



COVID-19: From Global Understanding to Personalized Action



**A 2020 Collection of Articles by
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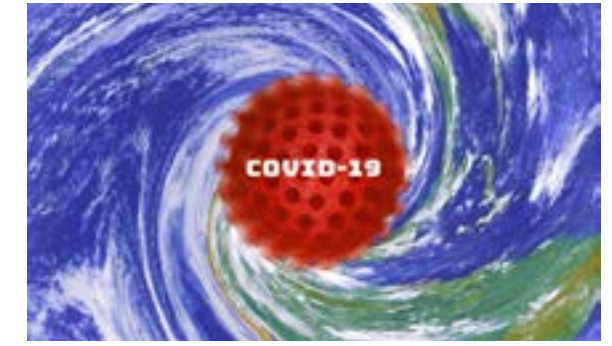
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Reflections on the COVID-19 Pandemic

I clearly remember the day in 1982 when my thinking about viral infections shifted from one point of view to another in the space of time it took me to listen to a lecture. I was living in Northern California then, and participating in a sabbatical year at the Linus Pauling Institute of Science and Medicine in Palo Alto. As I sat in a lecture hall among colleagues, a prominent young physician from the University of San Francisco Medical Center stepped up to the podium to give a presentation. His name was Paul Volberding. In July 1981, Dr. Volberding had identified one of the first reported cases of Human Immunodeficiency Virus (HIV) infection. Not long after, it was determined that HIV was

caused by a mutant RNA retrovirus, and its origins were tracked to transmission from animals to humans in Africa. Social contact was a hallmark of this virus. Everyone in the room that day was stunned by Dr. Volberding's account of the severity of the infection and its infectivity. Nearly 40 years on, data related to HIV continues to be sobering. The World Health Organization reports that more than 75 million people globally have been infected with the virus since it was identified, and of those, 32 million have died. It's important to understand that this is still very much an active and unresolved medical crisis that impacts people all over the world. In 2018, 34 million people were reported to be infected and 770,000 deaths were recorded. Although there is no immunization to prevent HIV infection nor is there a drug that truly eliminates it, somehow the passage of time, and perhaps also the awareness that antiretroviral drugs are used for treatment, has somehow dampened concerns about this virus in the United States and other western countries.

Today, as I write this, the world is grappling with the coronavirus (COVID-19) pandemic. This is also an infection involving a mutant RNA retrovirus, but fortunately it is less pathogenic than HIV. Public health crises like HIV and COVID-19 can prompt an array of cultural changes. It should never be forgotten that many health care workers lost their lives while treating patients with HIV/AIDS in the early 1980s. During that era, fear was a constant presence, and indeed we are again seeing widespread fear as we watch the number of COVID-19 cases rise while extreme attempts at control involving social distancing and stay-at-home orders are enacted. Historically it has been the case that truthful information can diffuse anxiety at the cultural level.

While exploring this concept, I came to recognize that viral pandemics occur on a regular basis. Here is a look back at some of the viral pandemics of the last century: the 1918 flu is estimated to have killed 20

to 30 million people; over two years, 1956 and 1957, the Asian flu is believed to have taken two million lives; in 1968, the Hong Kong flu killed one million people; and more recently, the 2009 H1N1 swine flu infected 61 million Americans and killed 12,500 people. With viruses, some are more infectious than others and some are more lethal than others.

In 2012, Anthony Fauci, MD, who is (and was then) the Director of the National Institute of Allergy and Infectious Diseases, published an article in the *New England Journal of Medicine* with David M Morens, MD, titled "The Perpetual Challenge of Infectious Diseases." They wrote: "Unlike many chronic and lifestyle-associated diseases resulting from multiple, interacting risk cofactors, most infectious diseases are caused

Although the review article by Drs. Fauci and Morens is very informative as it relates to the origin of viral epidemics, I question the statement that infectious diseases are caused by a single agent.

by a single agent." They continue: "Given their nature, infectious diseases are potentially preventable with personal protection, general public health measures, or immunologic approaches such as vaccination."^[1]

Although the review article by Drs. Fauci and Morens is very informative as it relates to the origin of viral epidemics, I question the statement that infectious diseases are caused by a single agent. My reasons stem from the study of the history of global viral pandemics and their pathogenicity and demographics. While there is no doubt that specific organisms are seen as the infectious vectors associated with specific pandemics, I believe history tells us that these viruses do not work alone. In fact, I believe a very different dynamic exists: these viruses work in combination with other factors — both social and biological — and some may be modifiable.

There is now evidence that certain lifestyle and environmental factors can serve as immunoadjuvants. Once identified, these factors can lend themselves to specific personalized intervention that is focused on renewal of immune system function, as well as increased resilience. I break down the social and biological categories mentioned in the preceding paragraph in the following way. Potentially modifiable social factors include things related to structure and behavior, such as housing, transportation, communication, health care systems, politics, and economics. What about biology? Here I would place potentially modifiable factors like stress, environmental toxicity, diet and nutrition, physical activity, sleep, hydration, intestinal microbiome composition, and biological rhythms. It is generally recognized that social factors are challenging to modify, whereas biological factors are personal and therefore an individual has a greater locus of control.

Hygiene, sanitation, and immunization are the three pillars of public health that are emphasized in the prevention of pandemic viral infections. All are important in reducing risk, but they do not adequately address the biological modifiable factors that play a very important and personal role in susceptibility to infection, as well as pathogenicity. I feel this observation has been validated by significant work done on HIV/AIDS pathology. There is strong evidence that personal factors such as diet quality, exercise, sleep, microbiome composition, and stress reduction can be significant in determining the course of HIV/AIDS in an individual who has become infected.^[2]^[3] This concept has been advanced recently with the recognition that an important way to approach the treatment of a viral or bacterial infection beyond that of immunization and antimicrobial/antiviral medications is through activation of specific components of the immune system. In a March 28, 2020 article titled “Activating Immunity to Fight a Foe — A New Path” that was published in the *New England Journal of Medicine*, Richard S Hotchkiss, MD and Steven M Opal, MD

highlight their belief that both the pharmaceutical industry and leaders at the National Institutes of Health need vision and courage to support trials that boost immunity in infectious diseases.^[4]

COVID-19: Is Risk and Severity Modifiable through Personal Lifestyle Factors?

From past pandemics we know that different viral infections influence differing percentages of people within a population, but that the majority is generally not infected. There are many reasons for this that are not fully understood. The biological factors I have outlined—environmental exposures, diet, stress, medications, and sleep — are becoming more well established as key factors that influence immune system integrity and defense against viral infection. It is now recognized that more than 20 million Americans are routinely taking various drugs that suppress the immune system and can change the way the body responds to viral and bacterial infections. This means that other lifestyle and dietary factors that influence the integrity of the immune system have become even more important in the age of globally transmitted viral diseases.

In a study of lifestyle factors and the incidence of community-acquired pneumonia in men and women living in the United States, it was found that smoking and weight-gain, along with reduced physical activity, were associated with increased incidence.^[5] Additionally, there is extensive research demonstrating that regular physical activity improves immune response to viral infections.^[6] In a March 2020 study published in the *Journal of the American Medical Association* titled “Association of Daily Step Count and Step Intensity with Mortality Among US Adults,” researchers found that a greater number of daily steps was significantly associated with lower all-cause mortality. This was independent of step intensity.^[7]

An overview of nutritional findings looks like this: a study of people who followed an unprocessed diet plan rich in plant foods, and also engaged in regular daily activity plus time spent outdoors in cooler temperatures, revealed that their immune system function and resistance to infection

A deeper look at individual nutrients is revealing. Numerous studies spanning 30 years have demonstrated the anti-viral influence of vitamin C and its importance in reducing the risk and severity of infections.

was improved.^[8] It has also been reported that the Mediterranean Diet improves immune function and lowers the incidence of recurring viral respiratory infections.^[9] Vitamin and mineral content of the diet may play an important role in reducing the risk to hepatitis C viral infection.

