SPECIAL PAPER

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

Financing: The author did not receive specific financing for this paper

Conflict of interest: The author declares there is no conflic tfo interest

Received: 5 March 2022

Accepted: 11 March 2022

Online publication: 29 March 2022

Corresponding author:
José Pacheco-Romero
jpachecoperu@yahoo.com

Cite as: Pacheco-Romero J. The coronavirus conundrum - Countries better prepared to face the pandemic - The Omicron variant and mutations - New vaccines? - The pregnant woman, the placenta, the fetus and the neonate. Rev Peru Ginecol Obstet. 2022;68(1). DOI: 10.31403/rpgo.v68i2388

The coronavirus conundrum - Countries better prepared to face the pandemic - The Omicron variant and mutations - New vaccines? - The pregnant woman, the placenta, the fetus and the neonate

El enigma del coronavirus – Países mejor preparados para enfrentar la pandemia - La variante ómicron y mutaciones – ¿Nuevas vacunas? - La gestante, la placenta, el feto y neonato

José Pacheco-Romero[1, MD, PhD, MSc, FACOG]

DOI: 10.31403/rpgo.v68i2388

ABSTRACT

Several western countries have initiated the return to pre-pandemic life with the reduction in the number of severe infections and deaths despite of the high infectivity of the Omicron B2 variant. This is occurring amid complaints from the population tired of the restrictions due to COVID-19, the consequent economic and labor problems and with an antivaccine sector with an important presence. SARS-CoV-2 will not disappear, new variants will emerge, and it will be necessary to be alert to its threats and design new vaccines. However, human beings are learning the measures to prevent infection, the importance of self-protection and of the family, and the surveillance of the virus. Imperfect vaccines have been developed that require boosters at relatively short intervals. However, many countries are not yet prepared to face the pandemic - now endemic - due to overconfidence in the eventual disappearance of the virus, lack of human and economic resources for better health care, and corruption. Women are more sensitive to viral infection and is getting vaccinated to avoid serious infection and death. Evidence finds that pregnant women with COVID-19 suffer more miscarriages, preterm deliveries, and intrauterine and perinatal death. The placenta is the unit most compromised in its defense of the fetus. The resulting placentitis causes placental insufficiency and fetal hypoxic-ischemic injury. Newborns are protected by the passage of maternal antibodies, with a longer duration of those originated by vaccines. Much remains to be known about the future of SARS-CoV-2 infection. But a complex and shocking problem resulting from the infection is already a reality – the prolongation of multi-organ damage, even with mild disease, mainly in the cardiovascular, pulmonary, and cerebral systems, as well as the alteration of mental health and shortening of life.

Key words: Coronavirus SARS-Cov-2, COVID-19, Pandemic, Endemic, Long-COVID, Gestation, Peru.

RESUMEN

Varios países occidentales han iniciado la vuelta a la vida prepandemia al disminuir el número de infectados severos y muertes a pesar de la gran infectividad de la variante ómicron B2. Esto ocurre en medio de reclamos de la población cansada de las restricciones por el COVID-19, los problemas económicos y laborales consecuentes y con un sector antivacuna con importante presencia. El SARS-CoV-2 no desaparecerá, se presentarán nuevas variantes y se deberá estar alerta a sus amenazas y diseñar nuevas vacunas. Sin embargo, el ser humano está aprendiendo las medidas para no infectarse, la importancia de la autoprotección y de la familia, y la vigilancia del virus. Se ha logrado vacunas aún imperfectas que requieren refuerzos en intervalos relativamente cortos. Pero, muchos países no están aún preparados para enfrentar la pandemia -ahora endemia-, por demasiada confianza a una eventual desaparición del virus, la falta de recursos humanos y económicos para una mejor atención en salud, corrupción. La mujer es más sensible a la infección viral y se está haciendo vacunar para evitar la infección grave y muerte. La evidencia encuentra que la gestante con COVID-19 sufre más abortos, partos pretérmino y muerte intrauterina y perinatal. La placenta es la unidad más comprometida en su defensa al feto. La placentitis resultante causa insuficiencia placentaria y lesión hipóxico-isquémica fetal. Los recién nacidos tienen protección dada por el pasaje de anticuerpos maternos, con mayor duración los originados por las vacunas. Aún queda mucho por conocer sobre el futuro de la infección por SARS-CoV-2. Pero ya es realidad

un problema complejo e impactante producto de la infección - la prolongación de los daños multiorgánicos ocurridos, aún con enfermedad leve, principalmente en los sistemas cardiovascular, pulmonar y cerebral, así como la alteración de la salud mental y el acortamiento de la vida.
Palabras clave. Coronavirus SARS-Cov-2, COVID-19, Pandemia, Endemia, COVID prolongado, Gestante, Perú.

In recent weeks, the number of new coronavirus cases and deaths has continued to decline worldwide, with only the Western Pacific showing an increase. This may be due to more people having antibodies provided by vaccines and by the viral infection itself. According to estimates from blood tests that reveal antibodies from coronavirus infection, the U.S. Centers for Disease Control and Prevention (CDC) consider more than 140M Americans (about 43 percent of the country) have had coronavirus. The blood tests count only antibodies from natural infection, including asymptomatic. Antibodies to the virus was lower in older age groups, with children having a seroprevalence of about 58 percent compared to 23 percent for those over the age of 65[1].

In the United Kingdom, Primer Minister Boris Johnson has hailed the British people for pulling through two of the "darkest years" since the Second World War as he brought the curtain down on the age of COVID lockdown laws. But he also axed all remaining rules and said it was too soon to declare victory over COVID just yet as more variants loom[2]. Although this process is occurring with much expectation in the Nordic countries, we should consider that we are not entering the same "normality" that we left when the new coronavirus started COVID-19. Many have even lost entire families and suffer chronic grief over the loss of loved ones, and others have developed post-traumatic stress disorder due to experiences with the disease. Many people are tired of the virus and protest the restrictions that still exist, driving the governments' decision to lift the restrictions and return to "normalcy". In addition, many people have developed resilience.

Which countries are best prepared to deal with the pandemic?

