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Omicron: What Happens Next?

Now that COVID is here to stay

Richard A. Marfuggi, MD
Fellow of the American College of Surgeons, DMH

Steve Brozak, DMH
Chief Executive Officer, WBB Securities

Inside this report

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 890,000 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). Figure 1 *(below)* and Figure 2, *(see following page)* 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.)

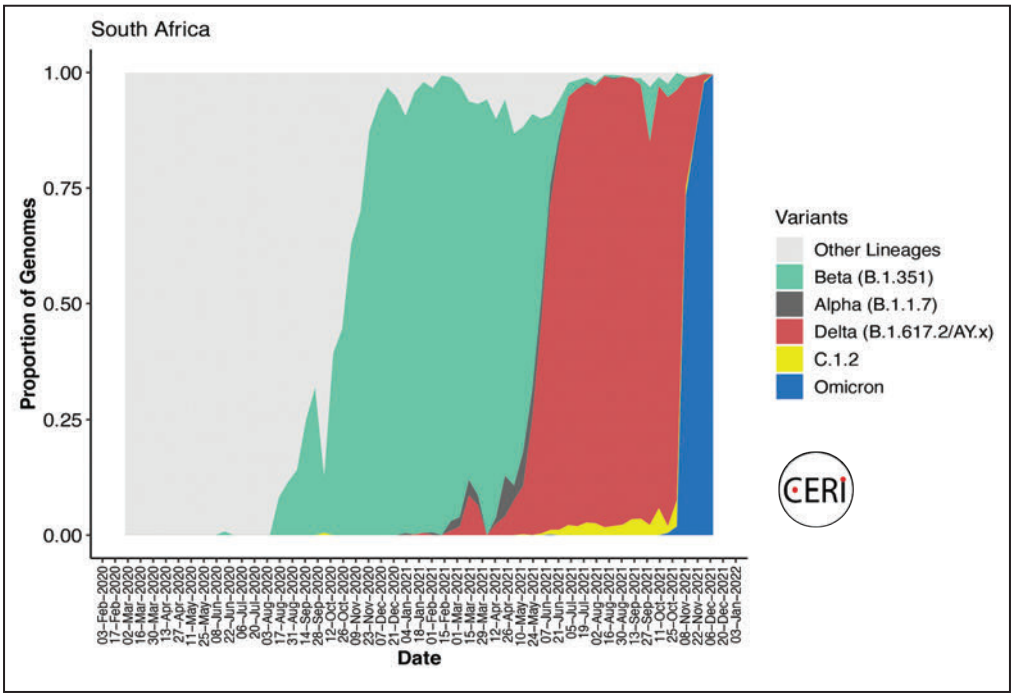

Figure 1. Analysis from the Centre for Epidemic Response and Innovation (CERI) showing the rapid variant infection progression in South Africa.
Diagram courtesy of Dr. Tulio de Oliveira.

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.

