Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus with a rapidly changing and highly mutable genotype. The available data are highly kinetic and dynamic, occurring in an environment of uncertainty but with periodic yet repeated surge-related morbidity and mortality coupled with and often driven by distorted human behavior. The reality is that much of what we think we know about SARS-CoV-2 is likely wrong, outdated, tinged with false presuppositions, and often based on belief-dependent realism and tribalistic thinking. Instead, the best way of knowing truth for a scientific issue is the scientific method, although that can often be incompatible with what the public wants to believe.

Everything we understand thus far about SARS-CoV-2 is conditional on time, variant, geography, type of host immunity, host factors and behavior, population structure, and levels of immunity at the macro and micro levels; community burden of transmission; and the interplay among these. The story of this pandemic, when it is written, is going to be seen as highly dependent on and perturbed by both human and viral behavior. We only get to influence the first factor (human behavior), although it obviously influences the second (viral behavior). Therefore, we will continue to see the evolution of viral variants—some of which have developed, are developing, and will continue to develop the ability to evade, in whole or in part, both vaccine-induced and illness-induced immunity as well as prevention and treatment with antivirals and monoclonal antibodies.

**Harsh Truths**

The unfortunate and harsh truth about coronavirus disease 2019 (COVID-19) in the United States is that more than a million COVID-19 deaths have occurred as of this writing. There have been 225,000 confirmed COVID deaths in the United States thus far in 2022 alone, despite the widespread availability of safe and effective vaccines. One of every 303 Americans is now dead of COVID-19, with a continuing toll currently of 300 to 400 deaths per day. We have had more deaths nationwide than deaths due to the 1918 US influenza pandemic. A major reason for this is that currently only 68% of Americans are fully vaccinated and only 33% are boosted. Less than 10% of eligible Americans have received the newer updated bivalent booster.

If we examine the data from other developed countries with the ability to accurately track vaccine uptake, the United States has among the lowest percentage of the
population that has received a booster dose, and therefore it is no surprise that we had more cumulative deaths per capita during the Omicron wave than any of these other countries. In fact, the United States has had the highest death rate of any of 21 other high-income countries. Although it is unthinkable that this could be the case, we must accept that the data are the data. Globally, the World Health Organization has estimated that approximately 15 million people have died of COVID-19.

**BRUTAL REALITIES OF COVID-19 IN THE UNITED STATES**

An examination of the current average daily new COVID-19 cases reveals that the unvaccinated have about 3 times the rate of acquiring new cases compared with the fully vaccinated in addition to a 6-fold higher risk of death. Whereas death rates have fallen as of May 2022, case rates soared to more than 100,000 new cases in the United States per day through the spring and summer of 2022, and this is likely to be a vast underestimate because of extensive home testing that is never reported. Yet, consistent with belief-dependent realism, no amount of data has swayed vaccine-hesitant and vaccine-rejecting individuals.

Multiple distorting human factors have an impact on the ability to manage the pandemic, from individual and collective human behavior patterns to a false epistemology by which the public attempts to understand and manage the pandemic. Human behavior during the pandemic has included vaccine hesitancy and rejection; rejection of masks; political and economic conflicts of interest; lack of leadership; and the discovery of animal reservoirs, such as the white-tailed deer and mink, that have been infected by human activity. In addition, we are dealing with pathologic cultural narcissism (a “me” not “we” mentality) and the false presupposition of the democratization of expertise. These factors are and have been injurious, self-defeating, and self-destructive. Ultimately, and indicative of massive issues that will occur into the future, we have lost any collective transcendent reference points by which we make decisions and act for one another’s and society’s interest.

**SARS-CoV-2 Variants and the Lies We Tell Ourselves**

The spike protein projecting from SARS-CoV-2 is composed of a number of parts, primarily the S2 and S1 domains, and contained within the S1 or distal part of the spike protein is the receptor-binding domain (RBD). The RBD binds to the human angiotensin-converting enzyme 2 receptor, allowing the virus to enter the cell and to hijack host cellular machinery to manufacture massive numbers of viral progeny. If we examine the number and location of mutations in 3 SARS-CoV-2 variants (wild type, Delta, and Omicron), one is struck by the significantly enhanced numbers of mutations from the original Wuhan ancestral strain to the Omicron variant. Not surprisingly, many of those mutations have accumulated in the RBD. As a result, as these types of variants arise, we begin to lose some level of effectiveness from illness-induced and vaccine-induced immunity as well as the efficacy of specific monoclonal antibodies as the virus mutates to evade immunity. The pattern of viral mutations often exactly matches the binding site between viral RBD and monoclonal antibody binding, accounting for loss of neutralizing activity.