^[10] Plant foods that contain phytochemicals such as flavonoids have been found to improve immune resistance to viral infection.^[11] Finally, probiotics that help support a healthy intestinal microbiome have been reported to enhance the antiviral effects of vaccination in elderly patients, which demonstrates the important role the microbiome has in immune function.^[12]

A deeper look at individual nutrients is revealing. Numerous studies spanning 30 years have demonstrated the anti-viral influence of vitamin C and its importance in reducing the risk and severity of infections.^{[13],[14]} Significantly, the resistance to viral infections that is linked to vitamin C has been demonstrated in children as well adults.^[15] Vitamin C use that exceeds dietary intake has also been shown to be valuable in improving immune response to viral infection.^[16]

It is well established that vitamin A also has a very important role in promoting proper immune function in response to viral exposure.^[17] Supplemental vitamin A use needs to be monitored because excessive,

long-term intake of this nutrient, which is stored in the liver, can cause damage. Zinc is an important mineral that works alongside vitamin A in influencing immune function.^[18] There are numerous studies demonstrating a synergistic relationship between zinc and vitamin A. Daily intakes that support immune function are 10–30 mg of zinc along with 2500 IU of vitamin A. Another nutritional trace mineral of importance in supporting immune function is selenium.^[19] Daily intake of selenium in the range of 50–100 mcg is considered important, but — like vitamin A — it should not be consumed in high amounts due to potential toxicity. Lastly, vitamin D has also been identified to be a very important nutrient for the support of immune function.^[20] Vitamin D is often called the “sun vitamin” because it can be synthesized in the skin upon exposure to full spectrum sunlight. With cold and flu more prevalent during winter months, it has been suggested that this may be due to a lower level of sun exposure at that time of year, and therefore reduced vitamin D production.^[21] Daily intake of vitamin D in the range of 800–2000 IU is considered safe and supports many functions, including bone formation as well as immune function.

In 2005, the Institute for Functional Medicine was privileged to host a presentation by Wafaie W Fawzi, PhD, MB, BS, from the Department of Nutrition, Harvard School of Public Health. Dr. Fawzi and his research group had published a landmark paper in the July 7, 2004 issue of the New England Journal of Medicine that was titled “A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality.”^[22] For this study, the investigators compared supplementation consisting of multivitamins alone, vitamin A alone, or both with placebo in women in Tanzania, Africa who had HIV infection. They found that women who were randomly assigned to receive multivitamin supplementation were less likely to have progression to advanced stages of HIV disease. These women were found to have better preservation of

CD4+ T cell counts and lower viral loads. They also had lower HIV-associated illness and mortality. Interestingly, it was found that vitamin A appeared to reduce the effect of the other multivitamins, and vitamin A alone had some negative outcomes. In a companion editorial commenting on the study, Barbara Marston, MD and Kevin M De Cock, MD stated the following: “Although definitive policy recommendations concerning multivitamin supplementation must await the appropriate evidence (ideally from a large, simple trial in a population with access to antiretroviral drugs), individual treatment programs and clinicians would be justified in routinely prescribing this nutritional support, since it may provide a benefit and does no harm.”^[23]

In the context of the many studies demonstrating that lifestyle, dietary, and environmental factors play important roles in improving immune defense capability, do we give these variables enough consideration when analyzing why some people contract a viral illness when exposed while others do not? COVID-19 is certainly not the last pandemic the world will face. In truth, it represents a unique opportunity for us to seriously examine modifiable factors that may influence both the infectivity and pathogenicity of viral infections. To do this we must expand our thinking beyond the traditional public health model for the prevention of viral infection. A more panoramic view would include personally modifiable biological factors that decrease the susceptibility to viral infections and the reduction in their virulence by the improvement in immune response, and a greater emergent understanding of immune mechanisms by these variables to help reduce the number of serious cases of infection. In turn, the burden on the disease care system, which can be strained to capacity during a pandemic event, would be reduced. Active application of the principles that underlie personalized lifestyle health care, as described in an article I authored with my colleague Deanna Minich, PhD, in 2013, and a focus on the modifiable biological factors associated with immune

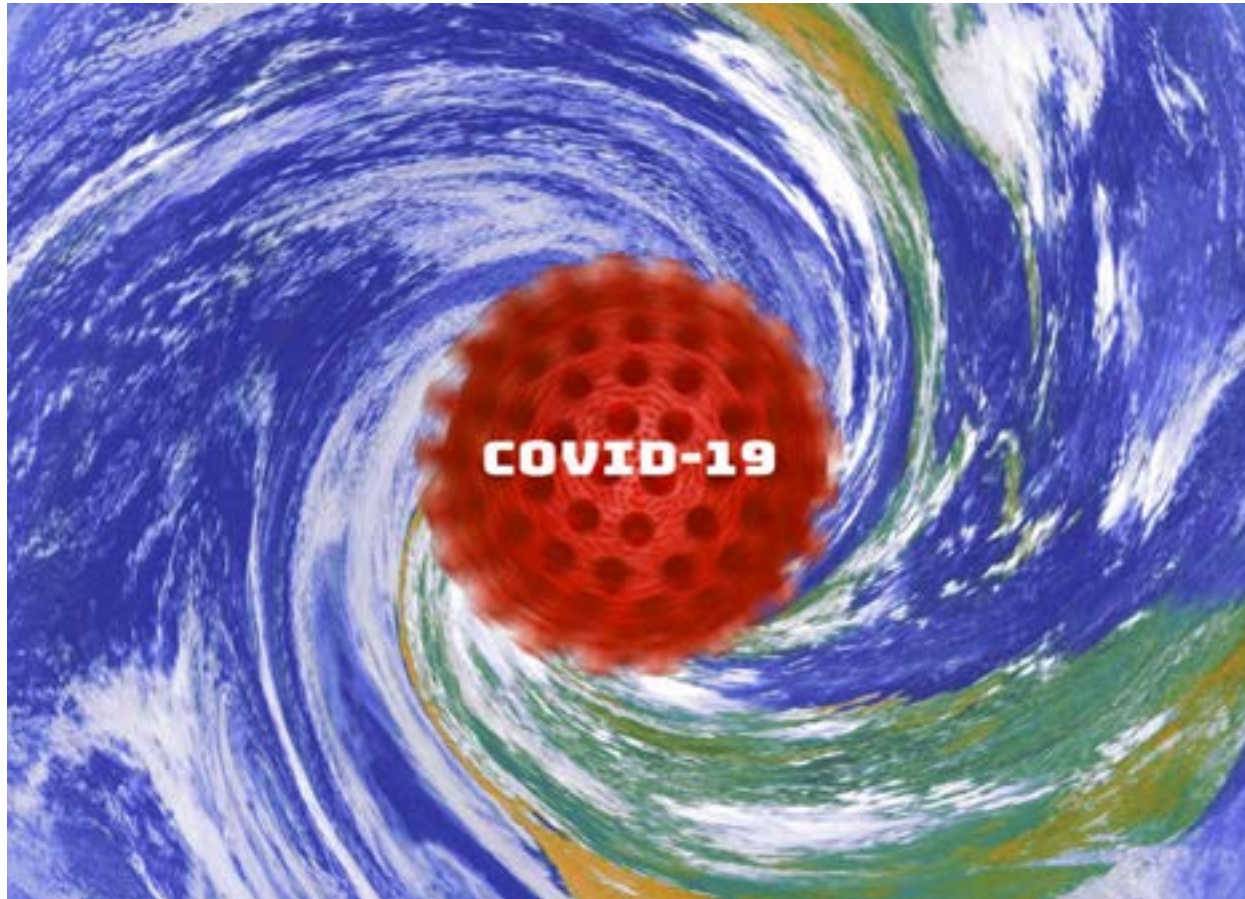
defense to viral infection creates a significant opportunity to reduce both morbidity and mortality associated with viral crises.^[24] This was a lesson we learned in the 1980s with HIV/AIDS, and this is an important lesson to relearn as the battle to contain and mitigate COVID-19 approaches new levels of global uncertainty and concern.

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Post-COVID: 5 Changes We Will See in Health Care

A perfect storm. This analogy has come to symbolize a series of events or factors that converge in a powerful way, often with a catastrophic outcome. As people seek answers about the trajectory of the COVID-19 pandemic — where it started, how it spread, when the curve will flatten, and how the world will navigate the long-term impact — some have suggested that the virus is the epidemiological equivalent of a perfect storm. But is that an accurate characterization?

In the April 16, 2020 issue of the *New England Journal of Medicine*, an editorial titled “Not a Perfect Storm — COVID-19 and the Importance of Language” was published.^[1] This opinion piece was written by two medical historians affiliated with Harvard University, Allan M. Brandt and Alyssa Botelho. These co-authors suggest that COVID-19 was not a random event, but rather one that was shaped in a very significant way by human actions. I find myself in agreement with their persuasive argument. They write: “This language creates a public health discourse that seems reactive rather than proactive, reductive rather than holistic, disempowering rather than empowering. Though its inherent drama may be appealing, the term ‘perfect storm’ invokes notions of randomness and volatility that may actually undermine our ability to address the Covid-19 pandemic and future disease outbreaks.”

With all “inherent drama” held firmly in check, I would like to take a logical look at five aspects of health care that I believe will change as a result of the COVID-19 global pandemic.

