American Society of Anesthesiologists

Volume 86 ■ Number 2 ■ February 2022
asamonitor.org

ASA Monitor®

THE LEADING SOURCE FOR PERIOPERATIVE HEALTH CARE NEWS

Omicron: Back to Square 1.1

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Editor-in-Chief

As of today (December 7, 2021), there are only 55 confirmed cases of the Omicron variant in the United States (asamonitor.pub/3rQQPXg; asamonitor.pub/333NABm). By the time you read this column, the Omicron variant will have eclipsed Delta as the dominant variant of SARS-CoV-2. The reason for this gloomy prediction is that it took just eight weeks for Omicron to eclipse the Delta variant in South Africa. Omicron is now quickly spreading throughout the world (Figure 1). We aren't exactly back to square 1, thanks to vaccines and therapeutics; however, it appears we are heading back to square 1.1.

This was expected

In a July paper in Scientific Reports, Rella et al. modeled the relationships between the rates of transmission for SARS-CoV-2 and the potential emergence of vaccine-resistant strains (*Sci Rep* 2021;11:15729). The most striking finding was counterintuitive: The highest risk for the establishment of a vaccine-resistant viral strain is when *"a large fraction of the population has already been vaccinated but the transmission is not*

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Figure 1: Worldwide spread of Omicron as of December 7, 2021 (asamonitor.pub/3DHIzw9). (From nextstrain.org. The Omicron representation is maintained by Trevor Bedford).

Why ASA Community Is My Go-To for Questions That Matter

Jennifer R. Root, MD, FASA

As a young physician in the late 1990s, I found myself in a very small town with just two partners covering a small community hospital, far from the sense of community I had enjoyed as a resident in a large academic center. The internet was just getting started at the time, and I recall wishing I could reach out via this new resource to experts within the many subspecialties of anesthesiology for insights and input on certain complex cases. Surely, I thought, this new "world wide web" could facilitate the timely sharing of information to help improve the care and safety of our patients... couldn't it?

Fast forward to today and the comparatively many opportunities for anesthesiologists to connect online. On the downside, and in contrast to in-person professional gatherings, social media platforms such as Reddit and Twitter can be a bit of Wild West in terms of information sharing. Enter the new ASA Community, a private discussion forum designed

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Reflections on an Exemplary Career and Life

Paul Pomerantz, FACHE

On Sunday morning, November 28, Chris Wehking, ASA's Business Events Strategy Executive, passed away following a long battle with cancer, surrounded by his loving wife and daughters. You've read about Chris in the ASA President's Monday Morning Outreach messages and in press releases. But in this column, I wanted to share some personal reflections.

Chris Wehking at Euroanaesthesia 2018 in Copenhagen.

I met Chris almost 20 years ago when he came to work for the American Society of Plastic Surgeons (ASPS) as Director of Meetings and Exhibits. He impressed ASPS, and later ASA, with his professionalism and humility. He was focused on interpersonal relationships, customer service, continuous improvement, and creating the best possible experiences.

Chris joined ASA in 2010 and rapidly transformed our planning and events team to be among the best in medicine. For those of you who attend ASA meetings, you have a sense of their quality.

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In the Know: Omicron: Back to Square 1.1

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controlled." Transmission must be controlled to prevent the emergence of strains that escape vaccine immunity. *"Plans to vaccinate individuals with a high risk of a fatal disease outcome followed by a drive to reach herd immunity while in uncontrolled transmission among the rest of the population is likely to greatly increase the probability that a resistant strain is established, annulling the initial vaccination effort."*

That is exactly what has happened. Uncontrolled transmission has continued due to delays in providing vaccines to low- and middle-income countries, delayed vaccination in children, and vaccine hesitancy in large swaths of the population worldwide. The emergence of the Omicron variant on approximately October 1, 2021, has undone much of the progress we have made against SARS-CoV-2 (asamonitor.pub/3DxyMrr).