Since December 2021, the predominant circulating variant in the United States has been the Omicron variant. Importantly, this was completely unpredictable as the expectation was that Delta subvariants would be next to arise. The Omicron variant was isolated in Botswana in November 2021 and then rapidly spread throughout South Africa and the rest of the world. Even though we have previously observed this type of pattern globally, if we go back to that early December 2021 time frame, most of the world believed Omicron would not be a problem. Omicron subsequently became widely geographically dispersed. It is significantly more transmissible than Delta but fortunately seems to have somewhat lower virulence compared with Delta, probably because of its propensity for upper rather
than lower airway infection, and some level of population immunity. Omicron demonstrated a larger genetic distance than any other variant of concern (VOC) from the ancestral strain\(^4\) and is better able to escape illness and vaccine-induced immunity compared with other VOCs as well as to evade the therapeutic effect of monoclonal antibodies. One consequence of this enhanced transmissibility is the significantly enhanced infection rate of children vs the other VOCs.

**BA.2—“Stealth” Omicron**

Although we again heard that it would not be an important public health issue, BA.2, the “stealth” Omicron, represented most new cases globally by April 2022. For example, the incidence in the Republic of South Africa went from about 22% of sequenced viruses to 86% between February 4 and February 11, 2022, and BA.2 subsequently outcompeted Omicron globally. It is approximately 30% more transmissible than Omicron. There is evidence of increased virulence and immune evasion capability with reduced efficacy of sotrovimab and a requirement for double the dose of tixagevimab-cilgavimab as prophylaxis. Since May, the United States and Europe have experienced yet another wave of COVID-19, this time due to Omicron subvariants—BA 2.12, BA 2.12.1, and BA 4/5. Currently, a variant under monitoring is the BA 2.75.2 subvariant, which may further evade illness and vaccine-induced immunity as well as all monoclonal antibodies except bebtelovimab. More worrisome has been the rapid evolution and spread of additional Omicron subvariants, including BA.5 variants (BQ.1, BQ.1.1, BF.7, BQ.X, XBB, BJ.1, other), BA.2 variants (BA.2.75.2, BS.1), BA.4 variants (BA.4.6), and others. Several of these arising variants may very well evade, in whole or in part, vaccine- and illness-induced immunity as well as monoclonal antibodies.

**What Should We Be Most Concerned With—Transmissibility or Virulence?**

In addition to viral virulence, we must also be concerned with viral transmissibility. As an example, let us take a baseline community that has a steady 10,000 infections. Let us assume that each new case generates an average of 1.1 new cases and that around 0.8% of new cases result in death. In 1 month’s time, approximately 129 deaths would be expected. However, what happens if the virus is 50% more lethal, like Delta? The number of deaths would jump to nearly 200 in 1 month. Instead of changing lethality, what if we instead make the virus 50% more contagious, like Omicron? Now, after a month, there are 978 deaths—or a 658% increase!\(^5\) That is what causes exponential spread. Human decision makers cannot deal, in a timely manner, with exponentiality. They always get it wrong, hence the astounding and continuing levels of COVID-19 morbidity and mortality.

Another way to think about exponentiality is by taking 2 scenarios, assuming 10 cycles of transmission in a naive population, where we vary R\(_0\), which is the basic reproductive rate of the virus—a measure of how many people, on average, an infected person would subsequently infect\(^6\):

- **Scenario A** with R\(_0\) = 2.5: leads to 9536 infections
- **Scenario B** with R\(_0\) = 6: leads to 60,466,176 infections

This important principle of exponentiality is what allowed us to predict that Omicron would lead to a worse surge and more deaths compared with Delta, which was counterintuitive to many decision makers. In fact, compared with the 2021 winter peak, Omicron cases rose 300%; hospitalizations, 115%; and deaths, 59%. Worse, the newer Omicron subvariants demonstrate R\(_0\) values closer to 12, accounting for the significant surge in new cases in the United States.

