

5 Concerns about SARS-CoV2 Biology: A Call to Pause, Deliberate and Revise Policy

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We have reached a crossroads in the SARS-CoV2 pandemic. Considering the risks of non-sterilizing immunization as a preventative measure, the precariousness of the current global situation cannot be underestimated. This review is intended to serve as a simple resource to help all people—from policy makers to families—better understand the biology of SARS-CoV2 and the potential ramifications of non-sterilizing immunization and offers recommendations and a call to action to protect all human health over the long term - in particular the developing immune systems of children and young adults.

From the start of the pandemic in 2020, immunization has been promoted by health agencies as the primary tool by which this pandemic should end. The decisions made to date have been made amid a crisis to address a crisis. Considering the number of cases and deaths in the United States and globally, it is understandable that there was a perceived immediate need to turn to vaccines as the most efficient human intervention option to contain and suppress the pandemic.

In the context of an ongoing crisis, however, there is also a need to regularly assess and recalibrate decisions going forward as scientists learn and the situation evolves. This is a new virus with new immunization technologies and evolving therapeutic discoveries. While decisiveness is critical, at the same time there is a need for an openness to shift course, depending on what we are learning, especially regarding treatment of severe COVID-19. This requires open paradigms for information sharing and discussion, integrity, and open public assessments of the core epidemiological aspects (beyond case numbers) of the pandemic to keep the public adequately informed. While we are acting to address short term tragedy in a crisis, we also should be proactive, as our decisions will have lasting and long-term ramifications. Fortunately, science offers us the ability to continually ask, test and answer questions about the potential benefits and costs of current recommendations to help re-evaluate and adjust responding policies for the rest of 2021 and beyond.

At this crossroads, the most vulnerable populations have been vaccinated using non-sterilizing immunization technology currently under Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration (FDA). The EUA was granted to help reduce the incidence of

severe COVID-19 disease and death, but while non-sterilizing immunizations can effectively protect vulnerable populations, such immunizations applied to an entire population for SARS-CoV2 are problematic. Already, we are seeing increasing reported variants in places like Brazil, the UK, and India. Assumptions have been made in the press that new variants emerge only from SARS-CoV2-infected masses, so by reducing the number of infections through immunization, variants will disappear. Evidence and growing scientific consensus suggest the contrary: variants are emerging in quasi-immunized individuals (e.g., only one shot) or fully immunized populations as either “breakthrough infections”—asymptomatic and symptomatic infections—in which more dangerous variants are creeping undetected within the immunized population. In many instances, with cases increasing in proportion to increased immunizations, and societies reopening and then closing again, authorities like the U.S. Centers for Disease Control (CDC) do not always have one clear control variable to understand what is driving certain phenomena. The possibility that asymptomatic and symptomatic transmission of stronger and more dangerous escape variants is already occurring *among immunized individuals* must be considered and new reporting systems to monitor such transmission should be established, especially if this transmission is spreading among healthy immunized individuals with stronger innate immunity to begin with¹.

