

SPECIAL ARTICLE

1. Expert Extraordinary Professor, Faculty of Medicine, Universidad Nacional Mayor de San Marcos, Lima, Peru. Honorary Academician, Peruvian Academy of Surgery, Lima, Peru. Editor, The Peruvian Journal of Gynecology and Obstetrics. ORCID iD: 0000-0002-3168-6717. Scopus Author ID: 34971781600

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Corresponding author:

José Pacheco-Romero

✉ jpachecoperu@yahoo.com

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The coronavirus conundrum - Covid-19 during the Bicentennial of the Independence of Peru - The postcovid syndrome - The vaccines - The pregnant woman

El enigma del coronavirus – Covid-19 durante el Bicentenario de la Independencia del Perú – El síndrome poscovid – Las vacunas – La gestante

José Pacheco-Romero¹, MD, PhD, MSc, FACOG

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ABSTRACT

Eighteen months have passed since the COVID-19 infection caused by SARS-CoV-2 was declared a pandemic. There is still no treatment for the virus other than symptomatic and recuperative. The rapid recognition of the novel coronavirus allowed the development of vaccines that are being used on an emergency basis and have led to a decrease in severe cases, hospitalizations, use of intensive care units, mechanical ventilation and deaths. But there are still unknowns about the genetic modifications and variants that the virus uses for better invasion and adaptation to human defenses, as well as about its immediate and long-term consequences in men, women and their children. Herd immunization seems distant to achieve, because we do not know the immunity provided by the infection and vaccines, as well as its duration, and because a large part of the population that does not want to be vaccinated. In addition, there is insufficient vaccine supply capacity, limited accessibility to health services, unfavorable economic situation, increased poverty and its consequences, temporary decrease in life expectancy and other complications secondary to infection by the virus. The present review is a brief account of recent advances in the knowledge and management of COVID-19, at a time when Peru is celebrating the Bicentennial of the country's Independence from Spanish rule, on July 28, 1821, and when Peruvians find themselves in the midst of an aggressive, elusive and deadly pandemic, with human, population, economic and political issues to be resolved.

Key words: Coronavirus infections, SARS-CoV-2 virus, complications, Pregnancy, complications, Newborn, Health services accessibility.

RESUMEN

Han transcurrido dieciocho meses desde que se declaró como pandemia la infección COVID-19 ocasionada por el SARS-CoV-2. No existe aún tratamiento contra el virus, salvo el sintomático y recuperativo. El rápido reconocimiento del nuevo coronavirus permitió la elaboración de vacunas que están siendo usadas de emergencia y han permitido disminuir los casos graves, hospitalizaciones, uso de unidades de cuidados intensivos, ventilación mecánica y muertes. Pero aún quedan incógnitas sobre las modificaciones genéticas y variantes que el virus utiliza para una mejor invasión y adaptación a las defensas del ser humano, así como sobre sus consecuencias inmediatas y a largo plazo en el hombre, la mujer y su niño. Parece distante alcanzar la inmunización de rebaño, porque desconocemos la inmunidad proporcionada por la infección y por las vacunas, así como su duración, y por la importante parte de la población que no desea vacunarse. Además, existe insuficiente capacidad de oferta de vacunas, accesibilidad limitada a los servicios de salud, situación económica desfavorable, incremento de la pobreza y sus consecuencias, disminución temporal de la expectativa de vida y otras complicaciones secundarias a la infección por el virus. La presente revisión es un recuento breve de lo avanzado recientemente en el conocimiento y manejo del COVID-19, en momentos en que el Perú celebra el Bicentenario de la Independencia del país del dominio español, un 28 de julio de 1821, y que encuentra a los peruanos en medio de una pandemia agresiva, elusiva y mortal, y con aspectos humanos, poblacionales, económicos y políticos a resolver. **Palabras clave.** Infecciones por coronavirus, Virus SARS-CoV-2, complicaciones, Embarazo, complicaciones, Recién nacido, Servicios de salud, accesibilidad.



