



# An Editorial overview and Perspective: Can the attenuated Omicron variant of Covid-19 virus resolve the pandemic in 2022?

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## Abstract

The highly transmissible Omicron variant of COVID-19 (SARS-CoV-2) emerged in late 2021 in South Africa and has now been found to represent over 70% of current infections in the USA and other Westernized nations. Its rapid spread is likely due at least in part to its apparent ability to escape neutralizing antibodies developed from previous exposure to covid and its variant subspecies. Currently over 1.35 million new COVID-19 cases were reported in the USA on Monday Jan 10th, 2022, accounting for the highest daily total for any country in the world since the onset of the pandemic. Among those individuals recently infected with the Omicron variant are included many previously vaccinated individuals and others who have gained natural immunity having recovered from COVID-19. Although the Omicron variant has been determined to be up to five-fold more contagious than its covid progenitor. it has a larger but overlapping molecular genome and the apparent capability to evade antibodies formed following prior exposure. To date it has resulted in only milder non-life-threatening illness compared to earlier forms of the virus, and consequently no deaths directly caused by the Omicron variant have been reported to date in contrast to more severe often dire outcomes for earlier forms of COVID-19. Thus, the question arises, can the Omicron variant produce a more broad-spectrum immune response to COVID-19 and its variants, and generate a longer-lasting immunity than current global vaccination and public health efforts, and finally, compared to earlier variant of COVID-19, will Omicron, should it become endemic or fully pandemic, finally contribute to the defeat of the COVID-19 pandemic in those regions where it may remain prevalent in 2022 due to its ability to result in only milder symptoms of covid-related illness while developing a broader based spectrum of protective neutralizing antibodies ?

**Keywords:** Coronavirus, Covid-19, Omicron

## Introduction

Coronaviruses are noted for causing respiratory and other illnesses in humans and some animal species.<sup>1</sup> The Coronaviruses that have caused illness in humans in recent years include the Middle East Respiratory Syndrome virus (MERS), the Severe Acute Respiratory Syndrome (SARS), and the current virus, the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2;

COVID-19), the emerging causative agent of the current pandemic. All the noted coronaviruses can cause respiratory and other symptoms of illness to varying degrees, but only the SARS-CoV-2 has evolved into an illness beginning in a localized epidemic and developing into a pandemic of serious magnitude within less than the first year of its discovery and subsequent existence. In contrast, microbial agents such as cholera for example, were typically well characterized including their mode of transmission and were easi-

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ly identified and effective treatment protocols established decades before causing the recent near decade long epidemic in Haiti following the devastating earthquake of 2010 and which inadvertently brought about the contamination of their waterborne mode of transmission in a major public water source for their nation.<sup>2</sup> The above mentioned respiratory coronaviruses may be transmitted by microdroplet transmission, however, which causes them to be a much greater challenge to control or eradicate via public health measures, due to their sub microscopic particle size, their moisturized respiratory in air, and their easy and virtually unlimited access to an airborne mode of release and dissemination. During this process, the virus-laden microdroplets are able to inoculate the surrounding air that nearby unsuspecting persons must breathe or otherwise make physical contact with. The inoculated airborne particles may also settle on virtually all nearby surfaces within air contact thus posing an additional infectious hazard to unsuspecting passers-by who may inadvertently come in contact with those surfaces and enabling their transfer to the awaiting respiratory passages of their new host, whether they be humans or susceptible animal hosts. Thus, the vital importance of addressing the modes of transmission becomes of paramount importance in constructive efforts to stem the continued spread and global expansion of the covid-19 pandemic and other infectious diseases.<sup>3-10</sup>

### Origins of the COVID-19 Virus

The origins of the pandemic link it to an outbreak in Hubei Province, Wuhan, China in late 2019, in close proximity to the nearby Wuhan Institute of Virology where it has now been established that research on closely related bat coronaviruses had been occurring. Although no direct link to the research lab to the origins of COVID-19/SARS-CoV-2 has yet been definitively established, considerable controversy continues to exist, but such suggestions are likely relegated to remain in the category of conspiracy theories until proven otherwise. Nonetheless, an outbreak of the novel virus later to be confirmed as a coronavirus was reported in Wuhan, via a suspected link to an unregulated open wet market, where a wide variety of foods including various freshly killed delicacy meats from civets and other animals capable of hosting the virus could be purchased. Coronaviruses may be transmitted from and between bats and other intermediate host animals and it has been presumed that the virus may have inadvertently contaminated the wet market via an intermediate animal host en route to its newfound human recipient. To date, the first human (patient zero) to have been infected with the COVID-19 has not been identified. During the initial reported outbreak, some two hundred individuals from Wuhan some of whom had visited the food market fell ill with a previously unknown form of viral pneumonia, which then spread rapidly among an immunologically naïve and likely unsuspecting population.