1. Pandemics, Redefined: The world has become more populated with people densely packed into large cities. Pollution, an environmental factor that negatively impacts the immune system, has increased. Global mobility — the ease with which we travel across countries and continents — fuels the transmission and spread of viral illnesses. In the last two decades, we have seen bird flu, swine flu, and Ebola become global health issues. Now we have COVID-19, and there is every indication that we will see more infectious disease pandemics in the future, perhaps with even greater frequency. People will need to adapt to this new reality that ignores borders and crosses cultural boundaries. In 2018, Bill Gates, tech pioneer and co-founder of the Bill & Melinda Gates Foundation, published an article in the *New England Journal of Medicine* that was titled “Innovation for Pandemics.”^[2] Presciently, Mr. Gates suggested

that a large-scale and lethal pandemic was a very real possibility. He was using historical precedent to guide his thinking about probability as well as preparedness. He wrote: “What the world needs is a coordinated global approach to pandemics that will work regardless of whether the next pandemic is a product of humans or of nature. Specifically, we need better tools, an early detection system, and a global response system.” How will pandemics be redefined? As an issue that connects humanity, not divides us.

2. Public Health, Redefined: Sanitation, hygiene, outreach programs, and awareness campaigns are the pillars that defined public health in the 20th century. But all of these efforts are broad brush — their effectiveness relies on averages and statistical models. Through better data analytics and a focus on personal health-related determinants that interrelate and amplify risk to infectious disease, we are going to see public health become much more precise in its application. The Institute for Health Metrics and Evaluation (IHME) has come to be recognized as the global leader in the field known as health metrics science. IHME’s work is powered by technological innovation and a worldwide collaborative network of research professionals. The value of this data-driven approach has already been demonstrated in a multitude of ways, and I feel it will revolutionize our ability to understand the potential impact of a pandemic by quantifying both the biological and social determinants of disease at a local level (an early warning system for every community in every nation). Data will guide decision-making about the allocation of resources to improve health and lower the risk to infection. At the same time, it will help with the early identification of sources and potential vectors that could trigger outbreaks. How will public health be redefined? It will become more precise, responsive, and targeted as a result of new data tools and technology.

3. Prevention, Redefined: Prevention, which has historically been identified with public health initiatives, has always been linked to population-based concepts such as immunization and the establishment of risk criteria for diseases. While these are important areas of concern, they are not adequate to prevent a pandemic, as our experience with COVID-19 clearly demonstrates. Another fact that is now indisputable is that the severity of response to a viral infection is highly variable among people who are exposed. Although the COVID-19 story is still unfolding, it did not take long to see patterns emerge with regard to incidence of infection. A wide range of possible outcomes also quickly became apparent. Men, older-age individuals, people with pre-existing diseases, and socio-economically disadvantaged populations all appear to be more vulnerable than other segments of society.

I offer a theory in the form of three questions:

- Could compromised immune resilience be a public health crisis that is not yet adequately measured or tracked in a way that encourages individuals to engage deeply and personally with this critical biological system?
- Is our current health care system responsible for this knowledge gap?
- Could awareness and self-monitoring of immune function save lives?

In 2010, the Affordable Health Care Act mapped out a sequence of first steps that would move prevention from the public health arena to the individual in the United States. By 2016, actionable efforts were underway. That same year, President Barack Obama published an article in the Journal of the American Medical Association that carried this title: “United States Health Care Reform: Progress to Date and Next Steps.”[3] In an editorial also published in that same issue of JAMA,

Stuart M. Butler, PhD, a Senior Fellow in Economic Studies at the Brookings Institution, wrote: “The health sector increasingly recognizes that it should focus more on ‘upstream’ determinants of health, not just medical services.”^[4] We have learned through our COVID-19 experience that compromised function of the immune system is a state that may be present in many people who appear otherwise healthy. How will prevention be redefined? Medicine will take a closer look at those “upstream” determinants of health. We will see new ways of assessing immune system function in development, and this focus will become incorporated into the standard of care that providers deliver to patients. The word “prevention” will no longer be disproportionately linked to a reduction of risk factors, but rather will encompass immune function and the management of lifestyle factors that can strengthen immune resilience.

4. Reimbursement for Medical Services, Redefined: When social distancing abruptly became our new normal, businesses — even the business of medical care — had to adjust quickly. Before COVID-19, the effectiveness of existing care models was already being called into question. Post-COVID-19, we need to find innovative ways of delivering care and streamlining reimbursement for medical services. Successfully preventing and managing future pandemics may depend on the evolution of the therapeutic relationship. A pre-COVID-19 statistic: more than 70% of medical expenditures in the US are for the diagnosis and treatment of chronic diseases. Chronic diseases, as I have already stated, may negatively impact immune resilience, making those who are living with these conditions high-risk candidates for infectious diseases. These chronic diseases have historically been treated with medications, although numerous studies have indicated that lifestyle interventions related to diet, exercise, sleep, and stress management may be more effective than pharmaceutical treatments. Designating primary care providers as gatekeepers who grant patients access to specialty medicine services

may not only be inefficient, but also ineffective. COVID-19 definitively showed us that chronic conditions can be linked to poor outcomes in a pandemic crisis. How will reimbursement models for medical services be redefined? We will see more emphasis on personalized lifestyle health care and how it can be effectively delivered in novel ways. This will include reimbursement for health coaching, group medical visits, and telemedicine. These are three care models that support people in making positive health changes that may translate into the reduction of risk to infectious disease.

5. Planetary Health, New Awareness: While the world was in lockdown for COVID-19, together we marked the 50th anniversary of Earth Day on April 22, 2020. Way back in 1966, Kenneth Boulding, who was an unusual combination of both economist and interdisciplinary philosopher, wrote about a concept of global connectiveness in which he referred to our planet as “Spaceship Earth.” Could there be a better and more profound example of how connected the biophysical web of Spaceship Earth is than a worldwide pandemic that has united us not through fear, but through the collective experience of slowing down and supporting one another through an event that has impacted each and every one of us?

There seems to be a greater recognition now that the resources of Spaceship Earth are not infinite. We all share the same water, air, and energy from the sun. COVID-19 has reminded us of the vulnerability of the human species and how our very survival depends upon the resources derived from our planet. You would be hard-pressed to find anyone who does not now appreciate the importance of our food supply and the global relationships that drive its production and distribution. There are currently 7.8 billion people inhabiting Spaceship Earth, and our crew is projected to grow to 12 billion by the end of the 21st century. The importance of our climate, soils, water, and plant diversity cannot be overstated.

Is there a silver lining to the COVID-19 pandemic? Are people now asking more questions about climate change, pollution, our reliance on ultra-processed foods, our sedentary lifestyles, our excessive alcohol intake, our use of medications and drugs, and our stress — SO MUCH STRESS — from being overscheduled and dependent on smart-devices? In 2017, an article titled “Planetary Health: Protecting Human Health on a Rapidly Changing Planet” was published in *The Lancet*.^[5] It was written by Samuel S. Myers, MD, who is a member of the faculty of the Harvard University Center for the Environment and also Director of the Planetary Health Alliance. Dr. Myers wrote: “The impact of human activities on our planet’s natural systems has been intensifying rapidly in the past several decades, leading to disruption and transformation of most natural systems. These disruptions in the atmosphere, oceans, and across terrestrial land surfaces pose serious threats to our health and survival and require a paradigm shift in how we deal with them.”

This is a field that I have an intense interest in. More than 40 years ago, I began my career as a professor of environmental science. My advocacy has remained strong over the decades, and earlier this year I was proud to co-author a paper with my colleague, Susan Prescott, MD, PhD, that appeared in the *International Journal of Environmental Research and Public Health*.^[6] Dr. Prescott and I wrote about the impact of the planetary health movement, and this is what we had to say: “In restoring human connectedness to the natural world, a sense of community and shared purpose must occur in tandem with technological solutions, and will enhance individual empowerment for personal well-being, as well as our collective potential to overcome our grand challenges. Such knowledge can help shape the use of metaphor and re-imagine solutions and novel ways for restoration or rewilding of ecosystems, and the values, behaviors and attitudes to light the path toward exiting the Anthropocene.” How will COVID-19 result in a new awareness of planetary health? What is a worldwide pandemic if

not a “grand challenge”? Spaceship Earth keeps spinning. On its beautiful surface, many of us are still in quarantine, awaiting humanity’s next chapter. Let’s write it collectively. Let’s get it right. We’re in this together.