SITUACIÓN DE LA PANDEMIA DURANTE LA CELEBRACIÓN DEL BICENTENARIO DEL PERÚ

When the first imported case of COVID-19 was reported in Peru on March 5, 2020⁽¹⁾, the first SARS-CoV-2 death in the country had occurred 2 days earlier, on March 3, in Saposo, San Martín, in the Peruvian jungle, and the virus had been circulating since February 2020⁽²⁾. On March 11, 2020, the World Health Organization (WHO) declared the existence of a COVID-19 pandemic due to the high number of cases in 112 countries outside China; it was the first pandemic caused by a coronavirus. And, although the Peruvian government took several control measures, these were insufficient for the advance of the viral infection, and the health system was not prepared for these emergencies. At the time of writing this note, cases of infection and deaths continue in the world with worrying oscillations, with 200 million infected cases and 4 million deaths and, in Peru, more than 2 million cases of confirmed infection, 200 thousand deaths and 20% of the population fully vaccinated⁽³⁾. Of the positive cases during 2020 (1.091.092) and 2021 (1.035.941), 57% occurred in adults, 17% in persons aged 60 years or older, 3% in children aged 0 to 11 years, 3% in adolescents aged 12 to 17 years and 20% in young people aged 28 to 29 years; 51.4% of the cases corresponded to women. The infection curve had more peaks in the first wave and was somewhat longer in the second wave, with more confirmed cases and higher incidence in Lima (capital of Peru) and Callao (main port of Peru, close to Lima). The trend in deaths was somewhat higher in the highlands and lower in the jungle, much lower in rural areas than in urban areas, with 86.879 deaths in the first wave and 110.227 in the second wave, which seems to be giving way to the third wave⁽⁴⁾.

WHAT HAVE WE LEARNED FROM SARS-CoV-2 INFECTION?

Since China's first COVID-19 pandemic report in December 2019, we have learned that people of all ages are at risk for SARS-CoV-2 infection as well as severe disease. The probability of severe disease from COVID-19 is higher in persons aged ≥ 60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions, primarily cardiovascular disease, diabetes, chronic lung disease, cancer, kidney disease, obesity, sickle cell disease, immuno-

compromising conditions, transplant recipients and pregnant women^(5,6). Longer viral shedding time has been found in symptomatic infections, infected adults, persons with chronic diseases, and in stool samples⁽⁷⁾.

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations that can potentially increase or decrease infectiousness and virulence, as well as increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This may lead to an increased risk of reinfection or decreased efficacy of vaccines⁽⁸⁾. When a virus replicates, it can change very slightly every time. Sometimes a change does cause a virus to behave differently, for example allowing it to spread more easily. There are already thousands of variants of the coronavirus SARS-CoV-2⁽⁹⁾. At the starting of 2020, a SARS-CoV-2 mutant with a D614G mutation in the gene encoding the spike protein appeared. The D614G mutation gradually replaced the original SARS-CoV-2 strain discovered in China and has become the dominant type of the virus circulating worldwide⁽¹⁰⁾. There is emerging evidence that the B.1.1.7 (Alpha) variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent⁽¹¹⁾. The B.1.351 (Beta) variant that was originally identified in South Africa is now the predominant variant in that region and has spread to many other countries, including the United States. The P.1 (Gamma) variant was originally identified in Manaus, Brazil, and has now emerged in the United States. The B.1.617.2 (Delta) variant, first identified in India and designated a VoC by WHO, is also circulating in the United States, responsible for 93% of current COVID-19 cases. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 (Epsilon) variants that were originally identified in California and select Vols such as the B.1.526 (Iota) variant originally identified in New York and the B.1.617.1 (Kappa) variant first identified in India.

On 14 June 2021, a variant assigned to Pango lineage C.37, GISAID clade GR/452Q.V1, NextStrain clade 20D, was designated as a global VOI, and assigned the WHO label "Lambda". This variant is now considered as meeting the VOI working definition based upon evidence of continued emergence and suspected phenotypic implications. Lambda has been associated with sub-



stantive rates of community transmission in multiple countries, with rising prevalence over time concurrent with increased COVID-19 incidence. The earliest sequenced samples were reported from Peru in August 2020. As of 15 June 2021, over 1.730 sequences have been uploaded to GISAID from 29 countries/territories/areas in five WHO regions. Elevated prevalence has been noted particularly in South America in countries such as Chile, Peru, Ecuador, and Argentina. Authorities in Peru reported that 81% of COVID-19 cases sequenced since April 2021 were associated with Lambda. In Chile, prevalence of Lambda has increased over time, accounting for 32% of sequenced cases reported in the last months – co-circulating at similar rates to variant Gamma (33%), but outcompeting variant Alpha (4%) over the same period. Lambda carries a number of mutations in the spike protein with suspected phenotypic implications, such as a potential increased transmissibility or possible increased resistance to neutralizing antibodies⁽¹²⁾. In Peru, the dominant Lambda variant (C.37; 70%) is followed in frequency by the Gamma variant (P1; 20%), which predominates in the regions bordering Brazil, and then the Delta variant with more than 100 cases⁽¹³⁾, which seems to be advancing rapidly. Zeta, Epsilon, Iota and other variants are also present. The new Minister of Health has reported a high possibility that the third wave of the coronavirus has already started in Peru. A new Covid variant, worse than the Delta and Lambda strains, could emerge in the U.S. as deadly outbreaks are revealed. The World Health Organization is also monitoring Eta, Kappa, Iota, and Lambda –which one study found can supposedly infect the vaccinated– as hospitalizations surge amongst the unvaccinated in the US. They can evade the person's antibodies and reduce the effectiveness of the Covid vaccine, leading to breakthrough infection; but the unvaccinated remain at a deadly risk accounting for 99 percent of ICU patients. The Delta variant is affecting young people, much like the 1918 Spanish flu killing young adults⁽¹⁴⁾.