National rates of COVID-19 infection and fatality have varied dramatically since the onset of the pandemic. The factors that explained the greatest variation in COVID-19 infection and fatality rates (IFR) in 177 countries over the same period were the age profile of the country (46·7% of variation), gross domestic product-GDP per capita (3·1% of variation), and national mean body mass index (BMI) (1·1% of variation). 44·4% (29·2–61·7) of cross-national variation in IFR could not be explained. Measures of trust in the government and interpersonal trust, as well as less government corruption, had larger, statistically significant associations with lower standardized infection rates and with higher COVID-19 vaccine coverage. If all countries had a national BMI equal to or less than that of the 25th percentile, standardized IFR would be reduced by 11·1%. Increasing health promotion for key modifiable risks is associated with a reduction of fatalities[3].

Strong protections against this coronavirus over the past two years have occurred through the tests, vaccine rollouts, new treatments, and the best scientific understanding of what this virus can do. An active epidemiological surveillance program in specific geographical areas consists of education about the virus, an intense genomic surveillance plan of the virus in the community - including a permanent study of sewage systems -, strengthening of the vaccination program, judicious use of masks and diagnostic tests, preparation of the health system to react to eventualities, rapid use of available drugs against infection, monitoring of the number of cases, hospitalizations, admissions to the ICU and deaths.

However, the return to pre-pandemic "normality" is resulting in a lack of protection for vulnerable people, such as those with comorbidity, the immunocompromised, those with cancer, among others. For at least 7 million immunocompromised people in the United States—a number that's already larger than the populations of 36 states-, the end of public-health protections means their lives are further curtailed. That number does not include the millions more who have diseases that also hamper immunity, such as AIDS and at least 450 genetic disorders. Close to 3 percent of U.S. adults take immunosuppressive drugs, either to treat cancers or autoimmune disorders or to avoid rejecting transplanted organs or stem cells. Should they get infected, their risk of hospitalization is higher, and their risk of death is one in ten. Flexible work policies, availability of testing and treatment, and paid leave will change. And perhaps worst

of all, immunocompromised people are beginning to be dismissed outright by their friends, relatives, and colleagues[4].

In a population-based study involving 358,487 adult patients with cancer in 2020, in Ontario, Canada, at the start of the pandemic, there was an immediate 34.3% decline in the estimated mean cancer detection volume for melanoma and cervical, endocrinologic, and prostate cancers. Incidence rates have not yet returned to prepandemic levels[5]. The same is happening with sexual and reproductive health prevention measures and access to contraception.

Types of SARS-CoV-2 tests

Three types of COVID-19 test continue to have a crucial role in the transition from pandemic response to pandemic control. Molecular tests such as PCR are highly sensitive and specific at detecting viral RNA, for confirming diagnosis in symptomatic individuals and for activating public health measures. Antigen rapid detection tests detect viral proteins and, although less sensitive than molecular tests, they are easier and faster to do, are lower in cost, and detect infection in those at risk of transmitting the virus to others. As such, antigen rapid detection tests can be used for screening individuals at enhanced risk of infection, to protect people who are clinically vulnerable, to ensure safe travel and the resumption of schooling and social activities, and to enable economic recovery. With vaccine roll-out, antibody tests (which detect the host's response to infection or vaccination) can be useful surveillance tools to inform public policy but should not be used to provide proof of immunity, as the correlates of protection remain unclear[6].

Omicron variant and properties

The Omicron variant is a variant of SARS-CoV-2, which causes the disease COVID-19. Present during the last months, Omicron's altered entry pathway leads to more rapid replication in the nasal epithelium, but less in the lower segments (lung). Previous SARS-CoV-2 isolates and variants, such as Delta, only enter cells efficiently by binding ACE2 and activating fusion via cell-surface protease TMPRSS2. This allows them to enter at the cell surface and bypass the endosome, where potent restriction factors are enriched. Omicron, conversely, is able to enter cells in both a TMPRSS2-dependent and -independent manner, having evolved the ability to avoid endosomal restriction. Hospitalization rates appear to be lower (50% to 80% lower), and cellular immunity (CD4+ and CD8+ T lymphocytes) would be preserved after vaccination, allowing it to cope with severe disease[7].

And a new strain of Covid dubbed "Omicron's sister" spreads 33 per cent faster, but it is no more severe. The sub-lineage is known as BA.2. Initial studies from Denmark, where the sub-variant has spread quickly and makes up half of all Omicron cases, shows no difference in hospitalization risk. BA.2 is missing a key mutation that allows labs to discover and then flag up cases, which could make it harder to track[8]. It also possesses immune-evasive properties that further reduce the protective effect of vaccination against infection. But both booster-vaccinated and fully vaccinated individuals are less like to get infected and transmit either subvariants[9]. Few people contracted BA.2 after infection with BA,1, indicating vaccination does give some protection.

The emergence of new variants with varying degrees of immune evasion is just a matter of time. Scientists are seeking to find out when the next variant of concern will emerge, whether it will cause severe disease and how it will cope against our arsenal of vaccines[10,11].

Genetic risk factors for severe COVID

Several genetic variants are associated with an increased risk of developing severe COVID-19 requiring critical care or hospitalization. A study used whole genome sequencing in 7,491 critically ill cases compared with 48,400 controls to discover and replicate 23 independent variants that significantly predispose to critical Covid-19. They identified 16 new independent associations, including variants within genes involved in interferon signaling (*IL10RB, PLSCR1*), leucocyte differentiation (*BCL11A*), and blood type antigen secretor status (*FUT2*). There was evidence implicating multiple genes, including reduced expression of a membrane flippase (*ATP11A*), and increased mucin expression (*MUC1*), in critical disease. Mendelian randomization provided evidence in support of causal roles for myeloid cell adhesion molecules (SELE, ICAM5, CD209)

and coagulation factor F8, all of which are potentially druggable targets. At least two distinct mechanisms can predispose to life-threatening disease: failure to control viral replication, or an enhanced tendency towards pulmonary inflammation and intravascular coagulation[12].

Reinfections with COVID-19

Recent evidence suggests that "natural" COVID-19 protection depends on many factors, including when the infection happened, the variant involved, whether someone has been boosted or not, and the overall strength of their immune system[13].