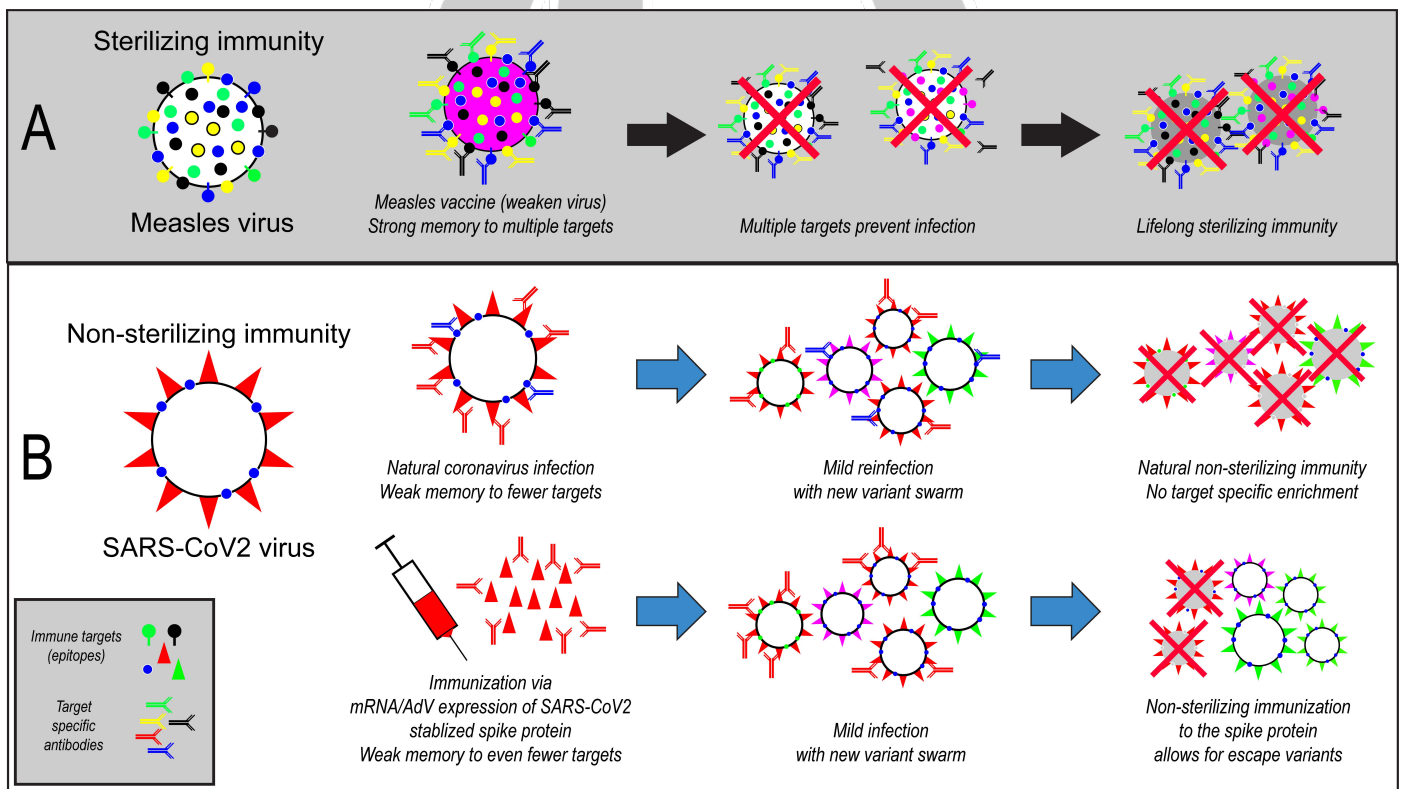
As such, now is the time to open the aperture of data collection and analysis to reassess whether the risks of non-sterilizing immunization beyond vulnerable populations is advisable policy moving forward. The potential consequences of biologically inappropriate immunizations are discussed in answers to five basic questions below:

1. What is non-sterilizing immunity and why do asymptomatic infections in immunized populations increase the risks of the current non-sterilizing immunization campaigns?

First, the biological difference between sterilizing and non-sterilizing immunity in relation to the development of dangerous “escape variants” of viruses should be understood by everyone. Sterilizing immunity—whether through vaccine or recovery from natural infection—creates an immune memory strong enough to prevent a virus from infecting previously infected individuals or others, as the virus no longer replicates sufficiently to be contagious. Non-sterilizing immunizations, on the other hand, reduce or prevent symptoms of disease, but they do not prevent viral infection. This difference under certain circumstances can result in unwanted evolutionary pressure on the virus and ample opportunity to strengthen, in effect creating (selecting for) viral virulence—stronger variants—and severe disease²⁻⁴. The difference between these two

immunological states can be illustrated with a simple hypothetical example. Two nurses with the same health history, “Vicky” and “Carol”, are infected with a more virulent strain of SARS-CoV2 while on shift. At the start of the pandemic, both nurses would have stayed home sick with severe symptoms and missed two weeks of work. In this case, Vicky was recently EUA- immunized and shows no symptoms to a silent infection and therefore takes no time off, while Carol, unvaccinated, remains home for two weeks with symptoms. Two weeks later, Vicky has potentially infected hundreds with this more virulent strain, while Carol stayed at home and infected only her daughter, who recovered in a few days. At the global population level, these hypothetical dynamics would be dangerous and not supportive of a blanket immunization policy. Although the biology of human immunity is incredibly complex, it is relatively well understood for certain viruses—polio, measles, mumps, and chicken pox—that generate sterilizing immunity after infection. The term “vaccination” traditionally refers to the life-long sterilizing immunity that is generated after immunization to a virus like measles. Sterilizing immunity is based on the recognition of a diverse

