancer, and heart disease may develop post-COVID mental disorders⁽¹²⁾.

The largest U.S. study looking at the long-term effects of COVID - the Veterans Administration healthcare system - included more than 9,000 patients treated with paxlovid within 5 days of symptom onset, during Omicron and subvariant surges. The mean age was 65 years, 12% were women, and they compared the results with ~47,000 controls. There was 26% reduction in cases of long COVID and its complications, as well as extended survival and avoided hospitalizations for up to one year. Pending further data, it appears that paxlovid treatment may have both acute and long-term benefits in COVID-19 infection⁽¹³⁾.

DIVERSE PUBLIC HEALTH GAPS IN THE PANDEMIC

The Pan American Health Organization (PAHO) points out that it is possible that public health measures essential to contain the spread of COVID-19, such as confinement and social distancing, could have been associated with atypical cases of influenza and respiratory syncytial virus, due to the reduced exposure of the immune system to common respiratory pathogens⁽¹⁴⁾. We add that also because of the pandemic, the management of chronic diseases such as hypertension, cardiovascular diseases, obesity, metabolic syndrome, diabetes mellitus and many others, including the preventive control of pregnant women and children, has been neglected. Due to COVID-19, it is estimated that, in the last 2 years, one million cases of cancer have gone undetected throughout Europe. In the first year alone, physicians saw 1.5 million fewer cancer patients and 1 in 2 people with cancer suffered delays in treatment⁽¹⁵⁾.



COVID-19 AND PREGNANCY

COVID-19 infection is known to be associated with increased maternal morbidity in pregnancy and adverse neonatal outcomes such as fetal death and prematurity. Little is currently known about whether the timing of infection during pregnancy affects these outcomes. In a prospective German prospective observational study involving 1,149 symptomatic pregnant women infected with SARS-CoV-2, infection in the first two trimesters of pregnancy was associated with an increased risk of early preterm delivery (≤ 32 weeks) and stillbirth compared with infection in the third trimester. The risk of preterm delivery was highest in the first 4 weeks after infection. SARS-CoV-2 infection should be prevented during pregnancy, and those infected during early pregnancy might benefit from extensive obstetric surveillance during the remainder of gestation⁽¹⁶⁾.

ON EFFICACY IN THE TREATMENT OF INFECTION BY NEW SARS-CoV-2 SUBVARIANTS WITH THE USE OF MONOCLONAL ANTIBODIES – PREGNANCY

The American College of Physicians has noted that some antiviral drugs and monoclonal antibodies may improve outcomes for outpatients with mild to moderate COVID-19. In 26 studies conducted prior to the emergence of the Omicron variant, nirmatrelvir-ritonavir and casirivimab-imdevimab combinations likely reduced hospitalizations, nirmatrelvir-ritonavir likely reduced all-cause mortality, and regdanvimab likely improved recovery. Casirivimab-imdevimab reduced recovery time with a mean difference of 4 days. Molnupiravir may reduce all-cause mortality, sotrovimab may reduce hospitalization, and remdesivir may improve recovery. Lopinavir-ritonavir and azithromycin may increase harms, and hydroxychloroquine may result in lower recovery rates. However, generalization of the findings to the currently dominant Omicron variant is limited⁽¹⁷⁾.

The SARS-CoV-2 subvariants BA.4.6 and BA.5 share the same amino acid substitutions in the receptor-binding domain of the spike protein, the main target of vaccines and therapeutic monoclonal antibodies against SARS-CoV-2. BA.4.6 also has an additional mutation not found in BA.5 (R346T), a worrisome finding that the efficacy of current vaccines and therapeutic

monoclonal antibodies against this subvariant is greatly diminished. Recent data from the National Institute of Infectious Diseases, Tokyo, Japan, suggest that remdesivir, molnupiravir and nirmatrelvir and the monoclonal antibodies bebtelovimab and imdevimab retain their efficacy against BA.4.6 in vitro. The results also indicate that the monoclonal antibodies casirivimab, sotrovimab, tixagevimab, and cilgavimab may not be effective against BA.4.6⁽¹⁸⁾.

However, in the case of BQ.1.1 and the 6+ mutations there is worrisome evidence of immune escape, by early loss of efficacy of the monoclonal antibodies evusheld or bebtelovimab. This affects preventive therapy for immunocompromised or back-up therapy when paxlovid is unsuccessful⁽¹⁹⁾.