THE SYMPTOMOLOGY OF THE VIRUS IS VARYING

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among

72.314 persons with COVID-19 in China, 81% of cases were reported to be mild (no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory compromise, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (respiratory failure, septic shock, and/or multiorgan dysfunction or failure)⁽¹⁵⁾. More recently, about 70% of patients experience fever, cough, or shortness of breath, 36% have muscle aches, and 34% headaches. Other reported symptoms include, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting. COVID-19 is primarily a pulmonary disease, but also leads to cardiac, dermatologic, hematologic, hepatic, neurologic, renal, thromboembolic events. Imaging may be normal early in infection and can be abnormal in the absence of symptoms, with bilateral multifocal opacities, bilateral peripheral ground-glass opacities, and areas of consolidation developing later in the clinical course⁽¹⁶⁾.

ON MANAGEMENT OF COVID-19 CASES

The SOARS (SpO₂, Obesity, Age, Respiratory rate, Stroke history) score uses constitutive and readily assessed individual characteristics to predict the risk of COVID-19 death. Deployment of the score could potentially inform clinical triage in preadmission settings where expedient and reliable decision-making is key. Its predictive accuracy (calibration) in external cohorts was consistently higher in patients with milder disease (SOARS 0-1), the same individuals who could be identified for safe outpatient monitoring. Prediction of a non-fatal outcome in this group was accompanied by high score sensitivity (99.2%) and negative predictive value (95.9%)⁽¹⁷⁾.

After WHO concluded late last year that none of four treatments - hydroxychloroquine (originally developed for malaria), the antiviral remdesivir, interferon, or the antiretrovirals lopinavir and ritonavir - achieved significant reductions in the duration of hospitalizations, deaths from COVID-19 or the number of people requiring ventilation. It now recognizes only two treatments as effective for severe cases of COVID-19: dexamethasone and interleukin-6 antagonists. And it has initiated Solidarity trials with three new treatments against the coronavirus: the drug artesunate (produced by the pharmaceutical company Ipca, and until now used in the treatment of severe cases of malaria), imatinib



(from Novartis, used in some types of cancer) and infliximab (from Johnson & Johnson, used for rheumatoid arthritis and diseases that attack the immune system)⁽¹⁸⁾.

The NIH COVID-19 Treatment Guidelines Panel also recommends against the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP) - hydroxychloroquine, anti-SARS-CoV-2 monoclonal antibodies, hyperimmune gamma globulin, convalescent plasma, ivermectin, interferons, tenofovir with or without emtricitabine, vitamin D- except in a clinical trial. The following sections are currently under revision: anti-SARS-CoV-2 monoclonal antibodies, corticosteroids, interleukin-1 and IL-6 inhibitors, kinase inhibitors, antithrombotic therapy in patients with COVID-19⁽¹⁹⁾.

Monoclonal antibodies are one of the few approved emergency therapeutic alternatives to treat COVID-19, and it is not available worldwide. In a large observational study, Mayo Clinic researchers demonstrated that two monoclonal antibodies - bamlanivimab or the combination of casirivimab and imdevimab - given as separate infusions helped prevent hospitalizations in 3.596 high-risk, COVID-19-infected patients, provided they were given early in the COVID-19 infection cycle. These antibodies are laboratory-made proteins that mimic the immune system's ability to fight harmful pathogens⁽²⁰⁾.

The more than 4 million deaths worldwide due to SARS-CoV-2 have not only led to family destruction, increased orphanhood, greater poverty, among others, but also to demographic changes. Thus, in the USA, life expectancy has decreased by one and a half years by 2020. The COVID-19 pandemic fueled America's largest life expectancy drop in nearly eight decades, with Hispanics hit the hardest. It marks the largest one-year drop since World War II, according to new data from the Centers for Disease Control and Prevention's National Center for Health Statistics. The drop brings life expectancy to its lowest level since 2003 and is the largest since a decline of 2.9 years between 1942 and 1943⁽²¹⁾.