Natural infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) elicits strong protection against reinfection with the B.1.1.7 (Alpha), B.1.351 (Beta), and B.1.617.2 (Delta) variants. However, the B.1.1.529 (Omicron) variant harbors multiple mutations that can mediate immune evasion. The effectiveness of previous infection in preventing reinfection was estimated to be 90.2% against the Alpha variant, 85.7% against the Beta variant, 92.0% against the Delta variant, and 56.0% against the Omicron variant. The effectiveness with respect to severe, critical, or fatal Covid-19 was estimated to be 69.4% against the Alpha variant, 88.0% against the Beta variant, 100% against the Delta variant, and 87.8% against the Omicron variant[14].

Vaccination - Effectiveness and duration – Breakthrough infections

Vaccination has been associated with a smaller reduction in transmission of the Delta variant than of the Alpha variant, and the effects of vaccination decreased over time (by 12 weeks in index patients who had received ChAdOx1 nCoV-19 and attenuating substantially in those who had received BNT162b2). PCR Ct values at diagnosis of the index patient only partially explained decreased transmission[15].

Vaccine effectiveness against COVID-19 beyond 6 months remains incompletely understood. A study investigated the effectiveness of COVID-19 vaccination against the risk of infection, hospitalization, and death during the first 9 months after vaccination for the total population of Sweden. The cohort comprised all individuals vaccinated with two doses of ChAdOx1 nCoV-19, mRNA-1273, or BNT162b2, and matched unvaccinated individuals, until October 4, 2021. For the outcome SARS-CoV-2 infection of any severity, the vaccine effectiveness of BNT162b2 waned progressively over time, from 92% at 15–30 days to 59% from day 181 onwards. Waning was also slightly slower for heterologous ChAdOx1 nCoV-19 plus an mRNA vaccine. With respect to severe COVID-19, vaccine effectiveness seemed to be better maintained, although some waning became evident after 4 months[16].

Estimates of COVID-19 mRNA vaccine effectiveness have declined because of waning vaccine induced immunity over time, possible increased immune evasion by SARS-CoV-2 variants or a combination of these and other factors. CDC recommends that all persons aged ≥12 years receive a third dose (booster) of an mRNA vaccine ≥5 months after receipt of the second mRNA vaccine dose and that immunocompromised individuals receive a third primary dose. All unvaccinated persons should get vaccinated as soon as possible and should receive a third dose when eligible[17].

We are aware that the newly emerged B.1.1.159 (Omicron) variant of severe acute respiratory syndrome coronavirus 2 has many changes[32] in its spike protein relative to that of the original virus (Wuhan-hu-1), particularly in the receptor-binding domain and the N-terminal domain, the primary targets of neutralizing antibodies. Although findings indicate that the Omicron variant shows an unprecedented degree of neutralizing antibody escape, they also suggest that boosting and promoting affinity maturation of antibodies in persons who have previously been infected or vaccinated, with the use of existing Wuhan-hu-1–based vaccine immunogens, will provide additional protection against infection with the Omicron variant and subsequent disease[18].

Many persons remain unvaccinated. A study used weekly publicly available CDC data from 26 U.S. jurisdictions, which include COVID-19 death rates by age and vaccination status, to estimate the number of excess deaths that might have been averted by vaccination from May 30 to December 4, 2021, among unvaccinated persons > 18 years old. There were an estimated 83,400 excess deaths among the unvaccinated

populations, the largest number in people aged 65–79 years old (34.7%), followed by those 50-64 years old (31.1%). Extrapolated to the U.S. population, the researchers estimated approximately 135,000 excess deaths during the study period in persons >18 years old[19].

In a cross-sectional assessment of 816 unvaccinated healthy adults (mean age, 48) recruited on social media, researchers assessed antibody status arising from SARS-CoV-2 infection rather than from vaccination. Although evidence of natural immunity in unvaccinated healthy U.S. adults up to 20 months after confirmed COVID-19 infection is encouraging, it is unclear how these antibody levels correlate with protection against future SARS-CoV-2 infections, particularly with emerging variants. In addition, the results suggest that many patients who say "I know I had COVID" — but without a confirmed diagnosis — weren't infected with SARS-CoV-2[20].

A study evaluated COVID-19 incidence and death rates among unvaccinated and fully vaccinated adults with and without booster doses during periods of Delta and Omicron variant emergence. The highest impact of booster doses against infection and death compared with full vaccination without booster doses was recorded among persons aged 50-64 and ≥65 years. Eligible persons should stay up to date with COVID-19 vaccinations[21]. In Peru, so far only 38% of the population > 12 years of age has been vaccinated with the three doses and 40% of children have been vaccinated. It is estimated that 80% of deaths due to COVID-19 have been among older adults; most of them had only received two doses[22].

Researchers consider SARS-CoV-2 is specializing by increasing the affinity of the spike protein to its receptor, angiotensin-converting enzyme 2 (ACE2). In addition to increases in infectivity and transmission, another important consequence is neutralizing antibodies; serum samples have reduced capability to block spike–ACE2 binding because they are outcompeted by the increasing affinity of the virus for ACE2, providing an "affinity escape" in contrast with a serotype escape. Consequently, vaccines should be optimized not only by considering antigenic variation but also by increasing the affinity of antibody responses[23].

Frequency of SARS-CoV-2 breakthrough infections in fully vaccinated individuals

The frequency of SARS-CoV-2 breakthrough infections in fully vaccinated individuals increased with the emergence of the Delta variant, particularly with longer time from vaccine completion. However, whether breakthrough infections lead to onward transmission remains unclear. In a study involving 125 patients comprised of 72 vaccinated and 53 unvaccinated individuals, to assess the levels of infectious virus in vaccinated and unvaccinated individuals, protection from culturable infectious virus waned significantly starting at 5 months after completing a 2-dose regimen of mRNA vaccines[7].

In short, vaccines are not 100% effective in preventing infection, so some of the fully vaccinated people will be infected by COVID-19 anyway.

Treatment for COVID-19 infection

Remdesivir, from Gilead Laboratories, was the first drug against Covid-19 approved by the U.S. FDA for emergency use in July 2020. This molecule inhibits viral replication in cultures. It is currently only used within 7 days of symptom onset in COVID-19 patients with low-flow oxygen requirements. Appears to be effective against the Omicron variant[24].

Molnupiravir is a small-molecule oral antiviral product that is active against severe acute respiratory syndrome coronavirus 2. In a randomized study with 1,433 participants, early treatment with molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19[25]. Molnupiravir, from Merck Laboratories, is also effective *in vitro* against the Omicron variant.

