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Omicron: What Happens Next?

Richard A. Marfuggi, MD, DMH
Commissioner
American Medical Association Foundation

Steve Brozak, DMH
Chief Executive Officer
WBB Securities

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Omicron may be the latest challenge the world faces in dealing with the SARS-CoV-2 virus (the one responsible for COVID-19), but it does not condemn us to relive the horrors of March 2020, when COVID-19 first appeared. We have learned, sometimes painfully, quite a lot about the virus, its mode of action, and what constitutes both effective and non-effective means of dealing with it. That said, there is much more to learn and to address.

COVID is Here to Stay

To many, virology and public health have been areas of study relegated to scientists, researchers, health care professionals, and departments of health. Most people deem both areas to be important, but they have considered them of little import in their day-to-day lives. But because *COVID is here to stay,* we would all do well to become more familiar with virology and public health. As of this writing, each of us would be hard-pressed to find a single individual who has not been affected by the pandemic. In the United States alone, we know of more than 840,000 deaths attributed to COVID. The actual number is likely much higher. Add to that the disruption of our economy, our schools, our social interactions, and our sense of personal well-being, and we quickly realize that no one is spared.

This report attempts to explain some of what we know about COVID-19, what we might expect from it, and what we might do to mitigate, or ideally prevent, its most harmful effects. We begin with a discussion of the South African experience, then move to a primer on virology, immunology, and the meaning of infection. We conclude with strategies for mitigation and prevention considered vital by most public health authorities.

What Happened in South Africa?

We recently interviewed Dr. Tulio de Oliveira, MSc and PhD, who is Director of the Centre for Epidemic Response and Innovation (CERI) at Stellenbosch University in South Africa, where he is Professor of Bioinformatics. Born in Brazil, he is also a professor at the University of KwaZulu-Natal in South Africa and affiliate professor of Global Health at the University of Washington in the United States.

He and his skilled laboratory staff identified not only the presence, but also the genetic code of Omicron in an incredible 36 hours after receiving the first patient sample. With great transparency and an exemplar sense of ethical responsibility, the information was quickly disseminated to laboratories and health agencies around the world.

The information was deemed so important that the journal *Nature* published an expedited article detailing the findings on January 7, 2022 (https://www.nature.com/articles/d41586-021-03832-5). Figures 1 and 2, below, come from the CERI work and depict the rapid transmissibility of Omicron. (As of January 6, 2022, twenty countries, spanning four continents, recorded record-breaking numbers of COVID-19 cases, according to *The Financial Times:* https://www.ft.com/content/0baf118c-68f7-448c-9a54-2e67debe46a1.)