Finally, when it seemed that the second wave of infections was ending in countries like the U.S. and Europe, and it was thought that adults could go back to work and children could go to school and be reunited with family and friends, the

COVID cases were reported to have risen again, with a slight increase in cases in the over-60s vaccinated adults, that could be due to waning immunity⁽²²⁾.

And the conservative scenario of a probable third wave of COVID-19 in Peru this year is 2.5 million infected cases and 67.000 deaths, the worst scenario being 4 million infected cases and 115.000 deaths. This increase could extend over a period of nine months⁽²³⁾. These figures would be added to the total of 2.1 million confirmed cases and 197.000 deaths so far in Peru, with only 20% of its population vaccinated⁽²⁴⁾.

PREGNANT WOMEN AND COVID-19

The characteristics and outcomes associated with giving birth with COVID-19 over the first year of the pandemic in the US has been studied in 869.079 adult women, including 18.715 women (2.2%) with COVID-19. They underwent childbirth at 499 US medical centers between March 1, 2020, and February 28, 2021. Women with COVID-19 were more likely to have preterm birth (16.4%), with no significant increase in cesarean sections, but increased mortality, need for intubation and ventilation, and intensive care unit admission. These findings suggest that COVID-19 was associated with an increased risk of morbidity and mortality for women giving birth, as well as preterm birth⁽²⁵⁾. On the other hand, in twenty-eight studies that included 790.954 pregnant women, among which 15.524 were diagnosed with both asymptomatic and symptomatic SARS-CoV-2 infection, the odds of developing preeclampsia were significantly higher among pregnant women with SARS-CoV-2 infection than among those without SARS-CoV-2 infection (7.0% vs 4.8%; $p < 0.00001$)⁽²⁶⁾.

In Peru, up to epidemiological week 30 of 2021 there have been 320 cases of maternal death, with an average of 10.6 maternal deaths per week, with an upward curve from 2019 (302 cases in total) and 2020 (439 cases in total). 62.5% of women were aged 30 years or older (overall average 31 years)⁽²⁷⁾. Up to epidemiological week 13 of 2021, 16% of deaths were complicated with preeclampsia and 19% with obstetric hemorrhage, 64% had COVID-19 infection, and 75% died in the puerperium. The estimated maternal mortality ratio was 82.6 per 100 thousand live births in 2020, compared with 56.8 in 2019 (28).



On the other hand, one in every 100 children has lost a parent or grandparent to COVID-19 in Peru⁽²⁹⁾. In the referent National Maternal Perinatal Institute of Peru, in the first half of 2020, 43 newborns of mothers with COVID-19 were registered, 93% of them asymptomatic. The most frequent obstetric complications were premature rupture of membranes (18.6%) and preeclampsia (11.6%) and 65.1% of births were vaginal. Only one newborn had positive RT-PCR for COVID-19, and 14% of the newborns presented morbidity, such as prematurity, low birth weight, sepsis and pneumonia requiring ventilation⁽³⁰⁾. At present, efforts are being made to vaccinate pregnant women and it is recommended to plan their pregnancies.

Conflicting reports have emerged for rates of preterm births and stillbirths during the COVID-19 pandemic. Evaluation of 2.465.387 pregnancies at an Ontario, Canada hospital including 13.781 that resulted in stillbirth, the mean preterm birth rate was 7.96% compared with the 7.87% during the previous 17.5 years, with no special cause variation. The mean stillbirth rate for the cohort was 0.56%, and from January to December 2020, the stillbirth rate was 0.53%, with no special cause variation⁽³¹⁾. We have seen in Peru that the percentage of preterm births increased during the pandemic in most regions of the country.

A study found that rates and severity of postpartum depression (PPD) and anxiety symptoms among women seeking treatment for PPD have worsened in Canada during the COVID-19 pandemic. However, treatment-seeking mothers have consistently maintained good relationships with their infants⁽³²⁾.

LONG-TERM SEQUELAE POST COVID-19

Most people who become ill with coronavirus 2019 recover completely within a few weeks. But some, even those who have had mild versions of the disease, continue to have symptoms after their initial recovery. This condition is referred to as persistent COVID-19 and the conditions as post-COVID-19 syndrome or prolonged COVID-19. While it is older adults and people with many serious medical conditions who have this syndrome, young or healthy people may also have it weeks or months after infection. Common signs and symptoms that persist over time