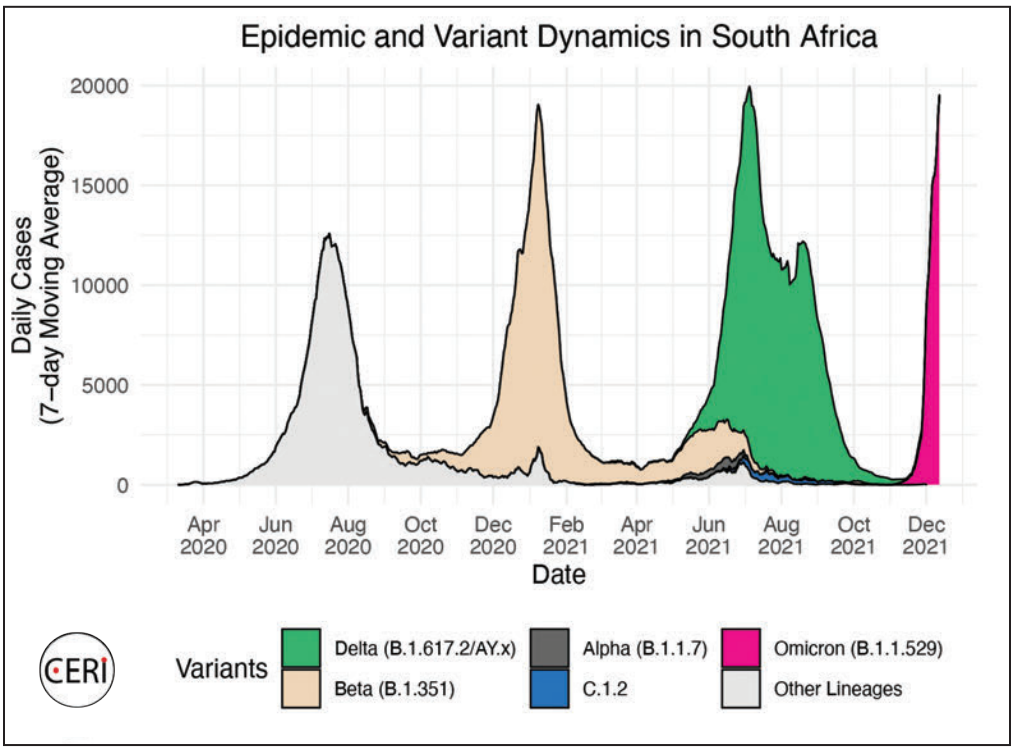

Figure 2. Epidemic and variant dynamics in South Africa, April 2020 to December 2021, from the Centre for Epidemic Response and Innovation (CERI).
Diagram courtesy of Dr. Tulio de Oliveira.

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.

[1]https://bit.ly/3qelXxs

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. 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, 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, which 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.

Glossary A

The following words and phrases, arranged in groups of related terms, are briefly explained in the context of this report. In ***Glossary B*** *(below)*, the same terms are arranged alphabetically.

Common terms for describing a disease

Epidemic
An outbreak of a disease in a certain geographical area.

Pandemic
An outbreak of a disease that has spread across several countries or continents.

Endemic
A constantly present disease within a particular geographic area or population.

Prevalence
The total number of individuals in a population who have a disease at a specific time, usually expressed as a percentage of the population.

Incidence
The number of people who develop a specific disease during a given time period, such as a month or a year.

Terms commonly used in relation to the COVID-19 pandemic

Virus
A sub-microscopic infectious agent that can only replicate and cause disease once it enters a living host cell. Hosts may be humans, animals, bacteria, or plants. Viruses have a simple structure consisting of a nucleic acid molecule encased in a protein coat. In humans, viruses cause diseases such as measles, mumps, and hepatitis.

Bacterium/Bacteria
Bacteria are ubiquitous single-cell microorganisms. Some are aerobic, only able to survive in the presence of oxygen. Others are anaerobic, not requiring, or not able to survive, exposure to oxygen. Most bacteria are beneficial; some cause disease. Once an individual is infected with a virus, a secondary bacterial infection exacerbates the disease process. When antibiotics are administered to a patient with COVID-19, it is to treat a secondary bacterial infection, not the COVID-19 virus. Antibiotics have no effect on viruses.

Coronavirus (CoV)
Coronaviruses are a family of viruses that cause illness in humans and animals. Seven different types have been found in people, including those responsible for the SARS, MERS, and COVID-19 epidemics.[1] An estimated 25 percent of colds are caused by a coronavirus. Protein spikes on the outer surface of the virus give it the appearance, under a microscope, of being surrounded by a corona or crown. The terms novel coronavirus (nCoV) and "variant of concern" refer to a new strain of disease-causing virus not previously identified in humans.

SARS
Severe acute respiratory syndrome is a contagious respiratory infection.

SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2 is the coronavirus that causes COVID-19.

COVID-19
A respiratory disease caused by the virus SARS-CoV-2, discovered in 2019. The virus spreads primarily from person to person through respiratory droplets produced when an infected person coughs, sneezes, or talks. Some people infected with the disease may be asymptomatic, while others may have symptoms ranging from mild to severe. COVID-19 does not need to cause severe disease or infect a person's internal organs to replicate and spread. The linings of the nose and upper airways provide fertile territory for the process. Individuals thus affected develop symptoms as mild as nasal congestion or a head cold.

COVID is an abbreviation for coronavirus disease. COVID-19 is an abbreviation for the disease caused by SARS-CoV-2.

Virus mutation
A change in the genetic code of a virus. Like all viruses, COVID-19 continually mutates: mutations do not necessarily change the character of the virus. Most viral mutations are harmless. Some mutations, however, make the virus better able to evade detection, better able to circumvent the body's immune protection, and/or better able to spread. When the virus achieves any, or a combination, of these capabilities, it becomes a so-called variant of concern. Such variants include Delta and Omicron *(see "Variant viruses," below)*.

