

SPECIAL ARTICLE

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The coronavirus conundrum - New subvariants of SARS-CoV-2 subvariants - COVID-19 and pregnancy - Is there a bright side to the pandemic?

El enigma del coronavirus – Nuevas subvariantes de subvariantes del SARS-CoV-2 – COVID-19 y embarazo - ¿Existe algún lado bueno de la pandemia?

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ABSTRACT

Since the late 2020's it was anticipated that the SARS-CoV-2 coronavirus would stay with us indefinitely, but there was hope that we would be able to combat it at some point effectively so that it would not produce the severe illness and death that we were seeing at that time. The pandemic has continued with this coronavirus continually modifying itself to enter the human body more easily. The Omicron variant preferentially infects the upper respiratory tract. And some of its mutations appear to affect parts of the spike protein that bind to ACE2. One of the latest subvariants of the variants, BA.212.1, infects more people more rapidly, although cases of severe infection and deaths have declined considerably. The following is a summary of what has been known in this first quarter of the year 2022 about the particularities of the virus, how it infects and its consequences, the protection of vaccination, what's new about the pregnant woman and her newborn, and whether there is any good side to the occurrence of the COVID-19 pandemic.

Key words: SARS-CoV-2 coronavirus, variants, subvariants, Omicron COVID-19, Pregnant woman, Fetus, Newborn.

RESUMEN

Desde fines del año 2020 se previó que el coronavirus SARS-CoV-2 se quedaría con nosotros de manera indefinida, pero había la esperanza que pudiéramos combatirla en algún momento con efectividad, de manera que no produjera la enfermedad severa y la muerte que veíamos en esos momentos. La pandemia ha continuado con este coronavirus que se modifica continuamente para ingresar con más facilidad al organismo humano. La variante ómicron infecta preferentemente las vías respiratorias superiores. Y algunas de sus mutaciones parecen afectar partes de la proteína de la espiga que se unen a la ACE2. Una de las últimas subvariantes de las variantes, la BA.212.1 infecta con mayor rapidez a un mayor número de personas, aunque los casos de infección severa y muertes han disminuido considerablemente. A continuación, se presenta un resumen de lo que se ha conocido en este primer trimestre del año 2022 sobre las particularidades del virus, la forma de infectar y sus consecuencias, la protección de la vacunación, lo nuevo sobre la gestante y su recién nacido y si existe algún lado bueno sobre la ocurrencia de la pandemia COVID-19.

Palabras clave. Coronavirus SARS-CoV-2, variantes, subvariantes, COVID-19, Gestante, Feto, Recién nacido.

SARS-CoV-2 EVOLUTION

As of the last Monday in May 2022, the seven-day average number of COVID-19 cases in the United States was more than six times higher than a year ago. According to the Johns Hopkins Coronavirus Resource Center, the seven-day average was 119,725 cases, a figure that stood at 17,887 cases on May 28, 2021. Meanwhile, the seven-day average of 470 deaths recorded on Memorial Day 2022 was a decrease from 637 on the same day in 2021⁽¹⁾.

The United States of America is now amid a new wave related to the BA.2 and BA.2.12.1 variants of Omicron, with more than 90,000 new



cases confirmed per day and a 20% increase in hospitalizations. The actual number of cases is probably less than 500,000 per day, but far higher than any of the previous waves in the United States, except with Omicron. The CDC suggests that the pandemic is over. As of last week, 43% of new cases were attributable to BA.2.12.1, which is outpacing BA.2 with its 25% higher transmission rate. BA.2.12.1 is distinct from both Omicron BA.1 and BA.2; a unique and key L452Q mutation is present in the spike. Multiple subvariants of Omicron compete for increased immune evasion; BA.2.12.1 (in parallel to BA.4 and BA.5) has a substantial transmission advantage over BA.2. There is a decrease in the effectiveness of vaccines and booster, from 90-95% to approximately 80%, as well as less hospitalization and death. There is a high probability of new, more harmful variants in the coming months. Although COVID vaccines and drugs are more effective than those for influenza, the number of deaths, already over 175,000 in 2022, is still >10 times higher than for seasonal influenza (about 30,000 per year), which is totally unacceptable⁽²⁾.

A significant proportion of COVID-19 transmission is asymptomatic or presymptomatic, potentially up to 60%, according to a 2021 JAMA Network Open modeling study. There is a higher percentage of asymptomatic infections with Omicron than with previous variants, which would relate to higher baseline levels of immunity in the population when that variant appeared. However, they can infect others, especially now when the spaces people visit are not always well ventilated, and where many individuals talk loudly while eating⁽³⁾.