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COVID-19: A Pandemic Within a Pandemic

“The race is on throughout the world to develop Covid-19 vaccines and therapeutics and end a pandemic that threatens to infect a substantial portion of the planet’s population, and perhaps kill millions of people, especially older adults. As billions of dollars flow into research and development efforts aimed at controlling the virus, the pandemic response remains hamstrung by our limited understanding of how to generate effective immunity, particularly in the elderly.”^[1]

COVID-19 officially became a pandemic on March 11, 2020. The World Health Organization (WHO) had been closely monitoring this novel coronavirus since early January, when a cluster of pneumonia cases in Wuhan, Hubei Province, China was reported. Past experiences with infectious respiratory viruses such as SARS and MERS informed decision-making in the weeks that preceded the declaration of a public health emergency. Two factors were of high concern: spread and severity. These concerns proved to be more than justified.

As of June 17, 2020, more than 8,000,000 cases of COVID-19 infection have been confirmed globally, and at least 440,000 deaths have been reported. COVID-19 has provided us with the opportunity to examine emerging data in real time. By tracking the history of the infection, it quickly became clear that there are significant differences among people in terms of both risk to infection and — if infected — severity of disease.

The Lancet, a highly respected professional journal, published the first international medical report about COVID-19 infection in Wuhan, China on February 15, 2020, and this article indicated that the infection was associated with acute respiratory symptoms and many other complex medical problems.^[2] A March 2020 follow-up study, also in Lancet, discussed the clinical course of the infection and risk factors associated with mortality.^[3] Specifically, they looked at how comorbidities (preexisting health conditions) might increase the risk for COVID-19 complications. The researchers noted that older age, hypertension, obesity, and diabetes were all associated with increased disease severity. As the virus spread, so too did support for this finding. From Seattle to New York, patients with COVID-19 did worse when comorbidities were present.^{[4],[5]}

Thankfully, there is some positive news. Among people with COVID-19, it appears that less than 20% become seriously ill, and for those who do

experience severe symptoms, the majority seem to fully recover. Outliers — patients who follow no established trend — have also been noted. The wide range of possible outcomes has created anxiety for both the public and the medical community alike. Why do some people fare so poorly while others have only mild symptoms? The answer may be tied to the functional status of an individual's immune system.

Certain chronic conditions, including the comorbidities mentioned above, result in altered immune system function, which can include unhealthy forms of inflammation. We have also come to understand that the COVID-19 virus can impact the function of many critical organ systems. So what's the link? Respiratory, cardiovascular, neurological, gastrointestinal, renal, and hepatic performance are all associated with alteration in immune system function. Inflammation is a hallmark of immune system dysfunction and is also strongly associated with COVID-19 infection. We know this because of a term that has recently entered the public dialogue: cytokine storm. A cytokine storm results when there is a breakdown in control of the immune system. An overwhelming inflammatory response takes place in the body, similar to a septic shock event.^[6] The title of an opinion piece published online in *Lancet Rheumatology* on May 29, 2020 perfectly captures the situation: “Coronavirus is the Trigger, but the Immune Response is Deadly.”^[7]

This means we have to think very carefully about how our immune systems can become dysfunctional. Are there early signals that might tell us when things are going wrong? As it turns out, there is a condition called metabolic syndrome which is characterized by altered immune function. In fact, it overlaps with the comorbidities that contribute to COVID-19 severity, and has been steadily rising in frequency over the last several decades. What happens when the world's most prevalent non-communicable health condition and a highly infectious viral disease collide? We

find ourselves in our new reality: a COVID-19 pandemic within a pandemic of metabolic syndrome.

Running the Numbers

Among 5700 patients hospitalized with COVID-19 in and around New York City, most had a comorbidity associated with metabolic syndrome. These included hypertension (56%), obesity (42%), and diabetes (34%). [8] Another report, this one published in the *Journal of the American Medical Association (JAMA)*, analyzed COVID-19-related data for the five boroughs of New York City. In this review, they found that, compared to other boroughs, the Bronx and Queens had the highest rates of hospitalizations and deaths per 100,000 residents. Notably, people in these two boroughs also had the highest prevalence of comorbidities.^[9]

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Clearly, there's an important connection here. In fact, researchers around the world have been examining this link from multiple angles and many hypotheses are being offered for consideration. Angela Saini, a noted science journalist, published an article in the

May 23, 2020 issue of *Lancet* that cautioned against associating comorbidities with genetic susceptibility based on race: “Such speculation runs the risk of forgetting that the demographic categories we recognise socially do not in fact have very much biological meaning and betrays a wider problem in medicine when it comes to race.”^[10] There has been a global effort to determine specific genetic linkages to infection with COVID-19, but to date no strong genetic determinants have been found.

Social determinants and lifestyle have emerged as the major factors determining risk to serious disease associated with COVID-19 infection.^[11]

My study of metabolic syndrome and inflammation — an undertaking that now spans more than 30 years — leads me down a different path of thinking. I believe these comorbidities result from the complex interaction of individual genetics, lifestyle, environment, diet, and the social determinants of disease.

In a number of ways, the pandemic of metabolic syndrome had already been on the radar of public health groups, as well as clinical care providers and planners. Morbidity and mortality related to non-communicable disease (NCD) was identified as a global concern in recent years. The World Health Organization had been tracking a constellation of NCDs for some time and was well aware that they had overtaken infectious disease as the most significant global cause of illness and premature death. An article published in the May 30, 2020 issue of *Lancet* addressed the fact that COVID-19 provided a new layer of urgency to the prevention and control of NCDs. The authors, who are affiliated with the WHO Regional Office for Europe write: “The COVID-19 response and continued and strengthened focus on NCD prevention and management are key and interlinked aspects of public health at the present time.”^[12]

As noted above, all of the comorbidities linked to both metabolic syndrome and COVID-19 severity are associated with altered immune function and a chronic state of inflammation.^[13] “Inflammaging” is a term that has come to be used as a descriptor for chronic inflammation related to aging or chronic non-communicable conditions such as hypertension, insulin resistance, and obesity.^[14] Right now, the attention of the world is clearly focused on threats like COVID-19 and the potential for additional outbreaks. With this in mind, certain important questions must be

prioritized. When did this state of altered immune function begin to be a global health issue? What is the cause of chronic inflammation that is impacting populations in so many countries? What can be done to rectify this situation?

Working the Problem

To answer these questions, we need to take a close look at the last 50 years. In the late 1970s, comorbidities started to become more prevalent in industrialized countries like the United States. Within a few short decades, the trend had reached developing nations. In April 2011, Margaret Chan, OBE, JP, FRCP (at that time was Director-General of the WHO), said the following: “The rise of chronic noncommunicable diseases presents an enormous challenge. For some countries, it is no exaggeration to describe the situation as an impending disaster; a disaster for health, for society, and most of all for national economies.”^[15] COVID-19 is the impending disaster that Dr. Chan predicted nine years ago.

David Stuckler, MPH, PhD, is currently a Professor of Political Economy and Sociology at the University of Oxford. In 2011 — the same year that Dr. Chan spoke about the WHO’s concerns about non-communicable diseases — Dr. Stuckler edited a textbook called *Sick Societies: Responding to the Global Challenge of Chronic Disease*. The arc of data that Dr. Stuckler has been tracking for more than a decade is compelling. In a 2008 article titled “Population Causes and Consequences: A Comparative Analysis of Prevailing Explanations,” he utilized four decades of male mortality rates to demonstrate that the division between infectious diseases and non-communicable diseases is shrinking and becoming increasingly problematic for health policy makers and health economists.^[16]

In 2006, British physician and global health analyst Luke Allen penned an article that was titled “Are We Facing a Noncommunicable Disease Pandemic?” The article abstract conveys a powerful message: “The global boom in premature mortality and morbidity from noncommunicable diseases (NCDs) shares many similarities with pandemics of infectious diseases, yet public health professionals have resisted the adoption of this label. It is increasingly apparent that NCDs are actually communicable conditions, and although the vectors of disease are nontraditional, the pandemic label is apt.” Dr. Allen proposed that the response to the global pandemic of chronic noncommunicable disease should be modeled after the WHO viral pandemic response plan because of shared features and impact on both population health and the global economy.^[17]

Let’s use Japan as a case study to examine this issue of the rising prevalence of comorbidities more closely. Japan historically had a very low incidence of obesity, hypertension, prediabetes, and diabetes. This started to shift in the 1980s. From 1988 through 2012, the rapid increase in these conditions was resembled the exponential growth of an infectious disease epidemic. In this case, there was no infectious agent. Rather, the population of Japan experienced dramatic changes in lifestyle, environment, diet, and stress.^[18]

Unfortunately, what happened in Japan was anything but an isolated event. Instead, it reflected a trend that was spreading across the world: a global epidemic of metabolic syndrome.^[19] Metabolic syndrome, as I’ve already stated, is defined as a state of chronic inflammation. It is also characterized by an imbalance of immune system function, and people with this condition typically have elevated blood pressure, blood triglycerides, and body mass index, as well as reduced levels of HDL cholesterol and impaired insulin sensitivity. Today, more than 30% of the adult population in the United States has metabolic syndrome.

