

## SPECIAL ARTICLE

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# The coronavirus conundrum - The end of the COVID-19 pandemic? - The woman, the pregnant woman and the fetus - Vaccines - Future

## El enigma del coronavirus – ¿El final de la pandemia COVID-19? – La mujer, la gestante y el feto – Vacunas - Futuro

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### ABSTRACT

WHO Director-General Tedros Adhanom Ghebreyesus has recently said that 'The end of the pandemic is near. We are not there yet, but the end is in sight'. And U.S. President Joe Biden, with about 400 deaths per day in the U.S., has repeated that assertion. From what we can read in the literature, we are not there yet and there may be a long way to go. Although more is known about the virus and its ability to transform into variants and subvariants in order to enter the host more easily, some of these transformations are cause for concern. We make a brief review of what we have learned about morbidity and mortality due to SARS-CoV-2, how women's health has worsened, some alterations in sperm, defenses against the virus, reinfections, its unhealthy action on the pregnant woman, the fetus and the newborn, vaccines and boosters, and a vision of what lies ahead.

**Key words:** Coronavirus SARS-CoV-2, COVID-19, Female, Pregnancy, Fetus, Neonate, Placenta, Vaccines.

### RESUMEN

El Director General de la OMS Tedros Adhanom Ghebreyesus ha dicho recientemente que 'El fin de la pandemia está cerca. Todavía no hemos llegado, pero el final está a la vista'. Y el presidente de los EE. UU. Joe Biden, con alrededor de 400 muertes por día en los EE. UU., ha repetido dicha aseveración. Por lo que podemos leer en la literatura, aún no estaríamos en tal situación y pudiera haber un buen trecho por recorrer. Si bien se conoce más acerca del virus y su capacidad de transformación en variantes y subvariantes de manera de ingresar con más facilidad al huésped, algunas de estas transformaciones son motivo de preocupación. Hacemos una revisión somera sobre lo aprendido sobre la morbimortalidad por el SARS-CoV-2, cómo ha empeorado la salud de las mujeres, algunas alteraciones en el esperma, las defensas ante el virus, las reinfecciones, su accionar malsano sobre la gestante, el feto y el neonato, las vacunas y refuerzos y una visión de lo que nos espera.

**Palabras clave.** Coronavirus SARS-CoV-2, COVID-19, Mujer, Embarazo, Feto, Neonato, Placenta, Vacunas.

### MORBIDITY AND MORTALITY CAUSED BY SARS-CoV-2

Daily global SARS-CoV-2 infections fluctuated between 3-17 million new infections per day between April 2020 and October 2021, peaking in mid-April 2021, primarily because of increases in India. Between the start of the pandemic and November 14, 2021, there were an estimated 3.80 billion combined SARS-CoV-2 infections and reinfections, and 3.39 billion (43.9% of the global population) were estimated to have been infected one or more times. The high-income subregion had the fewest infections (239 million). The cumulative proportion of the population ever infected varied widely among countries and territories, with rates above 70% in 40 countries and below 20% in 39 countries<sup>(1)</sup>.

In the first year of the COVID-19 pandemic (through April 2021), many governments tolerated progressively higher infection rates before implementing 'stay-at-home' orders in successive waves, perhaps because of concerns about the economic costs of lockdown or because they



were desensitized to the large number of cases. In contrast, a few governments - notably those that had eliminated SARS-CoV-2 locally such as Australia and China - activated the immobilization measures, resulting in progressively lower counts<sup>(2)</sup>.

The United States of America accounts for just over 4% of the world's population but is responsible for about 16% of the world's deaths from COVID-19. Among the many reasons are failure to take advantage of life-saving vaccines, resistance to simple precautions such as wearing masks in crowded spaces, and high rates of health conditions such as coronary artery disease and obesity<sup>(3)</sup>. In addition, the pandemic has caused Native Americans to fall further behind other major racial/ethnic groups in terms of life expectancy. The estimated loss in life expectancy at birth is between 1-3 years worldwide. But, for Native Americans during the two-year COVID-19 pandemic this loss has been 4.5 years in 2020 and 6.4 years in 2021 relative to 2019, despite having the higher vaccination rates than those of other racial/ethnic groups<sup>(4)</sup>.