A recent article in the journal Nature refers to the fact that millions of variants will probably continue to emerge every day. But most mutations do not improve the virus's ability to survive and reproduce and are overtaken by more suitable versions. Pango's committee uses a hierarchical system that indicates the evolutionary history of the variant following an alphabetical sequence from A to Z, then AA to AZ, BA to BZ, and so on. Separated by a dot, the following numbers indicate the order of the branches of that lineage, e.g., BA.1, BA.2, BA.3, BA.4 and BA.5, the first five branches of the original ancestor of the Omicron. BA.2.12.1 is the twelfth lineage branching from BA.2 and the first named branch in that twelfth bush. So far, only five variants have met

the WHO criteria for being termed variants of concern by being more transmissible, virulent, or able to escape an immune response than other versions. This sequencing of SARS-CoV-2 is almost non-existent in some parts of the world, and some countries with intense outbreaks have reduced genomic surveillance⁽⁴⁾.

SARS-CoV-2 has had billions of opportunities to reconfigure itself as it spread across the planet, and it continues to evolve, generating new variants and subvariants. Two and a half years after it first spread to humans, the virus has repeatedly changed its structure and chemistry. The latest of the virus variants and subvariants is the misnamed BA.2.12.1, which is part of the Omicron variant. It is 25% more transmissible than the BA.2 subvariant. No vaccine or booster can create a perfect shield against SARS-CoV-2 infection. However, vaccines greatly reduce the risk of severe disease. All currently used vaccines are based on the genomic sequence of the original 2019 strain of the virus from Wuhan, China, and essentially mimic the spike protein of that version of the virus and trigger an immune response that is protective when the real virus appears. But the variants can evade many of the neutralizing antibodies that are the immune system's first line of defense. Omicron was more transmissible than delta, delta more than alpha and alpha more than earlier variants that did not have a Greek alphabet name. When a mutation offers some advantage, the process of natural selection will favor it. South African scientists have identified BA.4 and BA.5 subvariants, which have mutations associated with immune evasion. The number of cases is increasing. The emerging subvariants are adept at evading neutralizing antibodies in people who recovered from infections with the original omicronic variant. The BA.4 and BA.5 subvariants have the potential to give rise to a new wave of infections. That is, subvariants of subvariants are being observed. When the Omicron variant swept through the U.S. population over the winter, almost as if it were an entirely new virus, the country was largely vaccinated. And yet approximately 80 million people were infected for the first time in that omicron wave. Future variants could be even more pathogenic⁽⁵⁾. BA.3 and BA.4 subvariants are circulating in Peru.

Investigators have searched PubMed, Embase, and the Cochrane Library database for all the



studies which evaluated the relationship between elevated cardiac troponins (cTns) and the risk of short-term all-cause mortality in patients with COVID-19. Compared with patients without myocardial injury, the group with elevated cTns was associated with increased short-term mortality (11 studies, 29,128 subjects, OR 3.17, 95% CI 2.19-4.59, $p = 0.000$, $I^2 = 92.4\%$, p for heterogeneity 0.00). For the dose-response analysis, the elevation of cTns $1 \times$ 99th percentile upper reference limit (URL) was associated with increased short-term mortality (OR 1.99, 95% CI 1.53-2.58, $p = 0.000$). The pooled OR of short-term mortality for each $1 \times$ URL increment of cTns was 1.25 (95% CI 1.22-1.28, $p = 0.000$). The authors found a positive dose-response relationship between myocardial injury and the risk of short-term all-cause mortality and propose elevation of cTns $> 1 \times$ 99th percentile URL was associated with the increased risk of short-term mortality⁽⁶⁾.

REGARDING THE LONG AND PERSISTENT COVID

Several pathophysiologic mechanisms have been implicated in the pathogenesis of postacute sequelae of SARS-CoV-2 infection (PASC). At the National Institutes of Health Clinical Center, Bethesda, Maryland, 189 self-referred adults with SARS-CoV-2 infection with at least 6 weeks from symptom onset were enrolled, 12% of whom were hospitalized during acute illness. The control group consisted of 120 individuals with no history of COVID-19 and negative antibodies. At enrollment, 55% of the COVID-19 cohort and 13% of the control participants manifested symptoms consistent with post-traumatic stress syndrome. An increased risk for PASC was observed in women and in those with a history of anxiety disorder. Participants reported lower quality of life on standardized tests. Abnormal findings on physical examination and diagnostic tests were infrequent. Neutralizing antibody levels against spike protein were negative in 27% of the unvaccinated COVID-19 cohort and in none of the vaccinated COVID-19 cohort⁽⁷⁾.