Variant viruses
Viruses continually mutate, and the resultant variant may appear, disappear, or persist. The Delta variant of SARS-CoV-2 has caused more infections and has spread

[1]https://coronavirusexplained.ukri.org/en/article/cad0003/

more rapidly than the original, called "wild-type," SARS-CoV-2 strain. Published data indicate that the Omicron variant multiplies about seventy times faster in the human respiratory tissue than the Delta variant does. The World Health Organization labels each variant of concern with letters of the Greek alphabet to simplify public communication and to avoid stigmatizing countries where variants are detected.

Omicron

This variant of SARS-CoV-2 was first detected in November 2021. By December 2021, it had been detected in most of the United States and rapidly became the most dominant strain.

Common terms related to the study of Omicron

Virology

The branch of science that studies viruses.

Genetic code

The genetic code is a complex structure arising from simple building blocks. Organic molecules called nucleotides form the basic structural unit of the naturally occurring chemical compounds known as nucleic acids. The two nucleic acids that both store and pass on genetic information are DNA (deoxyribonucleic acid, a double-strand helix molecule) and RNA (ribonucleic acid, a single-strand molecule). A group of three nucleotides (also called a nucleotide triplet or codon) specify each amino acid. Amino acids combine to form proteins, the building blocks of life.

DNA and RNA are, in simplest terms, long chains of amino acids. That chain, when *read*, directs the production of all the body's proteins. The sequence of amino acids in a DNA or RNA chain is specific to each organism, be it human or viral, so knowing that sequence defines the organism. Any changes to the genetic code produce a variant or mutant of the organism.

Genome sequencing and Genomic surveillance

In the context of SARS-CoV-2, genome sequencing is a laboratory method used to determine the genetic code of the virus. Genomic surveillance monitors the presence of the virus in a population and identifies variants before they become widespread. Both processes are central to public health efforts to identify virus hot spots, alert health authorities, and promote timely, targeted responses.

Terms commonly associated with infection and disease

Infection
Infections are classified as bacterial, viral, fungal, or parasitic, depending on the infecting agent. Disease cannot occur unless an infection is present. Infection, however, does not always cause symptomatic disease. This means that an asymptomatic, yet infected, individual may spread the infection to others.

Disease
Any harmful deviation from the normal structural or functional state of a person or organism. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Disease cannot occur in the absence of infection, but infection does not always result in symptomatic disease.

Pathogen
An organism that causes disease.

Antigen
A toxin, chemical, or foreign substance, such as a bacteria or virus, that induces an immune response. Because they generate this response, antigens are sometimes referred to as immunogenic.

Antibody
A blood protein produced in response to an antigen *(see "Antigen," above).* Blood proteins help the body produce substances that it needs to function, and antibodies attempt to neutralize antigens. Antibodies seek out antigens and chemically combine with them, making them vulnerable to processes that inactivate or eliminate them. Each type of antibody is antigen specific: an antibody to a specific virus will have no effect on another unrelated virus. While antibodies help prevent infection, they have little effect in preventing or mitigating symptomatic disease. *(See "Infection" and "Disease," above, for the distinction between the two.)*

Neutralizing antibody
A type of antibody that inactivates a specific antigen. Some COVID-19 variants overcome antibody neutralization, producing breakthrough infections.

Monoclonal and polyclonal antibodies
Both monoclonal and polyclonal antibodies are molecules produced in the laboratory and designed to act as substitutes for antibodies produced by the body. Monoclonal antibodies are derived from a specific kind of immune cell, while polyclonal antibodies are produced from several different types of immune cells. Monoclonal and polyclonal

antibody infusions currently are the primary means of defense against COVID-19 for immunocompromised people—that is, people who are unable to produce their own antibodies.

Immunity
The ability of an organism to resist a particular infection.

Active immunity
The result of an immune system response when exposed directly to a pathogen or an antigen or when indirectly exposed through vaccination. Once exposed to a specific pathogen, the immune system produces specialized cells, which, in turn, produce antibodies to that particular pathogen. Upon exposure to the foreign substance, the human immune system produces B cells, which circulate in the blood. Over time, they become memory B cells (MBCs), which remember the pathogen or vaccine that stimulated their production. Re-exposure to the pathogen or a close relative of the pathogen (delivered, for example, by a vaccine) stimulates antibody production directed against the pathogen. Some evidence suggests that prior exposure to other coronaviruses confers a bit of protection against the Omicron variant.