set of molecular targets associated with the pathogen. The primary reason vaccinations create sterilizing immunity for e.g. measles virus is that like natural infection, immunization against a weakened/dead measles virus produces immune memory to multiple unrelated molecular targets (Fig. 1A)^{5,6}. The same is not true for other RNA viruses like influenza, making inoculation against influenza imperfect at best^{7,8}. The biology of coronaviruses offers human immune systems an even less diverse set of molecular targets than the measles example (Fig. 1B)^{9,10}. Reinfection from these viruses is expected more often than for influenza, and *sterilizing immunization against coronaviruses remains impossible*. There is strong evidence, however, that natural infection builds immunity to a broader set of targets that crucially also includes non-spike proteins present in coronaviruses¹¹. Unlike natural infection, infection after non-sterilizing immunization may be producing variants of concern (VOCs), all of which have their relevant mutations within the coronavirus spike protein.



Sterilizing versus non-sterilizing immunity. **A.** Sterilizing immunity developed after vaccination against measles virus. Multiple targets (epitopes) are the basis for lifelong immunity. **B.** Natural non-sterilizing immunity to coronaviruses and EUA immunization to SARS-CoV2 spike protein are shown. Natural immunity to SARS-CoV2 recognizes targets (blue circles) other than the spike protein (red triangles)¹⁰. Immunization to the spike protein alone selects for variants from future infections that can escape spike protein antibodies. Because spike protein biology is key to severe COVID-19, enriching for spike protein variants could be potentially catastrophic.

Fortunately, the consequences of non-sterilizing immunization on viral evolution have been observable in livestock for decades. One pertinent example of how non-sterilizing immunization can lead to quiet but dangerous escape variants in chickens is evident in Marek's disease^{12,13}. In this example, what started out as a mild disease that rarely led to death has evolved after years of blanket non-sterilizing immunization into a disease that causes wide-spread lymphoma and near 100% mortality in unimmunized birds. Similar case examples include infectious bursal disease virus in poultry¹⁴ and feline calicivirus¹⁵. In no uncertain terms, non-sterilizing immunizations are expected to cause an increase in asymptomatic transmission of stronger, more dangerous, viral variants over time. In the current case of SARS-CoV2, these stronger variants would be the strains that escape neutralization by spike protein-targeting antibodies, which is already unfolding globally: Geographies with significant immunization are starting to allow for more virulent breakthrough strains¹⁶. Logically, prevalent breakthrough infections among immunized individuals (as recently reported^{17,18}) also render a health COVID-19 vaccine passport program meaningless. In effect, applying the biology of non-sterilizing immunization to human populations is creating a generation of more dangerous variants - not because of the sheer number of global infections, but because non-sterilizing immunization programs encourage the virus to evolve in this extremely undesirable direction heading into 2022.

Currently, the public understands the EUA for immunization against SARS-CoV2 was granted with the knowledge that non-sterilizing immunity was the only expected outcome. The public remains relatively unaware of the extent of potential breakthrough infection risks, and not enough effort has been made to date to collect and assess *to what extent* immunized individuals can be infected and contagiously shed active virus. Therefore, an assessment by public health authorities should commence immediately to quantify the scope and duration of both asymptomatic and symptomatic infections of immunized individuals. If even only a small fraction of immunized individuals can be infected and spread the virus with less severe disease manifestation (as can be inferred from recent data)^{19,20}, these individuals are a primary potential source for more dangerous new variants (VOCs) of SARS-CoV2. *If there is any significant asymptomatic infection of vaccinated individuals, continued immunization beyond vulnerable populations should stop immediately; otherwise, the list of VOCs will continue to grow unabated*²¹.

