C Nicodemus **Pandemic Month 18** 1 August 2021

With the roll out of vaccines in 2021, the promise that the COVID 19 pandemic would disappear into the background of active community disease seemed promising, and indeed that is still the overall trajectory in which we as a global society are headed. I shall maintain my reverse chronological series of perspectives on this site however as my perspectives are best appreciated when reviewed with the benefit of hindsight. We have yet to reach a period of comfortable hindsight and contemplating why may provide inspiration for refreshed thinking beyond the constraints of the various medical subspecialties and the political climate of the modern world.

The politicization of the pandemic has been a most unfortunate turn and it may well ultimately result in the needless deaths of millions of people across the world. Populist hostility to science and technology as well as resistance to change within scientific and medical paradigms have been two constants throughout the ages. Galileo was imprisoned for his heretical observations regarding planetary motion. Phobic attitude toward vaccines as well as a confusion between one's freedom to harm oneself versus freedom to harm others are playing an increasingly important part of the continuing story.

I have convinced a few vaccine avoiding friends to become vaccinated through my argument around background mutation rates in an actively spreading viral population. If we continue to harbor Covid-19 in the community it will continue to have opportunity to mutate into new and differing variants. Variants that may prove more infectious or more toxic as well as variants that are more indolent. Perhaps the indolent variant will displace the more lethal variants and eliminate Covid-19 from our daily news feed but the opposite is equally possible. Reducing mutation rates by reducing burden of infection is our wisest strategy.

Most vaccine avoiders fear the vaccines and their possible consequences more than the disease itself. They consider themselves especially at risk from the vaccine and prefer the choice not to be vaccinated. For some however, it's a political response tied to concepts of freedom and individual liberty. The opportunity to exercise their right to remain unvaccinated supersedes the clear risk benefit calculus. The risk of severe disease or death from infection for the unvaccinated is orders of magnitude greater than any risk directly from the vaccine or for severe infection occurring post vaccination. If the calculus only mattered to the individual perhaps choosing the risky path is justified. The issue for society however is that by being a culture media for continuing growth and mutation of the virus and its continuing spread, the unvaccinated are proactively endangering their families and the community. They need to justify that truth to themselves if they elect to remain unvaccinated.

Meanwhile, in these commentaries I have repeatedly referred to the value of a “CAISS” model of prospective clinical research to identify promising leads to alter the outcomes of pandemic infection using readily available community interactions. I was emphatic about the approach before vaccines had proven to be a viable approach to managing this brand of corona virus. Precedent for successful Corona Virus vaccines was lacking and in other acute viral infections sometimes pre-existing immunity can exacerbate the consequences of an acute infection and not ameliorate or prevent disease. The success of the vaccine initiatives is a true testament to the power of modern biotechnology. The success of the vaccines is a testament to the technology but also to the luck of the draw with the actual virus.

As the virus continues to smolder and replicate around the globe variants will continue to emerge and the possibility that a future variant will not be controlled by vaccine should not be forgotten.

My argument for the establishment of a CAISS model in the regulatory world of clinical research and drug development is to allow the tool to be available on short notice in a future global public health emergency. I am hoping these ideas are registered by policy makers as the current pandemic continues to play out.

For pathogens whose toxicity is mediated by a toxin therapeutic intervention must focus on the toxin and the growth of the pathogenic organism. In contrast for organisms whose pathogenicity is the byproduct of the immune response to the organism itself and thus immune related, the calculus can be different. This is the circumstance with Covid-19.

For Covid, by chance pre-existing immunity very much reduces the likelihood of the severe sequela future infection, thus the vaccines are the community actionable intervention of choice that can virtually eliminate the severest forms of the disease. It is possible other carefully timed immune interventions that alter the pattern of the acute immune response to infection might accomplish in the same thing. Except in geographies where vaccine does not yet exist exploring this possibility is now impossible for COVID-19. Vaccine distribution is the highest priority. Nevertheless, if COVID mutates to a new more lethal variant that again proves more toxic to those previously immunized or infected we may once again need to prospectively hunt for a community actionable intervention using a screening study model. My next update to this series will be in time for the 2021 holiday season.

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