Pfizer Laboratories' Paxlovid, protease inhibitor PF-07321332, administered with ritonavir, reduces the risk of hospitalization and death by 89% when used within three days of symptom onset. The Paxlovid pill is authorized for emergency use in children 12 years of age and older and there are no oral antiviral treatments for younger children.

Monoclonal antibodies (MCAs) are immunoglobulins that specifically target the virus's spicule protein, attach to, and block the binding of SARS-CoV-2 to cellular receptors. Regdanvimab and the combination of casirivimab and imdevimab received European Medicines Agency (EMA) approval; they show reduced 28-day mortality, reduced progression to mechanical ventilation and reduced hospitalization to a median of 4 days. Sotrovimab should be effective against the Omicron variant. Tocilizumab is an MCA against the interleukin-6 receptor (IL-6R) that has shown earlier cessation of ventilatory support and reduced mortality in COVID-19 patients, especially with low-flow and high-flow oxygen therapy, when administered 1 to 2 days after hospital admission. Similar results have been obtained with sarilumab[24]. Early laboratory data hint that sotrovimab could lose effectiveness against the rapidly spreading BA.2 variant. US regulators have given emergency approval to another MCA, bebtelovimab, that inhibits both the original Omicron strain and BA.2 in laboratory assays[26]. Recently, the Food and Drug Administration has halted the use of two COVID-19 monoclonal antibody therapies -Regeneron Pharmaceuticals [casirivimab and imdevimab] and Eli Lilly [bamlanivimab and etesevimab] - because they are ineffective against the dominant Omicron variant[27].

Unfractionated heparin has anticoagulant, antiviral and anti-inflammatory effects by neutralizing chemokines, cytokines, and others. Hospitalized patients with COVID-19 should receive antithrombotic prophylaxis with low molecular weight heparin (enoxaparin, dalteparin, tinzaparin, certoparin, nadroparin), if there are no contraindications, since arterial and venous thromboembolism are common complications of coronavirus infection. Fondaparinux is an alternative. Do not administer therapeutic anticoagulation without indication in intensive care patients.

Dexamethasone is indicated with the onset or worsening of oxygen dependence. Early use is unlikely to be beneficial; rather, it may be detrimental.

In a retrospective and non-randomised nationwide Swedish registry-based study, 14,685 women between 50 and 80 years of age were included in a study with 11,923 (81%) in the control group; 227 (2%) women in group 1 were women with previously diagnosed breast cancer and receiving endocrine therapy – 'decreased systemic estrogen levels', and 2,535 (17%) women in group 2 were women receiving hormone replacement therapy (HRT) – 'increased systemic estrogen levels'. In this study, estrogen supplementation in postmenopausal women was associated with a decreased risk of dying from COVID-19. Further randomised intervention trials are warranted[28].

Although vaccines remain the most important way to curb the pandemic, there is still a desperate need for better therapies to treat people who cannot - or choose not - access the vaccines, whose immune systems cannot respond fully to vaccination, or who experience breakthrough infections. Hundreds of COVID-19 drug trials are underway around the world, and the US National Institutes of Health (NIH) ACTIV programme has included more than 30 studies looking at possible treatments[29].

On long COVID

Having COVID-19 with a mild clinical course does not prevent the possibility of presenting long-term complications, since the disease is a systemic infection, with multiple pathways to produce short-term damage. It attacks not only the respiratory system, but also other areas, such as the brain, heart, liver, intestine, testes, and lymph nodes. In the CoVHORT study, limited to patients who did not require hospitalization, 68% prevalence of 1 or more COVID-19 symptoms was found at 30 days, which increased to 77% at 60 days. These findings are consistent with other cohorts with longer follow-up time, which found that 61% of patients who had COVID-19 continued to have symptoms up to 6 months later. Fatigue has been described in 14% to 70% of patients up to 6 months after infection and is associated with poor quality of life and activity limitation. Other implications are anosmia and parosmia, with decreased desire and ability to eat, weight gain or loss, decreased social interactions[30].

Other researchers used a U.S. Medicare Advantage insurance database to identify 88,000 older patients (age, ≥65) with COVID-19; 27% were hospitalized. One third of these patients sought medical attention for problems that either emerged during the postacute period (lat-

er than 20 days after diagnosis of COVID-19) or began during the acute period and continued into the postacute period. Compared with propensity-matched controls, the proportion of patients with late sequelae was 11% higher in the COVID-19 group overall and was 24% higher in the subgroup of hospitalized patients. Risk differences were greatest for respiratory failure (7.6%) and hypertension (4.4%); hazard ratios were highest for respiratory failure, thrombotic conditions, and encephalopathy[31]. And, in an exploratory prospective multicenter cohort study conducted in ICUs of 11 Dutch hospitals, 452 patients with COVID-19, aged 16 years and older, and alive after hospital discharge were followed up for 1 year: 74.3% reported physical symptoms, 26.2% reported mental symptoms, and 16.2% reported cognitive symptoms. The most frequently new physical problems were weakened condition (38.9%), joint stiffness (26.3%), joint pain (25.5%), muscle weakness (24.8%) and myalgia (21.3%)[32].

On the other hand, there is a long-term, substantial rise in risk of cardiovascular disease, including heart attack and stroke, after a SARS-CoV-2 infection, even in mild disease. The risk is elevated even for those who are under 65 years of age and lack risk factors, such as obesity or diabetes. Comparing more than 150,000 veterans in the U.S. Veterans Affairs (VA) healthcare system who survived for at least 30 days after contracting COVID-19 with two groups of uninfected people, people who had recovered from COVID-19 showed stark increases in 20 cardiovascular problems over the year after infection. For example, they were 52% more likely to have had a stroke than the contemporary control group[33]. In another study, the same researchers found that patients recovering from COVID-19 were at significantly elevated risk for all 28 prespecified mental health disorders (e.g., anxiety disorders, depressive disorders, stress and adjustment disorders, opioid and nonopioid substance abuse disorders, neurocognitive decline, sleep disorders). Risks for all diagnoses were elevated significantly in those who were not hospitalized for acute COVID-19 and were even higher in those who were hospitalized. Patients recovering from COVID-19 also had significantly greater risks than those recovering from seasonal influenza and those who had non–COVID-19-related hospitalizations[34].