**COVID-19 VACCINE—EFFICACY AND EFFECTIVENESS**

When it comes to vaccine efficacy, there is a complex interplay between host characteristics, pathogen characteristics, vaccine type, time since vaccination, and geography. Host characteristics include demographic differences, genetic factors, existing
immunity, and comorbidities. Virus characteristics include the specific variant, inoculum size, and portal of entry.

**What Is Vaccine Efficacy?**

Vaccine efficacy can be viewed as a gradient of protection. Like virtually all our vaccines, SARS-CoV-2 vaccines are far better at blocking disease vs blocking infection. If we look at prevention of death, the mRNA vaccines were reported as 95% efficacious (against the Alpha variant); but if we look at asymptomatic infection and transmission, depending on the amount of time lapsed since last dose, it could be 0% to 40%. Vaccine efficacy depends on multiple factors, such as the underlying immune system health (innate, adaptive humoral, adaptive cellular) in the host, preexisting immunity, predominant circulating variant, community burden of transmission, and genetic factors. Overall, for the population, we can consider that there are 3 “enemies” to the development of immunity after vaccination: age, variant, and time.

With age comes immunosenescence and decreased vaccine immunogenicity along with a growing number of medical comorbidities. In general, if we look at people who were immunized in their 20s to 40s, they develop an abundant antibody response. On the other hand, people immunized in their 60s to 80s with the same vaccine under the same conditions develop a much lower level of antibodies. So, with age, we generally become more susceptible to infection and develop less robust immune responses to vaccines, a condition known as immunosenescence.7

With new variants have come mutations and recombination events resulting in immune evasion and the decreased ability of neutralizing antibody to bind virus and to block attachment to cell receptors. We see a similar trend in looking at the effect of VOC plus age. For example, if we measure neutralization of both the WA1/2020 strain and P1 variant, we find that not only does neutralizing ability wane with time, but at any one time point there is a difference (decrease) in the amount of measurable neutralizing antibodies by increasing age.7 In 1 study, there was a measurable and highly significant 22-fold drop in neutralization of the Omicron variant by Pfizer vaccine—elicited immunity.8 So logically, even vaccinated individuals are going to become more susceptible to infection in a shorter time due to Omicron and Omicron subvariants circulating, and of course, this is exactly what has happened.

If we look at the first 3 approved vaccines in the United States and track the hazard ratio for becoming polymerase chain reaction positive (ie, infected) after adjusting for age, race, ethnicity, sex, and comorbidities, Janssen wanes the fastest, followed by Pfizer, followed by Moderna, the last being most likely a dose effect.9 Thus, with increasing time, antibody levels and therefore protection do decrease. Vaccine effectiveness for infection over time also differs among the 3 vaccines. During a 6-month period, effectiveness against infection for adults in the United States wanes from about 89% to 58% with Moderna, from 87% to 43% with Pfizer, and from 86% to 13% with Janssen.9 Effectiveness against death and severe disease, however, is relatively well maintained, which reflects the gradient of protection previously discussed. This likely reflects the fact that prevention of disease tends to be more T-cell mediated, whereas prevention of infection is B-cell mediated.10 Unfortunately, we do not have a suitable standardized method for routine measurement of cellular immune responses to vaccination for clinical use. Newer data on Pfizer vaccine effectiveness showed the same trend.11 During an Omicron-predominant time period, effectiveness in healthy 12- to 15-year-olds against emergency department/urgent care visits after 2 vaccine doses (14 to 149 days earlier) was 45%, with no measurable efficacy after 150 days. We see the same phenomenon if we look at the same data for healthy 16- to 17-year-olds, but if they received 3 doses, vaccine effectiveness was boosted back up to 81%. Regardless, in both age groups, vaccine effectiveness against hospitalization was relatively maintained at very high levels even after 150 days.
Why Do Breakthrough Cases Occur?
Breakthrough cases are the predictable and expected result of a collision of waning immunity, new variants with immune-evading capability, high community burden of transmission, and inherent host factors as discussed here.