Emergence in South Africa

In early November, a surge of COVID-19 cases was noted in the Gauteng province of South Africa (asamonitor.pub/3y8tuRQ). Although the Gauteng province is the smallest province in South Africa, it is home to approximately one-fourth of the population (~15 million individuals) and includes Johannesburg, among the largest cities in the world, and Pretoria, the capital of South Africa.

On November 25, the Network for Genomic Surveillance South Africa announced that a highly mutated SARS-CoV-2 variant was responsible for the November surge. The following day, the World Health Organization designated the variant "Omicron," noting that "given mutations that may confer immune escape potential and possibly transmissibility advantage, the likelihood of potential further spread of Omicron at the global level is high" (asamonitor.pub/3pCnsFv). The European Centre for Disease Prevention and Control (ECDC) similarly noted, "given its immune escape potential and potentially increased transmissibility advantage compared to Delta, we assess the probability of further introduction and community spread in the EU/EEA as HIGH" (asamonitor.pub/3oA1VxU).

Emergence in the U.S.

On December 1, 2021, the CDC issued a statement regarding the first confirmed case of the Omicron variant within the U.S., a California resident who had returned from South Africa on November 22, 2021 (asamonitor.pub/3oAILrt). The following day, there was a confirmed case from Minnesota in a man who had recently traveled to New York City to attend an anime convention (asamonitor.pub/3yb64LD). Roughly half of his 35 contacts at the conference have since tested positive for SARS-CoV-2 (asamonitor.pub/3dzQ7p0). As of this writing, Omicron has been reported in 17 states (asamonitor.pub/3EyD42Z).

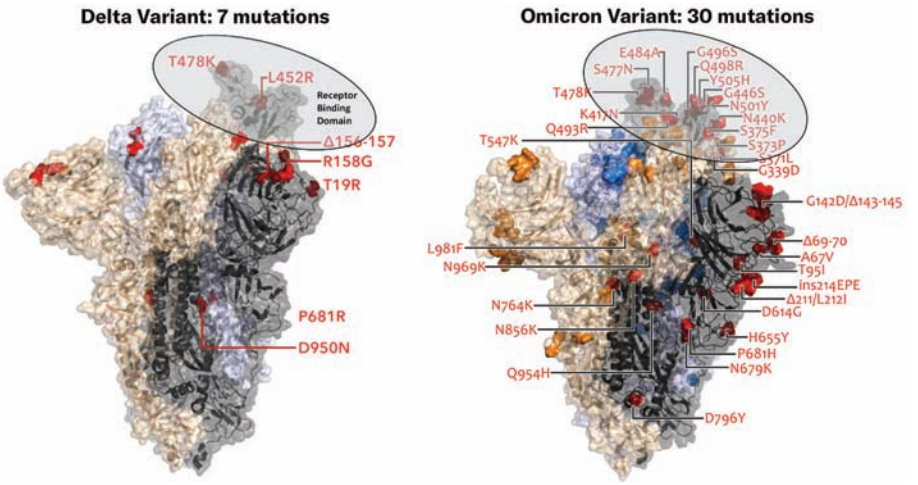

Figure 2: The seven mutations on the spike protein of the Delta variant increased infectivity, allowing Delta to out-compete all prior variants. The spike protein of the Omicron variant has 30 mutations. The receptor binding domain is the part of the spike protein that recognizes the human ACE2 receptor. The receptor binding domain of the Delta variant has only two mutations The receptor binding domain of the Omicron variant has 15 mutations. (Image credit: COG-UK Mutation Explorer: https://sars2.cvr.gla.ac.uk/cog-uk).

Mutational profile

Omicron emerged with 30 mutations in the spike protein, the surface protein that recognizes the human ACE2 receptor (Figure 2). The part of the spike protein that binds to the ACE2 receptor initiating entry into the cell is called the "receptor binding domain." Extensive analyses of the receptor binding domain have shown that increased binding affinity leads to increased infectiousness (*Nat Microbiol* 2021;6:1188-98; *bioRxiv* February 2021).

Fifteen of the 30 mutations in the Omicron spike protein are in the receptor binding domain (Figure 2). This is in marked contrast to the Delta variant, which only has two mutations in the receptor binding domain. Computational analysis has demonstrated that the Omicron variant will likely have significantly higher affinity for the human ACE2 receptor (*bioRxiv* December 2021). This will likely lead to greater infectiousness than Delta.