Vaccines reduce the risk of developing COVID-19, but studies disagree on their protective effect against long COVID. Neurological rehabilitation clinics used to treat about 50 people each week with conditions such as chronic pain, Parkinson's disease, and sports injuries. After COVID, now they treat another 50–100 people each week with issues such as extreme fatigue, breathlessness, difficulty concentrating or any of the many other symptoms of long COVID. Vaccination might only halve the risk of long COVID — or have no effect on it at all. The cause of long COVID is as unclear as its definition. One possibility is that a reservoir of the coronavirus lingers after the acute infection in various tissues — such as the intestine, liver, or brain — and continues to cause damage. Another possibility is that the broad immune response triggered by the initial infection can generate antibodies and other immunological reactions against the body's own tissues. Vaccination then further reduces the risk of long COVID in those who develop a breakthrough infection by another half. In October 2021, the UK Office for National Statistics, which is collecting data on long COVID, reported that the first dose of a COVID-19 vaccine was associated with a 13% decrease in self-reported long-COVID symptoms among those who already had the condition. The second dose yielded a further 9% drop relative to the first[35].

A new report by Dr. Philip Wild, head of clinical epidemiology at the Universitätsmedizin Mainz, Mainz, Germany, and director of the Mainz Gutenberg COVID-19 study on persistent COVID-19 remains to be explored. He sees it as a challenge to discriminate whether the constellation of more than 60 symptoms associated with post-COVID-19 syndrome - such as fatigue, memory problems or sleep disturbances - has such an origin or different causes, as is evident from the fact that many patients in a cohort of more than 10,000 people in Germany have also presented some of its characteristic manifestations despite having no history of SARS-CoV-2 infection[36].

Vaccination in women undergoing assisted fertilization treatment

In a study that included a total of 400 patients undergoing IVF during January-April 2021, 200 vaccinated women and 200 age-matched unvaccinated women, COVID-19 mRNA vaccine did not

affect the ovarian response or pregnancy rates in IVF treatment. Women should be vaccinated for COVID-19 prior to attempting to conceive via IVF treatments, given the higher risk of severe illness in pregnant women[37].

The pregnant woman and COVID-19 - The placenta - The fetus and newborn

Pregnant women with COVID-19 are at increased risk of intensive care unit (ICU) admission, mechanical ventilation, and death compared with both pregnant individuals without SARS-CoV-2 infection and nonpregnant adults with COVID-19. It remains unknown whether SARS-CoV-2 infection specifically increases the risk of serious obstetric morbidity. In a retrospective cohort study of 14,104 pregnant and postpartum patients delivered between March and December 2020 at 17 US hospitals, mean age 29.7 years, 2,352 patients had SARS-CoV-2 infection (80.1% tested positive in the third trimester, 17.6% in the second trimester and 2.3% in the first trimester) and 11.752 did not. A composite outcome of maternal death or serious morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2 occurred significantly more frequently in individuals with SARS-CoV-2 infection compared with individuals without SARS-CoV-2 infection (13.4% vs 9.2%, respectively). All 5 maternal deaths were in the SARS-CoV-2 group. SARS-CoV-2 infection was not significantly associated with cesarean birth (34.7% vs 32.4%). There were 14,471 neonates (2,297 delivered by patients who were SARS-CoV-2 positive during pregnancy and 12,017 delivered by patients without SARS-CoV-2). SARS-CoV-2 exposure was significantly associated with preterm birth at less than 37 weeks' gestation and NICU admission. Most of the preterm births among patients with SARS-CoV-2 were medically indicated or not resulting from spontaneous preterm labor (58.8%). Among live births in the exposed group with a SARS-CoV-2 test (n = 1,323), 1.2% of neonates tested positive for SARS-CoV-2 before discharge[38].

Of the 994,268 obstetric patients in another US study cohort, 742,113 (74.6%) delivered prepandemic and 252,155 (25.4%) delivered during the COVID-19 pandemic. The percentage of short postpartum hospitalizations increased among all births (28.7–44.5%), vaginal births (25.4–39.5%), and cesarean births (35.3–55.1%). Although short postpartum hospitalizations were more common during the COVID-19 pandemic, there was no change in readmission in the unadjusted (1.4% vs 1.6%, standardized difference=0.009) or adjusted (aOR 1.02, 99% credible interval 0.97–1.08) analyses for all births or when stratified by mode of delivery. Short postpartum hospitalization -less than two midnights for vaginal births and less than three midnights for cesarean births was significantly more common during the COVID-19 pandemic for obstetric patients with no change in hospital readmissions within 6 weeks of postpartum hospitalization discharge. The COVID-19 pandemic created a natural experiment, suggesting shorter postpartum hospitalization may be reasonable for patients who are self-identified or health care professional–identified as appropriate for discharge[39]. This experience has been similar in Peruvian maternity hospitals.

Perinatal death is an increasingly important problem as the COVID-19 pandemic continues, but the mechanism of death has been unclear. The role of the placenta in causing stillbirth and neonatal death following maternal infection with COVID-19 and confirmed placental positivity for SARS-CoV-2 was evaluated by clinico-pathological analysis by a multinational group of 44 perinatal specialists from 12 countries. They studied placental and autopsy pathology findings from 64 stillborns and 4 neonatal deaths having placentas testing positive for SARS-CoV-2 following delivery to mothers with COVID-19. All 68 placentas had increased fibrin deposition and villous trophoblast necrosis and 66 had chronic histiocytic intervillositis, the three findings constituting SARS-CoV-2 placentitis. Sixty-three placentas had massive perivillous fibrin deposition. Severe destructive placental disease from SARS-CoV-2 placentitis averaged 77.7% tissue involvement. Other findings included multiple intervillous thrombi (37%) and chronic villitis (32%). The majority (63%) of the 30 autopsies revealed no significant fetal abnormalities except for intrauterine hypoxia and asphyxia. Among all 68 cases, SARS-CoV-2 was detected from a body specimen in 16 of 28 cases tested, most frequently from nasopharyngeal swabs. Four autopsied stillborns had SARS-CoV-2 identified in internal organs. In summary, the pathology abnormalities composing SARS-CoV-2 placentitis cause widespread and severe placental destruction resulting in placental malperfusion and insufficiency.