The outbreak was first reported to the World Health Organization (WHO) in late Dec 2019, and was first diagnosed in the USA on Jan 20, 2020, in an individual who had recently travelled from Wuhan, China to Washington State, USA. The International air travel routes likely facilitated the origins of the infections in the USA and other nations, and the rapid transition from an epidemic in China to the unsuspecting current global pandemic via numerous trans-international travel itineraries initially originating in Wuhan, China occurred with previously unprecedented rapidity. Because the virus may be transmitted from asymptomatic individuals, it presents an additional challenge to develop fully effective control procedures that can protect naïve passers-by from inadvertent exposure.

### Clinical Considerations of COVID-19

The overall clinical impact of the virus is now becoming more evident as the pandemic enters its third year of existence. Initially thought to be predominantly a respiratory illness, it is now recognized that the virus may also infect multiple organ systems including CNS and brain tissue, the cardiovascular system, liver, adrenals, musculoskeletal tissues, and gastrointestinal tract among others in addition to the respiratory epithelium, thus providing some explanation for the diverse array of signs and symptoms which may develop following an infection. Not surprisingly, individuals who have comorbidities including pulmonary disorders, diabetes, hypertension, obesity, and others commonly associated with aging are placed at a higher spectrum for risk of the more severe consequences and may succumb likely due to the combined effects of the comorbidities as impacted by the virus, while younger, healthier individuals typically recover from the virus often without lingering consequences and lower risk for development of chronic sequelae. Recently, the term 'long covid' has been introduced to acknowledge the lingering sequela that may develop following an active infection. The SARS-CoV-2 virus has irrevocably altered the life and wellbeing of individuals worldwide, with catastrophic impact on the health-care systems throughout the globe. While no specific therapies yet exist to prevent or cure the virus, research has resulted in a number of therapeutic strategies to treat the symptoms and clinical manifestations of the illness, which can often result in respiratory and multiorgan failures that require lifesaving intensive care attention, due at least in part to excessive cytokine mediated inflammatory responses that can initially severely damage pulmonary alveoli in addition to broader systemic effects, and can result in the most dire of outcomes in the absence of supportive heroic, therapeutic lifesaving measures.<sup>11-15</sup>

### Preventative Protocols

Preventative protocols have been published, but due to the airborne microdroplet mode of transmission most such efforts have

not yet become fully effective due to multiple physical constraints and the virility and nature of the virus itself in its apparent quest to survive. The primary preventive measures employed in attempts to slow the viral spread and transmission since the onset of the pandemic include personal protective equipment (PPE) for potentially exposed medical workers whose duties require close contact with infected individuals, vaccination with any one of the approved vaccines, social distancing including unnecessary contact with infected individuals or others at risk, frequent hand washing with soap and water, and restricted regional and International travel to minimize person-to-person and airborne contact, and chemical disinfectants applied to hands and presumed contaminated surfaces and which can disrupt the integrity of the coronal lipid and impede tissue uptake of the viral particles. To date however, none of these measures alone or in combination have achieved a 100% success rate. While social distancing is nominally determined to be approximately six feet (approximately 2 meters) of distance between individuals, the airborne microdroplets may be carried considerably further depending on the specific air movement in the immediate vicinity of the source, presumably an asymptomatic passersby, thereby enabling infected microdroplets to contaminate individuals and exposed surfaces well beyond the nominal six foot or approximately 2 meters established for conventional social distance interface parameters. Thus, it is not surprising that currently recommended preventive protocols have not been one hundred percent effective in containing the spread of COVID-19.

### **The Masking Dilemma**

Masking of individuals has been widely recommended, with mandates for compliance in a large number of jurisdictions. To date, however, masking as currently practiced in the community, has not been fully effective. A wide variety of mask types have been utilized, from the modified neck scarf or gaiter to the medical standard equivalent to the N95 or KN95 mask and the copper microparticle imbedded masks which may provide an additional level of viral prevention and reassurance to the wearer. Surgical masks have been used in medical and surgical practice for many decades, where along with surgical hand washing, they were introduced to reduce the potential transmission of bacterial contamination during medical and surgical procedures and where they have most deservedly earned wide acceptance. Viral particles however are remarkably smaller in diameter and overall size than bacterial cells, and not only are prone to being more easily transported in airborne microdroplets than bacterial organisms during normal respiration, the more loosely woven cloth fabric of many of the currently exercised masking options is likely ineffective in limiting virally enhanced microdroplets during their release during normal breathing from an unsuspecting COVID-19 virus donor. Neck scarfs or gaiters may be used as legal face covers, as can bandanas, beanies, buffs and other