Orphanhood and caregiver deaths associated with COVID-19 have left some 10.5 million children without parents and caregivers. Only two countries, Peru and the United States, have committed to addressing COVID-19-associated orphanhood. Urgent responses to the pandemic can combine equitable vaccination with life-changing programs for affected children to help them mitigate lasting adverse consequences, a public health imperative. Three essential components stand out: (1) preventing caregiver deaths by accelerating vaccinations, containment, and treatment; (2) preparing families to provide safe and nurturing alternative care; and (3) protecting orphaned children through economic support, violence prevention, parenting support, and ensuring access to school<sup>(5)</sup>.

CDC has stated that most SARS-CoV-2 transmission occurs early in the illness, one to two days before symptom onset and two to three days thereafter. However, there are no data to support five days or anything less than ten days of isolation. Barczak's own research, published on the medRxiv preprint server, suggests that one-quarter of people who have contracted the Omicron variant of SARS-CoV-2 may still be infectious after eight days<sup>(6)</sup>.

In a study of 1,238 women from ten Latin American countries, aged 40-64 years, 304 (24.6%) had a positive history for COVID-19. Postmenopausal status and family history of dementia were more frequent among women who had had COVID-19, and infection was less frequent among current or past users of menopausal hormone therapy and those with less physical contact<sup>(7)</sup>.

### SURVEY REVEALS THAT WOMEN'S HEALTH WORSE- NED IN 2021

According to a Gallup poll, Covid-19 brought more health problems for women around the world in 2021 than 2020. Women were more stressed, worried, sad, and angry in 2021 than at any time in the past decade. No country scored more than 70 out of 100, with Taiwan, Latvia, Austria, and Denmark at the top. Three countries scored less than 40 points: Afghanistan, Congo, and Venezuela. The United States ranked 23rd, with 61 points out of 100<sup>(8)</sup>.

### COVID-19 AND SEMEN

Semen is not infectious with SARS-CoV-2 a week or more after COVID-19 infection (mean, 53 days). However, couples wishing to conceive should be cautioned that sperm quality after COVID-19 infection may be suboptimal. The estimated recovery time is 3 months, but further follow-up studies are underway to confirm this and to determine whether permanent damage occurred in a minority of men<sup>(9)</sup>.

### HUMAN DEFENSES TO SARS-CoV-2

In a retrospective cohort study at the Mayo Clinic, samples from 455 participants with COVID-19 were analyzed. The control cohort consisted of 182 anonymized, age- and sex-matched plasma samples stored prior to the COVID-19 pandemic and available at the clinic's biorepository. In-depth profiling of circulating cytokines and other proteins, lipids, and metabolites from both cohorts were performed. Biomarkers were determined by applying an AutoGluon-tabular classifier to a multi-omics dataset, producing a stacked set of state-of-the-art machine learning algorithms. Global proteomics and glycoproteomics were also performed on a subset of matched pre-COVID-19 patient samples. A total of 1,463 cytokines and circulating proteins were quantified, along with 902 lipids and 1,018 metabolites.



By developing a machine learning-based prediction model, a set of 102 biomarkers was discovered that predicted severe and clinical outcomes of COVID-19 better than the traditional cytokine set. These predictive biomarkers included several novel cytokines and other proteins, lipids, and metabolites. It was concluded that a multiomics molecular signature in the plasma of patients with COVID-19 prior to hospital admission can be exploited to predict a more severe course of the disease<sup>(10)</sup>.

### CLINICAL OUTCOMES OF SARS-CoV-2 REINFECTION

First infection with SARS-CoV-2 is associated with an increased risk of acute and post-acute death and sequelae in the pulmonary and extrapulmonary organ systems. Concerned that reinfection would add to the risk incurred after first infection, the U.S. Department of Veterans Affairs health databases were reviewed to construct a cohort of persons with first infection (n = 257,427), reinfection (2 or more infections, n = 38,926), and an uninfected control group (n = 5,396,855). It was found that, compared with those with first infection and the uninfected control group, reinfection contributed additional risks of all-cause mortality, hospitalization, and adverse health outcomes in the pulmonary system and several extrapulmonary organ systems (cardiovascular disorders, coagulation and hematologic disorders, diabetes, fatigue, and gastrointestinal, renal, mental health, musculoskeletal, and neurologic disorders). Risks were evident in those who were unvaccinated or who had 1 or more vaccinations before the second infection, and most were still evident at 6 months after reinfection. Risk and burden increased gradually with the number of infections. Thus, reducing the overall burden of death and disease due to SARS-CoV-2 will require strategies to prevent reinfection<sup>(11)</sup>.

