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After Omicron

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Editor-in-Chief

That was fast. Writing this column in early December, we stated "As of today (December 7, 2021), there are only 55 confirmed cases of the Omicron variant in the United States. By the time you read this column, the Omicron variant will have eclipsed Delta as the dominant variant of SARS-CoV-2" (*ASA Monitor* 2022;86:1-7). The next month we wrote about Omicron virulence, noting that it was reduced from prior variants but still deadly (*ASA Monitor* 2022;86:1-5). Since then, Omicron cases have peaked worldwide and are now declining. What's next?

Most of us are "sort of" immune

Understanding our post-Omicron trajectory requires a basic understanding of the adaptive immune system. Our dendritic cells constantly scan for pathogens. When a pathogen is identified, dendritic cells eat it and migrate to lymph nodes, where they present the pathogenic antigen to activate cytotoxic (CD8, "killer"*) T cells, helper (CD4) T cells, and B cells. The cytotoxic T cells identify and kill any cells with the antigen on the surface (e.g., cells infected with the virus). The helper T cells activate B cells, which proliferate into plasma cells

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We Have Met the Enemy (and They Are Us)

Ronald L. Harter, MD, FASA

The origin of the title of my Leadership Perspective, for those of you unfamiliar with it, is a cartoon character named Pogo, dating back more than five decades. True historians may recognize it as a play on a famous quote by U.S. Navy Master Commandant Oliver Perry during the War of 1812, written in a letter to Major General William Henry Harrison: "We have met the enemy and they are ours."

The origin of Pogo's quote was a poster that Pogo's cartoonist Walt Kelly made for Earth Day 1970, depicting Pogo in a wooded area, surrounded by litter strewn across the ground as far as the eye could see. The obvious message being that we are the source of many of our own problems.

As we assess the list of challenges facing physician-delivered and physician-led anesthesia care in the U.S., there is a component of "they are us" for at least one of the primary items on that list.

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SPECIAL SECTION

Incident Command System: The Time to Prepare Is Now 25-30

Guest Editor: Stacey Watt, MD, MBA, MHPE, FASA

Health Equity Curriculum for Anesthesiology and Surgery Residents: A Necessary Step Toward Addressing Perioperative Disparities

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Health disparities are defined as particular types of health differences closely linked with economic, social, or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater social or economic obstacles to health based on their racial or ethnic group, religion, socioeconomic status, gender, age, or mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion (Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. 2002). Health care disparities are differences in access to and delivery of health care itself due to the above factors.

Health disparities are pervasive across all aspects of medicine, though they are relatively under-recognized in surgery, anesthesia, and pain management. Several studies illustrate the existence of perioperative health inequities, which result in health and health care disparities that negatively impact patient outcomes and experiences. One

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PERIODICALS

In the Know: After Omicron

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(factories that produce antibodies) and memory B cells (quiescent factories primed for future infections). Some helper T cells become memory T cells, ready to trigger another response should the pathogen invade again.

When we were children, we were all exposed to the endogenous coronaviruses HCoV-HKU1, HCoV-NL63, HCoV-OC43, and HCoV-229E (*J Clin Virol* 2012;53:135-9). Our antibodies waned over a few months to years (*J Infect Dis* 2018;217:1728-39; *Nat Med* 2020;26:1691-3), which is why we kept getting sick from these viruses. Fortunately, our memory B and T cells were ready to respond when we got reinfected. Remember the "worst cold you ever had in your life?" That was probably a coronavirus. While it made you pretty sick, thanks to immunity dating back to childhood, you didn't die.

Between vaccination and infection, almost everyone now has some immunity to SARS-CoV-2. In the United Kingdom, more than 99% of adults have antibodies to SARS-CoV-2 (asamonitor.pub/3H-8B7Ld). The Centers for Disease Control and Prevention does not conduct similar surveillance. However, a U.S. survey of 1,555,745 blood donations through June 2021 demonstrated 87% seropositivity by the end of the study (*Clin Infect Dis* February 2022). Ongoing vaccination efforts along with the subsequent Delta and Omicron surges have likely brought that near 100% in the U.S. as well.