relatively loose forms of facial coverings, as long as they cover the nose and the mouth when worn. When it comes to the barrier of physical restraint of microbe passage through the mask, however, since viruses are some 200-fold smaller than most typical bacterial organisms, the potential for physical containment of microbes vs viruses within the fabric of the masking material, the viral particle would seem to enjoy a more efficient transmissibility since their small relative size relative to the looser mesh of the masks easily permits viral passage even after hydration with the respiratory microdroplets. Pathogenic viruses including SARS-CoV-2 are obligate intracellular parasites, incapable of prolonged survival or replication without a suitable mammalian host that can provide the enzymatic and nutritional support needed for continued survival and replication. In contrast, many bacterial organisms are complete organisms including nuclear and enzymatic functions and can survive independently outside a cell as long as adequate essential nutrients and otherwise favourable conditions are made available, as is typical of bacterial culture media such as standard agar preparations that capable of providing those essential nutrients are provided. Parasitic organisms capitalize on different modes of transmission between hosts, are likely to occur only very rarely if at all in respiratory emissions, are often larger multicellular organisms and are an even larger size than the largest of bacteria likely to pose a medical issue in conventional medical practice.<sup>16-20</sup>

### **Composition and Biophysical Nature of the Coronavirus**

The chemical and biophysical nature of the corona viruses present complications not encountered to the same extent in the manifestation of illness as occurs with other infectious viruses. Two such critical locations on the COVID-19 virus are the coronal lipid coat that encompasses the particles, and the complex spike proteins extending from the corona that are attributed to their infective capacity via binding to ACE2 receptors to gain cellular entry in respiratory and other tissues. Once internalized, the viral particles associate with the host cellular RNA replication mechanisms where they begin to replicate almost immediately, in advance of the initial host immune responses and before such responses are fully active, thereby giving the viral illness an early chronologic advantage over the immune responses in the early stages of covid-19 induced illness. Prior viral exposure or vaccination may result in an acquired or natural immune response, thereby enabling a more rapid response to the viral exposure via activation of previously developed circulating antibody-generating plasma B cells and bone marrow memory B cells formed following the vaccination or prior exposure processes. Peak concentrations of covid-19 antibodies typically occur within a week to a few weeks post-exposure but decrease to suboptimal levels in the weeks and months that follow the infection being cleared. The declining circulating antibody levels may

then predispose the individual to be subjected to reinfection one or more times within six to eight months of the original exposure, including previously vaccinated individuals. The residual plasma and bone marrow memory B cells have proven beneficial however, as re-exposure typically results in a less severe magnitude of illness and more rapid recovery than might have occurred in naïve individuals who had never been exposed to either immunogenic source. Because the post infection antibody levels are considered transient in nature, reinfection is common in this as also occurs in EHV-1 and other viral illnesses. Ref The recent recommendations for administration of booster immunizations six or months after initial Immunization or exposure lends credibility and traction as such boosters may re-engage the immune system soon enough after administration and enabling the memory B cells of plasma and bone marrow to become reawakened, thereby improving circulating antibody levels to a more protective level should re-exposure occur during the immediate weeks and months following the booster re-immunization. It is not yet known if additional boosters beyond the first year may be in order in the future.<sup>21-25</sup>

### **Development of Effective COVID-19 Vaccines**

Vaccination has proved its effectiveness in the prevention and control of numerous pathogenic viruses, including smallpox, polio, the common viruses associated with influenza and the common childhood illnesses among others, and attempts to develop an effective COVID-19 vaccine became an early incentive in the quest to overcome the COVID-19 pandemic. Using current state-of-the-art technologies, at least three vaccines were quickly developed via joint incentives between private and public entities, successful candidate vaccines were developed mostly based on new RNA methodology, tested for safety and efficacy in early clinical trials, and ultimately granted emergency use authorization (EUA) by the FDA, all in less than one calendar year from the onset of the pandemic. Subsequently widespread immunization programs were initiated and deemed successful, with most vaccines reporting over 90% effectiveness when administered as recommended, also all accomplished within the first year of the pandemic and giving meaning to the name 'warp speed' coined by the US developers. COVID-19 immunizations have now been administered to well over two hundred million Americans in addition to additional millions worldwide, representing approximately over two thirds of the US population, and establishing among the highest COVID-19 vaccination rates of any nation. However, to date the vaccination experience has been found to be insufficient to establish a reliable 'herd immunity' in the US or other populations due to a variety of complications. Notwithstanding the considerable efforts undertaken at home and abroad to decrease the progression of the pandemic and to afford some measure of protection to those individuals most at risk of the