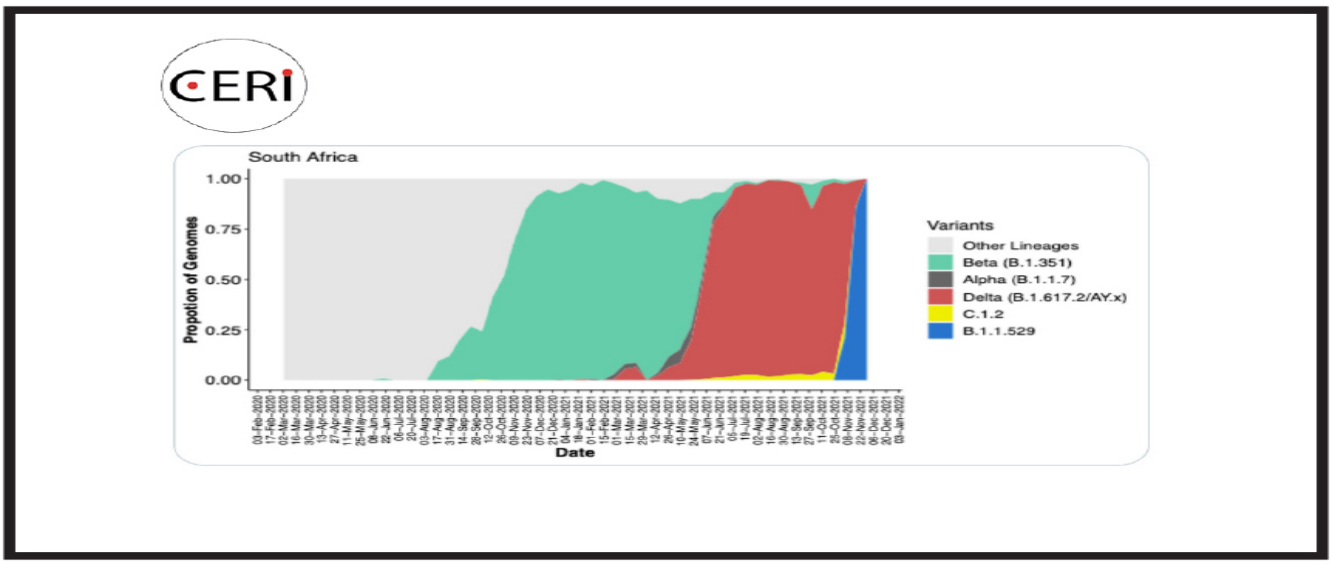

Figure 1. Analysis from the Centre for Epidemic Response and Innovation (CERI) showing the rapid variant infection progression in South Africa. Diagram courtesy of Dr. Tulio de Oliveira.

As discussed in the January 7 *Nature* article, initial data seem to suggest that Omicron produces a less severe form of COVID. That marginally positive observation is tempered by the fact that *Omicron has the capacity for substantial evasion of neutralizing antibody responses, and modeling suggests that immune evasion could be a major driver of the observed transmission dynamics*. Rapid transmission of the variant through a population does not equate with rapid progression of the disease through individual people. It may, in fact, take several weeks for disease progression and/or hospitalization to become evident.

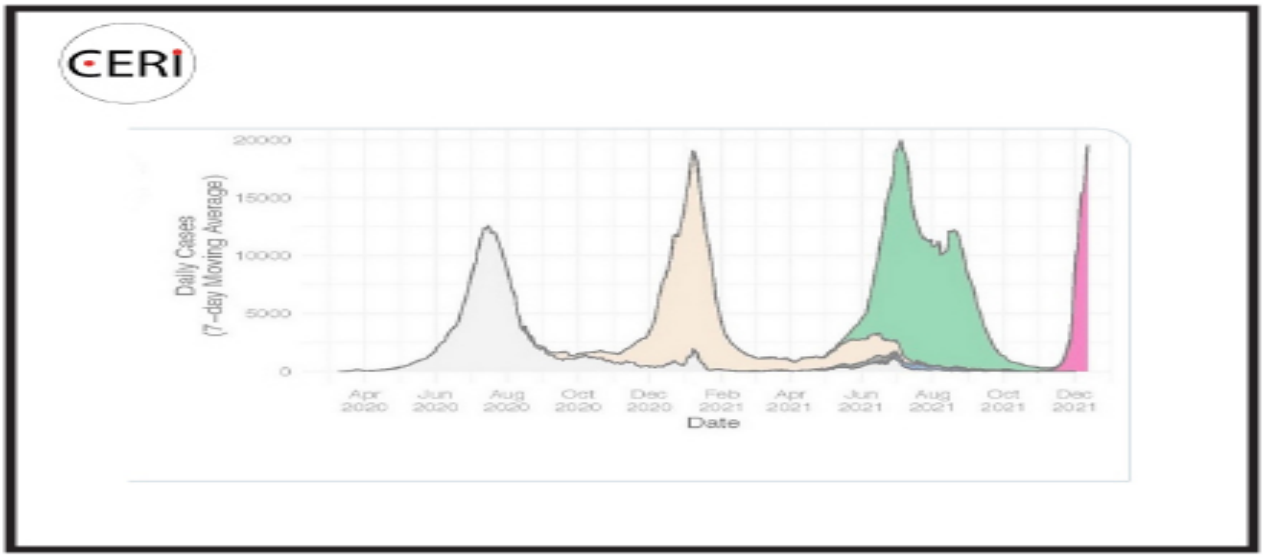

Figure 2. Epidemic and variant dynamics in South Africa, April 2020 to December 2021, from the Centre for Epidemic Response and Innovation (CERI). Diagram courtesy of Dr. Tulio de Oliveira.