Regarding women, 552 pregnant women aged 12 years or older seen at the University of Pittsburgh Health System (UPMC) with any documented positive test for SARS-CoV-2, 62% of whom were fully vaccinated, were treated with the monoclonal antibodies (mAb) bamlanivimab and etesevimab, casirivimab and imdevimab, or sotrovimab and were compared with 392 non-mAb-treated pregnant women. The median gestational age was 179 days and 69% received sotrovimab. Drug-related adverse events occurred in 8 (1.4%) pregnant women, with no differences in obstetric outcomes. There were no deaths among mAb-treated patients compared with one death in untreated control patients⁽²⁰⁾.

EFFECTIVENESS OF VACCINES

It is difficult to keep track of the new SARS-CoV-2 variants with esoteric designations and many unnamed. But several of them are quite worrisome because their growth advantage compared to BA.5 (the wave being overtaken) is substantial, mainly because of their ability to evade immune response. The fact that the variants converge on the same and multiple mutations (at sites R346, L452, K444, F486, N460) indicates how the virus is evolving in response to pressure from previous infection and vaccine-induced immunity⁽²¹⁾. The efficacy of a third dose of COVID-19 mRNA vaccine (booster) against the B.1.1.529 Omicron variant is uncertain, especially in elderly and high-risk populations. Among the 490,838 people in the U.S. Department of Veterans Affairs health care system who had received two



doses of COVID-19 mRNA vaccine (BNT162b2 or mRNA-1273) at least 5 months previously, predominantly male (88%), with mean age 63.0±14.0 years and mean follow-up of 80 days, the effectiveness more than 10 days after booster was 42.3% against infection, 53.3% against hospitalization, and 79.1% against death from SARS-CoV-2⁽²²⁾.

In a mid- and late-phase study and compared with its original vaccine, Moderna Inc. indicates that its Omicron-adapted vaccines produced improved immune responses against BA.4/5 subvariants when administered as booster doses. However, neutralizing antibody response levels were reduced nearly 5-fold against the emerging BQ.1.1 subvariant, although virus-neutralizing activity remained 'robust'. Pfizer Inc. and its German partner BioNTech SE have claimed that after one month their Omicron-adapted injection targeting BA.4/5 subvariants produced a stronger antibody response in older adults than the original injection⁽²³⁾.

The most immune-evasive variants are BQ.1.1 and XBB (BA.2.75.2 as well), demonstrated in part by resistance to bebtelovimab, the only remaining monoclonal antibody that worked well against earlier versions of the virus, and to evusheld, the antibody combination used for prevention in immunocompromised individuals. But the level of immune escape is also seen with hybrid immunity, i.e., the combination of vaccination and infection after vaccination. Neutralizing antibodies against BQ.1.1 and XBB (and BA.2.75.2) are missing after 3 injections (Coronavac) and 7 months after BA.1 infection. In the U.S. wave of BA.5, 2 boosters have been shown to reduce deaths (91%) and hospitalizations in persons aged 50 years and older, as well as fewer hospitalizations (72%) in persons aged 18-49 years. This body of data adds to the marked reduction in mortality for those 50 years and older by a 4th booster compared to a 3rd booster. Also, systematic reviews indicate that vaccines help protect against long Covid by 30 to 50%⁽²¹⁾.

A recent joint press release from the Peruvian Ministry of Health and the Peruvian Society of Obstetrics and Gynecology stated that vaccination continues to be promoted in the country with the regular schedule in order to protect pregnant women and their babies from various immune preventable diseases, and they call on

pregnant women and their families to join in their protection by completing their vaccination process, remembering that vaccines are free, safe, effective and of high quality⁽²⁴⁾.

Monovalent COVID-19 mRNA vaccines were known to be less effective against symptomatic infection during the period of predominance of the Omicron variant of SARS-CoV-2. Bivalent COVID-19 vaccines, not yet available in Peru, include a component of the original virus strain to provide broad protection against COVID-19 and a component of the Omicron strain for better protection against COVID-19 caused by that mutant⁽²⁵⁾. Bivalent messenger RNA (mRNA) vaccines containing the ancestral sequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and version B.1.1.529 (Omicron) have recently become available to address waves of coronavirus 2019 infection and disease caused by Omicron variants. The bivalent vaccine mRNA-1273.214 containing the Omicron BA.1 mutation, currently licensed for use in many countries, elicits strong neutralizing antibody responses against the Omicron BA.1 variant and the epidemiologically dominant BA.4 and BA.5 subvariants. The Omicron BA.2.75 subvariant, whose prevalence has steadily increased in at least 36 countries, contains potential spike mutations that escape antibodies. In one study, mRNA-1273.214 elicited a potent neutralizing antibody response against the BA.2.75 subvariant, independent of prior SARS-CoV-2 infection. This response was 2.1-fold higher than that against the BA.4 and BA.5 subvariants and 3.4- and 1.6-fold lower than that of the SARS-CoV-2 ancestral strain D614G and the BA.1 subvariant, respectively⁽²⁶⁾.