untoward health effects of infection, including premature death to over five million people worldwide and 800,000 in the USA, the global vaccination efforts were deemed incomplete and to date have failed to adequately control the pandemic in contrast to the effectiveness of other types of vaccines. The industrial and direct healthcare costs of this pandemic are extraordinary and continuing virtually unabated, now reaching billions of dollars, and lost industrial productivity annually across the globe. The rapid combined and well-coordinated responses of the industrial and governmental public health endeavours to develop and implement effective COVID-19 vaccines in addition to continued research and clinical evaluations of oral medications and other approaches are believed by many to have played a significant role in limiting the global damage from the pandemic where these endeavors are likely to continue to contribute to the resolution of this pandemic.

### **The Chemical and Biophysical Nature of the Corona Viruses**

The chemical and biophysical nature of the corona viruses present complications not encountered to the same extent in the manifestation of illness as occurs with other infectious viruses and microorganisms. Two such critical locations on the COVID-19 virus are the essential coronal lipid coat that encompasses the particles, and the complex spike proteins extending from the corona that are attributed to their infective capacity via binding to ACE2 receptors, in concert with the lipophilic coronal membrane to facilitate viral entry, which enable the viral particle to gain cellular entry in respiratory and other tissues. Once internalized, COVID-19 viruses behave as obligate intracellular parasites, and the viral particles rapidly associate with the host cellular RNA replication mechanisms where they begin to replicate almost immediately, and in advance of the initial host immune responses. The viral replication appears to commence before the immunogenic responses are fully active, thereby giving the viral illness an early chronologic advantage over the immune responses in the early days of a COVID-19 induced illness. Prior viral exposure or vaccination may result in an acquired or natural immune response, thereby enabling a more rapid response to the viral exposure via activation of circulating antibody-generating plasma B cells and bone marrow memory B cells that had been formed from the vaccination or prior exposure processes. The process of viral replication during a reinfection or in a previously immunized individual may still precede a substantive early immune response by several days, thereby providing only a partial immune antibody generating response in the early days of the re-exposure. Peak concentrations of newly generated COVID-19 antibodies typically trail the peak viral replication processes in both scenarios and occur at maximal levels within a few days to a few weeks post-exposure but tend to decrease to suboptimal ful-

ly protective levels in the weeks and months that follow the active infection being cleared. The phenomena of low circulating levels of COVID-19 antibodies months after an infection or vaccination may leave the individual subject to reinfection one or more times following an original immunogenic exposure. The residual plasma and bone marrow memory B cells are clearly beneficial however, as re-exposure typically results in a more rapid response than may occur in naïve individuals, resulting in a less severe magnitude of illness than might have occurred in naïve individuals who had never been exposed to either immunogenic source. The recent recommendations for administration of booster immunizations approximately six months after initial Immunization or exposure lends credibility as such boosters may re-engage to immune system to improve circulating antibody levels to a more protective level should re-exposure occur.

### **Viral Mutations in Coronaviruses**

Many viruses including those that cause the periodic influenza or common cold are prone to periodic mutation, some more frequently than others. The COVID-19 virus began to demonstrate mutations on its infective spike proteins soon after being characterized, resulting in the Delta, Omicron and among multiple other lesser known variants, and both of the currently dominating variants continue to circulate widely. Of interest, both Delta and Omicron appear to be more highly transmissible than their progenitor, but only the Delta but not the Omicron have been associated with serious illness resulting in mortality. While both of the current variants have generated multiple variations on the spike protein, the Omicron appears to have developed the most biochemical changes so far and the greatest molecular footprint of the multiple variants characterized to date. All variants contain multiple potential epitopes that by themselves are necessarily immunogenic, and thus the larger molecular footprint of the Omicron may enable that entity to establish a broader spectrum of antibody protection once it is encoded in the host immune system B cells than has been produced from the original progenitor virus, analogous to the reported greater magnitude of effectiveness of natural vs. vaccine-mediated (acquired) immunity. The Omicron variant has been determined to be at least five-fold more contagious than its COVID-19 progenitor, but to date has resulted in only mild illness and no reported deaths that can be directly linked to the Omicron variant have been reported to date. Thus, Omicron appears to have all the makings of a naturally attenuated strain of the COVID-19 virus, which is somewhat analogous to the observations of a century ago with the cowpox vs. the smallpox virus and it is proposed that the naturally attenuated character of the Omicron variant may result in a welcome amelioration of the dire signs and symptoms of the COVID-19 pandemic.<sup>26-31</sup>