Both vaccination and infection induce the full panoply of adaptive immune responses: plasma cells crank out antibodies for a couple of months, cytotoxic T cells hunt and destroy infected cells, helper T cells regulate the process, and memory B and T cells multiply, preparing for the next infection. For a few months, antibodies prevent us from getting infected again by destroying the virus before it reaches the target cells. However, antibody protection wanes over a few months. Cytotoxic T cells lose interest, albeit a little more slowly than antibodies wane (*Nat Immunol* 2021;22:620-6). Within a few months we are again vulnerable to infection.

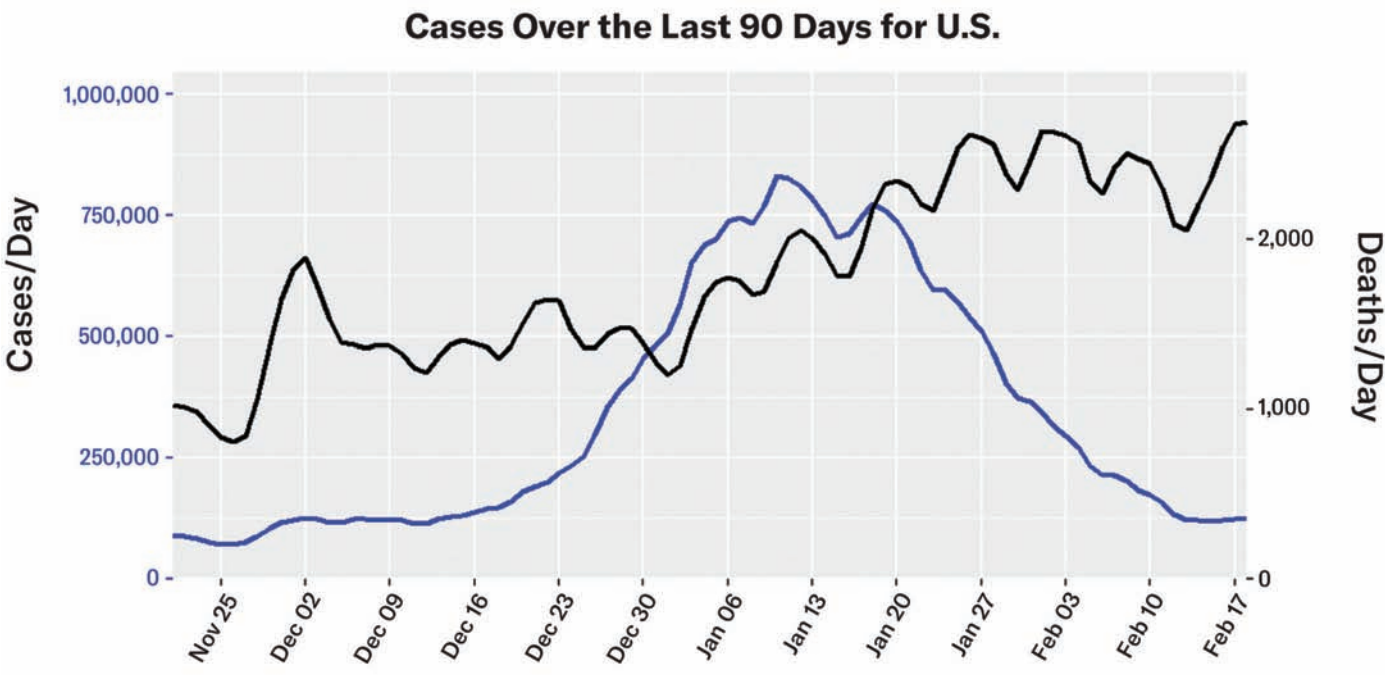

Figure 1: Cases (blue line) and deaths (black line) over the past 90 days for the United States.† Note the y-axis values for cases is on the left and deaths is on the right. The Omicron surge in cases peaked the second week in January. Daily death rates reached a plateau about four weeks later but have slowly decreased through February.

Fortunately, our adaptive immune system is primed for battle. In response to a booster vaccine, or infection with SARS-CoV-2, the memory cells respond quickly. Memory B cells proliferate as plasma cells, cranking out another round of antibodies. Memory T cells spawn new populations of cytotoxic and helper T cells. Cytotoxic T cells trained on prior variants readily recognize Omicron (*Nature* January 2022). We may get sick, but our primed immune system will get us through it. This is the real purpose of vaccination. Not getting COVID-19 in the short term is a big plus, but the real goal is inducing memory cells to protect us over the long term.