Booster Doses and the Wobble Stage. There is a theoretical construct vaccinologists use when thinking about delivering vaccines to a population in the context of an emerging pathogen for which there is no prior immunity. The main principles of this construct include the following:

- Building population-level immunity quickly. Unfortunately, we were not successful in doing that because of vaccine hesitancy and rejection.
- Rebuilding immunity as it wanes with time. Boosters are required, but even they will wane with time, and far fewer people received timely boosters.
- Eventually, as in the case of SARS-CoV-2 BA.4/5 and subvariants, a new variant develops that requires refocusing immunity to that viral variant with a variant-focused vaccine booster. This is the wobble stage that we are in right now.

Real-World Effectiveness Data. Individuals who received the primary Pfizer series and then were boosted barely accumulate any measurable risks of hospitalization, whereas those who received only 2 doses suffer from more hospitalizations. This is true for both severe disease and death. If we analyze homologous vs heterologous boosting, after the administration of 2 doses of Pfizer vaccine, there is waning of vaccine effectiveness against the Delta variant but much faster and significant waning of vaccine effectiveness against variants like Omicron. When we add a Pfizer booster dose, we get a profound boost in vaccine effectiveness that begins to wane quickly. On the other hand, when the booster dose is Moderna (heterologous boosting), effectiveness seems to be better. Thus, a “mix and match” strategy may offer some slight benefit.

Pfizer vaccine data in the elderly reveal a similar story. Measurable neutralizing ability was somewhat depressed for the Delta strain vs the Wuhan strain but profoundly depressed for Omicron. The neutralizing ability improves with boosting but wanes again and is more suppressed with Omicron compared with Delta and Wuhan. Moderna vaccine was also effective against infection after the second dose with waning over time, especially against Omicron. When boosted, effectiveness improves, but similarly more waning of immunity was observed with Omicron than with Delta. There seems to be consistency across the vaccines, with slightly better neutralization capability of Moderna vs Pfizer. The major point is that allowing continued viral transmission in the population will continue to result in the development of variants that will “learn” how to evade immunity by means of mutation and recombination.

Vaccine Effectiveness Against Hospitalizations. During the Omicron-predominant period through January 2021, after 2 doses of an mRNA vaccine, effectiveness against infection fell dramatically after 5 months to the 50% range. However, with a third dose (booster dose 1), it goes back up into the 90% range but subsequently falls into the 80% range and continues to gradually wane with time. Thus, booster doses are critical in providing the maximum amount of protection against infection, hospitalization, severe disease, and death.

Vaccine Recommendations
As a result of the preceding, we have seen the evolution of recommendations for vaccination. The Centers for Disease Control and Prevention (CDC) now allow that the second dose can be delayed up to 8 weeks after the first dose for those who are otherwise healthy and who are older than 12 years and younger than 65 years. The reason is that the longer the interval between doses, the better the immunogenicity and durability with reduced adverse effects. In fact, there is early evidence that we can decrease the already small risk of myocarditis by
expanding that interval. The issue is that until 2 doses have been received, protection against disease is compromised. As for the Janssen vaccine, the most recent recommendation is to subsequently boost with an mRNA vaccine. In the immunocompromised host, 2 doses are given, with a later additional dose (third dose) followed by a booster dose (fourth dose) 2 or more months after the third dose. For nonimmunocompromised persons, a newer bivalent mRNA booster is available, as is a protein subunit vaccine for use as a booster 2 or more months after the last vaccine dose. These recommendations will continue to evolve as more data become available and with the advent of new boosters and new variants that threaten health, and the CDC vaccine guidance charts should be consulted.17

Vaccine Safety

It is important to communicate that there is no such thing as “safe” with any human-made product. There is only the balance between risk and benefit and therefore the concept of “safer.” Wisdom, then, resides in guiding patients in which risks to undertake for the most benefit as there is no risk-free pathway. There are only 4 choices: COVID-19 infection, COVID-19 vaccination, passive immunity, and absolute isolation. As the Janssen vaccine is no longer a preferred vaccine, here we primarily comment on the issue of myocarditis.

Myocarditis/Myopericarditis. The predominant risk discussed in the media due to COVID-19 vaccination is myopericarditis. There is relatively little risk of myocarditis/myopericarditis after the first dose regardless of which mRNA vaccine is administered. The second dose appears to be the issue, hence the recommendation of increasing the time interval between doses. There appears to be a greater risk with Moderna vaccine (probably because of dose) compared with Pfizer vaccine.18 If we look at a 7-day risk interval per million doses given, we find that this is a male-predominant adverse effect that happens significantly less often in female patients. It is more common during the pubertal period but can still happen in older individuals but with much less frequency.19

Examining risks vs benefits reveals that if we administer 1 million doses of an mRNA vaccine to men aged 16 to 17 years, we prevent about 57,000 cases of COVID-19, 500 COVID-19–related hospitalizations, and 170 COVID-19–related intensive care unit admissions. The price we pay is 73 cases of vaccine-associated myocarditis.