Technically, metabolic syndrome is not a disease. It is probably better described as a state of lowered resilience to disease, as is evidenced by the number of associated comorbidities. People with metabolic syndrome are at increased risk to both non-communicable and infectious diseases such as COVID-19. In a May 2020 publication titled “Diabetes and Metabolic Syndrome as Risk Factors for COVID-19,” a group of authors affiliated with the University of Maribor in Slovenia point out that the disturbances associated with metabolic syndrome not only result in increased susceptibility to COVID-19 infection, but also reflect alterations in the immune system that sets the stage for more serious outcomes.^[20]

Connecting the Dots

COVID-19 is a new virus within the coronavirus family. As we all know now, it has a very high infection rate. Additionally, COVID-19 has some unusual infectivity features: it can be transmitted by asymptomatic individuals, plus the severity and clinical manifestations of the infection can vary widely (from mild to life-threatening). Seemingly, all body systems can be impacted by a COVID-19 infection; serious cases of respiratory, cardiovascular, immunological, kidney and liver, gastrointestinal, and neurological crises have all been reported.^[21] In the organ systems affected by COVID-19, cells have been found to express the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is thought to represent a target for the virus which allows it to bind to and enter our cells.^[22] Recent studies show that the virus binds to the ACE2 receptor more easily in the presence of inflammation.^[23]

The COVID-19 virus has spike-like proteins on its surface. These give the virus the unique ability to bind tightly to the ACE2 receptors. The spike-like proteins are also what differentiate the COVID-19 virus from other coronaviruses. These spikes have what are called high affinity furin

binding sites (furin is an enzyme in human blood that activates specific proteins).^[24] Researchers believe a slight change in the genetic architecture of the virus resulted in a modification at the furin binding site in the spike proteins. This is what makes COVID-19 such a formidable foe. How? It enables the virus to hijack furin, which allows it to attach to the ACE2 receptors on tissues more readily and facilitate penetration into cells. Given that so many tissues express the ACE2 receptor, this mutation and sequence of events makes COVID-19 uniquely more infective than other coronaviruses.^[25]

Furin belongs to a family of nine proteins that are called proprotein convertases (PCSKs). The function of these proteins is to regulate various biochemical processes, both in times of good health and when a disease state is present.

Regulation of furin levels in the blood is influenced, in part, by the immune system and inflammation. When cholesterol in the blood is elevated, furin is more vulnerable to being hijacked by the virus, and there is a greater opportunity for COVID-19 to convert

to its more infective form. It is speculated that this can contribute to the comorbidity-related priming of COVID-19 in people with elevated cholesterol who are at risk to cardiovascular problems.^[26] The ability of this virus to impact furin and increase infectivity is unique to COVID-19 (SARS-COV-2); it does not occur (to the same extent) with other coronaviruses, including SARS-COV-1.

Furin belongs to a family of nine proteins that are called proprotein convertases (PCSKs). The function of these proteins is to regulate various biochemical processes, both in times of good health and when a disease state is present. Furin is produced by a number of different cell types, including some within immune cells.^[27] In people who have comorbidities

that are associated with metabolic syndrome (hypertension, obesity, elevated triglycerides, impaired insulin sensitivity, and inflammation), furin levels have been found to be abnormal.^{[28],[29]} Interestingly, David Harrison, MD, who leads a research team at Vanderbilt University School of Medicine, published work in 2015 indicating that hypertension is related to inflammation derived from an activated immune system.^[30]

In 2018, researchers at the Department of Clinical Sciences at Lund University in Sweden and the School of Pharmacology at Helsinki University in Finland collaboratively reported the results of a study involving 4678 individuals with metabolic syndrome and diabetes that revealed elevated levels of furin in the blood.^[31] Prior to that, a group representing several clinical and academic institutions in Japan had reported that certain variations in the genes that control furin production were related to metabolic syndrome.^[32] This work suggests that the influence of furin on the comorbidities associated with COVID-19 may have a genetic connection. Finally, it's well established that furin levels are elevated in people with inflammatory autoimmune disorders.^[33] In sum, this research shows furin may be a key link between metabolic syndrome, inflammation, and COVID-19 complications.

Let's now draw a straight line between the non-infectious pandemic of metabolic syndrome pandemic and the infectious pandemic of COVID-19. Metabolic syndrome dramatically increases our risk of developing comorbidities like hypertension and diabetes. These in turn predispose us to contracting COVID-19 and for developing more severe systems after infection. This is likely due to the chronic inflammatory state (altered immunity) associated with metabolic syndrome. Furthermore, the comorbidities associated with metabolic syndrome may compromise our immune function through increased levels of furin in the blood. Let's put this together. When an individual with metabolic syndrome is exposed

to COVID-19, the virus gets the benefit of a compromised immune system and extra furin to facilitate binding to our cells. This is a mechanistic explanation of the situation that the world now finds itself in: a pandemic (COVID-19) within a pandemic (metabolic syndrome).

Mapping a Strategy

We know quite a lot about COVID-19. Its genetic profile has been sequenced, and we understand the unique composition of its spike proteins. Within the body, we know that infectivity depends upon the action of the virus binding to ACE2 receptors, which are expressed on many tissues. We know that COVID-19 has the ability to hijack an enzyme in our blood — furin — and when this happens the spike protein architecture is remodeled, making the virus even more active and pathogenic. We know that the comorbidities associated with COVID-19 infection and its severity are all associated with a dysfunction in our first line of immune defense, which is called our innate immunity. Innate immunity is known to be heavily involved in chronic inflammation.^[34]

How can this information inform our actions, not only in terms of mitigating the spread of the present pandemic, but also in preparing for future pandemic events? The best and most logical step is to reduce the prevalence of metabolic syndrome. Many lifestyle, environmental, and dietary factors are associated with abnormal immune function related to chronic inflammation and metabolic syndrome.^[35] Studies of the COVID-19 pandemic are being published every day, and some researchers are already positing that diet and metabolic syndrome could be partially responsible for the high variability that has been noted in infection and death rates.^[36] The Mediterranean diet — which is plentiful in fresh vegetables, fruits, whole grains, virgin olive oil, nuts, seeds, and fish that are high in omega-3 fats, while also low in sugar and processed foods —

has been extensively studied for its positive influence on the comorbidities associated with metabolic syndrome and its ability to reduce chronic inflammation.^[37] Food as medicine? A recent article suggests that it's a valid concept to consider for the prevention of coronavirus disease.^[38] Emerging evidence even shows that dietary intervention could potentially reduce the probability of infection with COVID-19 or the severity of symptoms in infected individuals.^[39] Recently, a multinational research consortium published work indicating that a diet associated with lowering the incidence of metabolic syndrome both improves immune system function and reduces inflammation, which — as already noted — are important considerations in minimizing the severity of COVID-19.^[40]

Why diet? Vegetables and fruits contain a class of nutrients called phytochemicals that play important dietary roles in reducing the comorbidities associated with metabolic syndrome.^[41] Certain phytochemicals, such as the flavonoids quercetin and luteolin, have been found to bind to the ACE2 receptor on COVID-19, which can potentially help to protect against infection.^{[42],[43]} A recent study evaluated how quercetin and vitamin D may contribute to the mitigation of COVID-19 through their impact on immune system function and the reduction of chronic inflammation.^[44] It is clear that improvement in the lifestyle, environmental, and dietary factors associated with the comorbidities that are linked to both metabolic syndrome and COVID-19 can have a positive impact on enhancing immunity.^[45] Studies have shown that improved physical fitness, reduction in obesity, and increased quality of sleep can all positively influence immunity and reduce the severity of viral infections like COVID-19.^{[46],[47],[48]}

In a sense, COVID-19 represents an alarm bell — “a tocsin to our aging and unfit society,” to paraphrase one author's recent work; I would add “immune compromised” to that description.^[49] In 2008, Scott M. Grun-

dy, MD, PhD, a researcher I greatly admire who is Director of the Center for Human Nutrition, Chairman of the Department of Clinical Nutrition at UT Southwestern Medical Center, published a seminal article titled “Metabolic Syndrome Pandemic.”^[50] Today, twelve years later, that pandemic swirls around an infectious threat called COVID-19. The good news is we know how to manage the pandemic of metabolic syndrome. Doing so, however, will require significant changes in how health care is structured and funded, as well as a shift in the cultural context of disease.^[51] Successful implementation of new thinking and new strategies has become critically important in this new era of pandemic awareness.