include: fatigue, shortness of breath, cough, joint pain, chest pain, problems with memory, concentration or sleep, muscle pain or headache, palpitations, loss of smell or taste, depression or anxiety, fever, dizziness on sitting up, worsening of symptoms after physical or mental activity, among others. Although COVID-19 is known to affect mainly the lungs, it can also damage many other organs. Thus, imaging tests show damage to the cardiac muscle, even in cases with mild symptoms of COVID-19, which may increase the risk of heart failure or other cardiac complications. The type of pneumonia associated with COVID-19 can damage the alveoli, with resulting scar damage. Even in young people, it can cause strokes, seizures and Guillain-Barre syndrome. COVID-19 can also increase the risk of developing Parkinson's disease and Alzheimer's disease. Some adults and children develop a multisystem inflammatory syndrome after having COVID-19. The infection can cause blood clots to form, resulting in heart attacks and strokes, as well as affecting the lungs, legs, liver and kidneys. Not much is yet known about how COVID-19 will affect people in the long term, but it is a subject under investigation⁽³³⁾. It seems reasonable to infer that the persistence of risk for several weeks after SARS-CoV-2 infection is consistent with COVID-19 causing an increased risk of thrombo-occlusive disease, as has been reported for other respiratory infections⁽³⁴⁾.

It is of interest to recall the descriptive analysis of 1.959.982 COVID-19 patients with no control group, conducted by FAIR Health, Inc. using longitudinal data from their computer database of over 34 billion private healthcare claims records from 2002 to the present. Of patients who had COVID-19, 23.2 percent had at least one post-COVID condition 30 days or more after their initial diagnosis with COVID-19, to a greater extent in patients who had more severe infection; 19 percent were asymptomatic. The five most common post-COVID conditions across all ages were pain, breathing difficulties, hyperlipidemia, malaise and fatigue, and hypertension. The conditions varied by age group, and most were associated with females than males. By age, the largest share (25.4 percent) with this condition was found in individuals aged 19-29. Of the four mental health conditions evaluated as post-COVID conditions, anxiety was associated with the highest percentage in all age groups. Depression was second, adjustment disorders third and tic



disorders fourth. The odds of death 30 days or more after initial diagnosis with COVID-19 were 46 times higher for patients who were hospitalized with COVID-19 and discharged than patients who had not been hospitalized. Of COVID-19 patients who were hospitalized and discharged, 0.5 percent died 30 days or more after their initial diagnosis. Among COVID-19 patients with pre-existing conditions, intellectual disabilities were associated with the highest odds of death 30 days or more after initial COVID-19 diagnosis⁽³⁵⁾.

An online survey from September 6, 2020 to November 25, 2020, included 3.762 participants with confirmed (diagnostic/antibody positive; 1.020) or suspected (diagnostic/antibody negative or untested; 2.742) COVID-19, from 56 countries, with illness lasting over 28 days and onset prior to June 2020. For >91%, the time to recovery exceeded 35 weeks. During their illness, participants experienced an average of 55.9+/- 25.5 (mean+/-STD) symptoms, across an average of 9.1 organ systems. The most frequent symptoms after month 6 were fatigue, post-exertional malaise, and cognitive dysfunction. 85.9% of participants experienced relapses, primarily triggered by exercise, physical or mental activity, and stress. Cognitive dysfunction or memory issues were common across all age groups (~88%). Except for loss of smell and taste, the prevalence and trajectory of all symptoms were similar between groups with confirmed and suspected COVID-19. By seven months, many patients have not yet recovered (mainly from systemic and neurological/cognitive symptoms), have not returned to previous levels of work, and continue to experience significant symptom burden⁽³⁶⁾.

Several new studies presented at the Alzheimer's Association International Conference have found that many COVID-19 patients experience "brain fog" and other cognitive impairments months after recovery. This adds to a growing body of research on COVID-19's apparent long-haul symptoms, which can include confusion, forgetfulness and other worrying signs of memory loss. Researchers at the University of Texas Health Science Center studied the cognition and olfactory senses of 300 older adult Amerindians from Argentina who contracted COVID and found that 50% had persistent problems with forgetfulness and 25% had additional problems with language and executive dysfunction. Damage to the blood-brain barrier caused by inflam-

mation can result in the brain's inability to send messages from the brain to other parts of the body. The poorer memory and thinking scores were associated with lower level of oxygen saturation during a short walk test⁽³⁷⁾.

The Clinical Guideline for the care of the Long COVID/persistent COVID patient, elaborated and agreed upon by the 48 scientific societies and patient associations most involved in the care of this pathology, summarizes the collaborative project coordinated by the Spanish Society of General and Family Physicians (SEMG) and the LONG COVID ACTS patient groups. It addresses the care of individuals, at least 10% of those affected by acute infection, who present signs and symptoms that are maintained for more than 4 to 12 weeks after infection and are not explained by an alternative diagnosis. The profile of the affected patient is female (almost 80% of cases), aged between 43 and 46 years, with average persistence of symptoms greater than 90 days and with an average of 6 to 9 affected systems or organs. Different approaches are presented, some aimed at etiological treatment (antivirals, monoclonal antibodies, anti-inflammatory drugs, patient plasma), others to replace nutritional deficits (vitamin D, B complex, folic acid, omega-3) and others local and symptomatic (physiotherapy, rehabilitation, speech therapy, psychological intervention and exercise), in addition to vaccination against coronavirus⁽³⁸⁾.