In evaluating the efficacy of the U.S.-licensed bivalent mRNA booster vaccine, it provided significant additional protection against symptomatic SARS-CoV-2 infection during the period when the BA.4/BA.5 Omicron lineages and sublineages predominated in persons who had previously received 2, 3, or 4 doses of monovalent vaccine. Because of the waning immunity of monovalent doses, the benefit of the bivalent booster increased with time since receipt of the most recent monovalent vaccine dose. Therefore, all persons should be up to date with recommended COVID-19 vaccines, including bivalent booster doses, if more than 2 months have elapsed since their last dose of monovalent vaccine⁽²⁷⁾.



HUMAN RIGHTS AND THE COVID-19 PANDEMIC

In relation to the COVID-19 pandemic, many countries and states failed to fulfill their human rights obligations. Initially, officials in Wuhan, China, suppressed information, silenced petitioners, and violated freedom of expression and the right to health. Then there have been inequities in many countries in fulfilling the human rights to non-discrimination, to attain the highest attainable standard of health and to take seriously the obligation of international assistance and cooperation. The response to these violations means much greater funding by high-income countries to support low- and middle-income countries in rights-based recoveries, in addition to implementing measures to ensure equitable distribution of COVID-19 medical technologies. New legal instruments and mechanisms are needed, from a treaty on the right to health to a fund for civil society advocacy for the right to health, so that the narratives of future health emergencies and people's daily lives are of equality and human rights⁽²⁸⁾.

ETHICS

The COVID pandemic has posed significant challenges to societies and health systems around the world, both technical challenges - developing effective vaccines and therapies - and ethical challenges - determining the 'right' course of action on critical issues, such as introducing the use of masks and vaccines, restricting travel, intentional research on participants to test vaccines, allocating scarce vaccines, among others. A 'right' decision in assigning resources includes maximizing benefits and preventing harms, mitigating disadvantages, reciprocity, instrumental value, and equal moral concern. Other frequently invoked ethical principles - transparency, commitment, and responsiveness to evidence - are procedural. However, for ethics to inform decisions, the policy-making process needs to change. This requires a competent team with complementary capabilities and skills that can fully consider the complex global, regional, and local impact of pandemic planning and decision-making such as COVID. It will consider existing knowledge of appropriate values and principles to guide policy, ensuring that ethical knowledge is present before an emergency response is conceived and effectively integrated into decision making⁽²⁹⁾.

THE FUTURE

Despite remarkable scientific and medical advances, political, socioeconomic and behavioral factors undermine the response to the COVID-19 pandemic. The Delphi study, the result of a multidisciplinary panel of 386 academic, health, non-governmental, governmental, and other experts from 112 countries and territories in response to the COVID-19 pandemic, has been published to recommend specific actions to end this global public health threat. The panel developed consensus statements and recommendations on communication, health systems, vaccination, prevention, treatment and care, and inequalities. Three of the top-rated recommendations call for whole-of-society and whole-of-government approaches, maintaining proven prevention measures using a vaccine approach, and a range of public health and financial support measures to complement vaccination. Other recommendations advise governments and other parties to improve communication, rebuild public trust, and involve communities in managing pandemic responses. Infection rates tend to increase when governments suspend social measures, including nonpharmaceutical interventions, regardless of the level of vaccination⁽³⁰⁾.

FAREWELL TO DR. ANTHONY FAUCI

Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases and leading infectious disease expert, plans to leave the U.S. federal government in December 2022. He urged Americans to get vaccinated with the updated COVID-19 booster vaccines from Pfizer and Moderna in the face of a potential rebound of infection during the fall and winter, as they give significant additional protection against symptomatic COVID-19 in people who have previously received two, three, or four doses of the original vaccine⁽³¹⁾. Furthermore, Dr. Fauci noted that there is no reason to believe today that the threat of emerging infections will diminish, as their underlying causes are present and, most likely, increasing. The emergence of new infections and the resurgence of old ones are largely the result of human interactions with and invasion of nature. Likewise, climatic changes help unstable infectious agents to emerge, jump species and, in some cases, adapt to spread among humans. In addition to the need to continue to improve capabilities to deal with established



infectious diseases such as malaria and tuberculosis, among others, emerging infectious diseases are now a perpetual challenge. Infectious disease specialists must always be prepared and able to respond to the perpetual challenge⁽³²⁾.

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