Caution is required in applying one population's experience to another, because no two populations are identical. For example, Omicron was detected in younger South Africans and had yet to affect the rest of the population. Even though the South African vaccination rate is a relatively low 27 percent,[1] there is a high degree of prior exposure to other strains of COVID-related viruses in the population. In relatively young and healthy individuals, prior exposure would be expected to provide some degree of immunity to new variants. The U.S. population is not as young, nor is it as healthy, as that of South Africa. Hence the admonition against direct comparison.

Immunity and Vaccination

Immunity refers to the ability of an individual organism, such as a human, to resist an infection. If a sufficiently high percentage of a population develops immunity to an infection, that population has acquired *herd immunity*, and the infecting organism is contained if not eliminated. An individual person may develop some degree of immunity to COVID-19 (usually through prior exposure or vaccination). It will be impossible for a population like that of the United States to develop herd immunity to COVID, given current levels of prior exposure and vaccination.

Both acute infections of SARS-CoV-2 and the COVID vaccines stimulate our immune systems to produce antibodies targeting the virus. That is good and desirable. The problem with our response to COVID is that the antibodies we produce, sometimes called *neutralizing* antibodies, live for only a short time: several weeks to a few months. As neutralizing antibody levels decrease, so does our protection. Ideally, we want antibodies to stay around indefinitely or, at least, until COVID no longer presents a threat to us.

B Cells, T Cells, Killer T Cells: A Primer

Imagine an epic movie production with a cast of thousands. In a sense, this describes our immune system. New actors are discovered, and new roles are written, on an almost daily basis. That said, identifying some of the leading stars and their roles will help in understanding immunology and the inner workings of our immune system. Three of the stars are called B cells, T cells, and killer T cells.

When we are exposed to either the COVID virus or a COVID vaccine, our immune system produces B cells, which circulate in the blood; initially, they do not do much. Over time they mature and become memory B cells (MBCs). As the name suggests, these cells *remember* the pathogen or vaccine that stimulated their production. B cells remain quiescent until re-exposed to that specific pathogen or a close relative of the pathogen. This exposure stimulates antibody production directed against the pathogen. In this way we develop so-called *long-term immunity*. MBCs that we produced from vaccines received in childhood against polio, measles, mumps,

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1 https://bit.ly/3qeIXxs

rubella, diphtheria, and tetanus give us protection for years. In an ideal world, we will one day have such protection against COVID.

Vaccines also stimulate production of memory T cells (MTCs). Working in a similar way, MTCs assist MBCs in making antibodies at a constant rate, and they too, when exposed to the virus or something that looks like it, begin antibody production.

Cytotoxic (killer T) cells constitute another component of the immune system. Viruses are only able to reproduce within host cells. Killer T cells work by destroying infected cells before a virus has a chance to reproduce and disseminate its progeny. Once all of these cellular components develop, long-term immunity becomes established.

The first dose of a vaccine prompts the immune system to produce MBCs and MTCs and helps them grow. The second dose shifts antibody production into high gear.

Infection and Disease

Infection is not the same as disease. Preventing infection prevents disease, but preventing disease is not the same as preventing infection. An infected person may never develop the signs and symptoms of the disease. This may seem counterintuitive, but if you think about it for a bit, it explains a lot and is why it is so important to identify individuals who are infected yet have no symptoms.

Antibodies, particularly neutralizing antibodies, may prevent infection, but they play a very minor role in preventing or resolving disease. Simply stated, *antibodies help protect against infection, but to protect against disease, we need good cellular immunity*, especially through robust MTCs.

Vaccines, Immunity, and Omicron

Vaccines, usually administered by injection, inhalation, or ingestion, stimulate our immune system to produce antibodies. Historically, most vaccines have contained a weakened or dead virus or bacteria. Vaccines of this type, in rare circumstances, have produced the disease they were intended to prevent. In the United States, the two most widely distributed vaccines avoid this potential problem by utilizing messenger RNA (mRNA) technology. Studied for over forty years, mRNA technology had never been used in the production of vaccines for humans.