If we examine the number of excess events due to vaccine exposure per million exposed, we find a significantly smaller number for myocarditis in those who received a dose or 2 doses of mRNA vaccines compared with myocarditis in those who became COVID-19 infected. When we look at pericarditis and cardiac arrhythmias, it is almost always related to the infection.20 As another example, the risk of myocarditis in patients with COVID-19 is about 16 times higher vs that in noninfected people. The myocarditis risk is 37 times higher for infected children younger than 16 years and 7 times higher for infected people aged 16 to 39 years compared with their uninfected peers.21

Another example is the risk of thrombotic thrombocytopenia syndrome (TTS) in women (30- to 49-year age group) after receipt of the Janssen vaccine. Per million doses administered in this age group, we prevent 10,000 cases of COVID-19, 900 hospitalizations, 140 intensive care unit admissions, and 20 deaths. The price we pay is 6 to 7 cases of Guillain-Barré syndrome and 8 to 10 cases of TTS.22 Fortunately, we have other choices, like an mRNA vaccine, with which we can eliminate the risk of TTS. As a result, the CDC now recommends that an mRNA vaccine be used preferentially to the Janssen vaccine.

In summary, the new recommendation for mRNA vaccines to increase the interval between the first and second doses increases immunogenicity, decreases the risk of myocarditis, and improves antibody durability. This is tailored primarily toward healthy individuals 12 years and older and younger than 65 years but creates some degree of tension as there is not full protection until full immunization.
More recently, the Food and Drug Administration has approved the use of a protein nanoparticle platform vaccine (Novavax). This vaccine presents the spike protein and an adjuvant to the immune system with robust antibody formation. Longer term data are not yet available, nor are real-world effectiveness data in the face of evolving viral variants. Currently, the vaccine has been submitted for use as a booster, and the FDA has now approved this vaccine for use as a first booster.

**Multiorgan-Specific Subclinical Function**

There are other highly significant risks of COVID-19 infection. The data to date reveal an alarming rate and breadth of end-organ long COVID complications and mental health issues.

In 1 study of 443 individuals after SARS-CoV-2 infection, there were multiple abnormal organ-specific findings that persisted 6 to 9 months after mild to moderate infection. Another study reported large numbers of SARS-CoV-2 RNA copies in the respiratory tract but also in the cardiovascular system, lymph nodes, skeletal muscle, nerves, ocular tissue, optic nerve, and brain. Autopsies revealed SARS-CoV-2 protein expression in human cerebellum and Purkinje system in addition to blood vessels in the brain.

Another study looked at risks and 12-month burdens of incident post–acute COVID-19 cardiovascular outcomes. Here again, regardless of age, COVID severity, and comorbidities, there was a profound excess risk burden per 1000 people of 20 different cardiovascular outcomes with a hazard ratio in the range of 2 to 4 for stroke, transient ischemic attack, arrhythmia, myocarditis, ischemic heart disease, heart failure, and thrombotic disorders. Finally, 1 study looked at mental health outcomes, particularly for those who were hospitalized with COVID-19, and found an elevated relative risk of a subsequent mental health diagnosis or mental health–related drug prescription. More recently, a CDC study revealed evidence of long COVID symptoms in 20% to 25% of all COVID-19 cases. To date, the nature of postinfection symptoms remains unclear and is also associated with a variety of infections beyond COVID-19.

**GLIMMERS OF HOPE AND WHAT HAPPENS NEXT**

The question we are most often asked is, Are we heading into the endemic phase? There is no way to know. We believe that less severe variants may indicate movement into endemcity; however, to date, there is no evidence for this. In addition, we do not understand the biologic, virologic, and immunologic “rules” by which viruses become endemic with one exception: high levels of immunity in the population have a “forcing” action toward endemcity in general; but if immunity is not high enough, it can also act as a mutational pressure.