Passive immunity
When a person has not mustered, or cannot muster, an active immune response, the person may be treated with monoclonal or polyclonal antibodies *(see "Monoclonal and polyclonal antibodies," above)* to provide some degree of passive immunity. Passive immunity is temporary, as the antibodies received have a limited life span.

Cellular immunity
The most effective and longest lasting protection against a pathogen or antigen is provided through cellular immunity. Pathogens and antigens are organisms or substances that the body perceives as both alien and harmful. To protect the body, the immune system is activated. Once activated, the immune system deploys specialized cells that act in unique ways toward the common goal of eliminating the pathogen or antigen. Here are some of the major components of cellular immunity:

T CELLS and **MEMORY T CELLS** (MTCs) function in similar ways to **B CELLS** and **MEMORY B CELLS** (MBCs) *(see "Active immunity," above)*, but while antibodies stimulated by MBCs seek out exposed areas of a virus, T cells seek out the more hidden and more structural parts of the virus.

PHAGOCYTES surround and ingest a pathogen or any cell infected by the pathogen. Once ingested, the phagocyte neutralizes or destroys the pathogen.

Antigen-sensitized killer T cells attach to an infected cell and release cytokines, which are toxic to the pathogen. These killer cells are also known as cytotoxic cells, meaning they kill foreign cells, cancer cells, and cells infected with a virus. Killer T cells destroy infected cells before a virus has a chance to reproduce and disseminate its progeny. (Killer T cells sometimes work against the body when, for example, they see an organ transplant as containing foreign cells, and their destructive work may lead to transplant rejection.)

Long-term immunity is dependent on each one of these cell types.

Herd immunity

Resistance to the spread of an infectious disease within a population because of pre-existent immunity among a high percentage of the population following previous infection or vaccination. Herd immunity, which presupposes that long-lasting immunity is possible, contains or eliminates a disease.

The already global spread of the virus and the low rates of vaccination in many countries, coupled with variable responses to public health recommendations—such as vaccine hesitancy, resistance to mask-wearing in public gatherings, and gathering in large numbers in enclosed places—make herd immunity an unrealistic means of containing COVID-19. Simply stated, it is too late in this pandemic to consider herd immunity a realistic option for control.

Immunology

The branch of medicine and biology that studies immunity.

Immunocompromised

A weakened immune system. Many conditions compromise the immune system, ranging from inherited immune deficiency diseases to cancer, post-transplantation, and other conditions treated with immunosuppression therapy. Other diseases such as diabetes and obesity also compromise a person's immune system. A person with a weakened immune system is especially vulnerable to severe disease from SARS CoV-2.

Vaccine

Usually administered by injection, inhalation, or ingestion, vaccines stimulate the immune system to produce antibodies targeting viruses and other pathogens. Historically, most vaccines have contained weakened or dead virus or bacteria.

Messenger ribonucleic acid (mRNA) vaccine

Studied for over forty years, messenger RNA (mRNA) technology had never been used in the production of vaccines for humans before development of the COVID-19 vaccines.

The mRNA vaccines contain only a small, altered piece of viral RNA *(see "Genetic codes," above)* resembling, but not identical to, the viral RNA found in the protein spikes appearing on the outer surface of the COVID-19 virus. (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 altered spike protein fragment in mRNA vaccines is sufficient to initiate an immune response but is incapable of causing disease. While mRNA vaccines are effective in stimulating production of antibodies that inactivate the COVID-19 virus, these vaccines appear to be less effective in stimulating cellular immunity, *(see "Cellular immunity" above)*.

Booster

Booster shots have the same ingredients as the current COVID-19 vaccines, although the dose of these ingredients in the booster may differ from the dose of primary shots. Booster shots stimulate additional antibody production, but the degree and duration of that production has not been determined for protection against COVID-19.

Vaccine efficacy

A measure of how well a vaccine performs under ideal conditions, as determined in a careful clinical trial. Clinical trials test whether a vaccine is safe to use and how well it protects people against a disease. In immunology, measurement of the amount or concentration of a substance in a solution is called a titer and usually refers to the number of antibodies in a person's blood. Titer decay, a decrease of antibodies, indicates a loss of efficacy.