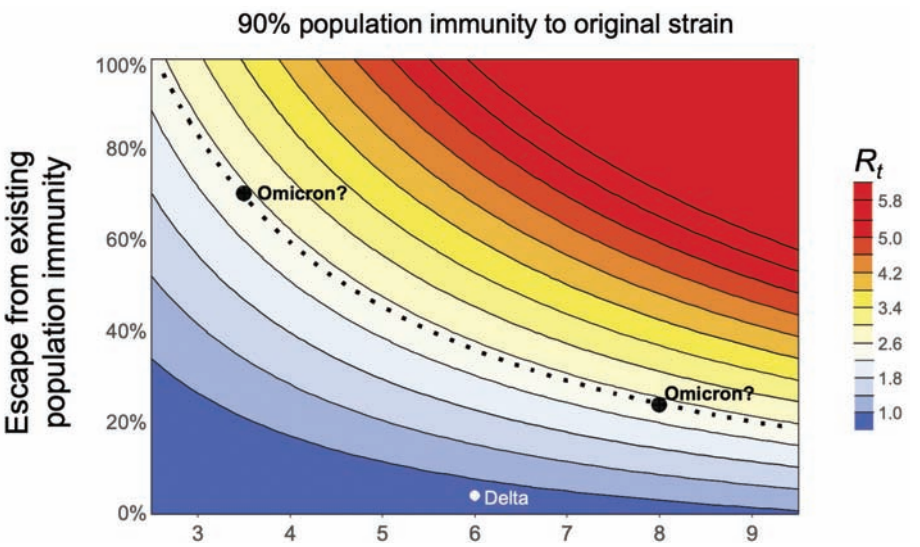

Figure 3: It appears that the current reproduction number (R_t) for Omicron is about 2.5, which is why it is outcompeting Delta in South Africa (current R_t <1). The dashed line shows immune escape vs. intrinsic infectiousness (R_0) for R_t = 2.5. Because most of the population now has pre-existing immunity from either infection or vaccination, Omicron may be outcompeting Delta either by virtue of higher intrinsic infectiousness (around 8 in the figure below) or higher immune escape (about 75% in the figure below). Adapted from Trevor Bedford (asamonitor.pub/31l145x).

All current vaccines target the spike protein. Investigators have identified many mutations in the spike protein that impair antibody binding (*Cell Host Microbe* 2021;29:44-57). At least eight of the mutations on the Omicron spike protein are known to impair antibody recognition (asamonitor.pub/3pHrD2Q; asamonitor.pub/3pFjvzL).

Infectivity and immune escape

R_t is the current "reproduction number," the number of new infections caused by each infected individual. Prior to the introduction of Omicron, R_t in South Africa was approximately 0.8, meaning that each person infected, on average, 0.8 individuals. As a result, COVID-19 cases were decreasing. Over the past two weeks, R_t in South Africa has surged to approximately 2.5 (asamonitor.pub/3oCr5f5). That is why cases are surging in South Africa: each individual who gets Omicron passes it along to about 2.5 individuals.

Initial data from South Africa show that Omicron is associated with a substantially higher risk of reinfection than previous variants (*medRxiv* December 2021). Thus, Omicron has substantially higher immune escape than previous variants. Put another way, a higher risk of reinfection means that vaccination or prior infection with COVID-19 isn't as protective against infection by the Omicron variant as it was against infection by the Delta variant.

Figure 3 shows the relationship between intrinsic infectiousness, called R_0, immune escape, and the current reproduction number (asamonitor.pub/31l145x). R_0 is the reproduction number when the virus was first introduced. It is estimated that the initial Wuhan strain had an R_0 of about 3 (*medRxiv* December 2021). Delta exploded worldwide, replacing earlier strains, because it was about twice as infectious, with an R_0 of 6. However, as immunity increased, the number of susceptible individuals dropped, so the current reproduction rate for Delta is less than 1.