Unfortunately, because of how we failed to deal with the pandemic, SARS-CoV-2 cannot now be eradicated. The multitude of reasons for this include human behavior and continued transmission, an animal reservoir (white-tailed deer, mink), waning immunity (both illness and vaccine induced), and importantly, continued viral mutation and recombination events. Therefore, we can confidently predict that our great-, great-, great-grandchildren will be getting COVID vaccines.

**Anticipations**

What shall we expect in the future? One scenario is that SARS-CoV-2, under mutational and selective pressure and recombination events, further changes, allowing either significantly or somewhat enhanced transmissibility and virulence. The evidence for this is the observation of the continued generation of VOCs, such as BA.2.12, BA.2.12.1, BA.2.75.2, and BA.4/5, and their subvariants; insufficient immunogenicity of the current vaccines against variants with greater antigenic distance, such as Omicron and Omicron subvariants; continued rejection of current vaccines; and escape from monoclonal antibody, convalescent plasma, and vaccine-induced antibodies.

The second scenario is that SARS-CoV-2 mutates into a virus with significantly less transmissibility and virulence, allowing
movement into the endemic phase, probably with periodic epidemic seasons. The evidence for this is currently lacking. There is no evidence for less transmissibility, and whereas the virulence of Omicron may be less in those previously vaccinated, that is not true for those who are unvaccinated.

**Next-Generation Vaccines**

New COVID-19 vaccine development continues. Second-generation vaccines will likely be reviewed by the Food and Drug Administration during 2022 and into early 2023. The first of these, Novavax (recombinant S protein in a synthetic nanoparticle + Matrix-M), has already been approved. This is likely to be followed by vaccines being developed by Medicago (recombinant S protein VLP + AS03) and Sanofi/GSK (S protein produced in insect cells through baculovirus vector + AS03). So-called third-generation COVID vaccines may include oral and nasal spray formulations, peptide-based vaccines, and other novel formulations. Such vaccines offer the hope of inducing mucosal immunity, thereby blocking viral transmission and infection.30

**CONCLUSION**

Finally, there is a significant likelihood of a worsening pandemic surge that the world will not be capable of mitigating in the face of the currently developing ultratransmissible Omicron subvariants. We must consider that SARS-CoV-2 is controllable with proper masking and distancing. If we add vaccines, it is eminently controllable. Yet in the third decade of the 21st century, with more scientific/medical knowledge and resources than at any time in our history, we have generally proven ourselves incapable, nationally and globally, of responding in a consistently rational manner. The evidence is overwhelming. Finally, over the horizon, areas of concern include unusual SARS-CoV-2 cryptic sequences that have been identified in New York City wastewater, early evidence of reverse zoonosis, and continued emergence of a variety of yet newer variants. We are also just starting to see the emergence and impact of the long-term population health effects of COVID-19 infection, including long COVID, predisposition to chronic illnesses, neuropsychiatric and behavioral/learning disabilities, and others that are yet to be recognized. The World Health Organization concluded in 2019 that vaccine hesitancy is one of the top 10 health threats to humans (that has turned out to be true), and wisdom dictates that unless we change our course of action, we will repeatedly see new variants that will drive continuing morbidity, mortality, and surge demands on the medical system. Such a course is untenable and immoral, given the profound suffering, morbidity, mortality, and effect on economies worldwide. Have we finally learned our lesson, or is it true that humankind never learns anything from history?

**POTENTIAL COMPETING INTERESTS**

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland provides consultative advice to AiZtech; AstraZeneca UK Limited; Eli Lilly and Company; Emergent Biosolutions; Exelixis, Inc.; Genevant Sciences, Inc.; GlaxoSmithKline; Janssen Global Services, LLC; Medicago USA; Merck & Co. Inc.; Moderna; Novavax; Pfizer-BNT; Regeneron Pharmaceuticals, Inc.; Sanofi; Syneos Health; and Vyriad. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. Dr. Poland holds patents related to vaccinia, influenza, and measles peptide vaccines. Dr. Poland has received grant funding from ICW Ventures for preclinical studies on a peptide-based COVID-19 vaccine. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies. Dr. Poland is an adviser to the White House and World Health Organization on Covid-19 vaccines and monkeypox.
**Abbreviations and Acronyms:** CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TTS, thrombotic thrombocytopenia syndrome; VOC, variant of concern

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