### PHYSICIAN BURNOUT INCREASED IN 2021

A study published in Mayo Clinic Proceedings found that about 63% of physicians surveyed experienced at least one manifestation of burnout in 2021, up sharply from 38% in 2020 and the highest number in a decade. Emotional exhaustion and depersonalization were higher in 2021, while work-life balance satisfaction decreased. Depression scores remained relatively stable.

Women have been more affected by this burnout which occurred against a backdrop of other stressors such as gun violence, economic concerns, and childcare obstacles<sup>(12)</sup>.

### COVID-19 IN PREGNANT WOMEN AND THEIR FETUSES AND NEONATES

#### COMPLICATIONS OF PREGNANCY BY COVID-19

In a cross-sectional study from the U.S. CDC's National Center for Health Statistics using data from all live births in the United States from January 1, 2018, through December 31, 2020, gestational weight and excessive gestational weight gain increased during the COVID-19 pandemic, especially in pregnant women younger than 25 years, non-Hispanic black, unmarried, and obese before pregnancy<sup>(13)</sup>.

Pregnant women are at increased risk of serious complications from COVID-19 infection, such as myocardial injury, arrhythmias, and heart failure, including the need for intensive care unit admission, mechanical ventilation, and the need for extracorporeal membrane oxygenation support compared with nonpregnant women of childbearing age. They should therefore be distinguished from unique complications of pregnancy associated with COVID-19 such as preeclampsia, peripartum cardiomyopathy, and spontaneous coronary artery dissections<sup>(14)</sup>.

COVID-19 has been associated with hypertensive disorders of pregnancy. The association is biologically plausible as COVID-19 causes endothelial injury and multiorgan inflammation. In one trial, serologic testing for SARS-CoV-2 was performed on 6,192 (92.7%) pregnant women, and 568 (9.2%) were seropositive. There appeared to be no association between SARS-CoV-2 infection and the presence of hypertensive disorders of pregnancy. Only 2% of the seropositive pregnant women had moderate or severe disease<sup>(15)</sup>.

### MATERNAL DEATH

As has been the case in many countries around the world, maternal deaths in the U.S. increased substantially (33.3%) after March 2020, when COVID-19 infection began, a figure higher than the estimated global excess deaths associated with the pandemic. Increases in maternal deaths may involve conditions directly related to COVID-19



(respiratory or viral infection) or conditions exacerbated by COVID-19 or other health care disruptions such as diabetes or cardiovascular disease<sup>(16)</sup>.

In pregnant women seen in 463 U.S. hospitals during the COVID-19 pandemic and whose information was in the PINC AI Healthcare database, maternal death during hospitalization for delivery increased from 5.17 to 8.69 deaths per 100.000 pregnant women (OR 1.75; 95% CI, 1.19-2.58). There was minimal change in mode of delivery (vaginal: OR 1.01; primary cesarean: OR 1.02; vaginal delivery after cesarean: OR 0.98; repeat cesarean: OR 0.96). Hospital stay for delivery decreased by 7%. Finally, the adjusted odds of gestational hypertension (OR 1.08), obstetric hemorrhage (OR 1.07), preeclampsia (OR 1.04), and preexisting chronic hypertension (OR 1.06) increased. The odds of maternal death, cardiovascular disorders, and obstetric hemorrhage were also increased. Further efforts are needed to ensure that the potential risks associated with the COVID-19 pandemic do not persist beyond the current state<sup>(17)</sup>.