As shown in Figure 3, Omicron's current R_t of 2.5 in a population that is mostly immunized by vaccination or prior infection is necessarily the result of its elevated levels of immune escape. Immunization from vaccination or prior infection is less effective at preventing infection. The intrinsic infectiousness (R_0) for the Omicron variant might actually be less than for the Delta variant. However, because most of the population is once again susceptible, the Omicron variant will produce another wave of infections.

Infection fatality rate

As of today, South Africa is not seeing a surge in deaths from Omicron. Initial anecdotal reports from physicians in South

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Africa have been positive regarding disease severity (*Nature* 2021;600:197-9). There are several possible explanations:

1. As shown in Figure 4, the surge started in mid-November. It may be too early to draw any conclusions from the lack of an increase in deaths. However, Figure 4 also shows hospitalizations, ICU admissions, and patients requiring mechanical ventilation. These are nearly unchanged, despite a surge in cases from about 300 per day to over 10,000 per day now.
2. Any immunity, even if reduced, will reduce the incidence of death. That has been a consistent finding since the beginning of the pandemic. If most of the infections are in vaccinated individuals, the vaccine may still be proving effective in preventing death.

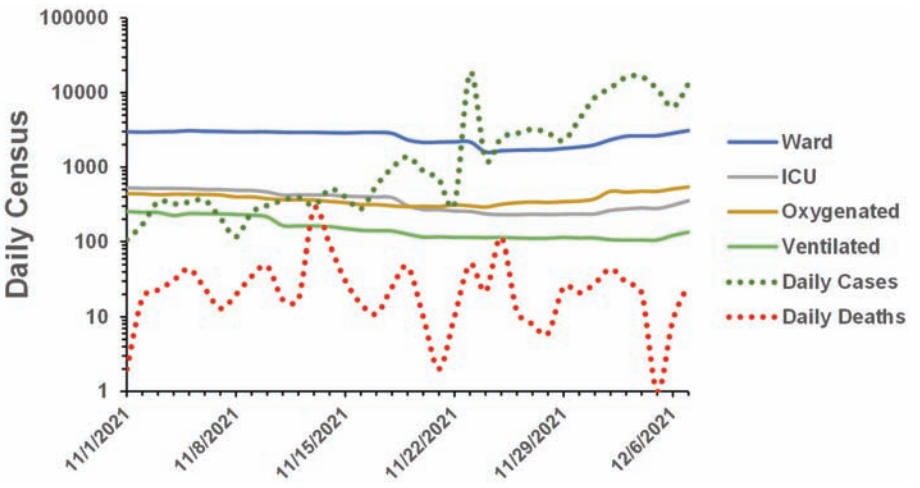

Figure 4: South Africa publishes a daily census of patients with rt-PCR diagnosed COVID-19. Since mid-November, cases in South Africa have increased from about 300 new cases/day to more than 10,000 case/day (dotted green line). Despite this surge, there has been no change in daily deaths (dotted red line) and only a modest increase in the number of patients hospitalized, transferred to the ICU, or requiring ventilation. (Case and death data from Hopkins, hospitalization data extracted from the daily NICD National COVID-19 Hospital Surveillance reports.)

"By the time you read this, we will know whether Omicron is truly less virulent than previous variants. This will have an enormous effect on whether we see just a wave of Omicron infections next year, or whether we see a wave of Omicron infections *and deaths*."

3. It is possible that Omicron is less intrinsically lethal than prior variants. The four endemic coronaviruses are not associated with a high mortality. While this may be a result of immunity acquired in childhood, it is possible they are intrinsically less virulent.

By the time you read this, we will know whether Omicron is truly less virulent than previous variants. This will have an enormous effect on whether we see just a wave of Omicron infections next year, or whether we see a wave of Omicron infections *and deaths*.