Glossary B

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T CELLS and **MEMORY T CELLS** (MTCs) function in similar ways to **B CELLS** and **MEMORY B CELLS** (MBCs) *(see "Active immunity," above)*, but while antibodies stimulated by MBCs seek out exposed areas of a virus, T cells seek out the more hidden and more structural parts of the virus.

PHAGOCYTES surround and ingest a pathogen or any cell infected by the pathogen. Once ingested, the phagocyte neutralizes or destroys the pathogen.

ANTIGEN-SENSITIZED KILLER T CELLS attach to an infected cell and release cytokines, which are toxic to the pathogen. These killer cells are also known as cytotoxic cells, meaning they kill foreign cells, cancer cells, and cells infected with a virus. Killer T cells destroy infected cells before a virus has a chance to reproduce and disseminate its progeny. (Killer T cells sometimes work against the body when, for example, they see an organ transplant as containing foreign cells, and their destructive work may lead to transplant rejection.)

Long-term immunity is dependent on each one of these cell types.

Coronavirus (CoV)

Coronaviruses are a family of viruses that cause illness in humans and animals. Seven different types have been found in people, including those responsible for the SARS, MERS, and COVID-19 epidemics.[1] An estimated 25 percent of colds are caused by a coronavirus. Protein spikes on the outer surface of the virus give it the appearance, under a microscope, of being surrounded by a corona or crown. The terms novel

[1]https://coronavirusexplained.ukri.org/en/article/cad0003/

coronavirus (nCoV) and "variant of concern" refer to a new strain of disease-causing virus not previously identified in humans.

COVID-19
A respiratory disease caused by the virus SARS-CoV-2, discovered in 2019. The virus spreads primarily from person to person through respiratory droplets produced when an infected person coughs, sneezes, or talks. Some people infected with the disease may be asymptomatic, while others may have symptoms ranging from mild to severe. COVID-19 does not need to cause severe disease or infect a person's internal organs to replicate and spread. The linings of the nose and upper airways provide fertile territory for the process. Individuals thus affected develop symptoms as mild as nasal congestion or a head cold.

COVID is an abbreviation for coronavirus disease. COVID-19 is an abbreviation for the disease caused by SARS-CoV-2.

Disease
Any harmful deviation from the normal structural or functional state of a person or organism. COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Disease cannot occur in the absence of infection, but infection does not always result in symptomatic disease.

Endemic
A constantly present disease within a particular geographic area or population.

Epidemic
An outbreak of a disease in a certain geographical area.

Genetic code
The genetic code is a complex structure arising from simple building blocks. Organic molecules called nucleotides form the basic structural unit of the naturally occurring chemical compounds known as nucleic acids. The two nucleic acids that both store and pass on genetic information are DNA (deoxyribonucleic acid, a double-strand helix molecule) and RNA (ribonucleic acid, a single-strand molecule). A group of three nucleotides (also called a nucleotide triplet or codon) specify each amino acid. Amino acids combine to form proteins, the building blocks of life.

DNA and RNA are, in simplest terms, long chains of amino acids. That chain, when *read*, directs the production of all the body's proteins. The sequence of amino acids in a DNA or RNA chain is specific to each organism, be it human or viral, so knowing that sequence defines the organism. Any changes to the genetic code produce a variant or mutant of the organism.

Genome sequencing and **Genomic surveillance**
In the context of SARS-CoV-2, genome sequencing is a laboratory method used to determine the genetic code of the virus. Genomic surveillance monitors the presence of the virus in a population and identifies variants before they become widespread. Both processes are central to public health efforts to identify virus hot spots, alert health authorities, and promote timely, targeted responses.

Herd immunity
Resistance to the spread of an infectious disease within a population because of pre-existent immunity among a high percentage of the population following previous infection or vaccination. Herd immunity, which presupposes that long-lasting immunity is possible, contains or eliminates a disease.

The already global spread of the virus and the low rates of vaccination in many countries, coupled with variable responses to public health recommendations—such as vaccine hesitancy, resistance to mask-wearing in public gatherings, and gathering in large numbers in enclosed places—make herd immunity an unrealistic means of containing COVID-19. Simply stated, it is too late in this pandemic to consider herd immunity a realistic option for control.