2. Why does the SARS-CoV2 origin and unique “spike” protein biology matter to developing effective pandemic solutions?

To be precise, it is not the entire SARS-CoV2 virus that is novel. Rather, it is the spike protein of SARS-CoV2 and its binding strength (affinity) for its target receptor—the human angiotensin converting enzyme 2 (ACE2) protein—that is novel and mysterious²². The spike protein is a glycoprotein (sugar coated protein) that protrudes from the SARS-CoV2 membrane and facilitates entry to host cells by binding to surface receptors. Not coincidentally, the SARS-CoV2 spike protein's unique biology is implicated in many aspects of severe pathologies seen in COVID-19 disease, including heart failure, pulmonary edema, encephalopathy, ischemia, and myalgia. The ACE2 protein is not only a cellular receptor, but also acts as an enzyme in circulation whose expression is tightly linked to blood vessel permeability and fluid regulation throughout the body. As such, ACE2 protein is expressed in a host of tissues, and importantly, ACE2 expression changes drastically throughout the body during severe COVID-19 infection. Unfortunately, how SARS-CoV2 spike protein's interaction with ACE2 causes this imbalance and how it manifests is not yet fully understood. By comparing human and mouse data from two prominent American labs, we can see why the field remains confused. In a powerful study done in 2020 by the Oak Ridge Laboratories, the knock-on consequences of system wide *upregulation* of ACE2 expression (identified as gene expression changes in human patients) is sufficient to explain all the symptoms of severe COVID-19²³. Contrastingly, the Salk Institute recently released a report detailing a *downregulation* of ACE2 expression as identified in mouse models of infection in severe COVID-19²⁴. These observations have two important implications:

- 1) Severe COVID-19 infection is a complex interaction between typical viral infection immune response symptoms (fever, inflammation, etc.) and those caused by the novel effects derived from the spike protein's physiological interactions with ACE2 and other proteins.
- 2) Researchers must better understand the mysterious biology of the SARS-CoV2 spike protein on human ACE2 and other human proteins.

Numerous recent reports of unexplained immunization associated events may be linked to the same poorly understood biology of this spike protein. To further complicate matters, most of these interactions seem to be significant only in cases of severe infection associated with chronic inflammation, obesity, etc., and this crucial connection is missing from any animal model of COVID-19 infection. Such connections (contradictions and complications) also are missing in the main-stream public health discussion.

Additionally, it has come to light that there appears to have been years of intensive gain-of-function (GOF) coronavirus research worldwide, or biological research in laboratories

increasing the virulence and lethality of pathogens and viruses using natural or manufactured biological mutation. This research included the collection²⁵, recombination, and serial passage of SARS-like coronaviruses²⁶, as well as laboratory leaks of SARS-like coronaviruses previously in China and elsewhere²⁷⁻³⁰, but with no significant data indicative of a recent natural zoonotic event ever reported. Nevertheless, the World Health Organization recently concluded that SARS-CoV2 was a zoonotic event, but left tea leaves for further analysis³¹. From the onset of the pandemic, the extraordinary affinity of the SARS-CoV2 spike for the human ACE2 protein has been cited as compelling evidence for a laboratory origin of the virus related to gain-of-function (GOF) experiments^{32,33}, but also paradoxically as evidence for why it could have emerged directly from wildlife³⁴. While still under investigation by U.S. Congress and numerous other international authorities, the possibility remains that the perplexing biology of SARS-CoV2 is the result of laboratory experiments involving intentional introduction of specific functional elements to wild type viruses, chimeric recombination of wild type viruses^{35,36}, and/or serial passage of wild type and/or laboratory viruses on a laboratory background of human ACE2 as host receptor specificity (human lung epithelial cultures³⁷, animal models with similar ACE2 proteins³⁸, and/or transgenic mice with human ACE2 protein substituted for their own).

Non-sterilizing immunization of low-risk populations to this unusual spike protein may put unwanted evolutionary pressure on it to change in a yet unexpected direction. In other words, immunizing *healthy* individuals to the spike protein of 2020 will challenge Mother Nature to find ways to change this protein to adapt to and escape the pressure from immunization. When this happens, it will be the weakest of the immunized who are put in danger all over again. *The unknown origin and unique spike protein biology of the SARS-CoV2 must be better understood before continuing large scale immunization in healthy, non-vulnerable citizens.*

3. How does the SARS-CoV2's binding strength for ACE2 protein relate to antibody dependent enhancement (ADE) in humans and why does this matter to immunization policy?

The spike protein of SARS-CoV2 and the ACE2 protein physically interact like a pair of complicated 3D magnetic puzzle pieces. Because this fit is optimized, not only can it explain the many novel disease mechanisms of COVID-19 as described above, but it is also expected to provide more potential for autoimmunity issues and antibody dependent enhancement (ADE), or antibody activity that makes a viral infection even worse. ADE in viral infection is thought to be dependent on maladaptive antibody

