



RESPONSE TO THE DEADLY CORONAVIRUS

Proaction vs. Reaction and Appropriate Aggression vs. Passive Aggression

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America is under attack, as is the rest of the globe, from a silent enemy. Most of us are unaware of the presence of the virus until symptoms suddenly appear. We are now in the midst of a pandemic, which will unfortunately kill hundreds of thousands, if not millions of individuals globally. Over the past few weeks, the incidence of the novel coronavirus (covid-19) infection has been on an exponential curve in many regions throughout the globe. Epidemiologists are attempting to predict when the incidence of new cases will peak in various regions. If they can accurately accomplish this, we would have a sense of hope regarding when the number of new cases will begin decreasing. These predictions are based on mathematical models, which of course, require data. Unfortunately, the data we are collecting is extremely fluid, yielding rapidly changing projections.

The purpose of this article is not to lay blame, but clearly, the response has been reactive, rather than proactive. Most nations' initial and primary responses have been to impose "partial" lockdowns, on the areas within the country, thought to be "hotspots." Those partial lockdowns were effective, but only in those limited regions. Similar to the child's game "Whac-a-Mole," new hot spots would suddenly appear. This process continued, and continues on, in each and every nation. In addition, many nations such as the U.S. impose "self-quarantines," relying on the individual(s) to "do the right thing." The problem with self-quarantine, is that most individuals are more concerned with self-preservation, rather than concern for the greater good. An example of this is an individual who was diagnosed with covid-19 in one state, and then traveled by plane to another state where she believed she would receive better care. A more proactive approach would have been a complete lockdown, enforced by the military, in every nation, every state, every city, and every town. This should not have been a gradual process, but rather an abrupt process, that likely would have required the imposition of martial law. Just recently President Trump was asked if he would consider locking down every state. He replied that would be unnecessary, as some states are doing well.

But the imposition of global martial law did not occur and a global and complete lockdown did not occur. Perhaps the opportunity to minimize casualties through sequestration and self-quarantine has long passed us by, at least in the U.S. I mention this because we truly do not know the percentage of the U.S. population that has been infected. This passive aggressive approach, at this late in the game, may save a relatively small percentage of the U.S. population, while deastating world economies. The few who are saved by this approach may be counterbalanced by failing economies, causing increased death through violence, starvation, and inadequate medical care.

Please be clear that I am not recommending opening up our states. To the contrary, I am recommending a complete nationwide lockdown, strictly enforced by patrolling military and police officers, effective immediately.



Currently, our president is allowing each governor to make an independent decision. This is unacceptable; our federal branch should and must make the best decision to protect our entire nation. Although I believe this would be a temporizing and somewhat helpful measure, it would not be enough.

Currently, in the U.S. if an individual develops symptoms suggestive of covid-19 infection, or even has confirmed covid-19 infection but is not ill enough to require hospitalization, the recommendation is to “self-quarantine.” If the individual becomes significantly ill, then they are hospitalized. If the individual requires hospitalization, the risk of death dramatically increases.

The primary reason for hospitalization is difficulty breathing. The alveoli of the lungs become filled with cells, debris, pus, and fluid, preventing the exchange of oxygen and carbon dioxide. If the process is extensive enough, the immune system’s response can also cause downstream complications at the cellular level, making it increasingly difficult to oxygenate, likely resulting in death. In the hospital, treatment options include antiviral drugs, such as remdesivir, lopinavir-ritonavir, and chloroquine/hydroxychloroquine (HCQ), with and without azithromycin (AZM). In addition, steroids are commonly used to attempt to calm the cytokine storm, which is an overwhelming hyper-immune response, commonly resulting in death. Of course, many of these patients require ventilator assistance.

Although some lives are saved with the above treatments, many are lost. Physicians and ICUs are overwhelmed, feeling helpless and unable to adequately treat their patients, not to mention fear for their own lives. If we continue down the same path we have been on, I do not anticipate improvement of our situation, within a month, 3 months, or even 6 months. So where do we go from here? How do we improve the mortality rate of those who do get infected? Of course, the devil is in the details, but the short answer is that we must become appropriately aggressive rather than passively aggressive.

We currently have limited data regarding the efficacy of antiviral therapies, such as HCQ, with and without AZM, remdesivir, and lopinavir-ritonavir. There is, however, preliminary/limited data suggesting efficacy of HCQ with AZM. While president Trump initially was perhaps overly enthusiastic about this combination being a “game-changer,” his enthusiasm was tempered by Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, where he explained that we have minimal data and the administration was not endorsing its use. Eventually, however, physicians began offering this combination in hospitalized patients. In addition, anxious physicians began prescribing it for demanding outpatients. Many states have done their best to limit and at times stop the prescribing of HCQ for outpatients.