Immunity
The ability of an organism to resist a particular infection.

Immunocompromised
A weakened immune system. Many conditions compromise the immune system, ranging from inherited immune deficiency diseases to cancer, post-transplantation, and other conditions treated with immunosuppression therapy. Other diseases such as diabetes and obesity also compromise a person's immune system. A person with a weakened immune system is especially vulnerable to severe disease from SARS CoV-2.

Immunology
The branch of medicine and biology that studies immunity.

Incidence
The number of people who develop a specific disease during a given time period, such as a month or a year.

Infection
Infections are classified as bacterial, viral, fungal, or parasitic, depending on the infecting agent. Disease cannot occur unless an infection is present. Infection, however, does not always cause symptomatic disease. This means that an asymptomatic, yet infected, individual may spread the infection to others.

Messenger ribonucleic acid (mRNA) vaccine
Studied for over forty years, messenger RNA (mRNA) technology had never been used in the production of vaccines for humans before development of the COVID-19 vaccines.

The mRNA vaccines contain only a small, altered piece of viral RNA *(see "Genetic codes," above)* resembling, but not identical to, the viral RNA found in the protein spikes appearing on the outer surface of the COVID-19 virus. (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 altered spike protein fragment in mRNA vaccines is sufficient to initiate an immune response but is incapable of causing disease. While mRNA vaccines are effective in stimulating production of antibodies that inactivate the COVID-19 virus, these vaccines appear to be less effective in stimulating cellular immunity *(see "Cellular immunity," above)*.

Monoclonal and polyclonal antibodies
Both monoclonal and polyclonal antibodies are molecules produced in the laboratory and designed to act as substitutes for antibodies produced by the body. Monoclonal antibodies are derived from a specific kind of immune cell, while polyclonal antibodies are produced from several different types of immune cells. Monoclonal and polyclonal antibody infusions currently are the primary means of defense against COVID-19 for immunocompromised people—that is, people who are unable to produce their own antibodies.

Neutralizing antibody
A type of antibody that inactivates a specific antigen. Some COVID-19 variants overcome antibody neutralization, producing breakthrough infections.

Omicron
This variant of SARS-CoV-2 was first detected in November 2021. By December 2021, it had been detected in most of the United States and rapidly became the most dominant strain

Pandemic
An outbreak of a disease that has spread across several countries or continents.

Passive immunity
When a person has not mustered, or cannot muster, an active immune response, the person may be treated with monoclonal or polyclonal antibodies *(see "Monoclonal and polyclonal antibodies," above)* to provide some degree of passive immunity. Passive immunity is temporary, as the antibodies received have a limited life span.

Pathogen
An organism that causes disease.

Prevalence
The total number of individuals in a population who have a disease at a specific time, usually expressed as a percentage of the population.

SARS
Severe acute respiratory syndrome is a contagious respiratory infection.

SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2 is the coronavirus that causes COVID-19.

Vaccine
Usually administered by injection, inhalation, or ingestion, vaccines stimulate the immune system to produce antibodies targeting viruses and other pathogens. Historically, most vaccines have contained weakened or dead virus or bacteria.

Vaccine efficacy
A measure of how well a vaccine performs under ideal conditions, as determined in a careful clinical trial. Clinical trials test whether a vaccine is safe to use and how well it protects people against a disease. In immunology, measurement of the amount or concentration of a substance in a solution is called a titer and usually refers to the number of antibodies in a person's blood. Titer decay, a decrease of antibodies, indicates a loss of efficacy.

Variant viruses
Viruses continually mutate, and the resultant variant may appear, disappear, or persist. The Delta variant of SARS-CoV-2 has caused more infections and has spread more rapidly than the original, called "wild-type," SARS-CoV-2 strain. Published data indicate that the Omicron variant multiplies about seventy times faster in the human respiratory tissue than the Delta variant does. The World Health Organization labels each variant of concern with letters of the Greek alphabet to simplify public communication and to avoid stigmatizing countries where variants are detected.

Virology
The branch of science that studies viruses.

Virus
A sub-microscopic infectious agent that can only replicate and cause disease once it enters a living host cell. Hosts may be humans, animals, bacteria, or plants. Viruses

have a simple structure consisting of a nucleic acid molecule encased in a protein coat. In humans, viruses cause diseases such as measles, mumps, and hepatitis.