sequences formed after immunization that can lead to novel severe disease upon subsequent infection in the future. While ADE can occur as a result of follow-on natural viral infections, the likelihood of ADE after natural COVID-19 infection is *minimized* because natural infection evokes a broader immunity response based on a wider range of molecular targets, as discussed earlier, including non-spike protein targets^{11,39,40} (see below). Previous data from Dengue Fever virus immunizations indicate that vaccinated individuals may also be more vulnerable to ADE upon exposure to future variants, even just one or many more years in the future⁴¹. Historically, immunization against the spike protein of SARS-1 and other coronaviruses in animal models has led to ADE⁴². In the case of SARS-CoV2, the unique shape and biology of the spike protein presents a molecular target with a high potential for the generation of autoimmune response and ADE⁴³. Several scientific papers published in 2020 discuss the risks of ADE, including specific response to coronaviruses. While vaccine developers reassure the public that vaccines are developed to avoid ADE risk, such risks can take time to emerge and may not be apparent during clinical trials, especially considering the perplexing relationship between this SARS-CoV2 spike protein and ACE2. Researchers can and should be looking for potential signs of ADE risk, and if necessary, recalibrating immunization and therapy approaches.

4. Why could this first EUA immunization present a risk to a child's developing immune system?

As stated earlier, coronaviruses do not offer multiple strong targets for our immune systems to remember. However, a wealth of data demonstrates that SARS-CoV2 infection does provoke a robust immune response in comparison to EUA immunizations^{11,39,40}. While the differences between traditional vaccination approaches and the current suite of immunization methodologies are beyond the scope of this brief, the current EUA immunizations have an additional compounding shortcoming in common: Their intended molecular target is a *stabilized* version of the spike protein of the SARS-CoV2 variant from 2020. In other words, whereas natural infection gives the body an opportunity to build immunity to any number of molecular targets, EUA immunization offers only a stabilized version of the poorly understood SARS-CoV2 spike protein.

This shortcoming is particularly risky for children in the context of known immunological mechanisms of life-long memory (research '*original antigenic sin*' to learn more). In brief, early immune challenges initiate cascades of native and adaptive immune responses that lead to immunological memory that lasts a child's lifetime. Subsequent related immunological challenges refine the existing molecular memories, and early infections remain a foundation for all

subsequent pathogen exposures. This is complicated by the immune system's tendency to modify existing memories, rather than make all new ones, an inertia that increases with age. The danger to immunizing healthy children for SARS-CoV2 is therefore acute: Immunization against this specific viral protein could permanently bias a child's immune system for a lifetime to a limited focus on a single subset of molecular targets from this one mysterious spike protein^{44,45}. *All considerations and/or trials to begin immunizing healthy children against SARS-CoV2 spike protein should be paused, and policymakers should consider the risks to children of continuing mass non-sterilizing immunization programs.*

5. What are “viral swarms” and why do they impact collective (herd) immunity and a path to end this pandemic?

The data demonstrates that natural COVID-19 infection provokes a vigorous and broader immune response than the protection offered by EUA immunizations⁴⁶. This outcome was expected, considering current knowledge about genetic swarm phenomena, a concept rarely discussed in the context of SARS-CoV2. Viral quasi-species and mutant swarms are relatively old concepts in evolutionary biology, but thanks to a multidisciplinary merging of physics, advanced A.I. and machine learning, scientists have come to understand how populations can evolve as a swarm of related genetic variants^{47,48}. The concept of a genetic swarm is important to understand how both individual and collective immunity are achieved and how this pandemic can end.

When a coronavirus infects a cell, it replicates. Few if any of these virus copies are perfect, but most go on to infect and reproduce in both nearby and remote tissues. A truer representation of the genome of a viral infection is that of a *viral swarm*: during infection, a swarm of imperfectly copied but closely related viral particles is responsible for infection. It is from this swarm of related but different variations of the virus that new dominant strains emerge in both individuals and populations. Even as a strain moves from person to person, it is a new swarm of nearly genetically identical viruses that causes the new infection. As a result of this phenomenon, different viral sequences can be found in the gut versus lungs during viral infections⁴⁹. Crucially, a natural infection represents an immune response to an entire genetic viral swarm, in contrast to an immunization responding to a single spike protein taken from a single 2020 viral sequence.

The sum total of all molecular targets available for a single infected patient's immune system to remember will be significantly higher than that of an immunized individual because each natural infection is a contemporary reaction to a current and existing viral genetic swarm. More

molecular targets mean natural infection will result in more durable long-term immunity for every recovered individual than immunization to the spike protein alone could produce⁵⁰. Across the global population, fully recovered COVID-19 patients⁵¹, using a range of archetypal and innovative therapies, candidate antiviral drugs (e.g. Ivermectin⁵² and others), will contribute more to lasting collective/herd immunity than EUA immunized patients whose immune memory is biased to the 2020 spike protein.