### **Therapeutic Options for COVID-19: the 'Off-Label' Dilemma**

At the onset of the pandemic, no standardized or consistent time-proven universal treatment protocols for the novel viral illness existed or had been developed. Early covid treatment options were typically based on recognized efforts to alleviate the symptoms, often with inadequate results in that older patients with one or more comorbidities all too often tended to succumb to the combined impact of the pre-existing conditions and the COVID-19 illness. Faced with no known pharmacotherapeutic agents for COVID-19 available, numerous treating physicians attempted using existing drugs and nutraceutical agents in off-label applications in the absence of existing and time proven pharmaceuticals. However, in the absence of controlled trials with those agents that included properly designed control groups it became difficult to interpret the results objectively. Not all of the potential drugs reviewed herein were approved for the treatment of COVID-19 in the USA, although most such drugs had been accepted for use in some other nations since at the onset of the pandemic, no approved therapeutic agents had yet been identified or approved by the FDA or the corresponding agencies of other nations. Among the early entrants to potential treatments included the longstanding antimalarial agent's quinine, chloroquine, and hydroxychloroquine, administered early in the course of the infection, in combination with vitamin D<sub>3</sub>, zinc and a broad-spectrum antimicrobial, all of which exhibited what was perceived by the treating physicians clinical efficacy for the illness. The above agents were usually administered with vitamin D<sub>3</sub>, zinc, and a broad-spectrum antimicrobial such as azithromycin which was presumed to minimize the potential for a secondary infection. The investigators reported less severe viral illness, and fewer hospitalizations and deaths when administering the off-label agents for COVID-19. The off-label applications indicated are believed to exert anti-inflammatory actions and were readily available and had been used successfully in other FDA approved applications including malaria and some Musculo-skeletal conditions for many years. Ref Their therapeutic potential was presumed to be linked to the anti-inflammatory actions of the agents, likely slowing, or otherwise impeding the inflammatory response of the invading COVID-19 virus on its human host. The antiparasitic agent ivermectin also demonstrates anti-inflammatory actions and was also found to be useful when administered early in the course of infection by the treating physicians. The more recently FDA approved intravenously administered antiviral agent remdesivir (RDV) in addition to several analogues of RDV have demonstrated antiviral activity in vitro and in vivo, and later in the course of the pandemic RDV was found to reduce the number of days of hospitalization and covid deaths by about one-third after 5 or more days of treatment and gained

FDA approval in 2021. RDV has now been used extensively in many countries as an appropriate standard of care for the treatment of COVID-19 illness but has not been approved for the prophylactic prevention of COVID-19 infection. Both Ivermectin and hydroxychloroquine have been approved for non-antiviral use for decades without significant side effects, and in recent COVID-19 studies, were found to be effective in decreasing both the magnitude of infection and the duration of illness when administered early in the course of infection. As with most infectious illnesses, early intervention is the most desirable and may enable a more complete recovery than if treatment is initiated later in the course of the illness being treated. Of note, in the afore mentioned off-label applications the clinical observations were recorded early in the course of their covid illness, with many patients in remaining in out-patient or early in-patient settings through their illness and it was reported that they experienced a high recovery rate. As is desired in treating most ailments and illnesses including COVID-19, in most of the reported studies reviewing off-label and natural remedies, or in locally approved applications of the above-mentioned agents they were consistently most effective when treatment was initiated early in the course of infection.

### **Monoclonal Antibodies and Convalescent Plasma**

Among the most effective treatment strategies for early COVID-19 yet developed is the intravenous administration of convalescent plasma and monoclonal antibodies, and which were also were granted an EUA for bamlanivimab plus etesevimab and casirivimab plus imdevimab by the FDA in 2020 and 2021 respectively.<sup>31</sup> Both of the antibody-based treatments are most effective when administered as early as possible as prophylactic or early treatment in high-risk patients as early in the course of the infection possible, and prior to the emergence of life-threatening signs and symptoms. When administered early in the course of infection, monoclonal antibodies and convalescent plasma have been shown to neutralize infective viral particles, reduce the number of hospitalization days, dramatically shorten the course of the infection, and significantly reduce morbidity, mortality, and chronic post-infection and long-covid sequelae especially in patients who may present with one or more comorbid conditions. Monoclonal antibodies, followed by convalescent plasma are deemed the agents of choice in the early treatment of COVID-19 by many practitioners and are gaining wide acceptance in the clinical community.