A prospective clinical study evaluating patients 28–60 days after hospitalization for COVID-19 reveals increased cardio-renal inflammation, reduced lung function and poorer self-reported clinical outcomes in patients relative to that in control participants. At 28–60 days after discharge, patients with COVID-19 showed increased incidence of cardio-renal involvement

and hemostasis pathway activation; worse health-related quality of life, according to EQ-5D-5L surveys; worse anxiety and depression, according to the PHQ-4 questionnaire; and diminished maximal oxygen utilization (and thus diminished aerobic exercise capacity). One in eight post-COVID-19 patients (13%) had an adjudicated diagnosis of myocarditis being highly likely. This result illustrates that multisystem illness severity due to COVID-19, rather than pre-existing disease, is one of the most important factors that drives post-COVID-19 syndrome. At follow-up (mean, 450 days), 15% of patients originally hospitalized for COVID-19 and 7% of control participants had been re-hospitalized or had died, with 68% of post-COVID-19 patients having received outpatient secondary care, compared with 26% of control participants⁽⁸⁾.

Swedish researchers have identified more than one million people who tested positive for SARS-CoV-2 between February 2020 and May 2021. They have studied the incidence of first deep vein thrombosis (DVT), pulmonary embolism (PE) and bleeding during the following 180 days. Controls were a matched cohort of 4 million people who did not have COVID-19. After adjustment, the risks of DVT, PE, and hemorrhage were significantly higher in the 30 days after COVID-19 diagnosis compared with those not diagnosed (hazard ratios: 5, 33, and 2, respectively), risks that remained significantly elevated for 3, 6, and 2 months, respectively, mainly in hospitalized patients⁽⁹⁾.

Whether SARS-CoV-2 antigen persistence underlies post-acute COVID-19 syndrome has been investigated. SARS-CoV-2 RNA expression was found in the intestinal mucosa ~7 months after mild acute COVID-19 in 32 of 46 patients with inflammatory bowel disease. Viral nucleocapsid protein persisted in 24 of 46 patients in intestinal epithelium and CD8+ T cells. SARS-CoV-2 antigen expression was not detectable in stool and viral antigen persistence was not related to the severity of acute COVID-19, immunosuppressive treatment, or intestinal inflammation. The results indicate that persistence of SARS-CoV-2 antigen in infected tissues serves as a basis for post-acute COVID-19. The concept that viral antigen persistence instigates immune perturbation and postacute COVID-19 requires validation in controlled clinical trials⁽¹⁰⁾.



Few longitudinal studies have reported on the persistent health effects of COVID-19, but with follow-up limited to one year after acute infection. A longitudinal, two-way cohort study of persons who had survived hospitalization with COVID-19 and were discharged has been published. Health outcomes were measured at 6 months (June 16-September 3, 2020), 12 months (December 16, 2020-February 7, 2021), and 2 years (November 16, 2021-January 10, 2022) after symptom onset, with a 6-minute walking distance test, laboratory tests, and a series of questionnaires on symptoms, mental health, health-related quality of life, return to work, and whether they received medical care after discharge. A subgroup of COVID-19 survivors received pulmonary function tests and chest imaging at each visit. 2469 COVID-19 patients were discharged from Jin Yin-tan Hospital (Wuhan, China) between January 7 and May 29, 2020, 1192 COVID-19 survivors completed assessments at the three follow-up visits and were included in the final analysis, 1119 (94%) of whom attended the face-to-face interview 2 years after infection. Regardless of initial disease severity, COVID-19 survivors had longitudinal improvements in physical and mental health, and most returned to their original job within 2 years. However, the burden of symptomatic sequelae remained quite high, and COVID-19 survivors had a markedly lower health status than the general population at 2 years⁽¹¹⁾.