Recommendations for an independent and public call to action:

Significant portions of the population remain at risk for severe disease, even after immunization. Using global data available, the key vulnerability factors that define at-risk populations should be identified, reported, and referenced to guide where remaining immunization interventions should be focused to prevent COVID-19 disease upon infection. It is likely that some age groups, without specific comorbidities, are at essentially minimal risk^{53,54}. At the same time, recommendations should be made to encourage behavioral changes among the otherwise healthy population to minimize susceptibility to severe COVID-19 disease⁵⁵. *By applying EUA immunizations only to vulnerable populations and continuing to promote and develop a suite of disease recovery therapies, a robust and effective collective/herd immunity can be maintained going forward to end to the pandemic.*

Society responded quickly to address tragedy during a crisis, and the time has come to ask, test and answer questions about emerging data and new discoveries about the virus. In the current climate, evaluating public health policies without political or financial conflicts-of-interest related to vaccine discoveries or digital health data collection schemes (e.g., digital vaccine passport or location tracking databases affiliated with business entities) seems nearly impossible. This can and should change to regain public trust. The extent to which we understand the current pandemic is largely due to crowdsourced independent investigation of the history and use of global gain-of-function viral research. Without the decentralized reporting efforts of citizens and academics such as those from the ad hoc research group D.R.A.S.T.I.C.⁵⁶ among others⁵⁷ who share analysis on platforms such as Twitter and Substack, the public would remain unaware of the extent to which such research on viruses in China and around the world has increased public health risks.

Additionally, ensuring the integrity and accountability of global health, science, and technology review boards is critical. U.S. President Biden recently held a new 46-person scientific integrity task force meeting on May 14 in an effort to review past practices and remove partisanship from evidence-based policymaking in the U.S. government.

Certainly, this effort should apply to pandemic management to improve public trust and strengthen government accountability.

The following recommendations may be considered by this new task force, the U.S. Centers for Disease Control (considering recently revised COVID-19 breakthrough case protocols⁵⁸), and other policy makers worldwide as part of their mandate:

- i. *Require accurate and transparent quantification and disclosure of significant asymptomatic infections of immunized individuals. If such cases are discovered, EUA immunization beyond the most vulnerable populations should discontinue.*
- ii. *Invest in research to identify previously infected adult healthy individuals, as well as those with significant overlapping innate immunity from previous coronavirus infections to assess the extent to which EUA immunizations are beneficial to this segment, or whether it is prudent to defer vaccination to preserve natural immunity acquired through infection.*
- iii. *Invest in convalescent plasma therapy research to capitalize on the diversity of molecular targets (swarms) identified by natural infections every day around the world.*
- iv. *Quantify the mutation rate of SARS-CoV2 relative to other known human coronaviruses to assess its genetic stability and extent to which variants are emerging from non-sterilizing EUA immunizations compared to natural case number.*
- v. *Investigate and understand better the novel biology of the SARS-CoV2 spike protein and possible side effects of off-target expression during EUA immunizations before continuing to promote mass immunization on healthy, non-vulnerable citizens.*
- vi. *Investigate global GOF research methodologies currently in use to identify unacceptable risk levels; apply precautionary principles (measures to be taken to prevent harm in several risk categories e.g., rules of choice or procedural requirements) to GOF research, as well as for cell lines and transgenic animal models with the potential to induce bias into laboratory virus experiments, intentionally or by happenstance.*
- vii. *Identify and promote a broader suite of prophylactic health measures and medical therapy solutions as part of a balanced, economically viable pandemic recovery portfolio, e.g., use of candidate off label antiviral treatments like Ivermectin⁵², humanized monoclonal antibody treatments like Lerolimab^{59,60}, nutrition adjustments, lifestyle changes, and weight loss.*

Conclusion:

In the challenge to make decisions and adjust direction in time of crisis, the global community is still learning about

the virus and the ramifications of human intervention. In this environment, access to information, analysis, and approaches are paramount. Decisions today have long term consequences for global health. While it is tempting to look to EUA immunizations as a single foolproof solution, there are personal and broader risks that are not yet well appreciated. Moreover, a multilayered approach that considers the full range of tools and options available will ensure greater resilience and success beyond 2021.

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