Intrauterine and perinatal death likely results directly from placental insufficiency and fetal hypoxic-ischemic injury. There was no evidence that SARS-CoV-2 involvement of the fetus had a role in causing these deaths[40].

Vaccination of the pregnant woman

COVID-19 vaccination in pregnancy generates functional anti-spike (anti-S) IgG antibodies in maternal circulation that are detectable in umbilical cord blood at birth and can protect the newborn and infant from COVID-19. Anti-S IgG titers in the umbilical cord are correlated with maternal titers and are highest after late second and early third trimester vaccination. The persistence of vaccine-induced maternal anti-S IgG in infant blood has been studied and the persistence of infant anti-S IgG after maternal vaccination versus natural infection has been compared. The study found that most infants born to COVID-vaccinated mothers had persistent anti-S antibodies at 6 months, compared with infants born to mothers with SARS-CoV-2 infection. Understanding the persistence of maternal antibody levels in infants is important because COVID-19 infections in this age group account for a disproportionate burden of pediatric SARS-CoV-2–associated morbidity and because COVID-19 vaccines are not currently planned for administration to infants younger than 6 months[41].

Regarding vaccination against COVID-19 (Pfizer-BioNTech, Moderna, or Johnson & Johnson/Janssen), before and during pregnancy, 1,359 pregnant women blood samples who delivered at 34 weeks of gestation or more, including 20 women who received a booster dose, and 1,362 umbilical cord samples were associated with detectable maternal anti-spike IgG levels at delivery. Among women with a history of SARS-CoV-2 infection, maternal and cord blood antibody response achieved with vaccination in early pregnancy was comparable with third-trimester vaccination in pregnant women without a history of SARS-CoV-2 infection. A booster dose in the third trimester was associated with maternal anti-spike IgG levels greater than third-trimester vaccination in women with or without a history of SARS-CoV-2 infection[42].

In 2021, the American College of Obstetricians and Gynecologists recommended booster doses for pregnant and post-partum women based on their increased risk of COVID-19-related complications. Unvaccinated pregnant women in low-income and middle-income countries are at much higher risk of dying from COVID-19 but are also less hesitant to receive vaccination. Furthermore, the absolute reduction in risk following a booster is likely to be small for most vaccinated pregnant women who do not have a comorbidity. Longitudinal profiling of immunogenicity induced by different types of vaccines in pregnant women is essential for informing booster timing. In the meantime, strategies for more equitable distribution of vaccines and reduction of vaccination hesitancy among the unvaccinated are likely to be more effective in reducing COVID-19 complications than offering boosters to all already-vaccinated pregnant women[43].

Maternal death in Peru and the COVID-19 pandemic

The reduction of maternal mortality in Peru was prioritized through various strategies to meet the commitment of the 2016 Sustainable Development Goals. There was a decreasing trend in maternal deaths (MD) until 2019, with an average weekly notification of 5.8 MD. With the onset of the pandemic due to COVID-19, starting in 2020, an increase in MD was observed, specifically during the II trimester, with 439 MD being notified. This represented an increase of 45.4% (+137) compared to 2019, with an average weekly notification of 8.3 MD, surpassing that presented in the last 8 years.

Now, the CDC of the Ministry of Health (MINSA) has reported that, during 2021, 471 maternal deaths (MD) were reported, with an increase of 7.3% (+32) compared to 2020 and with fewer MD per week in the last quarter; 130 MD occurred due to COVID-19 disease[44]. The average weekly notification was 11.4 MD -minimum 3 (week 34) and maximum 22 (week 09)-, an increase that surpassed that presented in the last 12 years. Of the MD reported, 63% (297) occurred in the first half of the year, coinciding with the peaks of mortality due to COVID-19 in women. An excess of 96 MD and 128 MD has occurred in 2020 and 2021, compared to the baseline trend[50] of MD in recent years (2016 to 2019), with an increase in hypertensive disorders and bleeding. MD due to COVID-19 were institutional in 93.1%.

In mid-June 2021, immunization of pregnant women against COVID-19 began in the country. As a result, during the III (6.3) and IV (7.1) quarters of 2021, fewer MD per week were reported compared to the I (11.1) and II (11.8) quarters, as MD caused by COVID-19 decreased (-32.7%).

The average age of the deceased was 30.9 years, with a range of 13-48 years. The age group of women aged 30-34 years (27.6%) was the most affected, while the group aged < 19 years (42; 8.9%) decreased compared to that observed in 2020. Regarding MD due to COVID-19, 5 (3.8%) deaths occurred in women < 19 years, 76 (58.5%) in women aged 20-34 years and 49 (37.7%) in women > 35 years. The puerperium represented the time with the highest number of MD (66.5%), with an increase of 5.5% compared to 2020. The puerperal MD due to COVID-19 (80%) was much higher than that observed in 2020.

50.8% (226) of MD in 2021 were due to direct causes and 49.2% (219) to indirect causes. The proportion of direct causes was lower compared to what was observed in 2020 (-5.3%) and to the five-year period 2015-2019 (-14.2%). From the beginning of the pandemic until the I semester 2021, COVID-19 infection represented the main cause of MD (40.4%), displacing the direct causes (hemorrhage and hypertensive disorders). However, in the II semester, there was an increase in direct causes, which came to represent 68.4% of MD in the country. Hemorrhage (23.4%) and hypertensive disorders (22.8%) returned to being the main causes of MD at the national level, displacing COVID-19 disease (8.9%) to third place.

A total of 24.2% (114/471) of MD had a positive reactive confirmatory test for COVID-19 infection. Of this group, 79 had COVID-19 infection as the basic cause of death. Regarding maternal death and immunization, from week 24 to week 52 of 2021, 203 MD were reported, 11.8% (24) died from COVID-19; 95.8% (23) were not immunized against COVID-19 and 1 deceased had only 1 dose of COVID-19[44].

Closing

At the beginning of March 2022, the Johns Hopkins Coronavirus Resource Center indicates the number of SARS-CoV-2 deaths worldwide has surpassed 6 million, as we are entering the third year of its presence[45]. It took the world seven months to record its first million deaths from the virus after the pandemic began in early 2020. Four months later another million people had died, and 1 million have died every three months since, until the death toll hit 5 million at the end of October[46]. The number of infected persons is close to 450 million and the number of vaccination doses administered has reached 10.6 billion[45].