The adaptive immune response decreases with age and certain conditions. The influenza vaccine for those over 65 years of age is a four-fold higher dose to compensate for the reduced immune response associated with age. Immunosuppression is another major cause of reduced adaptive immunity. Patients who have undergone transplantation or who have cancer, inflammatory arthritis, or autoimmune disease may take drugs that suppress the immune system.

We are all "sort of" immune, depending on age, our health, and exactly how and when our adaptive immune system met SARS-CoV-2.

What will happen this spring?

As shown in Figure 1, daily case rates in the U.S. peaked during the second week in January and have decreased to pre-Omicron rates. Daily death rates reached a plateau in late January and have been gradually decreasing throughout February. The reason that death rates decrease more slowly than case rates is the high variability in the interval between diagnosis of COVID-19 and death.

"COVID-19 remains a deadly disease for the elderly, the frail, and the immunosuppressed. Those with compromised immunity need to avail themselves of boosters when they are available and maintain effective masking, social distancing, and avoiding indoor crowds. They should take Paxlovid as soon as they are diagnosed with COVID-19."

Figure 2 shows the most recent data from South Africa. The Omicron surge peaked in mid-December. A few weeks later, ward hospitalizations, the census of patients in high care or ICU, and the number of patients requiring ventilators started to decrease. However, U.S., deaths in South Africa have not decreased since reaching a plateau.

The most recent briefing document from the Institute for Health Metrics and Evaluation (IHME) at the University of Washington notes that the recent decline in cases is "likely due to the exhaustion of susceptible individuals in the population" (asamonitor.pub/3p0tkbR). That is their way of saying that most of us have some immunity. The IHME predicts that deaths will drop precipitously in late February and that by June there will be *only* 29,000 additional deaths. The sustained peak in deaths shown in Figures 1 and 2 suggests that the IHME forecast may be optimistic.

Most states are lifting mask mandates and removing other non-pharmaceutical interventions. Since most of the population has some immunity, the IHME notes that removing mandates should have little effect on daily case rates.

COVID-19 remains a deadly disease for the elderly, the frail, and the immunosuppressed. Those with compromised immunity need to avail themselves of boosters when they are available and maintain effective masking, social distancing, and avoiding indoor crowds. They should take Paxlovid as soon as they are diagnosed with COVID-19 (*N Engl J Med* February 2022). Paxlovid can be hard to find, but healthdata.gov lists pharmacies with available inventory (asamonitor.pub/3BKsYeL). There was hope that prophylactic cilgavimab/tixagevimab (Evusheld) might ward off infection, but it may be ineffective against Omicron (*Clin Infect Dis* February 2022).

What will happen next summer?

This summer the Omicron surge will have lost steam with nearly 100% population immunity. The surge in deaths shown in Figures 1 and 2 will vanish. For those with healthy immune systems, life will seemingly have returned to normal.

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** Not to be confused with natural killer T cells, which are part of the innate immune system.*

†From SL Shafer Weekly COVID-19 update for February 28, 2022. The update is freely available from steven.shafer@stanford.edu.

SARS-CoV-2 will continue to circulate, finding susceptible individuals among the unvaccinated, the immunocompromised, and those with waning immunity. Fortunately, additional booster shots should be widely available this summer. Booster shots will help compensate for waning immunity or deficient immune systems. While the booster shots will help prevent infection, long COVID, and secondary transmission, that's not the primary reason to get boosted (asamonitor.pub/3v2cNIj; *Science* January 2022). The main reason for a booster shot is to enhance your B and T memory cells, allowing a quick and robust response from future infections long after your antibodies have waned.

In additional to the existing vaccines, you will likely be able to get one of the Omicron-specific mRNA vaccines under development by Pfizer and Moderna. It isn't clear that you should prefer an Omicron-specific vaccine. In animal studies, the original mRNA vaccines used against the ancestral strain efficiently boost antibodies to Omicron (*N Engl J Med* January 2022; *JAMA* 2022;327:639-51). Animal studies suggest that the Omicron-specific mRNA vaccines are no better at boosting against Omicron than the original mRNA vaccines (*Nature* February 2022; *bioRxiv* February 2022; *bioRxiv* February 2022). They may even provide *less* protection against non-Omicron strains (*bioRxiv* January 2022). Unfortunately, the Omicron-specific vaccine trials have slowed down because the Omicron surge left very few susceptible subjects to enroll in vaccine trials. Additionally, during periods of low transmission, it may be more difficult to accurately assess efficacy endpoints.

