

A Time to Look Forward: Thoughts on the Covid-19 Pandemic

A message from
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The Path Forward:

- First, Social Distancing should remain in place to limit but it will not eliminate dissemination of virus. Our supply chains must remain open, businesses must remain viable, but precautions to reduce rapid spread should be followed. This need not last indefinitely or follow some multiyear formula gated to death rates if the steps we recommend below are prioritized and executed.
- The prevalence of the disease in individual communities or geographies needs to be established as rapidly as possible. Rapid testing needs to be available and not restricted to those afflicted or likely afflicted. The risks within individual communities can then be gauged and policies adjusted to local situations.
- A serologic test that identifies prevalence of prior infection also needs to be established as quickly as possible. This will allow appreciation of the presence or not of occult carrier states in the community and much better define the practical limits of infectivity to immune naïve individuals.
- The **critically important immediate additional step** is to rapidly study prospectively in a coordinated fashion, possible interventions ([actionable interventions](#)) that might prevent lower respiratory involvement of COVID-19 from progressing to acute respiratory distress syndrome (i.e. severe pneumonia and respiratory failure). This can be done rapidly at acute care centers by establishing an emergency expedited protocol assess each patient presenting with early signs of lower respiratory COVID-19 disease to the best supportive measures as is the current practice *plus the addition of a brief course of one of several alternative randomly assigned interventions* with a focus on preventing an “inflammatory storm” from occurring in the lung. The interventions studied need to be readily available and have the potential to be easily used as an outpatient without supervision. They should not be associated with extreme toxicity, but caution is advised at this stage because modulating immunity in the setting of a poorly characterized pathogen may have unexpected risk. Thus, the organization of an emergency protocol to guide this step is critical. It is likely based on my professional experience that the process of rapid evolution to ARDS is an immune mediated process associated with a cytokine storm. If this storm is dampened the immune mediated damage to the lungs may be prevented. If the panel of alternative agents or interventions is evaluated in parallel and any given cohort shows early signs of an adverse impact on early systematic review, that cohort may be eliminated from further evaluation. In contrast if a cohort shows signs of a favorable pattern of progression that cohort would be expanded. Current communication technology will make it possible to orchestrate such a study centrally on immediate notice and adjust it in an urgent and unprecedented manner such that if any of the possible interventions included proves to be a clear winner, it can be identified and instituted globally with minimal delay. Such a step has not been a focus of the widely dispersed public announcements, or news & policy discussions to date, but in our view this

approach should be an absolute urgent priority. There are several possible interventions meeting the criteria to be appropriate candidates and are readily available. We have communicated our recommendations to leading authorities, and welcome dialog with interested professional to consider additional candidates. The system to organize such a coordinated effort stretches beyond current food and drug regulation but should be done under a common guidance by emergency international consensus.

- The steps most frequently discussed are the identification of an effective anti-viral compound to directly control the infection and the development of a vaccine. Both are equally important and deserve continuing priority development, but the realistic timeline to actionable implementation of a winning solution is likely too long to address the current urgent global economic need in a satisfactory near-term fashion. Both solutions will ultimately be critical to eliminate the threat and provide the backstop if a solution for the prevention of respiratory progression does not rapidly emerge. Both anti-viral and vaccine are likely to be successful in the intermediate term (e.g. months to 1-2 years) but they are not actionable for most infected patients in the current time frame.

Why is the additional step of “actionable intervention” above so important?

The reason that COVID-19 is a major threat is that the global population is immune naïve and thus susceptible to infection. Once most of the population is immune resistant the disease will disappear into the background of known pathogenic diseases and while outbreaks may occur regionally, global pandemic will be over. If COVID-19 infection did not carry a significant risk of acute respiratory failure (e.g. 0.5 to 5% as estimated currently) and infections could be safely managed as outpatients with mortality rates/severe complications 10 to 100 fold less than the current experience, then disease management would not be so dire to communities acute care capacity and economic activity could proceed without stopping the world. In the absence of a vaccine the infection itself would naturally immunize exposed individuals and the pandemic would fizzle out over time. The availability of convalescent serum from recovered patients with infection would provide a route to passively immunize patients at highest risk and economic activity could resume before global paralysis becomes politically toxic.

The prospect that a solution to rapid progression to respiratory failure might be found immediately is only possible because the clinical circumstance that allows design of a rapidly implementable approach to prospectively find a solution is uniquely upon us at this moment in time. Under normal circumstances, clinical cases that progress to acute respiratory failure occur unpredictably but with fair frequency in medicine and those patients do fill intensive care units on an ongoing basis. Most often the cases present with unexpected respiratory failure at which time all our medical efforts to reverse that firmly established pathologic process have modest success at best. The current pandemic provides a unique opportunity to prospectively evaluate putative solutions that would prevent the dire outcome from occurring at all. In normal settings the circumstance is virtually impossible to anticipate prospectively. From this pandemic if a simple and relatively innocuous solution preventing progression to ARDS is found, it may have likely also have application in other clinical settings where unexpected progression to respiratory failure also occurs. The lung is an organ that exposes the blood to oxygenation from the inspired air through a delicate matrix of thin membranes that separate the blood, the immune system and the air at microscopic distances. Any uncontrolled inflammatory response and scarring of those membranes can prevent

oxygenation and lead to death through asphyxiation. The recent respiratory complications of vaping selective flavors is analogous to the process being encountered in some COVID-19 patients. If we can prevent fatal lung disease complications of COVID-19, the infection becomes only unpleasant but fully manageable and need not cause global paralysis. A simple community based actionable interventions study could be introduced at minimal distraction to critical efforts of our front line triage facilities and offer a “take home kit and purpose” for patients presenting with fever and symptoms suggestive of covid-19 but not exhibiting signs of significant respiratory progression, and very simple data collected centrally using simple technology to organize the critical data from patients and their caregivers.