Vaccine efficacy

So far there is only one study looking at the efficacy of a vaccine against Omicron (asamonitor.pub/3DDen4g). The authors documented a 41-fold reduction in neutralizing capacity of the Pfizer BNT2b2 mRNA vaccine against Omicron, a deeply concerning finding. All subjects had received the BNT2b2 vaccine. Half of the subjects had also been infected with SARS-CoV-2. Similar reductions were seen in all individuals. However, because those who were infected in addition to being vaccinated had higher antibody titers, most still had sufficient immunity to prevent infection. Since booster shots also increase antibody titers, booster shots may increase immunity to Omicron.

This supports the finding of high levels of immune escape (the left point in Figure 3) as the primary reason for the rapid surge of the Omicron variant. It also provides strong impetus for the introduction of mRNA vaccines specifically directed toward the Omicron spike protein. Both Pfizer and Moderna have stated that they plan to introduce new vaccines within a few months.

Should you still get vaccinated? Yes, yes, yes, yes, yes. As has been emphasized for the past year, vaccination is the single most important intervention toward ending the pandemic (asamonitor.pub/3DxyMrr). However, vaccine alone isn't sufficient. To minimize the Omicron surge, we will need to maintain nonpharmaceutical interventions such as testing, tracing, mask-wearing, and social distancing.

SARS-CoV-2 therapeutics

Monoclonal antibody cocktails have proven to be reasonably effective therapies in hospitalized patients. However, there is growing evidence that monoclonal antibodies and antibody cocktails may prove less effective against Omicron (*bioRxiv* December 2021). This is a result of the same immune escape mutations that account for the current surge in South Africa.

Next year, we will see two new oral drugs specifically directed against SARS-CoV-2: Molnupiravir (Merck) and Paxlovid (Pfizer). Molnupiravir reduced the risk of hospital admission by 30% in the pivotal trial, a modest benefit (the drug was only narrowly recommended by the FDA panel for approval) (*BMJ* 2021;375:n2984). Pfizer's Paxlovid is 89% effective at preventing hospitalization (*BMJ* 2021;375:n2713). Importantly, both drugs interfere with highly conserved viral proteins, meaning they should be effective against Omicron. It is likely that these two oral therapies will be available in early 2022. They may be game-changing in reducing the death toll from SARS-CoV-2 next year.

In August 2021, William Haseltine proposed a four-pronged approach for the long-term control of COVID-19 (asamonitor.pub/2Z45MsR). The first prong is vaccination. Vaccination is critically important. However, vaccination alone is insufficient. The arrival of Omicron has driven this point home.

The second prong is antiviral treatment and prophylaxis. We do not yet have prophylactic drugs for SARS-CoV-2. However, molnupiravir and Paxlovid can be given orally in the early phase of the disease, when the greatest viral replication occurs. These would reduce morbidity, mortality, and transmission.

The third prong is public health interventions. These include testing, contact tracing, and isolation, as well as common-sense interventions such as masks and social distancing. As emphasized by Rella, these must be maintained until the pandemic is behind us (*Sci Rep* 2021;11:15729). Failure to do so will bring additional variants with enhanced immune escape.

The last prong is global coordination. Haseltine emphasizes the critical importance of sharing vaccines and pharmaceuticals with low- and middle-income countries. He also emphasizes the need for global collaboration among scientists and medical specialists. The rapid identification of Omicron by South African scientists shows how critical global cooperation is for ending the pandemic. Had South Africa not had extensive genomic surveillance, we might have only discovered Omicron when we saw an extraordinary and unexplained surge in the U.S.

It is this last point that requires emphasis. South Africa has provided an enormous service to global health by rapidly identifying the Omicron variant. In the process, our colleagues in South Africa have illustrated that we live in a tightly interconnected global community. As Figure 1 shows, what occurs in one part of the world has an immediate impact on the rest of the world.

The SARS-CoV-2 pandemic will not be over anywhere until it is over everywhere. ■

Editor's note: We would like to notify readers of an error in the January 2022 editorial "The New Normal." The sentence "Part of the New Normal for elective surgery will be positive strand RNA testing for patients with a history of infection to determine whether patients remain infectious" should have used the terminology *"negative strand RNA testing."* The online version of the article has been corrected and can be accessed at **asamonitor.pub/3EtUqgN**. We apologize for any confusion this may have caused.