In another study, 81.337 participants with self-report of suspected and confirmed COVID-19 infection and respiratory symptoms undertook a clinically validated web-optimized assessment as part of the Great British Intelligence Test. People who had recovered from COVID-19, including those no longer reporting symptoms, exhibited significant cognitive deficits versus controls when controlling for age, gender, education level, income, racial-ethnic group, pre-existing medical disorders, tiredness, depression and anxiety⁽³⁹⁾. Their score fell "greater than the average 10-year decline in global performance between the ages of 20 to 70", and more than in people who had suffered a stroke.

A clinical problem arising from mechanical ventilation in the intensive care unit in severe cases of COVID-19, is tracheal stenosis resulting from intubation for a long period; this occurs in 20% of patients. It presents with the sensation of



shortness of breath, coughing and stridor accompanying breathing. CT scan of the trachea, neck and thorax can confirm the diagnosis of the narrowed tracheal area, being necessary to perform tracheoplasty in these cases⁽⁴⁰⁾.

VACCINES – CLINICAL OVERVIEW

Currently, no SARS-CoV-2 vaccine has been approved by the Food and Drug Administration (FDA). In December 2020, the FDA issued Emergency Use Authorizations (EUAs) for two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). In February 2021, the FDA issued an EUA for a human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen). BNT162b2 can be administered to individuals aged ≥ 12 years, whereas mRNA-1273 and Ad26.COV2.S can be given to individuals aged ≥ 18 years. Clinical trials for these vaccines in younger age groups and clinical trials for other SARS-CoV-2 vaccine candidates are currently ongoing⁽⁴¹⁾.

After one dose the Pfizer vaccine is 36 per cent effective against symptomatic illness from the Delta variant, and the Oxford/AstraZeneca vaccine is about 30 per cent effective against getting ill. Two weeks after the second jab, Pfizer gives 88 per cent protection against catching the Covid strain and AZ gives 67 per cent protection. And after two doses, the Pfizer vaccine is 96 per cent effective against hospitalization and the AstraZeneca jab slashes the risk by 92 per cent⁽⁴²⁾.

The B.1.617.2 (Delta) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has contributed to a surge in cases in India and has now been detected across the globe. The effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant has been unclear. Only modest differences in vaccine effectiveness have been noted with the Delta variant as compared with the Alpha variant after the receipt of two vaccine doses. Absolute differences in vaccine effectiveness were more marked after the receipt of the first dose. This finding would support efforts to maximize vaccine uptake with two doses among vulnerable populations⁽⁴³⁾.

Among 1.497 fully vaccinated health care workers with Pfizer BNT162b2 messenger RNA vaccine, for whom RT-PCR data were available, 39

SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls. Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur⁽⁴⁴⁾.

A countrywide mass vaccination campaign with the use of an inactivated severe acute respiratory syndrome coronavirus 2 vaccine (CoronaVac-Sinovac) was conducted in Chile starting on February 2, 2021 through May 1, 2021; the cohort included approximately 10.2 million persons. The adjusted vaccine effectiveness was 65.9% for the prevention of Covid-19 and 87.5% for the prevention of hospitalization, 90.3% for the prevention of ICU admission, and 86.3% for the prevention of Covid-19-related death⁽⁴⁵⁾.

Efficacy of the COVID-19 Vaccine BIBP, also known as Inactivated COVID-19 (VERO CELL) was estimated to be 78% in adults 18-59 years of age. The vaccine was shown to be immunogenic and no safety concerns have been identified in clinical studies. The evidence to support the COVID-19 Vaccine BIBP comes from a phase 3 study (COVIV02), conducted in the United Arab Emirates (UAE), Bahrain, Egypt, and Jordan, involving 45.000 participants 18 years of age and above. Two other phase 3 studies are also ongoing, but no results are said to be available. These are double-blind, randomized, placebo-controlled-trials conducted in Peru (COVIV03) and Argentina (COVIV04) in, respectively, 6.000 and 3.000 participants from 18 years of age⁽⁴⁶⁾.