The new mRNA vaccines contain a copy of the virus's RNA that is the instruction set of what is found on the outer membrane of the COVID-19 virus *spike*. (The surface of each SARS-CoV-2 virus has dozens of spike proteins, which are instrumental in enabling the virus to fuse with human cells.) The spike protein fragment is sufficient to initiate an immune response but is incapable of causing disease.

While mRNA vaccines are effective in stimulating antibody production, they appear weaker in stimulating cellular immunity. This weakness manifests itself in lower antibody levels (titer decay) detected as early as two months after the second dose of vaccine. It remains to be seen whether modifying dose schedules (for example, lengthening the interval between the primary dose and booster or administering additional booster injections) can overcome this deficit. Protection against severe disease after full vaccination holds up better than protection afforded by viral infection

alone. This fact suggests that vaccines produce better long-term cellular immunity. The extended protection, unfortunately, does not apply to people with compromised immune systems.

Some may wonder how, if cellular immunity arising from previous variant infections and/or vaccines seems to mitigate the severity of Omicron disease, Omicron infections still occur? The answer is found in the location of the mutations within the virus. (See the section "Mutations and Variants of Concern," below.) The immune system is a *reactive system*. It does not anticipate threats; it reacts to them. Once threats appear in the form of pathogens (bacterial, viral, fungal, or parasitic microorganisms that can cause disease), the system is activated to muster a defense.

Back to our Primer

The components of our cellular immunity system are very targeted in their actions. Continuing our movie metaphor, each of the major actors memorizes their lines but not those of other cast members. Think of antibodies as performing cameo roles: they add to the overall picture but are not the major players. The main immunology actors are those providing longer-term cellular protection.

Remember: memory T cells (MTCs) result from specific stimuli. The stimulus is not the entire pathogen but rather a portion of that pathogen. MTCs only need to see that specific portion of the virus to begin producing antibodies. Once you see a dorsal fin in the water, you do not need to see the entire shark before reacting!

Mutations and Variants of Concern

Antibodies work by attaching to a specific portion of the virus and making it vulnerable to destruction. To protect itself, the virus mutates to change that specific portion of itself recognized by the antibody. Genome sequencing and genomic surveillance of SARS-CoV-2 (laboratory methods of determining and monitoring the genetic makeup of the virus) tell us what portions of the virus have changed. Each significant mutation produces a new *variant* like Omicron.

Unlike antibodies, T cells target viral areas that do not mutate often and remain largely unchanged. This explains why new variants can overcome antibody neutralization and produce breakthrough infections and why previously established cellular immunity remains potent. Simply stated, antibodies look for and see exposed viral areas, while T cells see the more hidden, and more constant, structural parts.

So why isn't the virus mutating in response to what the MTCs detect? Step back from anthropomorphizing the virus. COVID is not trying to hurt or kill us. *All the virus wants to do is make more of itself.* It can do that well enough just in your nose. It can, after all, enter, multiply, and escape to infect somebody else. All it needs to do is mutate sufficiently to overcome antibody neutralization in our noses and it's good to go. COVID doesn't need to cause severe disease or infect our internal organs to propagate and flourish. Mutating the more hidden structures (susceptible to T cell detection) doesn't help the virus in terms of allowing it to make more of itself and spread to more susceptible hosts.

MTCs can only see infected cells. If a specific variant can make enough progeny virus to transmit efficiently to others with just a simple (head cold) infection, then that variant will be happy and merrily transmit throughout a community.

What have we learned? What's ahead?

During our conversation, Dr. de Oliveira made several predictions. He expects a new variant that, like Omicron, will be highly transmissible and will be able to evade the antibody protections afforded by vaccination and/or prior infection. While he hopes that any new variant will be less severe, it is impossible to make predictions with certainty: so much depends on the variables of vaccination rates and personal behavior.

He noted that the world's response to South Africa's discovery of Omicron offers a stark and troubling lesson in how *not* to react to a crucial discovery during a pandemic. Instead of being lauded for the efficiency and transparency of the discovery, South Africa was burdened with (ineffective and unnecessary) travel restrictions. The restrictions, not based on science but on politics, not only hurt the South African economy, but sent a tacit message to all researchers that transparency might be damaging to them and their countries. If allowed to continue, such limiting reactions will deal crippling blows to the world of public health and, at minimum, stifle research.