### **Complementary Options for COVID-19**

Complementary therapies have also been applied in the treatment of COVID-19, and are sometimes added to the above agents. Complementary nutraceutical and other agents included the Vitamins C and D<sub>3</sub>, recognized for their antioxidant and immune-stim-

ulatory effects, respectively. In addition, an intestinally absorbable form of Zinc such as zinc glycinate was often recommended. Zinc is an important component of the early phase of most RNA antiviral therapies, as the DNA-dependent RNA replicase enzyme needed for the host viral replication mechanism has demonstrated to be sensitive to zinc inhibition and is believed to slow the early phase of the intracellular viral replication process in vivo in the newly acquired host. Antioxidants, including quercetin and some organically bound residues such as the glycinate forms facilitate luminal and cellular absorption and may facilitate zinc uptake in peripheral tissues by acting as a metallophors. Other antioxidant nutraceuticals including curcumin, turmeric, ginger and others may also slow the inflammatory responses attributed to the COVID-19 virus during its infective processes and result in a diminution in the manifestation of COVID-19 symptoms in both its early and long COVID-19 forms.

The nutraceutical resveratrol, (RSV, trans-3'5'trihydroxystilbene) can provide additional antioxidant activity to tissues, and has also been proposed and an effective agent in facilitating the oxygenation of tissue myoglobin in hemoglobinopathies including  $\beta$ -thalassemia and sickle cell disease (SCD), where it may also stimulate the generation of fetal hemoglobin. Fetal hemoglobin can easily transport oxygen to myoglobin during intrauterine and early extra-uterine development in the presence of low ambient pO<sub>2</sub>. In SCD, RSV can contribute to a decreased incidence of acute sickling episodes and fewer hospitalizations where it is believed to minimize the pathophysiologic impacts of sickling episodes in SCD by improving the net capacity for peripheral oxygen transport and myoglobin uptake under conditions of low pO<sub>2</sub>. As such, it may also facilitate improvements oxygenation of peripheral tissues in COVID-19 under conditions of low pO<sub>2</sub> by virtue of its capacity to stimulate the production of fetal hemoglobin, with its more favorable propensity to transport oxygen to peripheral tissues in addition to antioxidant activity similar to that provided by other nutraceutical compounds.

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der conditions of low pO<sub>2</sub> by virtue of its capacity to stimulate the production of fetal hemoglobin, with its more favorable propensity to transport oxygen to peripheral tissues in addition to antioxidant activity similar to that provided by other nutraceutical compounds. Supplemental Oxygen therapy, provided by line oxygen or via ventilator assist is also a standard of care in most instances including pulmonary decompensation, especially when the pO<sub>2</sub> becomes significantly decreased and in the presence of respiratory inflammation and impaired respiration. Where available, hyperbaric oxygen therapy at up to three times atmospheric pressures have been applied successfully to improve pO<sub>2</sub> and oxygen saturation levels. Although the blood and tissue oxygen saturation effects tend to be transient within a few hours after discontinuation, thus oxygen therapy is typically continued until satisfactory pO<sub>2</sub> levels can be maintained unassisted. Oxygen therapy can effectively oxygenate both adult and fetal hemoglobin effectively thereby enabling blood saturation to remain at or above 90 percent under normal conditions.

### Glucocorticoids and COVID-19

A common observation in infected individuals is the release of a family of inflammatory cytokines and chemokines in the days and weeks following COVID-19 infection, termed the 'cytokine storm' which may often be followed by dire pathophysiologic consequences. Approximately one third of COVID-19 patients may experience a cytokine storm, especially those who may have pre-existing comorbidities including compromised respiratory function, including current or prior smokers which may result in an exacerbation of their COVID-19 illness. Because adrenal glucocorticoid hormones are naturally occurring stress hormones that are typically released with a circadian or ultradian rhythm under the control of the adrenal-hypothalamic (HPA) axis under normal physiologic conditions, augmentation of glucocorticoid actions in peripheral tissues are often a desirable therapeutic objective in the presence of extraordinary noxious stimuli. Stress stimuli can activate the HPA axis following noxious stimuli resulting in the release of pro-inflammatory cytokines including IL-6, TNF, IL-1 $\beta$  and others that may act on the HPA resulting in increased adrenal glucocorticoid production. Under normal conditions, the glucocorticoids can exert strong immunomodulatory effects and bring about a profound constraint in inflammatory processes. The adrenal glucocorticoid hormones also modulate their own production through a negative feedback on the HPA axis thereby limiting the duration and magnitude of their activity via 11 $\beta$ -hydroxysteroid dehydrogenase activity (11 $\beta$ -HSD1, 11 $\beta$ -HSD2) that facilitate the inactivation of the bioactive hormone cortisol to its physiologically inactive form cortisone in target tissues. Inflammatory signals can further contribute to the regulation of 11 $\beta$ -HSD1 and 11 $\beta$ -HSD2, to further determine the extent of lo-