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The Challenge of COVID-19: What Should We Do?

It takes a lot to frighten someone who has circumnavigated the globe several times in a small sailboat. Consider the challenges of a life spent on the open water: rogue waves, wild weather, physical injuries, failing technology. This is what I was thinking while reading a column in my favorite boating magazine recently. The writer is a man who is well-known to serious global sailors. He has a colorful name and a reputation to match: Cap'n Fatty Goodlander. The good Cap'n Goodlander and his wife of 50 years, Carolyn, have countless friends — and fans — all over the world. Decades ago, they traded the comforts of a traditional home for the freedom of a modest boat cabin. As of this writing, the couple is on their boat in Singapore. They are well-stocked with supplies and they have access to services. Family is nearby. But after a lifetime of adventures filled with risks and uncertainties, the Goodlanders find themselves both anxious and frightened about a threat they cannot control: COVID-19.

What about you? Have you also been feeling the stress and the worry and the emotional exhaustion that hangs like a cloud over so many of us? Lately I have been wondering if we have crossed a threshold with COVID-19. Here's what I mean: is it now a simple fact that all of us will eventually be exposed to the virus? With each passing day, I believe we inch closer to this reality. But obviously not all of us who are exposed will die, and some of us who are exposed will not even become ill. These are things we know based on the events of 2020 thus far. In the absence of a safe and effective immunization to prevent COVID-19 infection, as well as the non-availability of a proven therapeutic drug treatment, what are our options for increasing personal resilience while we wait, watch, and hope for this pandemic to end?

Is Experience the Best Teacher?

I recently attended an online conference sponsored by the Royal Society of Medicine in London that drew more than 8000 virtual participants. One of the presenters was Dr. Monica Musenero, who holds a leadership position in the Ministry of Health in Uganda. Not long ago, Uganda struggled to contain an Ebola outbreak that became a crisis for that small nation. Dr. Musenero recounted learning about the COVID-19 virus infection in China earlier this year, and quickly recognizing that Uganda needed to immediately introduce social controls and contact tracking to prevent another health disaster among their population. These efforts and actions are considered a success. To date, Uganda has recorded less than 2000 cases of COVID-19 and only 20 deaths.

Taiwan also used past experience to their advantage when the threat of COVID-19 emerged. For context, the island of Taiwan is situated less than 100 miles from China. More than one million Taiwanese citizens work in China and routinely travel between the two countries. In 2003,

many lessons were learned as a result of the SARS epidemic, and Taiwan took steps to prepare for a future viral outbreak. As concerns about COVID-19 ramped up in the early days of 2020, the leadership of this country, including President Tsai Ing-wen (the first female president of an Asian country) and Vice President Dr. Chen Chien-jen (a Johns Hopkins University-trained epidemiologist and virologist), implemented standards designed to safeguard their country from this viral threat. It is believed that the early application of testing, contact tracing, isolation, and masks, as well as the use of electronic health record data resulted not only in low infection rates, but also minimal impact on daily life and the Taiwanese economy.

On a per capita basis, the United States has experienced approximately 1200 times as many COVID-19 deaths as Taiwan. It's a stunning contrast. Preparedness has proven to be a successful strategy for flattening of the curve of disease spread and allowing society to continue

On a per capita basis, the United States has experienced approximately 1200 times as many COVID-19 deaths as Taiwan. It's a stunning contrast.

to function. Taiwan has not experienced the catastrophic economic consequences that the United States is struggling with. Within the US, geographic examples support the validity of the preparedness model. In the August 11,

2020 issue of Wired magazine, an article was published under the title "San Francisco Was Uniquely Prepared for COVID-19." Like Uganda and Taiwan, San Francisco experienced a public health crisis in the not-so-distant past that imprinted both its citizens and leaders with a sense of urgency unknown in other areas of the country. Specifically, they experienced the HIV/AIDs epidemic, which was heavily concentrated in Northern California in the 1980s and 90s. This crisis was met with early

action and community support for activities such as testing, contact tracing, and sheltering at home. Significantly, that region has experienced a lower COVID-19 infection rate than other urban centers.

What's the takeaway? It's this: early introduction of — and compliance with — methods that are known to reduce potential virus exposure can have a tremendous and measurable impact on the containment of an epidemic. Can the actions taken by a relatively small population be scaled to have impact in a large country? Let's take a look at Canada. On August 25, 2020, the Journal of the American Medical Association (JAMA), published: "COVID-19 in Canada: Experience and Response." Canada, a country with more than 37 million citizens, implemented an integrated national COVID-19 response plan that included social distancing, reduced travel, personal hygiene guidelines, and a public awareness initiative that featured scientific experts sharing information about the seriousness of the situation. Canadians have also demonstrated widespread support for the use of masks. The infection rate in Canada is currently noted to be 19 cases per 100,000 people. In the United States, which has not organized a national response plan, the infection rate is greater than 1000 cases per 100,000 people. (According to this article, Taiwan — a country I have already highlighted — has an infection rate of just 2 cases per 100,000 people.)

Given this powerful combination of real-world experience and data, why is there still considerable and acrimonious debate about the value of wearing a mask to protect oneself from COVID-19 exposure? In another August 2020 JAMA article — an editorial co-authored by three physicians affiliated with the Centers for Disease Control and Prevention — the results from a number of research studies are summarized, including one that captured information from both employees (more than 75,000 of them) and patients in the largest health care system in Massachusetts.

This large-scale sampling indicates that there is a significant reduction in infection and illness among those who routinely wear masks in public versus those who do not. The authors write: "It is probably safe for individuals and safe for others to drive alone or to walk or jog alone on an uncrowded route without a face covering. But when individuals choose to go out or must be close to others in public, a cloth face covering can help reduce the spread of COVID-19 from asymptomatic individuals or others. With cloth face coverings, personal protection is derived from their use by all members of the community."

Immunity is everything and it's also unique to every individual. Your immune status is not my immune status, and vice versa. When a person's immune system is optimized, so is their resilience.

In the US, the outcry about masks has been volatile. Seemingly, no matter how high the evidence base for mask wearing is stacked, it's a subject that has become an emotional trigger and a social divider. The contri-

bution I would like to add to our national discourse is information about why masks are particularly important for protection from COVID-19. Cell is a top tier and highly respected scientific journal. In July, it published an article entitled: "SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract." More than 40 professionals are listed as contributing authors and participants in the research. It is complex work, however the summary points are quite accessible. The most vulnerable tissues for infection with the COVID-19 virus turns out to be the surfaces of the nasal passages and sinuses. Why? Because this part of the body has the greatest number of ACE2 receptors that can bind to COVID-19. With this knowledge in hand, the scientific logic becomes very clear. Using a cloth mask to cover the nose and mouth will reduce exposure of the upper respiratory tract to the virus. A mask, therefore, is a very important tool for personal protection against infection.

Making Prevention Personal: Your Decisions are the Key

Public health is everyone's responsibility. During a worldwide pandemic, you cannot rely solely on government interventions and increased vigilance of your personal hygiene. Immunity is everything and it's also unique to every individual. Your immune status is not my immune status, and vice versa. When a person's immune system is optimized, so is their resilience. And when resilience is strong, so too is your ability to fight the virus, even if you are exposed and infected.

Early in this article, I asserted my belief that everyone will eventually be exposed to COVID-19. With this in mind, we have to consider two things that you have some level of control over: minimizing exposure risk and maximizing resilience potential. In your own home and social environment, you can proactively choose to use the same measures that have kept infection numbers low in places like Taiwan, Uganda, San Francisco, and Canada. That is, you should wash your hands frequently, keep your social distance, limit group interactions, ventilate your personal space, and wear a mask in public. These are all choices that are easy to make.

But what about resilience? While it may feel harder to wrap your head around that concept, day-to-day decision-making is also the key feature of a successful personal immune resilience strategy. First, you need to determine if you are more vulnerable than others — both in terms of exposure and disease severity — based on what we know about COVID-19. Do you have one or more comorbidities? These are conditions such as obesity, diabetes, hypertension, or cardiac disease. Other factors may also be relevant. For example, data has shown that being older, medically underserved, or socioeconomically disadvantaged is linked to a higher incidence of serious illness among infected individuals.