Based on the following limited available data, there is some optimism regarding the efficacy of HCQ/AZM:

1. First clinical results were reported in a news briefing by the Chinese government in February 2020, revealing that the treatment of over 100 patients with chloroquine phosphate in China had resulted in significant improvements of pneumonia and lung imaging, with reductions in the duration of illness. No adverse events were reported. It appears that these findings were a result of combining data from several ongoing trials using a variety of study designs.
2. On the 17th of March 2020, the first clinical trial data were published by Gautret and colleagues in France. The researchers conducted an open-label non-randomized controlled trial with 36 patients diagnosed with SARS-CoV-2. Six of these patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty patients were assigned to the treatment group, and received HCQ 200mg three times a day for ten days. The control group received usual care. Six of the patients in the treatment group were also prescribed azithromycin to prevent bacterial superinfection. The main outcome of the trial was SARS-CoV-2 carriage at Day 6, tested using PCR of SARS-CoV-2 RNA from nasopharyngeal swabs. The results showed that patients in the treatment group were significantly more likely to test negative for the virus on Day 6 than patients in the control group (70% vs 12.5% virologically cured, $p < 0.001$). Moreover, all of the six patients who were treated with a combination of HCQ and azithromycin tested negative on Day 6.

Based on the above, there are multiple trials underway in multiple countries, evaluating the efficacy of HCQ/AZM. The first large-scale U.S. clinical study is seeking volunteers and looking to get underway. The study

will be conducted by the Henry Ford Health System, which is seeking 3,000 volunteers from healthcare and first responder working environments.

The design of the study will be a true blinded study, with participants split into three groups that receive “unidentified, specific pills” (possibly anti-virals or some equivalent); hydroxychloroquine; or placebo pills, respectively. They won’t know which they’ve received, and they’ll be contacted weekly by researchers running the study, then in-person both at week four and week eight to determine if they have any symptoms of COVID-19, or any side effects from the medication. They’ll get regular blood draws, and the results will be compared to see if there’s any difference between each cohort in terms of how many contracted COVID-19.

Large randomized clinical trials are what all credible scientists want to see before a drug or drug combination is recommended for prevention or treatment of disease. Finally, we will collect several months of data and be able to advise and recommend appropriate treatment (or not) to our health care practitioners. So why don’t our citizens stay calm and let the scientist to their work, instead of trying to hoard medicines, without even knowing their effectiveness?

Because thousands of people are dying daily, and we are not in a position to wait! Currently, this drug combination is mostly used on sick inpatients, when the drug combination is least likely to be effective! When patients present with significant pulmonary disease, with their alveoli filled with cellular debris, and inflammatory cytokines raging, it often does not matter whether the virus is eliminated. The vicious cycle has begun, causing an endless cascade of inflammation and scarring. I am not suggesting that we cease using this combination in sick inpatients. I am suggesting that we become appropriately aggressive in those who are not yet ill, not requiring hospitalization, with the hope that we can significantly alter the exponential spread of Covid 19. We simply cannot wait for the data!

So what are the risks associated with using these drugs? Using low dose HCQ as a preventative is extremely unlikely to cause any untoward effects. We have had plenty of time to evaluate this drug for safety, as hydroxychloroquine was first approved for medical use in the United States in 1955. In higher doses, and in combination with AZM, based on the limited data, again, we are unlikely to see significant problems, when using it for 7-10 days. Having said that, prior to treatment with the combination, patients should have an EKG performed to ensure they do not have a prolonged Q-T interval; a prolonged Q-T interval may increase risk for an abnormal heart rhythm.

What are the possible benefits? We could greatly alter the curves for incidence and mortality. An astute scientist, must not just evaluate the data, rather they must simultaneously observe the risk-benefit ratio.

What I am suggesting is the following: Consider testing a segment of the population with the rapid IgM/IgG antibody test. All individuals who have been acutely exposed (positive IgM), should be treated with agents that appear possibly efficacious, such as the combination HCQ/AZM, remdesivir, or other agents that have been approved via randomized controlled data read-outs. Over time, that region will be followed for incidence of new cases of Covid-19, hospitalization, recovery, and mortality. As resources permit, individuals who have not been exposed (negative IgM and IgG), may periodically be re-tested. This process can initially be started on a segment of the population, while extending it nationally if/when the results appear promising. Simultaneously, it is reasonable to consider using a drug such as low dose HCQ preventatively, in high-risk individuals. While this approach may seem aggressive, until a vaccine is available, the risk-benefit ratio is in favor of its implementation.

Citizens become aggressive and unruly, when the very administration that is supposed to protect the people, fails to do so. This is the reason that individuals are attempting to take matters into their own hands. We must be aggressive at this time, but appropriately aggressive! By heeding the warnings of our scientific experts and the Centers for Disease Control, including appropriate social distancing, proper hygiene including adequate and frequent hand washing techniques, as well as appropriate use of protective equipment while not jeopardizing our supply to frontline healthcare workers, we will get through this pandemic in due time and plan for the next inevitable outbreak with a much more resolute focus and preparedness.