cal glucocorticoid activity. The synthetic glucocorticoids dexamethasone, prednisolone, n-methyl prednisone and their congeners are immunosuppressant agents that tend to exert a longer plasma and tissue half-life than their naturally occurring analogues.<sup>31,30</sup> As such, they may be administered in a wide variety of inflammatory disorders with favorable therapeutic outcomes due to their ability to exert a more effective suppression of the release of inflammatory cytokines over a longer duration than their naturally occurring analogues. The above-mentioned synthetic glucocorticoids have now been recommended as a fundamental therapy early in the course of the COVID-19 infection where they may exert their broad-spectrum and more prolonged anti-inflammatory actions in a dose related manner, and where the glucocorticoid typically results in an amelioration some acute symptoms due to their ability to inhibit the release of pro-inflammatory and inflammatory cytokines. Due to their inhibitory effects on the HPA-mediated circadian or ultradian rhythm of adrenal glucocorticoid regulation synthetic hormone administration now occupies a central role especially when administered early in the course of COVID-19 infection. Overall, the therapeutic administration of glucocorticoids typically may exert potent anti-inflammatory effects across both the innate and adaptive immune system and are a mainstay of immunosuppressive therapies. Synthetic glucocorticoid compounds, such as dexamethasone and prednisolone, show greater efficacy compared to cortisol owing to their longer plasma half-life, improved parenteral absorption, reduced binding to cortisol binding globulin (CBG) thereby increasing the free to bound ratio, and enabling a greater potential for passive absorption in peripheral tissues. The magnitude of the inflammatory responses during diagnosis and treatment may be estimated by quantifying plasma C-reactive protein (CRP), a diagnostic marker of inflammation during the course of COVID-19 infection including variants where indicated.<sup>30,31</sup>

### Prophylactic Antimicrobial Therapy During COVID-19 Infection

It is undisputed that antimicrobial agents can bring about lifesaving actions during the treatment of confirmed microbial infections, and care must be exercised in dosing and administration protocols to minimize the potential for development of microbial resistance during such treatment.<sup>22,30,31</sup> Antimicrobial agents however, while lacking recognized antiviral activity and sometimes considered to be an 'off-label' application of an approved pharmaceutical when administered during confirmed viral infections, may also contribute an important safeguard during glucocorticoid therapy. In viral respiratory infections the potential always exists for a secondary opportunistic respiratory microbial infection to develop, especially in the presence of respiratory compromise. Thus the concurrent administration of an antimicrobial agent such as azithromycin or

other broad-spectrum drug has often been added prophylactically to minimize the potential risk of developing a compound viral plus multi-microorganism respiratory opportunistic infection. The management of the cytokine storm and its broad ramifications during COVID-19 infection remains a crucial but somewhat controversial issue due to the broad effects such agents may impact in peripheral tissues beyond the intended target. While the anti-inflammatory and immunosuppressive effects of the glucocorticoid agents may exert a profound impact on respiratory and other inflamed tissues, thereby limiting the progression of the inflammatory response and accelerating recovery from the noxious COVID-19 insult, their immunosuppressive actions on cellular elements of hemopoietic immunity may suppress molecular mechanisms of leukocyte recruitment and maturation, thereby impeding optimal cellular responses to potentially lurking microbial infections. Thus, the overuse of glucocorticoid immune suppressive agents while they may effectively inhibit cytokine-mediated tissue damage from noxious inflammatory cytokines, at the same time they may also impede cell-mediated immunity responses including antigen presentations interactions needed for optimal leukocyte and macrophage associated clearing of opportunistic microbial pathogens. Based on the greater magnitude of transmission for Omicron than earlier COVID-19 prophylactic therapy early in the course of infection best not be overlooked. Based on the observation that the Omicron is about 5-fold more highly transmissible, has a larger and overlapping molecular genome, and to date has produced only mild illness with no deaths reported to date in any age group directly from Omicron, it may provide an effective naturally occurring mechanism to decrease the most severe impact of the COVID-19 pandemic on the global health and longevity of individuals and the prosperity of nations impacted by the pandemic.