Age groups with the lowest vaccination coverage have seen the largest increase in seroprevalence. The 2021 U.S. Omicron COVID-19 surge in 2021 had a record number of cases but reporting of asymptomatic infections and home testing use has been lacking. Researchers from the U.S. CDC have used a nationally representative segment of blood samples tested in commercial laboratories for reasons unrelated to COVID-19 to estimate the proportion of people with antibodies to the SARS-CoV-2 nucleocapsid, which indicates a naturally occurring infection. Analysis of convenience samples from 45,000 to 75,000 specimens every 4 weeks between September 2021 and February 2022 found that seroprevalence increased in all age groups from 34% in December 2021 to 58% in February 2022. The largest increases occurred in children (age range, 0 to 11 years, from 44% to 75%) and adolescents (age range, 12 to 17, from 46% to 74%). By February 2022, three-quarters of children and adoles-

cents had been infected with SARS-CoV-2, and approximately one-third of these infections occurred during the Omicron surge⁽¹²⁾.

COVID-19 GLOBAL FATALITY TALLY

WHO has estimated that between January 2020 and December 2021, between 14 and 9 million excess deaths (uncertainty range: 13.3 million to 16.6 million) from COVID-19 occurred worldwide (in 194 countries). This represents more than 2.5 times the number of reported COVID-19 deaths. It was higher for men (57% vs. 43% for women) and more in middle-low-income countries. The highest number of excess deaths per 100,000 people in 2020 and 2021 occurred in Peru (437), Russia (367), South Africa (200), India (171) Brazil (160), Turkey (156), and the United States (140). Countries with low excess mortality rates include China, Australia, Japan, and Norway^(13,14). The WHO global estimates are lower than the 18.2 million deaths (17.1 million to 19.6 million) reported by the Institute for Health Metrics and Evaluation (IHME) and the 17.7 million deaths (13.9 million-21.1 million) estimated by The Economist for the same period. In contrast, government counts of global COVID-19 deaths in 2020-21, collected in Coronavirus App, suggest that the figure is less than 6 million. The difference of 3 million deaths between the three models is not trivial. First, gaps in the actual mortality data persist into the 21st century. In the WHO analyses of 194 countries, mortality data were not available for 85 countries, 41 of which are in Africa. Second, India is the country that misses the most deaths from COVID-19 (2.5 million-4.5 million). It misses 3 million of India's 10 million deaths annually, with the largest gaps occurring in the poorest states and among women. Third, the severe blockade of Wuhan (China) in the early 2020s resulted in very few deaths in the rest of the country. However, China is now facing a large omicronic wave, with large numbers of unvaccinated or under-vaccinated elderly people, which in the case of Hong Kong led to sharp but brief spikes in mortality rates. Fourth, the biggest surprise in COVID-19 mortality may come from Africa. Preliminary data suggest that populations in many urban settings in Africa, with various viral surges, have SARS-CoV-2 seropositivity above 60%, but relatively few deaths. Finally, of the 55 million people who died worldwide in 2019, nearly 50 million were over 15 years of age. However, most demographic surveys focus



on child and maternal deaths, paying little attention to adult mortality⁽¹⁵⁾. And recently scientists working with the World Health Organization (WHO) have corrected some surprising errors in its estimates of how many deaths the pandemic has caused. In a revision to a technical paper on their methods, researchers cut Germany's pandemic-related deaths estimate by 37%, pulling its excess death rate below those of the United Kingdom and Spain. They also raised their estimate for Sweden by 19%⁽¹⁴⁾.

LIFE EXPECTANCY TWO YEARS INTO THE PANDEMIC

Many countries have seen their average life expectancy decline during the pandemic. The United States lost more than 2 years of average life expectancy during 2020-21, the same as Poland but less than Bulgaria, more than Chile, Greece, England and Wales, Spain, Italy. Life expectancy in some countries has recovered. However, life expectancy estimates tend to give more weight to premature deaths of the youngest, because in those cases more years of life are lost. In the United States, there was also a notable excess of deaths in the youngest age groups. The greatest uncertainties in studies of excess deaths are not in data-rich European nations, but in countries that do not publish timely data on all-cause mortality⁽¹⁴⁾.

As of late May 2022, there has been more than 80 million cases of COVID-19 in the U.S., with the disease taking the lives of more than a million people. Mortality from COVID-19 is two to three times higher for Latinos than for non-Hispanic whites, and this pandemic has diminished the so-called Latino (or Hispanic) paradox – the fact that for years Latinos living in the U.S. have had an advantage in life expectancy over non-Hispanic whites. In 2019, data from the CDC showed Latino's life expectancy was 81.9 years, 3.1 years longer than the life expectancy for whites. COVID-19 deaths shortened life expectancy in 2020 for all people in the U.S. by a little more than a year – to about 77.5 years – and life expectancy for Latinos plummeted by a little more than three years, to 78.8 years⁽¹⁶⁾.