Conclusions:

When Europeans explored the world on crowded sailing ships in the 17th and 18th centuries they introduced deadly pandemics to countless isolated immune naive populations. When the Panama Canal was built in the late 19th and early 20th centuries countless conscripted laborer’s, engineers, and support personnel died shortly after arrival at the project sites. In that case, the victims immune naive state to yellow fever and other tropical pathogens sealed their fate. Populist rhetoric might suggest that the current experience should mandate the elimination of globalism. COVID-19 is nothing new to the world as a phenomenon. As a pathogen it is relatively innocuous, but disordered immune response in the lungs is leading to significant mortality and the disease agent is highly transmissible. The great flu pandemic was a century ago and other prolific pandemics will continue to emerge from time to time as a reality of life on our planet global or isolated.

Any isolated population is at risk from a novel pathogen. The current social distancing must be self-limited and of brief duration to allow the response to infection to catch up before we return to business as normal. Once the population is no longer immune naive and the serious pulmonary consequences of infection can be better prevented and controlled, the current experience will just be another experience to recall just as the “Spanish flu” is now. With clear leadership and direction this problem can pass more quickly than many fear. The initiative may be difficult to implement in our tertiary care centers and university institutions currently being stressed to capacity but could be rapidly implemented in the community using simple documentation and data collection techniques and minimal administrative burden. It will allow our communities standing on the side lines to contribute to a possible early solution while the rest of the battle rages on in search of the definitive cure. It is a critical moment, but I have confidence in our ability to channel immunity and to prevail.

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Background Appendix: Since its founding in 2008, AIT Strategies has found a unique role working with collaborators from around the world in academia, biopharma, contract research as well as regulatory authorities with a highly specific focus of advancing the practical application of immune pathway modulation with therapeutic intent. The organization has the advantage from existing outside the constraints that characterize the separate perspectives of our collaborators. While the majority of our attention and published work has been centered around tumor immunity and the potential of the human immune system to be activated to better control or eliminate cancer, this work has focused on unexpected combinations that modify clinical outcomes by modulating immunity. We have studied with interest the

capacity of many molecules and drugs to impact the character of an emerging immune response often in anticipated directions. Applications of these insights are relevant to cancer, infectious disease, as well as allergy and rheumatology. AIT strategies has always focused on molecules of interest and establishing relevant models to explore these interactions. Most often the simplified models of pharmacology, cell culture and analogous animal model system fail to recapitulate all the relevant factors needed to understand the human condition, and methods of experimental medicine and clinical trials are required to definitively address these questions. The major lesson we have learned in the past two decades is that standard understanding of the immune response process is very incomplete and that much of the dogma that dictates acceptable professional paths forward in given fields of medical specialty can paradoxically prevent finding the better alternative paths. The time constraints of grant cycles and research department budgets can require branch point decision making that reject approaches before they have been adequately explored. Thus, AIT Strategies is working on long term projects that extend beyond the constraints of individual institutions and are finally bearing fruit primarily for the benefit of future patients. The efforts of patients and researchers who have participated throughout must be appreciated because without that preliminary effort the true progress would not be possible.

Social media, and the current news cycles have raised panic and fear to unprecedented global levels in following the rapid outbreak and dissemination of the Corona Virus (COVID-19). Never has humanity had the communication tools to follow the progress of a pandemic so closely. The analogy might be watching a baseball game pitch by pitch without understanding the rules of the game. The experts attempting to handle the situation are besieged by second guessers looking over their shoulders, and one must ask whether all this attention is in fact influencing the decisions being taken at all levels of response ranging from clinical diagnostic laboratories, public health field workers and the urgent care clinics to the institutional and government decision makers setting policy across the world.

The opportunity for our society to effectively handle the crisis is unprecedented based on available technology and advancements in science. At the same time if we stop the world in our response, the damage of such paralysis may surpass the risk associated with the pathogen.

The decision to try to stop the exponential spread of the virus in our global population of COVID-19 immune naïve individuals is appropriate. What we have not seen is a clear delineation of the path forward to get us beyond this “momentary pause in life as we know it”. To AIT Strategies the path is clear. This message is intended to outline the prudent path in the context of the hysteria that is otherwise clouding individual judgment. This path needs to be understood by global leaders as well as media pundits. If this path is taken, not only will we have fundamentally advanced our knowledge, but the world will be a better place.