#### FETONEONATAL MORBIMORTALITY

A retrospective cohort study included all women with a positive SARS-CoV-2 RT-PCR test during a single non-ectopic pregnancy between February 21, 2020, and July 2, 2021. A total of 2.753 /2.789 (98.7%) eligible women who were infected during pregnancy could be matched; 17.4% and 48.4% were infected during the first and third trimester, respectively. While infections in the first and second trimester were not associated with preterm delivery (PTB) ( $p>0.8$ ), infections in the third trimester and, in particular, after 34 weeks' gestation had an increased risk of PTB, with adjusted ORs of 2.76 and 7.10, respectively. The risk of PTB was further increased in symptomatic third trimester infections (OR = 4.28). The risk of small for gestational age was comparable between study groups in all trimesters of infection, and pregnancy loss was similar in both groups. SARS-CoV-2 infection was associated with an increased risk of PTB only among women infected during the last trimester of pregnancy, particularly among symptomatic women<sup>(18)</sup>.

Pregnant women with SARS-CoV-2 infection experience higher rates of stillbirth and preterm delivery. A unique pattern of chronic histiocytic intervillitis (CHI) and/or massive perivascular

fibrin deposition (MPFD), coined SARS-CoV-2 placentitis, has emerged. In one study, 59 mothers gave birth to 61 infants with SARS-CoV-2 placentitis. Gestational age ranged 19-41 weeks, and the majority of cases (78.6%) were third trimester. Thirty babies (49.1%) were stillborn or were late miscarriages. Obese mothers had higher rates of pregnancy loss compared with those with BMI >30 vs 41%. SARS-CoV2 placentitis is a distinct entity associated with an increased risk of pregnancy loss, especially in the third trimester. Women can be completely asymptomatic and still experience severe placentitis. In contrast to 'classic' MPFD, placentas with SARS-CoV-2 are usually of normal size and have an adequate fetoplacental weight ratio<sup>(19)</sup>.

Seventeen observational studies reported on 2.769 pregnant women with a positive SARS-CoV-2 PCR test and 13.807 with a negative test. Pregnant women with a positive PCR test gave birth at an earlier gestational age (MD -0.19 weeks), smoked less (OR 0.75), and were associated with higher odds of preeclampsia (OR 1.30), NICU admissions (OR 2.37), stillbirths (OR 2.70), and perinatal mortality (OR 3.23). Eleven studies included neonatal PCR testing for SARS-CoV-2 performed on 129 infants, of which 20 were positive. Pregnant women testing positive for SARS-CoV-2 were more likely to have preeclampsia/hypertensive disorders of pregnancy, NICU admissions, stillbirths, and perinatal mortality<sup>(20)</sup>.

A report presents data on fetal mortality at 20 weeks or more reported in 2020 in the U.S. The fetal mortality rate was 5.74 fetal deaths per 1.000 live births and fetal deaths, not different from the rate of 5.70 in 2019. Although the fetal mortality rate in 2020 between 20-27 weeks' gestation was 2.97, deaths occurring at 28 weeks' gestation or more of 2.78 was not significantly different from 2019 (2.73). Rates were higher for women younger than 15 years and older than 45 years, women who smoked during pregnancy, and women with multiple pregnancies. Five causes accounted for 89.6% of fetal deaths and were as follows: 1) fetal death of unspecified cause; 2) fetus affected by complications of placenta, umbilical cord and membranes; 3) fetus affected by maternal complications of pregnancy; 4) fetus affected by maternal conditions that may not be related to the current pregnancy; and 5) congenital malformations, deformities and chromosomal abnormalities<sup>(21)</sup>.



In a cohort of 7.772 infants born during the COVID-19 pandemic, those born to the 222 mothers with a positive SARS-CoV-2 polymerase chain reaction test during pregnancy were more likely to have a diagnosis of neurodevelopmental sequelae in the first 12 months after delivery, even after accounting for preterm delivery. These preliminary results suggest that COVID-19 exposure may be associated with neurodevelopmental changes and highlight the need for prospective investigation of outcomes in children exposed to COVID-19 in utero<sup>(22)</sup>.

In another cohort study of 1,884 SARS-CoV-2 seropositive children with 90-day follow-up, 5.8%, including 9.8% of hospitalized children and 4.6% of discharged children, reported post-COVID conditions. SARS-CoV-2 seropositive children were more likely to report conditions at 90 days compared with those who tested negative, both among those who were not hospitalized and among those who were hospitalized. In addition, they reported systemic health problems, such as fatigue, weakness, fever. Counseling and follow-up of hospitalized children with numerous acute symptoms and who are older is necessary<sup>(23)</sup>.