EFFICACY OF VACCINATION AGAINST COVID-19

To gain insight into the efficacy of homologous and heterologous COVID-19 vaccine booster, a case-control (with negative test result) anal-

ysis was conducted to evaluate the efficacy of four vaccination regimens against symptomatic SARS-CoV-2 infection during a period when the Omicron variant was predominant: a) a single priming dose of Ad26.COV2.S; b) a single priming dose of Ad26.COV2.S plus a booster dose of Ad26.COV2.S (Ad26.COV2.S/Ad26.COV2.S); c) a single priming dose of Ad26.COV2.S plus a booster dose of mRNA vaccine (Ad26.COV2.S/mRNA); and, d) two priming doses of an mRNA vaccine plus a booster dose of mRNA vaccine (mRNA/mRNA/mRNA). In regimens that included an mRNA vaccine, BNT162b2 vaccine (Pfizer-BioNTech) or mRNA-1273 vaccine (Moderna) was used. The efficacy of Ad26.COV2.S vaccine (Johnson & Johnson-Janssen), compared with no vaccination, against symptomatic infection was 17.8% (95% confidence interval [CI], 4.3-29.5) during the period 14 days to 1 month from receipt of the last dose and 8.4% (95% CI, 1.5-14.8) during the period 2 to 4 months from receipt of the last dose. The corresponding values for the Ad26.COV2.S/Ad26.COV2.S regimen were 27.9% (95% CI, 18.3-36.5) and 29.2% (95% CI, 23.1-34.8); for the Ad26.S/mRNA regimen, 61.3% (95% CI, 58.4-64.0) and 54.3% (95% CI, 52.2-56.3); and for the mRNA/mRNA/mRNA regimen, 68.9% (95% CI, 68.3-69.5) and 62.8% (95% CI, 62.2-63.4). These results show that all regimens that included a booster dose, compared with no vaccination, provided protection against symptomatic Omicron infection (95% confidence intervals did not include 0). However, vaccine efficacy was higher for regimens that included a booster dose of an mRNA vaccine and was lower for the homologous Ad26.COV2.S/Ad26.COV2.S regimen⁽¹⁷⁾.

MORTALITY IN COVID-19 AMONG WOMEN ON HORMONE REPLACEMENT THERAPY

Recent limited observational data have suggested that there may be a protective effect of estrogens on COVID-19 disease severity. Authors investigated the association between hormone replacement therapy (HRT) or combined oral contraceptive pill (COCP) use and the likelihood of death in women with COVID-19 in the computerized medical records of the Royal College of General Practitioners of Oxford Research and Surveillance Centre. A cohort of 1,863,478 women over the age of 18 years was identified. There were 5,451 cases of COVID-19 within the cohort. HRT was associated with reduced all-cause mor-



tality in COVID-19 (adjusted OR 0.22, 95% CI 0.05-0.94). No all-cause mortality events were reported in women prescribed COCP⁽¹⁸⁾.

COVID-19 AND PREGNANCY

Expectant parents around the world have experienced changes in the way they care for child-birth because of COVID-19, including restrictions on access to delivery rooms and the presence of birth partners during delivery, as well as changes in birth plans. One paper reports the experiences of 477 families in England. The proportion of parents reporting birth interventions (e.g., emergency cesarean section) was higher than previously known, as were birth-related uncertainties and poor communication, leading to increased feelings of anxiety and high levels of negative emotions⁽¹⁹⁾.

Data based on 99.9% of all 2021 birth records received and processed by the U.S. National Center for Health Statistics indicate that the provisional number of births for the United States in 2021 was 3,659,289, up 1% from 2020 and first increase in the number of births since 2014. The total fertility rate was 56.6 births per 1,000 women aged 15-44, up 1% from 2020 and the first increase in the rate since 2014. The total fertility rate was 1,663.5 births per 1,000 women in 2021, up 1% from 2020. Birth rates decreased for females in the 15-24 age groups, increased for females in the 25-49 age groups, and remained unchanged for adolescents aged 10-14 in 2021. The birth rate for adolescent girls aged 15 to 19 declined by 6% in 2021, to 14.4 births per 1,000 women; rates declined for both younger (aged 15 to 17) and older (aged 18 to 19) adolescents. The cesarean delivery rate increased to 32.1% in 2021; the rate of low-risk cesarean delivery also incremented to 26.3%. The preterm birth rate increased by 4% in 2021 to 10.5%, the highest rate recorded since 2007. In summary, 2021 has seen the highest number of births and augmentation in the general fertility rate since 2014, with birth rates increasing in women aged 25-49 years and decreasing in adolescents. Cesarean sections and premature births have risen⁽²⁰⁾.