### Discussion and Conclusions

The evolution and treatment of the covid-19 RNA virus has posed many challenging issues. The virus has now migrated to virtually every corner of the planet and to every country of the world with devastating impacts to both health and economic issues since the initial report to the WHO in December 2019. The virus typically impacts individuals over 60 years of age more severely than has been reported in most of the younger, more healthy individuals who have contracted COVID-19, although individuals of any age including youth presenting with comorbid conditions may be at increased risk. The older individuals aged 60 and beyond who may contract covid often present with one or more age-associated comorbidities and typically suffer with more severe consequences including premature mortality than younger age groups. Consequently, for the first time in recent recorded history, the expected age of longevity experienced a decrease since 2020 for the first time in recent history attributed to the greater mortality rates among the older

age groups. The direst impact was found to occur in those people presenting with significant pulmonary, cardiovascular, immunologic and other chronic conditions as pre-existing comorbidities upon covid exposure and resulting in infection in both unvaccinated and vaccinated individuals. Individuals with prior vaccination or previous covid illness however tended to suffer less severe illness than immunologically naïve individuals. The recent emergence of the even more highly transmissible Omicron variant, albeit it with less severe clinical outcomes had inserted additional challenges to the pandemic in that it is resulting in surges in hospital and clinic visits and is threatening to overwhelm the already strained availability of medical and healthcare resources. Preventative and therapeutic options for the coronavirus remain limited however and may be best directed towards elements of the biochemistry of the infectious process with the same cautious strategy and protocols applied to earlier variants of the COVID-19 virus.

It has been observed that those individuals who have had vaccinations or prior COVID-19 illness have a lower risk of developing the most severe illness, hospitalizations and death, but may still become reinfected at a later time after several months have passed. Reinfection can also progress to 'long covid' following immediate partial recovery. While previous exposure to the antigenic epitopes results in formation of plasma B cells and bone marrow B cells, capable of continuing production of COVID antibodies, the circulating antibody concentrations decreases to residual levels several months post exposure that are inadequate to prevent future infections from taking hold but the delayed immune response typically occurs earlier than in a naïve subject, thereby preventing the most dire effects of the illness and likely enabling the recovery to occur more quickly. A debate occurs as to whether natural vs acquired immunity can provide the most robust immunity to COVID-19, and not all jurisdictions have yet accepted natural immunity as an effective protective measure. A limited number of studies completed in Israel and elsewhere however suggest that natural immunity attained via prior covid exposure and illness may be at least as effective as or superior to vaccination-induced immunity. The National Collegiate Athletic Association has recently decided to recognize athletes who have had COVID as equivalent to being fully vaccinated, but that endorsement has not yet received universal acceptance.<sup>32-34</sup> Hopefully, other organizations will follow as more studies on natural vs acquired immunity become available. In the interim it will be important to continue all available preventive measures known to contribute to infection control, in individual measures and in both close indoor and outdoor environments in concert with public health recommended procedures. While this may contradict the narrative that ignores the efficacy of natural immunity, it does appear to provide strong support for the benefits of natural immunity. In a recent study it was found that natural immunity provided

an average of 90% protection against previous versions of COVID and nearly 60% protection against reinfection with the Omicron variant, which is still better than the variable somewhat transient protection vaccination provides, and which may last for only 4 to 6 months post-vaccination. It was also found to provide “robust” protection against hospitalization and death from all known variants.<sup>8,9</sup> Natural immunity like immunization also has been demonstrated to become diminished over time, but was still found to be effective one year or more after recovery from COVID-19 infection.<sup>9</sup>

In conclusion, based on the observation that the Omicron is about 5-fold more highly transmissible and now has become present Internationally within a month of its reported discovery, its less severe pathophysiologic expression has the potential of contributing to the demise over the pandemic in the longer term, where the existing vaccines have been unable to due to logistic and other concerns. Specifically, despite the reported vaccine effectiveness in the initial vaccine trials, it became a virtually unsurmountable challenge to immunize a large enough segment of the global population within a short enough timeframe to accomplish herd immunity as has been achieved with other less mutation prone and less highly transmissible viral entities that could generate a longer lasting effective immune response. Specifically, the Omicron variant has a larger and overlapping molecular genome than earlier iterations, and to date has produced only mild illness with no deaths reported to date in any age group directly from Omicron/ As such it may provide an effective naturally occurring mechanism to decrease the most severe impact of the COVID-19 pandemic on the global health and longevity of individuals and the emerging future prosperity of nations impacted by the pandemic.

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### Conflicts of Interest

Author declares that there is no conflict of interest.

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