What will happen next winter?

SARS-CoV-2 variants of concern emerge every six to 12 months, so it is likely a new variant will appear later this year. This next variant may already be here. The BA.2 strain of Omicron that is gradually replacing BA.1 is so genetically distinct from the BA.1 strain that it may earn its own Greek name (likely Pi). Omicron variant BA.2 is more infectious than variant BA.1 (*medRxiv* January 2022). It may also be more virulent (*bioRxiv* February 2022). Omicron BA.2 is outcompeting BA.1 in Denmark and the U.K., including reinfecting some individuals who have recovered from BA.1 (asamonitor.pub/3LLpWLU).

SARS-CoV-2, like influenza, prefers cold, dry winter air. There will likely be a surge next winter, possibly exacerbated by a more immune-escaping variant. However, SARS-CoV-2 will encounter a worldwide population with substantial baseline immunity. Waning antibodies may lead to a surge in infections, but B and T memory cells are primed and ready. Our memory cells from vaccination or infection are broadly potent, at least against Omicron (*Nature* January 2022). Our adaptive immune system will prevent the winter surge in infections from causing a proportional surge in deaths.

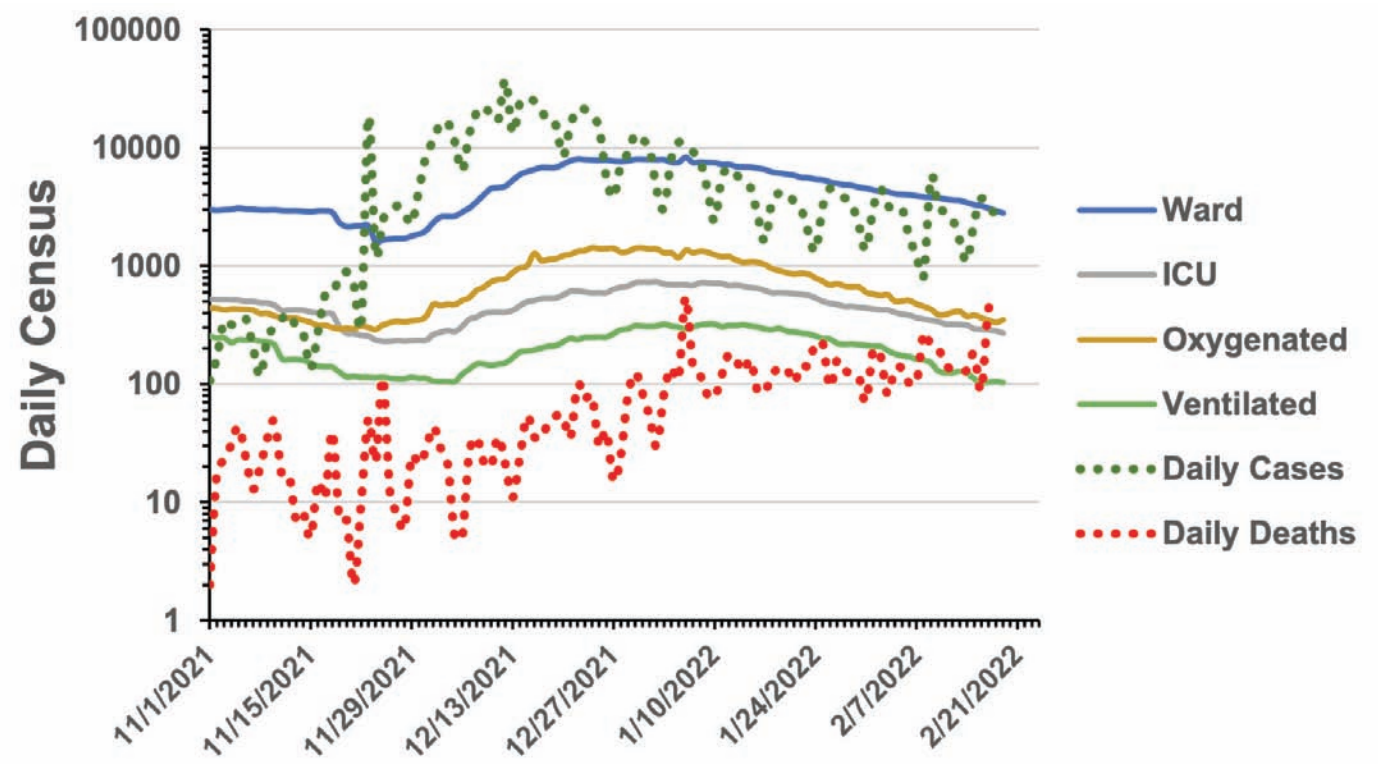

Figure 2: Case rates, death rates, and hospitalization census from South Africa. Cases have been declining since the second week of December. The number of patients requiring oxygen has declined since the end of December. The number of patients on ventilators has declined since the second week in January. However, deaths reached a plateau in mid-January and have not declined since. (Case and death rates are from the Center for Systems Science and Engineering at Johns Hopkins University. Daily census data are from the National Institute for Communicable Diseases of South Africa.)

Is the pandemic over?

No. According to the Dictionary of Epidemiology, a pandemic is "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, and usually affecting a large number of people" (A Dictionary of Epidemiology. Fourth Edition, 2001). With hundreds of thousands of new cases every day, the pandemic is certainly not over. The pandemic will be with us at least until the end of next year's winter surge. This is similar to the fourth wave of the 1918 influenza in 1920, months after the pandemic supposedly ended (asamonitor.pub/3sXpamw).

SARS-CoV-2 has changed in the past two years, but so have we. Most of us have acquired some immunity. Everyone in developed countries (except for the very young) has access to vaccines. We will have increased access to booster shots.

There is no herd immunity for SARS-CoV-2, but that was always a mirage (*Nature* 2022;601:165). Instead, widespread adaptive immunity anchored in our immune systems will protect us from severe illness, a result of vaccination, infection, or both.