If you are wondering about genetics, recent studies have been unable to identify common genetic characteristics that result in an increased risk to COVID-19-related disease. While there could be rare mutations of specific genes in the immune system that alter response to the COVID-19 virus, accumulating research indicates that this should not be a widespread concern for people at this time. Robert M. Plenge, MD, PhD wrote an opinion piece in a recent issue of JAMA under the title “Molecular Underpinnings

When you control personal factors that have already been noted — lifestyle, diet, environment — you can achieve a reduction in comorbidities that could lead to an improvement in immune system function.

of Severe Coronavirus Disease 2019.” Dr. Plenge summarizes work from multiple research groups, and with regard to the rare genetic variations that have been identified, he suggests that these are too infrequent to account for the significant number of specific groups of individuals who have

experienced increased illness and death from infection with the virus. However, Dr. Plenge also suggests that if additional genetic loci are identified, this could lead to improved diagnostics and therapeutics for those at risk.

Here's a recap of what we know: comorbidities put a huge number of people at risk, but genetics don't seem to be a major player. Lifestyle, diet, as well as environmental and social determinants (which include factors like poverty, crowding, stress, and unemployment) play significant roles in regulating the function of the immune system. Initially, it was believed that a COVID-19 infection only affected the lungs. Yet it quickly became clear that symptoms vary considerably from person to person. The liver, intestines, kidneys, brain, heart, skin, pancreas, and blood are all influenced by the virus. Unsurprisingly, all of these organs communicate with the immune system.

Can you eliminate or at least mitigate the presence of comorbidities and improve your immune function? For the most part, the answer is yes. When you control personal factors that have already been noted — lifestyle, diet, environment — you can achieve a reduction in comorbidities that could lead to an improvement in immune system function. Avoiding exposure to the virus entirely is the best way to protect oneself from infection and illness, but as the pandemic wears on and people begin the process of resuming daily activities, this strategy becomes more and more challenging for most people. It is important for people with comorbidities to understand that implementing changes now could represent an extra layer of protection should a future exposure become inevitable. Many people don't realize that the entire immune system turns itself over rapidly — millions of new cells every second, and a complete turnover every 100 days — which means you have the opportunity to change the cycle with the decisions you make about personal variables that are under your control.

Targeting Obesity, Hypertension, and Pre-Diabetes in the Battle Against COVID-19

Are you thinking that reducing comorbidities is easier said than done? It's true that the United States is not a healthy country. Children born today have a statistically lower life expectancy than that of their parents. That's a startling fact, and it's the first time this has happened in the US. A poor diet has been identified as one of the major contributors to this problem; according to a September 2020 article published in the *New England Journal of Medicine*, it is now the leading underlying cause of death in the US, having surpassed tobacco use in related mortality. A group of experts has come together to address this challenge. Together, they formed the Federal Nutrition Research Advisory Group. In July 2020, this group published a paper in the *American Journal of Clinical Nutrition* indicating that about

46% of adults in this country have an overall poor-quality diet. This number goes up to 56% for children. This problem is most acute in population groups that suffer from health disparities, increased frequency of comorbidities, and immune system problems. Among people between ages of 17 and 24, 71% do not meet the criteria for military service, and obesity is the leading medical disqualifier.

In the conversation around COVID-19, we are increasingly recognizing the role of diet. In fact, improving nutrition through dietary modifications is emerging as a key objective in lowering the negative effect of comorbidities on risk and severity of the infection. Francis Collins, MD, PhD has been the Director of the National Institutes of Health since

In fact, improving nutrition through dietary modifications is emerging as a key objective in lowering the negative effect of comorbidities on risk and severity of the infection.

2009. He recently published an important article in *JAMA* with his colleague Griffin Rodgers, MD called: "Precision Nutrition — the Answer to 'What to Eat to Stay Healthy.'" Significantly, Dr. Collins and Dr. Rodgers state the following: "Exploring how diet

and nutritional status modify immune response could help explain some of the variability in COVID-19 morbidity and mortality, even in individuals without diet-related chronic disease."

When you eat, you are feeding your immune system (and every other system in your body). Processed foods and empty calories can lead to compromised immune reserves, which is an imbalanced state that makes it more difficult for the body to manage the stress of the COVID-19 virus. Philip C. Calder, PhD is a respected global nutrition expert. With several collaborators, he authored a 2020 article called "Optimal Nutrition Status for a Well-Functioning Immune System is an Important Fac-

tor to Protect against Viral Infections.” I find the following excerpt quite compelling: “Public health practices, such as vaccinations and hygiene measures, are important measures that help limit the spread and impact of infections, including against acute respiratory viruses. However, the present situation with SARS-CoV-2 infection and severe outcomes of COVID-19 and the annual morbidity and mortality figures for respiratory infections overall make it clear that these practices alone are not sufficient. . . . As such, additional safe and cost-effective strategies are needed to support the immune system, and further protect individuals and populations from harm.”

While well-described in the scientific literature, it can sometimes seem difficult to connect diet and immune function. That’s why it’s important to recognize that the conditions we usually associate with diet are actually representations of immune dysfunction. We now understand that body fat is a key part of the immune system. There is a strong connection between excessive body fat and infiltration of that fat with activated immune cells that are in a proinflammatory state. This situation is a result of changes in the overall function of the immune system. Researchers have taken note that there is a high prevalence of obesity in countries with a high percentage of severe COVID-19 cases. In May of this year, Randy Q. Cron, MD, PhD published an article in *Lancet* with a provocative title: “Coronavirus is the Trigger, but the Immune Response is Deadly.” When obesity is coupled with exposure to the virus, the result can be a fatal alliance. Here’s why: chronic inflammation results from damaging alterations in the immune system. These same alterations are associated with obesity. If the controls of the immune system are disabled because of associations related to comorbidities, an individual is not only at greater risk for COVID-19 infection, but also for what has been called a “cytokine storm,” which essentially describes an overwhelming state of inflammation. In the most serious cases of COVID-19

infection, an individual does not die as a direct result of the virus, but rather from the collateral damage that takes place in the body.

Immune Regulation, Not Activation

Why would you want to “boost” an immune system that is already poised for overreaction? It does not make sense, and it also would not improve your resilience to either COVID-19 or other viral threats. Your goal should not be to activate the immune system, but rather to support its proper balance and control. I have coined the term “immuno-rejuvenation” to describe this concept. Recent advances in the understanding of our immune system have opened the door for new approaches to improving immune function. Personalizing your diet and undertaking evidence-based lifestyle interventions are the first steps in restoring immune system regulation. Individually and as a whole, these actions can help to clear away damaged immune cells, including those stored in fat cells. A successful immuno-rejuvenation reboot promotes a healthy, balanced immune system. It grants us the tools to mount a defense against COVID-19 and other illnesses.

Over the last few decades, numerous public awareness campaigns tried to get us to pay attention to the risks posed by chronic preventable conditions like diabetes, obesity, cardiovascular disease, and hypertension. COVID-19 has put them all to shame. We finally see clearly just how significant these comorbidities are to our health. An unexpected spokesman for the cause has recently emerged in the form of British Prime Minister, Boris Johnson. In April 2020, Mr. Johnson fell ill with COVID-19. He required hospitalization in an intensive care unit, and when he emerged, he did so as a man who had experienced a profound perspective shift.

Back in 2004, as a member of Parliament, Mr. Johnson openly rebutted calls for the government to become involved in fighting obesity in the United Kingdom. After a battle with COVID-19 that by most accounts was serious enough to warrant concern for his life, Mr. Johnson went on-the-record with the following statement: “The facts are simple: Extra

Public Health England is launching a new campaign focused on exercise and weight loss, and restrictions on junk food advertising are being tested. Of course, not everyone is happy with this plan.