### SHORTENED LIFE EXPECTANCY

Retrospective analysis of census data on economic income and mortality in California from 2015 to 2021 showed a decrease in life expectancy in both 2020 and 2021 (decreased from 81.40 years in 2019 to 79.20 years in 2020 and 78, 37 years in 2021) and an increase in the life expectancy gap by income level relative to the pre-pandemic period (increased from 11.52 years in 2019 to 14.67 years in 2020 and 15.51 years in 2021), which has disproportionately affected some racial and ethnic minority populations<sup>(24)</sup>.

### FEWER AND FEWER BIRTHS IN PERU

Births in Peru have declined from 738.945 in 2012 to 594.280 in 2019, with sharp drops in 2020 (427.481) and 2021 (318.007). Similarly, marriages decreased from 122.432 in 2012 to 28.313 in 2019, 45.699 in 2020 and 22.675 in 2021. Meanwhile, deaths increased from 212.383 in 2012 to 161.543 in 2019, 242.482 in 2020, with a return to 159.182 in 2021<sup>(25)</sup>.

## VACCINES

Vaccination against COVID-19 has substantially altered the course of the pandemic, saving tens of millions of lives worldwide. However, inadequate access to vaccines in low-income countries has limited impact in these settings, reinforcing the need for global vaccine equity and coverage<sup>(26)</sup>.

As of November 4, 2021, 191,360 women aged 15-49 years with known pregnancy status had completed the first-dose vaccine survey and 94,937 had completed the second-dose survey in seven Canadian provinces and territories. COVID-19 mRNA vaccines have had a good safety profile in pregnancy. These data can be used to adequately inform pregnant women about the reactogenicity of COVID-19 vaccines during pregnancy and should be considered along with efficacy and immunogenicity data to make appropriate recommendations on the best use of COVID-19 vaccines in pregnancy<sup>(27)</sup>.

In February 2021, the Peruvian Ministry of Health approved the emergency use of inactivated SARS-CoV-2 vaccine (Vero Cell) and initiated vaccination with healthcare workers nationwide. Using data from the Peruvian Ministry of Health, a retrospective cohort study of 520.733 healthcare workers was conducted in the period February 23-June 26, 2021. 415.212 had two doses of vaccine and 105.521 were unvaccinated. The mean age was 40 years and 65.6% were women. With respect to the unvaccinated cohort, the inactivated Vero Cell SARS-CoV-2 vaccine used in two doses had acceptable efficacy against death (90.9%) and against the risk of hospitalization (67.7%), while it had less efficacy in preventing COVID-19 infection (26.3%)<sup>(28)</sup>.

The increase in hospitalization rates among adults aged  $\geq 65$  years, compared with rates among younger adults, was more pronounced during the Omicron BA.2 prevalence. Among hospitalized nonpregnant patients, 44.1% had received primary vaccination and  $\geq 1$  booster or additional dose. Hospitalization rates among unvaccinated adults were approximately triple those of vaccinated adults<sup>(29)</sup>.

Mucosal IgA can provide immunity against respiratory viruses. Vaccination against SARS-CoV-2 potentiates mucosal IgA responses, and neutral-





izing IgA, including neutralizing IgA against the B.1.1.529 Omicron variant, has been detected after infection with wild-type SARS-CoV-2. These results suggest that mucosa-specific IgA of wild-type SARS-CoV-2 is protective against omicron B.1.1.529 infection<sup>(30)</sup>.

### IF A PERSON HAS HAD COVID-19, IS AN OMICRON BOOSTER NECESSARY?

The answer is yes because it provides additional immune protection against COVID-19. Natural immunity may not last more than a few months. And vaccines produce antibodies and immune T-cells. People who have already had COVID-19 and are not vaccinated after recovery are more likely to get severe and prolonged COVID-19 again<sup>(31)</sup>.