We are now armed with effective treatments, like Paxlovid and its successors, that can halt the progress to severe disease. More vaccines and therapies are on the way.

There is no reason to be resigned to getting COVID-19. Vaccines provide equivalent immunity without the risk of long COVID or transmission to others. Non-pharmaceutical interventions prevent infection, just as they always have. In a recent perspective in the Washington Post, Robert Wachter, Professor and Chair of the Department of Medicine at the University of California San Francisco, explains in glorious detail his risk analysis for whether to wear a mask to a reunion of friends and family (asamonitor.pub/3p3LSbc). The wise choice is to continue to wear a mask when around others, avoid indoor crowds, and practice social distancing until the local incidence drops below 1%.

The endgame

SARS-CoV-2 is now endemic (*Nature* 2021;590:382-4). To avoid illness, complications of COVID-19, and transmission to others we will likely receive regular vaccinations, just like the flu vaccine, for many years. Despite yearly vaccination programs, influenza kills 12,000 to 50,000 Americans every year. SARS-CoV-2 may continue to kill tens of thousands every year despite the availability of vaccines. Vaccines decrease the burden of disease but cannot eliminate it, particularly for vulnerable populations.

By infecting tens of thousands each day, SARS-CoV-2 has plenty of opportunity to evolve, creating new variants with increased infectivity and immune escape (*Sci Rep* 2021;11:15729; *ACS Infect Dis* February 2022). Moreover, since novel variants with heightened immune escape may be evolving within single immunocompromised individuals (*Science* 2021;374:1179; *Nature* 2022;602:26-8), immune-escaping variants may even emerge with low rates of infection.

We don't know if SARS-CoV-2 will continue to be as deadly as it becomes endemic. As noted by Singh et al., "Reduced pathogenicity of SARS-CoV-2 combined with mounting population-level immunity will likely cause a reduction of severe cases of COVID-19, leading to an apparent abatement of the pandemic, followed by endemic circulation of low pathogenic SARS-CoV-2 variants. A similar evolutionary trajectory may have led to the establishment of current low-pathogenic endemic human coronaviruses." (*Virol J* 2021;18:166)

As the editors of *Nature* summarize the endgame: "*SARS-CoV-2 will become endemic rather than extinct, with vaccines providing protection from severe disease and death, but not eradicating the virus. The virus will continue to circulate and change, and governments must continue to rely on the guidance and advice of scientists. We will not always be able to predict the virus's path, and we must be ready to adapt with it*" (*Nature* 2022;601:165). ■