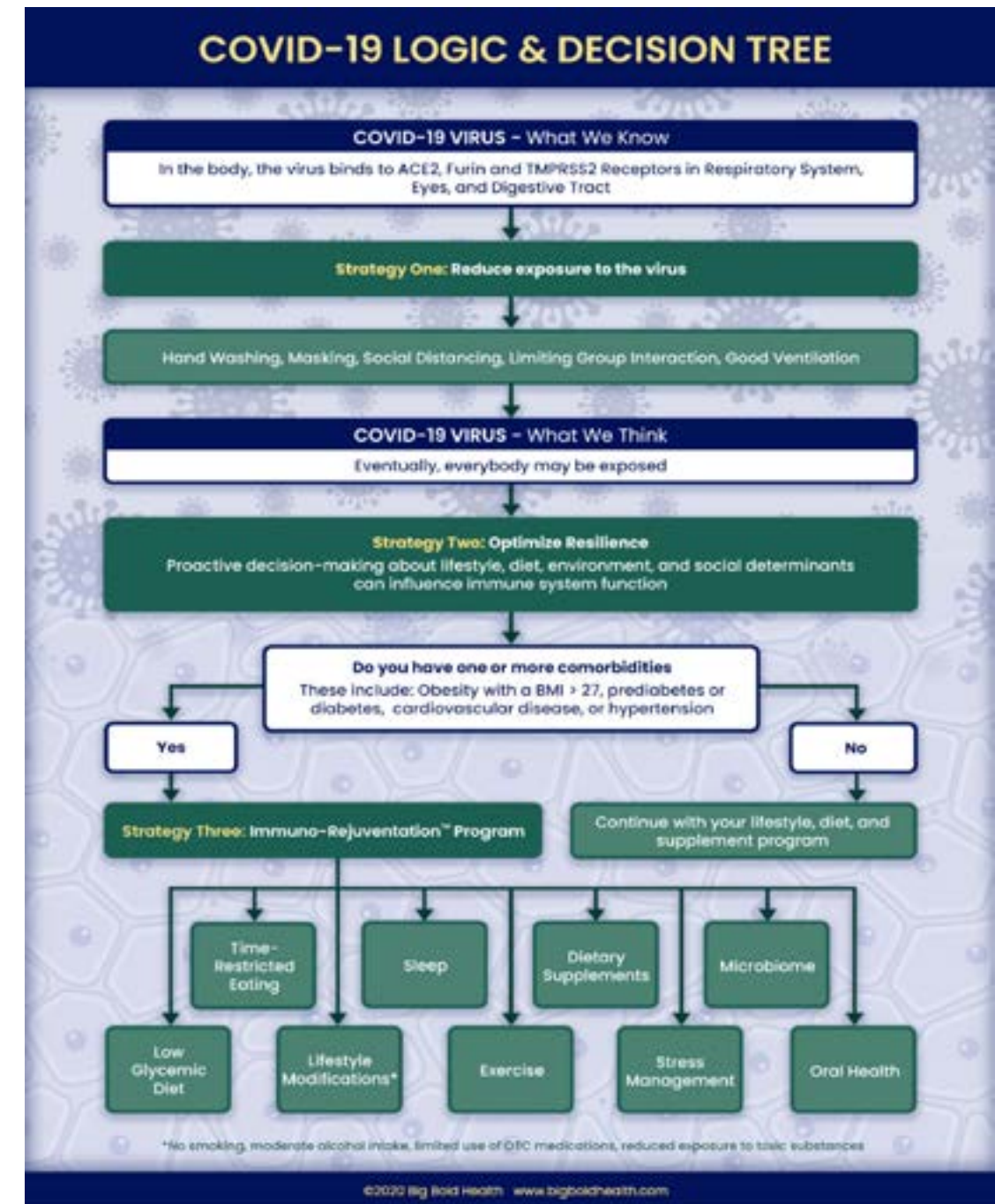
weight puts extra pressure on our organs and makes it harder to treat heart disease, cancer, and — as we have found — coronavirus. This was true in my case, and it’s true in many thousands of others. It was a wake-up call for me, and I want it to be a wake-up call for the

whole country.” Public Health England is launching a new campaign focused on exercise and weight loss, and restrictions on junk food advertising are being tested. Of course, not everyone is happy with this plan. There has been outcry about the potential impact on economic recovery and small businesses. But the significance of these crucial first steps cannot be overstated. Caroline Cerny, an executive with the UK’s Obesity Health Alliance, effectively summarized the situation this way: “The pandemic has thrown the need to improve our health sharply into focus.”

The COVID-19 Logic and Decision Tree

Most of us can still remember the first time we heard about COVID-19. The pandemic timeline is still defined by months, not years. We have learned quite a lot about the virus in a relatively short period of time. Can we harness what we know to reduce our personal risk and maximize our resilience? There are steps we can take — ways that we can be empowered — that are not dependent on the development of either a

vaccine or treatment drugs. The infographic below summarizes logic and decision-making strategies that you can apply in your life:



Individuals need to assess their own unique lifestyle, dietary, environmental, and social factors to create and manage a personal COVID-19 plan. The following categories and recommendations serve as the foundation of my immuno-rejuvenation concept:

- **Lifestyle** — Do all that is required to reduce the risk of exposure to the virus, including compliance with social distancing, limited group interactions, regular hand washing, and routine use of masks in public.
Sleep — Focus on getting 7–8 hours of restful sleep daily. Sleep plays an important role in immune system health.
- **Exercise** — Regular daily activity — as light as one hour of brisk walking — can have a very positive impact on immune system function. In contrast, over training has been found to have an adverse effect on the immune system. Finding your personal balance is the key.
- **Environment** — Avoid exposure to chemicals in the air, water, and food. This includes the excessive use of over-the-counter drugs, home care products, and certain personal care products that can potentially place a burden on our immune systems. Try to spend at least 20–30 minutes outdoors each day.
- **Stress** — Set aside time each day to do something that gives you a sense of peace. This could be reading, listening to music or a podcast, watching a video, or engaging in quiet meditation.
- **Diet** — Nutrition is not one-size-fits-all. No single diet will optimize immune function for everyone, but the following guidelines are foundational to an immuno-rejuvenation approach:

- Don't overeat. Control your calories to promote proper body weight.
- Don't consume excessive sweet foods or beverages. High sugar intake has an adverse impact on the immune system.
- Limit excessive intake of foods that are high in saturated fats, especially those found in meat products because they are known to have an adverse impact on immune function.
- Eat a low-glycemic-load diet that puts minimal stress on insulin and metabolism. The Mediterranean diet is an excellent example of this approach. This pattern of eating prioritizes consumption of vegetables, nuts, olive oil, fish, lean meats, beans, and fruits.
- Eat foods higher in soluble and insoluble fiber. This would include minimally processed fruits, vegetables, and grains.
- Consume vegetables of many colors to feed your body an array of immune-supportive phytonutrients.
- **Time-Restricted Eating** — This practice involves consuming all of your food during a 10-hour period of each day, and then avoiding both food and beverages for 14 hours. Time-restricted eating has been found to be helpful in stabilizing both metabolism and immune function.
- **Supplements** — Through extensive research and study over the past 20 years, it has been determined that a number of nutrients are very important for the support of immune function. There is evidence that many of these nutrients may not be adequately consumed in the diet, therefore daily supplementation at the appropriate level may be advisable:

- Vitamin A — 1500 to 3000 IU
- Vitamin C — 100 to 1000 mg
- Vitamin D — 1000 to 5000 IU
- Vitamin E — 100 to 400 IU (as a natural mixture of tocopherols and tocotrienols)
- Zinc — 15 to 30 mg
- Magnesium — 50 to 200 mg
- Vitamin B12—250 to 1000 mcg
- Vitamin B3 (as niacinamide) — 50 to 500 mg
- Quercetin — 200 to 1000 mg (a bioflavonoid found in onions, apples, grapes, buckwheat, and green leafy vegetables)
- Omega-3 fatty acids- 1000 to 3000 mg
- **Microbiome Integrity** — A high fiber diet that is rich in prebiotic nutrients to support a healthy intestinal microbiome has been found to be important in supporting the intestinal immune system. There is also evidence that a well-balanced probiotic supplement can also help in establishing a healthy intestinal environment.

Safe Harbors and Freedom from Fear

Where is your safe harbor right now? For most of us, it's our home in whatever form it takes — on land or on water. Many of us think wistfully about the freedom we enjoyed before 2020. Many of us also think about how this pandemic is shaping a new reality. Anthony Fauci, MD, is the director of the National Institute of Allergy and Infectious Diseases (NIAID) in the US, and he has become a familiar figure this year. Earlier this month, he published an article in *Cell* with David M. Morens, MD, a Senior Scientific Advisor at NIAID, that includes these thoughts about the historic and philosophical significance of these times: “COVID-19 is among the most vivid wake-up calls in over a century. It should force us to begin to think in earnest and collectively about living in more thoughtful and creative harmony with nature.”

Freedom, as we are all learning, can take many forms. While no one can predict when a sense of normalcy will return, wouldn't it be a relief to at least be free from constant fear and anxiety? You can start by using the COVID-19 Logic and Decision Tree to help identify a personal approach for minimizing your risks and vulnerabilities. We have tools at our disposal that can disrupt the spread of the virus and increase our personal resilience. If widely adopted, these efforts will help all of us navigate a course back to work, school, and our lives, and in the process restore the health of our economy, culture, and society. As we move forward, we will learn valuable lessons for future health crises that might impact our local communities, or — perhaps once again — our beautiful planet and global citizenry.

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