On a very positive note, Dr. de Oliveira detailed the benefits of rigorous testing, tracing, and genomic surveillance. These measures allow both governments and health care agencies to formulate and implement strategies based on the data collected. This vital information facilitates proper planning in areas as varied as hospital staffing, business activities, and social interaction. As an example of social benefits, South Africa was able to extend the hours for celebrating the New Year based on low levels of serious infection and low hospital occupancy rates. The extension provided not only a boost to local economies, but also an even more significant boost to public morale.

Remember that in the absence of good cellular immunity, you're entirely dependent on high levels of circulating antibodies for protection from infection and disease. For most people, especially the younger, healthier crowd, Omicron will likely be experienced asymptomatically, as annoying as a bad head cold. For people who have not mounted, or cannot mount, effective cellular responses, the risk of severe disease will remain high.

Who are these people? They are populations that the United States has in abundance: the frail elderly, the obese (body mass index [BMI] of 30 or higher), diabetics, and the immunocompromised (cancer patients, transplant recipients, those with autoimmune diseases, individuals on immunomodulator therapy, and others). Until we develop other therapies, monoclonal and polyclonal antibody infusions will remain their primary means of defense. (Both monoclonal and polyclonal antibodies are molecules that are produced in the laboratory and are designed to act as substitute antibodies. Monoclonals are derived from a specific kind of immune cell, while polyclonals are created from several different types.) For the immunocompromised, these antibody infusions will be their only defense. Remember: the infused antibodies have a short life span once administered. Once infused antibody levels drop, immunocompromised patients will be left defenseless, as they are unable to produce antibodies of their own.

In South Africa, prior waves of COVID have led to an ever-increasing degree of population immunity. Once adequate levels of cellular immunity develop, COVID will devolve to an endemic, rather than epidemic, infection. This situation will likely produce seasonal outbreaks like the other known coronaviruses, which are responsible for about 25 percent of common colds. In

the United States, at-risk populations will continue to require targeted protection until alternative therapeutics become available.

Future Vaccines and Treatments

The next generation of vaccines must target the less mutable portions of the coronavirus. Such vaccines would provide better protection against variants. Finding better ways to stimulate sluggish immune systems, especially in high-risk populations, will be essential. Once COVID devolves from pandemic to endemic, we must have in place a strategic response like that for influenza but, we hope, a more effective response. Be mindful that our current seasonal flu vaccines vary in efficacy from 10 percent to 60 percent.

Currently, cellular immunity is proving to be more cross-reactive (a phenomenon of the immune system in which an antibody directed against one antigen is successful at binding to a different antigen), thus protecting against another disease. For younger, healthier, leaner individuals, Omicron presents minimal concerns. For those at high risk, Omicron is likely to be no worse than prior variants. But its greater transmissibility, coupled with more asymptomatic disease within the community, will increase their risk of exposure.

Booster doses will provide a transient window of antibody protection, but early results from the U.K. suggest this protection wanes quickly, by about ten weeks, and there seems to be little effect on overall cellular immune response. As discussed above, monoclonal and polyclonal antibody infusions represent a stop-gap treatment that may be sufficient for the Omicron wave, but the next variant may not prove as susceptible to such treatment.

Call to Action

In the years to come, if nothing changes in our behavior and preparedness, people in at-risk groups will die at an accelerated rate. Only through a global public health response will this be prevented. No nation or peoples will be spared while its weakest are at risk.

Our message here is not a cry of despair, but rather a call to action. SARS-CoV-2 is a warning. With global surveillance and detection, equitable distribution of resources, targeted response to deal with local outbreaks, and nationally supported, transparent, and ethical research, we will deal with this pandemic, adequately prepare for the next one, and achieve a healthier planet.

Report authors:

Richard A. Marfuggi, MD, Fellow of the American College of Surgeons, and DMH, is a Commissioner of the American Medical Association Foundation.
https://amafoundation.org

Steve Brozak, DMH, is Chief Executive Officer of WBB Securities.
https://wbbsec.com

www.fpa.org

551 Fifth Avenue, 30th Fl.
New York, NY 10176