Maternal humoral immunity following SARS-CoV-2 infection has been found to decrease during pregnancy, resulting in low or absent titers of protection for a significant proportion of patients. A single booster dose of BNT162b2 mRNA vaccine

induced in one study a strong increase in protective titers for both the mother and the newborn, with mild symptoms following vaccination⁽²¹⁾.

One study has quantified how certain comorbidities might affect the risk of a case of COVID-19, defined as contracting a COVID-19 infection after being fully vaccinated. Many of the groups of people with comorbidities are known to be at increased risk for intermittent infection. The study found that pregnant people are 1.91 times more likely to be infected, people with a solid organ transplant are 1.83 times more possibly, and people with an immune system deficiency are 1.63 times more likely. However, cancer or Down syndrome were not found to increase the risk of a COVID infection. These results support the CDC recommendation that patients with a high-risk comorbidity -in this case pregnant women- may need further monitoring beyond vaccination to minimize the risk of COVID-19 infection⁽²²⁾.

In a retrospective cohort study, 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 persons with SARS-CoV-2 infection compared with persons without SARS-CoV-2 infection (13.4% vs. 9.2%, respectively). The study included 14,104 pregnant and postpartum patients, mean age 29.7 years, who gave birth between March 2020 and December 2020 at 17 hospitals in the U.S. Overall, 2,352 of the included patients tested positive for SARS-CoV-2 infection with nucleic acid or antigen testing, while the remaining 11,752 patients did not. Among those positive for SARS-CoV-2 in pregnancy, 80.1% were positive in the third trimester and 4.4% were positive 18 days after delivery. The primary outcome was a combination of maternal death or severe morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection other than SARS-CoV-2. SARS-CoV-2 infection was significantly related to the primary outcome: 13.4% vs. 9.2% of patients without a positive result. All five maternal deaths occurred in the SARS-CoV-2 group. On the other hand, moderate or higher severity of COVID-19 was significantly related to primary outcome, 26.1% vs. 9.2%, and cesarean delivery, 45.4% vs. 32.4%, respectively. Mild or asymptomatic infection was not significantly associated with primary outcome or with cesarean delivery⁽²³⁾.



SARS-CoV-2 infection during pregnancy and COVID placentitis are associated with an increased risk of stillbirth. Scientists investigated the presence of maternal viremia in persons with SARS-CoV-2 infection during pregnancy who had histologic placentitis versus those without placentitis. SARS-CoV-2 qRT-PCR was performed on plasma from 6 patients with COVID placentitis and 12 matched controls without placentitis. SARS-CoV-2 infection occurred between 4/2020 and 1/2021; latency between SARS-CoV-2 diagnosis and delivery was 0-76 days. Two cases of placentitis demonstrated viremia (1 stillborn and 1 healthy infant), while 12/12 controls were negative. Future research could consider viremia as a possible marker for COVID placentitis⁽²⁴⁾.

Compared with infants born before the COVID-19 pandemic, those born during the pandemic have had decreased fetal brain development which was associated with higher levels of distress in women who gave birth during the pandemic. The MRI study revealed that the pandemic cohort had smaller fetal white matter volumes (least-squares mean, 93.3 cm³ vs. 99.1 cm³; $p < 0.01$), hippocampus (least-squares mean, 8.2 cm³ vs. 8.7 cm³; $p = 0.01$) and cerebellum (least-squares mean, 1 cm³ vs. 1.1 cm³; $p < 0.01$) compared with the prepandemic group. In addition, the cortical surface area of all four lobes was significantly smaller in the pandemic group. Local four-lobe gyration indices were also significantly lower in the pandemic cohort, indicating less cortical folding. The pandemic cohort also had significantly lower sulcal depths in the frontal, parietal, and occipital lobes compared with the prepandemic cohort⁽²⁵⁾. Should we suggest that young couples who wish to have offspring consider postponing gestation until we know more about the outcome of the SARS-CoV-2-infected pregnant woman and her newborn?