Although reported COVID-19 deaths between January 1, 2020, and December 31, 2021, totaled 5,94 million worldwide, the COVID-19 Excess Mortality Collaborators estimate that 18,2 million (95% uncertainty interval 17,1–19,6) people died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period. The number of excess deaths due to COVID-19 was largest in the regions of South Asia, North Africa and the Middle East, and Eastern Europe. At the country level, the highest numbers were estimated in India (4,07 million), the USA (1,13 million), Russia (1,07 million), Mexico (798,000), Brazil (792,000), Indonesia (736,000), and Pakistan (664,000)[47].

We conclude this eighth fascicle on the coronavirus conundrum by noting that the Omicron B2 variant has proved to be more infectious than previous SARS-CoV-2s but causes fewer hospitalizations for severe cases and deaths. The population in various parts of the world would have become aware of infection preventive measures, vaccination and booster vaccination, and adaptation to changes. But this is not yet the case in all countries. Whole genome sequencing can help us determine the genetic variants associated with an increased risk of developing severe COVID-19 requiring critical care or hospitalization, with specific drug treatment to control viral replication or increased tendency to pulmonary inflammation and intravascular coagulation. The concern is that this viral disease is leaving as a sequel prolonged COVID with physical and mental health problems of varying magnitude, affecting personal, family, and social life, work, and reconstruction of living, often mourning with resilience the loss of family and friends. We health professionals must prepare ourselves to care for these new patients and to anticipate the new medicine based on genetics, immunology, appropriate anticoagulation, and compassion.

References

1. Keating D. More than 140M Americans have had coronavirus, CDC estimates. The Washington Post. February 28, 2022.
2. Elsom J. Boris Johnson hails Britain's 'pride and hope' as he finally rips up Covid rules – but warns of worse variants to come. The Sun. 21 Feb 2022.
3. COVID-19 National Preparedness Collaborators. Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021. Lancet. February 01, 2022. DOI: https://doi.org/10.1016/S0140-6736(22)00172-6
4. Yong E. The millions of people stuck in pandemic limbo. The Atlantic. February 16, 2022. https://www.theatlantic.com/health/archive/2022/02/covid-pandemic-immunocompromised-risk-vaccines/622094/
5. Eskander A, Li Q, Yu J, Hallet J, Coburn NG, Dare A, et al. Incident cancer detection during the COVID-19 pandemic. J Natl Compr Canc Netw. 2022 Feb 1:1-9. doi: 10.6004/jnccn.2021.7114
6. Peeling RW, Heymann DL, Teo Y-YT, Garcia PJ. Diagnostics for COVID-19: moving from pandemic response to control. Lancet. February 19, 2022;399(10326):757-68. Published: December 20, 2021. DOI: https://doi.org/10.1016/S0140-6736(21)02346-1
7. Peña-Hernández MA, Klein J, Malik AA, Coppi A, Kalinich C, Vogels CBF, Silva J, Yale SARS-CoV-2 Genomic Surveillance Initiative, et al. Comparison of infectious SARS-CoV-2 from the nasopharynx of vaccinated and unvaccinated individuals. medRxiv 2021.12.28.21268460; doi: https://doi.org/10.1101/2021.12.28.21268460
8. Cambridge E. New Covid variant dubbed 'Omicron's sister' is under investigation', health chiefs war. The Sun. 21 Jan 2022.
9. Cambridge E. Omicron's 'stealth sister spreads 33% quicker and can evade vaccines but isn't more severe. The Sun. 10 Feb 2022.
10. Ledford H. The next variant: three key questions about what's after Omicron. Nature News Explainer. 28 February 2022.
11. Zhao X, Li D, Ruan W, Chen Z. Effects of a prolonged booster interval on neutralization of Omicron variant. N Engl J Med. 2022;386:894-6. DOI: 10.1056/NEJMc2119426
12. Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, Walker S, et al. Whole genome sequencing reveals host factors underlying critical Covid-19. Nature. 7 March 2022). https://doi.org/10.1038/s41586-022-04576-6
13. Ramirez-Felman L. How strong is your immunity against Omicron? Yahoo!news February 14, 2022.
14. Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, Coyle P, Yassine HM, et al. Protection against the Omicron variant form previous SARS-CoV-2 infection. N Engl J Med. February 9, 2022. DOI: 10.1056/NEJMc2200133
15. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, Walker AS, Peto TEA. Effect of Covid-19 vaccination on transmission of Alpha and Delta variants. NEJM. January 5, 2022. DOI: 10.1056/NEJMoa2116597
16. Nordström P, Ballin M, Nordström A. Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden. Lancet. February 4, 2022. 2 https://doi.org/10.1016/S0140-6736(22)00089-7
17. Thompson MG, Natarajan K, Irving SA, Rowley EA, Griggs EP, Gaglani M, Klein NP, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance - VISION Network, 10 States, August 2021-January 2022. MMWR Morb Mortal Wkly Rep. 2022 Jan 21;71(4):139-45. doi: 10.15585/mmwr.mm7104e3
18. Schmidt F, Muecksch F, Weisblum Y, Da Silva J, Bednarski E, Cho A, et al. Plasma neutralization of the SARS-CoV-2 Omicron variant. N Engl J Med. February 10, 2022;386:599-601. DOI: 10.1056/NEJMc2119641
19. Jia KM, Hanage WP, Lipsitch M, Swerdlow DL. Excess COVID-19 associated deaths among the unvaccinated population ³18 years old in the US, May 30 – December 4, 2021. medRxiv preprint doi: https://doi.org/10.1101/2022.02.10.22270823; this version posted February 13, 2022.
20. Alejo JL, Mitchell J, Chang A, Chiang TPY, Massie AB, Segev DL, Makary MA. Prevalence and durability of SARS-CoV-2 antibodies among unvaccinated US adults by history of COVID-19. JAMA. Published online February 03, 2022. doi:10.1001/jama.2022.1393
21. Johnson AG, Amin AB, Ali AR, Hoots B, Cadwell BL, Arora S, et al. COVID-19 incidence and death rates among unvaccinated and fully vaccinated adults with and without booster doses during periods of Delta and Omicron variant emergence - 25 U.S. Jurisdictions, April 4-December 25, 2021. MMWR Morb Mortal Wkly Rep. 2022 Jan 28;71(4):132-8. doi: 10.15585/mmwr.mm7104e2
22. Suárez Bosleman D. COVID-19. El lento avance de la tercera dosis es un riesgo. Solo el 38% de la población objetivo ha completado este esquema de vacunación. Los adultos mayores son los más perjudicados. Diario El Comercio. 11 marzo 2022.
23. Bachmann MF, Mohsen MO, Speiser DE. The future of SARS-CoV-2 vaccination. N Engl J Med March 3, 2022; 386:899-900. DOI: 10.1056/NEJMc2119437
24. Eppinger U. Dos años de COVID-19: ¿Qué fármacos se ha estudiado y cuáles ayudan realmente a los pacientes? Medscape 8 febrero 2022.
25. Bernal AJ, Gomes da Silva MM, Musungaie DB, Kovalvhuck E, Gonzalez A, Delos Reyes V, et al., for the MOVe-OUT Study Group. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. Feb 10, 2022;386:509-20. DOI: 10.1056/NEJMoa2116044
26. Kreier F. Will a rising Omicron variant scramble antibody treatments? Nature 23 February 2022.ACOG Today's Headlines. The FDA halted use of two COVID-19 monoclonal antibody therapies. Good morning, January 25, 2022
27. ACOG. The FDA halted use of two COVID-19 monoclonal antibody therapies. Today's Headlines, January 25, 2022.
28. Sund M, Fonseca-Rodríguez O, Josefsson A, Welen K, Connolly A-MF. Association between pharmaceutical modulation of