### ADVERSE EFFECTS OF VACCINATION AGAINST COVID-19

In the period February 9 to December 31, 2021, a total of 31.760 reports with one or more adverse effects of vaccination (AEVI) have been registered in the VigiFlow pharmacovigilance database in Peru out of the 50.695.207 doses administered of the vaccine against COVID-19, which represents 0.06% of the doses administered. 55.7% were from the Sinopharm laboratory, 37.6% from the Pfizer laboratory and 6.7% from the AstraZeneca laboratory. Of the cases, 67.5% (21.417) occurred in the female population, 60.4% (19.170) in adults aged 30 to 59 years and 2% (650) in adolescents (12-17 years). The disorders were mostly pain in the vaccination area, malaise and pyrexia, headache and dizziness, diarrhea and nausea, myalgia, arthralgia, among others. Of the cases, 76.3% (24.236) were mild, 23.4% (7.436) moderate and 0.3% (87) severe<sup>(32)</sup>.

In a sample of women and through an Internet survey, 42% of those with regular menstrual cycles bled more than usual, while 44% reported no change after vaccination. Among respondents who do not usually menstruate, 71% of those taking long-acting reversible contraceptives, 39% of those taking gender-affirming hormones, and 66% of postmenopausal women reported intermittent bleeding. Increased irregular bleeding was found to be significantly associated with age, systemic vaccine side effects (fever and/or fatigue), history of pregnancy or childbirth, and ethnicity. In general, changes in menstrual

bleeding are not uncommon or dangerous, but attention to these experiences is necessary to build confidence in medicine<sup>(33)</sup>.

In order to describe reactions to the booster or third dose of COVID-19 vaccine and experiences with the vaccine among pregnant and lactating women, a follow-up Research Electronic Data Capture (REDCap) survey was sent to 17.504 participants beginning in October 2021; 17.014 (97.2%) completed the survey. The majority (82.8%) reported a local reaction and 67.9% reported at least one symptom<sup>(34)</sup>.

The benefits of maternal vaccination to the infant by transfer of maternal antibodies across the placenta have long been recognized. Supported by reassuring safety data on the use of other vaccines during pregnancy and accumulating data on the safety of Covid-19 vaccination for the mother and fetus, CDC and professional organizations (e.g., the American College of Obstetricians and Gynecologists) have strongly recommended vaccination in pregnant women. A booster dose is also recommended after completion of the initial vaccination series<sup>(35)</sup>.

Analysis of the antibody profile after vaccination with Ad26.COV2.S, mRNA-1273 or BNT162b2 in 158 pregnant women and transplacental transfer of antibodies by analysis of maternal and umbilical cord blood in 175 maternal-neonatal dyads reveal that vaccine-induced functions and Fc receptor binding are lower after vaccination with Ad26.COV2.S compared with mRNA vaccination and with subtle advantages in titer and function with mRNA-1273 versus BN162b2. Vaccines with mRNA have higher titers and function against the SARS-CoV-2 variants of interest. Vaccination in the first and third trimester, relative to the second trimester, results in increased maternal antibody-dependent NK cell activation, as well as cellular and neutrophil phagocytosis and complement deposition. The higher rates of transplacental transfer after vaccination in the first and second trimester may reflect placental compensation for decrease in maternal titers<sup>(36)</sup>.

### A VISION OF THE FUTURE WITH COVID-19

A warmer world means more disease in the future. Extreme temperatures are leading to more encounters between people and pathogens, which means more outbreaks of infectious diseases<sup>(37)</sup>.



During the COVID-19 pandemic, hospitals treated sicker patients requiring more frequent and prolonged use of catheters and ventilators. There were supply problems, staffing reductions, and longer visits. These unprecedented challenges may have contributed to a reduction in comprehensive prevention practices which are key to stopping antimicrobial-resistant infections and their spread. The COVID-19 pandemic has made it clear: prevention is preparation for unknown emerging threats in the future<sup>(38)</sup>.

A paper in the journal Nature reports that researchers in San Diego, California, detected the Alpha and Delta variants of coronavirus in the sewage of about 2.3 million people up to two weeks before the strains were collected by swabs and testing at clinics. They also detected Omicron about ten days before the first person tested positive in San Diego and tracked the rise of the BA.1 variant of Omicron in the population. However, the prospect of a variant-specific early warning system could take time, as it takes about two weeks to process the results after a sample is collected. But it has already been possible to reduce the sample sequencing time from weeks to days<sup>(39)</sup>.