Sputnik V -also known as Gam-COVID-Vac- is an adenovirus vaccine, which means that it uses an engineered adenovirus -a family of viruses that generally cause only mild illness- as a delivery mechanism for inserting the genetic code for the SARS-CoV-2 spike protein into human cells. It is similar to the Oxford-AstraZeneca and Johnson & Johnson vaccines. It was the first COVID-19 vaccine to be registered for use in any nation, and it has since been approved in 67 countries, including Brazil, Hungary, India and the Philippines. But the vaccine has yet to receive approval for emergency use from the European Medicines Agency (EMA) or the World Health Organization (WHO). Mounting evidence suggests Sputnik COVID vac-



cine is safe and effective. It is 91.6% effective at preventing symptomatic COVID-19 infection and 100% effective at preventing severe infection. Several countries, including South Korea, Argentina and India, are already manufacturing Sputnik V. Studies so far suggest that they are similar to those of the other adenovirus vaccines, with the notable exception of rare blood-clotting conditions⁽⁴⁷⁾. Sputnik V is more effective against the Delta variant of the coronavirus than Pfizer and Moderna, according to its manufacturers, the Gamaleya laboratory. They claim that the Russian vaccine is 83.1% effective against this variant of coronavirus (reduction x6) and 94.4% effective against hospitalizations (reduction x18). This is higher than the estimated effectiveness of Moderna (76%) or Pfizer (42%)⁽⁴⁸⁾.

Rare serious adverse events have been reported after COVID-19 vaccination, including Guillain-Barré syndrome (GBS) and thrombosis with thrombocytopenia syndrome (TTS) after Janssen COVID-19 vaccination and myocarditis after mRNA (Pfizer-BioNTech and Moderna) COVID-19 vaccination. On July 22, 2021, the Advisory Committee on Immunization Practices reviewed updated benefit-risk analyses after Janssen and mRNA COVID-19 vaccination and concluded that the benefits outweigh the risks for rare serious adverse events after COVID-19 vaccination⁽⁴⁹⁾.

The sanitary measures imposed in each country or state differ in relation to the need to be vaccinated against COVID-19, limiting in some cases the accreditation of having been vaccinated with the drugs approved in a certain region, and in others without exempting the tourist from tests to rule out the coronavirus. In the United States at the moment, it is not a requirement to be vaccinated to travel, but to enter that country it is necessary to present a PCR or antigen test with negative result. Canada announced that since August those vaccinated in the United States with Pfizer, Moderna, Johnson & Johnson / Janssen and AstraZeneca drugs can enter the country. The European Medicines Agency (EMA) has certified vaccines manufactured by four laboratories, namely Pfizer / BioNTech, Moderna, Johnson & Johnson / Janssen and Oxford / AstraZeneca. In Peru, the health authorities have approved the use of drugs developed by Pfizer, AstraZeneca and Sinopharm - Beijing. Most countries consider vaccination to be valid 14 or 21 days after the last dose has been received⁽⁵⁰⁾.

The latest Kaiser Family Foundation (KFF) Vaccine Monitor finds the share of adults who say they have either received a COVID-19 vaccine (67%) or say they will get vaccinated as soon as they can (3%) is relatively unchanged from June. The poll, conducted July 15-27th, may not capture any recent uptick in vaccinations after the most recent data from the CDC citing the increased risk of the Delta variant to both unvaccinated and vaccinated people. The gender gap in vaccine uptake that emerged last month is still present with women still eight percentage points more likely to report being vaccinated than men (71% vs. 63%), and a larger share of men saying they will “definitely not” get the vaccine (18% vs. 10%)⁽⁵¹⁾.

WHAT'S PROMPTING ALL THE BOOSTER DEBATE?

U.S. health officials say that people one day might need a booster - simple third doses, mix-and-match tests using a different brand for a third dose, or experimental boosters tweaked to better match different variants. Pfizer and its German partner BioNTech announced that in August, they plan to seek FDA authorization of a third dose because it could boost levels of virus-fighting antibodies, possibly helping ward off worrisome mutants. The World Health Organization said there is not enough evidence to show that third doses are needed. It said the scarce shots should be shared with poor countries instead of being used by rich countries as boosters⁽⁵²⁾. Germany and the United Kingdom will administer third doses starting in September, as agreed by their respective governments, following Israel's third dose strategy, which inoculates people over 60 years of age and those with immunosuppression, in view of the advance of the Delta variant. The Delta variant makes up around 99 per cent cases found in Britain with a recent rise of 34 per cent. And whilst the vaccines offer excellent protection, they do not offer 100 per cent protection. Laboratory analysis also found a single dose of either the Pfizer or AstraZeneca vaccines provided just 10 per cent protection against the mutation which originated in India. The Delta variant is four times more likely to overcome protective antibodies from a previous infection compared to the UK's Alpha variant⁽⁵³⁾. Israel, USA and Chile have authorized the administration of the third dose of vaccines, Chile with the AstraZeneca vaccine. And Uruguay, which admirably vaccinated its population with Sinovac, will administer a third dose with



Pfizer vaccine, despite the fact that almost 7 out of 10 people have the two doses of vaccine and 10% of its inhabitants achieved immunity through natural infection⁽⁵⁴⁾. The Peruvian Medical Association has requested the government to consider the application of the third dose due to the risks involved in their medical care.