oestrogen in postmenopausal women in Sweden and death due to COVID-19: a cohort study. BMJ Open. 2022;12:e053032. doi: 10.1136/bmjopen-2021-053032

29. Ledford H. Hundreds of COVID trials cold provide a deluge of new drugs. Nature News Feature. 01 March 2022.

30. Pérez-Cortés Villalobos A. La errónea concepción de que COVID-19 causada por ómicron es un resfriado común. Medscape. 7 de enero de 2022

31. Cohen K, Ren S, Heath K, Dasmariñas MC, Jubilo KG, Guo Y, Lipsitch M, Daugherty SE. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ. 2022 Feb 9;376:e068414. https://doi.org/10.1136/bmj-2021-068414

32. Heesakkers H, van der Hoeven JG, Corsten S, Janssen I, Ewalds E, Simons KS, et al. Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19. JAMA. 2022;327(6):559–565. doi:10.1001/jama.2022.0040

33. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nature Med. 07 February 2022. https://www.nature.com/articles/s41591-022-01689-3

34. Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with covid-19: cohort study. BMJ, 2022 Feb 16;376:e068993. https://doi.org/10.1136/bmj-2021-068993

35. Ledford H. Do vaccines protect against long COVI? What the data say. Nature. Nov 2021;599:546-8. doi: https://doi.org/10.1038/d41586-021-03495-2

36. Loewy MA. "COVID-19 persistente" en personas que nunca se infectaron. En: COVID-19: el resumen semanal (11 al 17 de febrero de 2022. Medscape.18 de febrero de 2022.

37. Avraham S, Kedem A, Zur H, Youngster M, Yaakov O, Yerushalmi GM, et al. COVID-19 vaccination and infertility treatment outcomes. Fertil Steril. 2022. doi: https://doi.org/10.1016/j.fertnstert.2022.02.025

38. Metz TD, Clifton RG, Hughes BL, Sandoval GJ, Gobman WA, Saade GR et al; for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network. Association of SARS-CoV-2 infection with serious maternal morbidity and mortality from obstetric complications. JAMA. 2022 Feb 22;327(8):748-759. doi: 10.1001/jama.2022.1190

39. Handley SC, Gallagher K, Lindgren EJD, Lo JY, Burris HH, Dysart KC, et al. Postpartum length of stay and hospital readmission before and during the coronavirus disease 2019 (COVID-19) pandemic. Obstet Gynecol. March 2022;139(3):381-90. doi: 10.1097/AOG.0000000000004687

40. Schwartz DA, Avvad-Portari E, Babál P, Baldewijns M, Blomberg M, Bouachba A, et al. Placental tissue destruction and insufficiency from COVID-19 causes stillbirth and neonatal death from hypoxic-ischemic injury: a study of 68 cases with SARS-CoV-2 placentitis from 12 countries. Arch Pathol Lab Med. February 10, 2022. https://doi.org/10.5858/arpa.2022-0029-SA

41. Shook LL, Atyeo CG, Yonker LM, Fasario A, Gray KJ, Alter G, Edlow AG. Durability of anti-spike antibodies in infants after maternal COVID-19 vaccination or natural infection. JAMA. Published online February 07, 2022. doi:10.1001/jama.2022.1206

42. Yang YJ, Murphy EA, Singh SBA, Sukhu ACBS; Wolfe IBS, Adurty SBA, et al. Association of gestational age at coronavirus disease 2019 (COVID-19) vaccination, history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and a vaccine booster dose with maternal and umbilical cord antibody levels at delivery. Obstet Gynecol. March 2022;139(3):373-80. doi: 10.1097/AOG.0000000000004693

43. Kalafat E, Magee LA, con Dadelszen P, Heath P, Khalil A. COVID-19 booster doses in pregnancy and global vaccines equity. Lancet. February 18, 2022. DOI:https://doi.org/10.1016/S0140-6736(22)00166-0

44. Ministerio de Salud Perú. Centro Nacional de Epidemiología, Prevención y Control de Enfermedades. Informe Técnico N° 020-2022.Situación Epidemiológica de la Mortalidad Materna en el Perú, SE 052 – 2021. 28 ene 2022. Nota Informativa N° 079-2022-CDC/MINSA

45. Johns Hopkins Coronavirus Resource Center. Johns Hopkins Coronavirus Report Map. 7 mar 2022. https://coronavirus.jhu.edu/map.html

46. Rising D. Death toll surpasses 6 million for pandemic now in 3rd year. yahoo!news. March 7, 2002.

47. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. March 10, 2022. DOI: https://doi.org/10.1016/S0140-6736(21)02796-3