Virus mutation
A change in the genetic code of a virus. Like all viruses, COVID-19 continually mutates: mutations do not necessarily change the character of the virus. Most viral mutations are harmless. Some mutations, however, make the virus better able to evade detection, better able to circumvent the body's immune protection, and/or better able to spread. When the virus achieves any, or a combination, of these capabilities, it becomes a so-called variant of concern. Such variants include Delta and Omicron *(see "Variant viruses," above)*.

About the authors

Richard A. Marfuggi, MD
Fellow of the American College of Surgeons, DMH

Dr. Marfuggi is a board-certified surgeon, educator, philanthropist, and medical ethicist. He is a Fellow of the Foreign Policy Association and an American Medical Association Foundation (AMAF) Commissioner for LGBTQ Health, as well as a presenter and advisor to the AMAF Leadership Development Initiative.

Dr. Marfuggi currently serves as Academic Director of the National Student Leadership Conference on Medicine and Health Care, as a member of the New Jersey Medical Society Biomedical Ethics Committee, and as a consultant to the New York State Office of Professional Medical Conduct.

The first physician to hold a Doctorate in Medical Humanities, Dr. Marfuggi wrote a thesis resulting in a program for educating health care students and professionals in ethical and equitable health care delivery. He is an external advisor to the Rutgers University T32 NIH [National Institutes of Health] Postdoctoral Training for Translating Research in Regenerative Medicine. He has taught at numerous institutions of higher learning, including the University of Wisconsin–Madison, the University of Richmond, Caldwell University, Centenary College, and Drew University.

Dr. Marfuggi is a member of the Board of Directors of Lighthouse Guild International, which serves people who are visually impaired, and a consultant to WBB Securities, an investment management, investment banking, and equity research firm.

Steve Brozak, DMH
Chief Executive Officer, WBB Securities

Dr. Brozak is CEO of WBB Securities a boutique investment bank and research firm specializing in the biotechnology, pharmaceutical, and medical device sectors. He is an award-winning analyst whose research has been recognized for accuracy and performance year after year by ranking organizations in the financial industry, including the StarMine financial modeling, FactSet data solutions, and TipRanks investing tool platforms.

A Fellow of the Foreign Policy Association, Dr. Brozak was previously Chairman and CEO of StormBio, Inc. This biotechnology company focused on the attenuation of Cytokine Storm, an immune system condition caused by virulent pathogens.

Dr. Brozak contributes regularly to *Forbes*, *STAT*, CNN, ABC News, and *Bloomberg Businessweek* on health care issues. He has appeared as a commentator on media outlets including Bloomberg, BNN, CNN, and CNBC, and his work has been published in *Nature*, *The British Medical Journal*, and *Brain Stimulation*. He is an outspoken advocate for the absolute need to change how we manage and finance health care in the United States and around the world.

As a retired U.S. Marine Corps Lieutenant Colonel who served multiple deployments, Dr. Brozak was appointed to the U.S. Secretary of the Navy's Navy and Marine Corps Retiree Council, where he focused on retiree health care matters. He received a Bachelor's degree and a Master's degree from Columbia University and a Doctorate in Medical Humanities from Drew University. His doctoral thesis presented a critique of the American health care system.

"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."

Dr. Richard A. Marfuggi
Dr. Steve Brozak
Co-authors of **Omicron: What Happens Next?**

"The public desperately needs accurate information about the SARS-CoV-2 pandemic, presented in a clear and understandable format. Drs. Marfuggi and Brozak provide an invaluable service in their attempt to do just that. This report helps explain why, in the race between the virus and vaccines, the virus gets way out in front while vaccines struggle to keep up. The authors also provide a framework for action: develop and deploy better therapeutics, ramp up testing and genomic surveillance, and engage world leaders in the development of a country-by-country strategy to get ahead of, and stay ahead of, COVID-19.

This is a global issue requiring a global response. Anything less will leave us at risk."

Dr. Rick Bright
Senior Vice President of Pandemic Prevention and Response
The Rockefeller Foundation

"This is a pithy and insightful look at the biggest health crisis of our time. Using straightforward language, the authors place scientific and policy challenges squarely in focus. This report is an important, if sobering read."

Ed Silverman
Pharmalot *columnist*
Recipient of the 2018 Gerald Loeb Distinguished Business and Financial Journalism Award for commentary