The Federal Drug Administration does not recommend antibody testing for vaccinated people, because it is not clear what level of antibodies is protective enough and because different tests yield different results. The Centers for Disease Control and Prevention reported more than 13.7 million people had received the Johnson & Johnson jab, and about 1% of them got additional shots for protection⁽⁵⁵⁾.

VACCINATION OF PREGNANT AND LACTATING WOMEN - PERU

Pregnant and lactating individuals were not included in the initial vaccine trials. A study that used data from three vaccine safety reporting systems in the United States reported that the frequency of adverse events among 35,691 vaccine recipients who identified as pregnant was similar to the frequency observed among non-pregnant patients⁽⁵⁶⁾. Developing a treatment plan should involve shared decision-making between the patient and the clinical team, with considerations based on the severity of maternal disease and the safety of the medication for the pregnant individual and the fetus. Breast-feeding in the setting of COVID-19 is not contraindicated, and decision-making surrounding feeding breast milk while the patient is receiving therapeutic agents for COVID-19 is addressed⁽⁵⁷⁾.

The U.S. Centers for Disease Control and Prevention recommends pregnant women be vaccinated against COVID-19, based on a new analysis that did not show increase risk for miscarriages⁽⁵⁸⁾. The American College of Obstetricians and Gynecologists and the Peruvian Society of Obstetricians and Gynecologists recommend that all eligible persons, including pregnant, lactating and recently pregnant individuals, receive a COVID-19 vaccine or vaccine series. The increased risk of severe illness for pregnant and recently pregnant people highlights the critical importance of vaccination for family members and clinicians caring for these individuals⁽⁵⁹⁾.

PROBLEMS ENCOUNTERED

The SARS-CoV-2 pandemic in India has adversely affected many aspects of population health. There was a significant decrease in hospital births per month during the pandemic period with a 4.8% decrease per 10% increase in the Government Response Stringency Index scores ($p < 0.001$). Hospital admissions from septic abortion was 56% higher (RR=1.56), the overall case-fatality of complications increased by 23% (RR=1.23, $p = 0.022$) and remained high across the different phases of the pandemic with a notable significant increase in deaths from heart failure in pregnancy. This study supports the legitimacy of the calls made to maintain sexual and reproductive health services as essential services during the pandemic⁽⁶⁰⁾.

The conclusion of a study to determine the differences in attitudes towards vaccination against covid-19 in a Peruvian sample, there was a higher percentage of acceptance by adult males with a higher university education level, mainly health professionals, educators and higher education students⁽⁶¹⁾.

And according to COVID-19 vaccinations per country, in US 55% of population is vaccinated and would need 132 days until 70% of the population is vaccinated against COVID-19; in Peru 25% of population is vaccinated and would need 269 days (nine months) until 70% of the population is vaccinated against COVID-19; Colombia has 31% of population vaccinated and would need 181 days until 70% of the population is vaccinated; Chile figures with 71% of population vaccinated⁽⁶²⁾, an example to be followed.

BY WAY OF COLOPHON

Every day we receive disturbing news about the virus' ability to modify itself to improve its invasion and infectivity in humans, being this a limitation for its timely follow-up and to obtain signs of a near and favorable end. Variations in the structure of the virus have had repercussions on the clinical presentation of the infection, with greater ease and expansion of contagion, but now fewer severe cases and deaths, which seems to have been influenced by the protective behavior of a segment of the population and by the vaccines applied worldwide at different speeds. On



the clinical side, the infected person is sought early in order to apply the management still in its perfection to alleviate their discomfort and reduce the severity of the infection, hospitalization, intensive care and death.

The form of presentation in symptomatic persons has been varying, as well as the ages of affectation, now also involving children, but always more frequently older adult and persons with comorbidities and immunocompromised. It is of concern that many asymptomatic patients already have organ involvement, and it is terrible to know the increasing cases of prolonged covid, i.e., post-infection sequelae that are disabling an increasing number of apparently recovered persons. We still do not know the degree and duration of immunity given by the disease and by the vaccine, but we remain hopeful that the vaccines will provide true protection against covid and the new viral variants for a prolonged period of time, so that we will move towards a new normality that reunites the family and allow the return to work, school and recreation, improving the quality of life, health and economy.

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