The U.S. FDA Advisory Committee recommended the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines this fall. Less than 48 hours later, the FDA announced that manufacturers wishing to update COVID-19 vaccines must add a spike protein component of the BA.4 and BA.5 Omicron subvariants (which differ only outside of the spike protein), to make bivalent boosters that can be used starting this fall<sup>(40)</sup>.

There is a disturbing new variant - B.A.2.75.2, a daughter of BA.2.75, with three new spike mutations that are worrisome. This variant has the largest immune escape that researchers at the Karolinska Institute have seen so far. The current strategy of searching for variants to catch up with BA.5 will probably not help counter BA.2.75.2. However, there is much evidence that a third or fourth booster vaccine (first or second) will help provide significant protection, and that is vital especially for people over 50, with a recommendation that everyone over the age of 12 receive boosters. The right question is about the 5th booster dose, for which there are no clinical data yet, will be able to have a high level of protection against severe Covid<sup>(41)</sup>.

## WHAT DRUGS COULD REDUCE THE RISK OF PROLONGED COVID INFECTION?

Research on prolonged COVID-symptoms lasting more than three months has lagged behind studies on the acute phase of infection. Nearly one-third of those discharged after COVID-19 treatment are readmitted within six months, and 12% die within six months of initial discharge. Researchers have proposed a number of causes, from persistent viral reservoirs, to autoimmunity, small blood clots, to a mixture of these factors. So far, vaccines represent the best way to prevent prolonged COVID by reducing the risk of SARS-CoV-2 infection by 40% or half. Some studies plan to analyze the impact of early treatment with antiviral drugs, such as oral molnupiravir, Paxlovid and remdesivir, with follow-up of participants, as in the SOLIDARITY study. An immunosuppressant drug called infliximab is also being tested; and imatinib may reduce inflammation of blood vessels. A trial in the United Kingdom, called HEALCOVID is testing two drugs targeting the cardiovascular system in people hospitalized for COVID-19: the anticoagulant apixaban and atorvastatin, which reduces cholesterol and blood vessel inflammation. Because of increased pulmonary fibrosis in prolonged COVID, the University of Chicago in Illinois has begun testing sirolimus, an immunosuppressive drug sometimes given to organ transplant recipients<sup>(42)</sup>.

## THE LANCET COMMISSION ON LESSONS FOR THE FUTURE FROM THE COVID-19 PANDEMIC

As of May 31, 2022, there were between 6 and 9 million reported deaths and between 17 and 2 million estimated COVID-19 deaths, according to the Institute for Health Metrics and Evaluation (IHME), representing a profound tragedy and a huge global failure on multiple levels. Too many governments have failed to respect basic standards of institutional rationality and transparency; too many people - often influenced by misinformation - have failed to respect basic public health precautions and protested them; and the world's major powers have failed to coordinate and collaborate to control the pandemic. The Lancet Commission has produced a series of recommendations that divide them into three main areas: (a) practical steps to finally control and understand the COVID-19 pandemic; (b) realistic, feasible and necessary invest-



ments to strengthen the first line of defense against emerging infectious agents in countries by strengthening health systems and expanding universal health coverage; and (c) ambitious proposals to ignite a renaissance of multilateralism, integrating the global response to the risk of future pandemics with actions to address the climate crisis and setbacks in sustainable development. It is mentioned that the COVID-19 crisis has exposed major weaknesses in the UN-based multilateral system, stemming from excessive nationalism, tensions between major powers, chronic underfunding of global public goods including the UN system itself, lack of flexibility of intellectual property regimes to ensure that global public goods are available to all, lack of adequate financing of sustainable development for low-income countries, and erosion of political support for multilateral solutions by major powers. The most basic recommendation is the strengthening of multilateralism in all crucial dimensions - political, cultural, institutional, and financial - to tackle pandemics, end poverty, maintain peace or address global environmental challenges. Member States are encouraged to enrich their deliberations and decisions with the voices of civil society, the private sector, local governments, parliaments, academia, and youth, among others. And recommit to the Universal Declaration of Human Rights - the moral charter of the UN - as it celebrates its 75th anniversary in 2023<sup>(43)</sup>.

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