A study from Norway revealed that, of 21,643 live births, 9,739 (45.0%) were born to women who received a second or third dose of COVID-19 vaccine during pregnancy. The incidence rate in the first 4 months of life of a positive test for SARS-CoV-2 was 5.8 per 10,000 days of follow-up. Infants of mothers vaccinated during pregnancy had a lower risk of testing positive compared with infants of unvaccinated mothers and a lower risk during the Delta variant-dominated period (incidence rate, 1.2 vs. 3.0 per 10,000 days of follow-up; adjusted hazard ratio, 0.29; 95%

CI, 0.19-0.46) compared with the Omicron period (incidence rate, 7.0 vs. 10.9 per 10,000 days of follow-up; adjusted hazard ratio, 0.67; 95% CI, 0.57-0.79). The results of this cohort study suggest a lower risk of testing positive for SARS-CoV-2 during the first 4 months of life among infants born to mothers who were vaccinated during pregnancy. Maternal vaccination against COVID-19 may provide passive protection to young infants, for whom COVID-19 vaccines are not currently available⁽²⁶⁾.

Misinformation surrounding COVID-19 vaccines has been widespread. The latest KFF COVID-19 Vaccine Monitor finds that 14% of adults and 24% of women who are pregnant or planning to become pregnant believe that pregnant women should not be vaccinated against COVID-19. While most of the public say they are at least somewhat confident in the safety of COVID-19 vaccines for adults in general, less than half say they are 'very confident' that the vaccine is safe for pregnant women. It is recalled that pregnant women were excluded from initial trials of the COVID-19 vaccine, and CDC estimates that about three in ten pregnant women remain unvaccinated. The CDC also recommends the COVID-19 vaccine for those who are breastfeeding, although 10% of adults and 17% of women who are pregnant or planning to become pregnant say they have heard and believe it is not safe for women who are breastfeeding to be vaccinated against COVID-19. And another 7% of adults and 16% of women pregnant or planning to become pregnant say they have heard and believe that COVID-19 vaccines have been shown to cause infertility⁽²⁷⁾.

VIRUSES THAT WERE ON HIATUS DURING THE COVID PANDEMIC RETURN

During these two years, as the COVID pandemic disrupted life around the world, other infectious diseases retreated. Now, as the world is rapidly scaling back measures to curb the spread of COVID, viruses and bacteria that were on hiatus are returning and behaving in unexpected ways. The past two winters have seen milder flu seasons, but flu is now on the rise, even in countries enjoying spring. Adenovirus type 41, which caused harmless outbreaks of gastrointestinal illness, may be triggering severe hepatitis in healthy young children. Respiratory syncytial virus (RSV), which causes illness in winter, caused



outbreaks of disease in children last summer and early fall in the United States and Europe. And now monkeypox virus, usually found only in West and Central Africa, is causing an unprecedented outbreak in Europe, North America, the Middle East, Australia⁽²⁸⁾ and South America. As of early June, WHO has reported that 780 cases of monkeypox have been confirmed in 27 countries where the virus is not endemic and maintains that the overall risk level is moderate. Despite limited epidemiological and laboratory information, WHO has recorded monkeypox in the United Kingdom (207), Spain (156), Portugal (138), Canada (58) and Germany (57), and some cases in Argentina, Australia, Morocco, and the United Arab Emirates⁽²⁹⁾; there are probably also cases in Brazil. Most patients are males aged 20 to 55 years, especially in those who have sex with other males. Countries such as Canada, the United Kingdom and the United States have begun to implement a strategy called 'ring vaccination' that attempts to stop the spread of monkeypox. It involves administering smallpox vaccines - which may be 85% effective against monkeypox because they are related viruses - to people who have been exposed through close contact with an infected person.

IS THE WORLD STILL UNPREPARED FOR THE NEXT PANDEMIC?

In May 2021, the Independent Panel for Pandemic Preparedness and Response called for the urgent implementation of a package of transformative interventions to end the COVID-19 emergency and make it the last pandemic of such devastation. The Panel's recommendations addressed the areas of leadership at the highest level, equity, new funding, a stronger WHO, modern disease surveillance, and national preparedness. However, in the year since the report's release, an additional 2 to 8 million people were reported to have died from COVID-19. Excess deaths from COVID-19 range from 14 to 21 million, a crisis that has weakened the ability of countries to withstand other global problems. The combined impacts of the pandemic, the Russian invasion of Ukraine, and rising inflation in many countries are estimated to push up to 95 million more people into poverty in 2022 compared to pre-pandemic projections. The consequences are more illness and death, strained health systems, deepening social divisions, wid-

ening economic inequalities, and more losses for households. Governments should report transparently on research and development funding and make public funding conditional on agreements that guarantee technology transfer and voluntary licensing to ensure equitable distribution. National coordination of pandemic preparedness should be overseen by heads of state and government, with sustained national investment in public health and broader health and social protection systems for preparedness and response, including policies that address inequities to protect the vulnerable⁽³⁰⁾.

Over six waves of COVID-19 in Japan, the number of cases and deaths per capita has been significantly lower than in other G7 countries, despite having the world's most aged population and being densely populated. Japan has high vaccination rates, especially among the elderly, and the use of face masks is common. The Japanese constitution prohibits strict closures, and social and economic activities have been maintained. At the start of the pandemic, more than 8,000 public health nurses at 400 public health centers were conducting 'retrospective' contact tracing for diseases such as tuberculosis to identify how people were infected, and that system was quickly adapted to COVID-19. By the end of February 2020, scientists had identified many transmission clusters and realized that most infected people did not infect anyone else, but a few infected many. Respiratory viruses were known to be transmitted mainly through aerosols, which led to warnings about the '3Cs' (*sanmitsu*): closed environments, crowded conditions, and close contact environments. People were asked to avoid karaoke bars, nightclubs, and indoor dining, which was largely complied with. In addition, there are booster vaccinations, antivirals, improved clinical care and public health measures such as CO2 monitors to control ventilation in public buildings⁽³¹⁾.

Meanwhile, and given the increase in COVID-19 infections, the U.S. Department of Justice on May 31 asked a federal appeals court to overturn a U.S. District Court judge's April order declaring illegal the government's mandate to require facemasks on airplanes, buses and at transit centers. Hours after the Florida federal judge declared the mandate illegal, the Biden administration said it would stop enforcing it⁽³²⁾.



THE BRIGHT SIDE OF THE PANDEMIC

At the beginning of the third year of the pandemic, millions of people have lost their lives and there are many patients with long COVID. Looking at the disaster wreaked on health systems, the economy, employment, family life, and the education of children and young people, it is hard to see whether this pandemic has left anything positive. However, Topol has found something that will transform the ability to prevent and treat a wide range of diseases in the coming decades. Prior to COVID-19, the combination of mRNA and nanoparticles had never been administered on a large scale, but now more than 2 billion doses have been administered in more than 170 countries around the world. The history of mRNA and nanoparticles had been building over many decades, starting in the 1960s, but the first clinical trials occurred around 2015 and the first approval by the Federal Drug Administration for testing in infectious diseases beyond SARS-CoV-2 was in 2019. Thus, mRNA + nanoparticle vaccination led to tick resistance and experimentally prevented infection with *B. burgdorferi*, the agent of Lyme disease. The potential of these multivalent mRNA + nanoparticle vaccines to protect against COVID, influenza and respiratory syncytial virus has also been evidenced in clinical trials and will form the basis for pan-sar-beocovirus and pan-β-coronavirus vaccines in development. This premise of inducing immunity against a target also applies to cancer, with notable success of immunotherapy directed at specific forms of cancer, intravenously or directly into the tumor. Similarly, genetic disorders would be targets for protein antigens, with clinical trials in conditions such as cystic fibrosis, ornithine transcarbamylase deficiency and transthyretin amyloidosis. There are also so-called tolerogenic vaccines, with the opposite effect, in an experimental model of multiple sclerosis and with important implications for all autoimmune diseases, such as type 1 diabetes, rheumatoid and psoriatic arthritis, systemic sclerosis, systemic lupus erythematosus and several others. Topol asserts that, someday, we will look back on the pandemic as an extraordinary renaissance in biomedicine, which has given rise to a validated pluripotent platform with seemingly limitless refinements and applications⁽³³⁾.

Finally, the Catholic University of Leuven in Belgium has announced that its researchers have

succeeded in identifying the key that allows the COVID-19 virus to attack cells, managing to close the lock to block the binding points of the S protein of the virus and prevent it from interacting with the cell, thus preventing infection. This opens the hope of an antiviral therapy administered by aerosol in case of infection or risky contact. This discovery is also of interest for counteracting other viruses with similar binding factors^(34,35).

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