Not a Pandemic of the Unvaccinated November 29, 2021

COVID is not the flu, and it is not Ebola. These simple facts explain much of confusion about our government's response to the pandemic. The 'superpower' which this virus has is that it is often highly contagious in people who have no significant symptoms. Even in people who do get symptoms, they are most contagious at the time symptoms start, and for 24 hours prior to and following the onset of symptoms. That is very different from the flu. Almost all of the admonitions issued by our government would be very practical if this were a flu pandemic, because flu symptoms typically mount quickly and include fever by the time the flu victim is very contagious. When a person feels bad and has a fever, wearing a mask and staying away from other people makes sense. Likewise, it is common sense for the people around the victim to be fastidious about hand washing and other hygiene measures. It is not common sense to live perpetually in that state, unless we are in the midst of an epidemic of an Ebola-like disease that spreads very easily and has a very high mortality. (About 50% or more of Ebola patients die, regardless of age or previous health status). It is easy to fall into the trap of thinking that COVID is like the flu. I remember many times when I told people that after they were fully vaccinated they could be around their 80 year-old relatives without worry or special precautions. I was especially encouraged after the initial reports showed that the mRNA vaccines were 94-95% effective in preventing COVID, and the Moderna vaccine was 100% effective in preventing severe COVID in the trials. I have been disappointed that my experience has taught me differently. Although the vaccines certainly do help to reduce the chance of symptomatic disease, it seems to be less than a 90% reduction. The reduction in severe disease seems to be closer to 90% than to 100%. Vaccination for COVID appears to make it more likely that the person will be completely asymptomatic, if they become infected. However, we know that they will shed just as much virus, but for a slightly shorter period of time. A recent article in the journal *Lancet* (November 20, 2021), titled "COVID-19: stigmatizing the unvaccinated is not justified," makes some of these same points. Stigmatization of the unvaccinated might be justified if COVID behaved like the flu; it doesn't, and to continue to act as if it does is dangerous as well as idiotic.

The vaccines worked better at first, and we are being told that the reason for diminished effectiveness is that the concentration of antibodies declines over time. That is part of the truth. A little-known fact is that the antibody level that is required for prevention of the now predominant Delta variant is 8 to 20 times higher than that required to prevent disease caused by the variants which were predominant previously. (Petra Mlcochova, "Delta variant emergence, replication and sensitivity to neutralizing antibodies" in *bioRxiv*. 2021) That is exactly what we would expect from a viral pathogen. Evolution of these viruses will always favor lineages that spread more easily and evade host defenses, whether natural or pharmaceutical. The reason typically given for the complete dominance of the Delta variant is that it spreads more easily, because to admit that COVID is changing to evade our vaccines would be politically incorrect, or perhaps even ideologically suspect. Well, that's okay, because Delta may very soon be supplanted by a new variant called Omicron. I have been worried about some other variants, such as Beta (from South Africa) or Gamma (from Brazil) would gain a foot-hold in this country, but they have not. The reason they haven't is that Delta is so successful, and it has effectively excluded them from the gene pool. The reason I have been worried about Beta or Gamma is that they have a particular mutation known as E484K that makes them able to evade most of our approved drugs and vaccines, but they lack the mutations that make Delta so highly contagious. Omicron has dozens of different

mutations, in a pattern that has not ever been seen before. Omicron is different, and its differences point up yet another important piece of misinformation. We are told, “Every time COVID is passed from one person to another, there is a chance for mutation.” That is another incorrect and frankly dangerous misunderstanding or falsehood. Almost certainly the collection of mutations seen in Omicron were the result of a long lasting COVID infection within one person. Very likely this was someone who had some type of immunosuppression, such as HIV, and took one or more COVID vaccines or treatments (possibly convalescent plasma). Each one of these acted as an evolutionary pressure, thinning the viral population so that the only virus remaining after each treatment/vaccine were immune to that vaccine or therapy. Omicron has several mutations that are typical of rapidly spreading variants, and it has a mutation that has not been seen previously in the wild: E484A. We know that E484K in the Beta variant results in substantial or complete evasion of all of our current vaccines, and may cause diminished effectiveness of our most commonly used monoclonal antibody therapies (produced by Regeneron and Eli Lily). In the March 10, 2021 edition of the journal Cell Host & Microbe, Zhuoming Liu *et. al* describe their efforts to predict and verify which potential mutations could be problematic; they indicate that E484A would likely cause diminished effectiveness of natural immunity. It would likely be otherwise equivalent to the E484K substitution.

It is worth noting that the spike protein on the surface of the viral particle which is responsible for COVID is the location of not only E484, but of all of the targets for the first generation of approved COVID therapeutics. There are a few different ‘hand holds’ where antibodies can ‘grab on’. Natural immunity utilizes several other sites for antibodies to grab, and natural immunity also utilizes cellular immunity that doesn’t require a hand hold. The repurposed drugs that have been found to be useful in COVID include inhaled budesonide and the antidepressants fluvoxamine and fluoxetine (Prozac). There is also evidence that hydroxychloroquine as well as ivermectin, colchicine and some antibiotics have some effectiveness, in addition to zinc and melatonin and vitamins C and D. All of these substances, as well as the new drugs discussed below, are likely to have maintained therapeutic benefit against Omicron.

We are very fortunate to just be getting new therapeutics to which Omicron has not been exposed. Sotrovimab is one such drug. The ending “mab” tells you that this is a monoclonal antibody, and thus it must be given IV. It is made by Glaxo-Smith Kline and is given as a one-time dose to those with COVID and at least one risk factor. It should be given as soon as possible and never after the 10th day of infection. Instead of attacking a portion of the rapidly mutating spike region of the virus, sotrovimab attacks the evolutionarily conserved envelope of the virus. Merck and Ridgeback Biotherapeutics have applied to the FDA for Emergency Use Authorization (EUA) for their oral antiviral drug molnupiravir for treatment of COVID-19. The application is to be discussed at the FDA's Antimicrobial Drugs Advisory Committee meeting on Nov. 30, 2021. The drug is an antiviral that has been under investigation for years, and works by introducing copying errors during the viral RNA replication process. In the trial it reduced the risk of hospitalization by approximately 50% (7.3% vs 14.1% with placebo). There were no deaths in the molnupiravir group compared to 8 deaths in the equally large placebo group. The dose is 4 pills (200mg each) twice daily for 5 days. Paxlovid is a new drug combination that has been developed by Pfizer, consisting of a new drug (PF-07321332) and ritonavir, currently used in HIV treatment. The company has asked for an EUA, “as soon as possible.” Paxlovid is given twice a day, 300mg (two 150mg tablets) of PF-07321332 with one 100mg tablet of ritonavir, and was found to reduce the risk of hospitalization by 89% compared to placebo. There were no deaths reported in patients who

received the drug, as compared to 10 deaths in the same number of similar patients who received placebo. Like molnupiravir, Paxlovid inhibits a step in the replication process, but at a later stage, preventing the necessary cleavage of proteins after they are produced under the direction of viral RNA.

Masks still work, and so does staying entirely away from other people, but I think that we have all begun to understand that “every form of refuge has it’s price.” (Eagles, “Lyin’ Eyes” from *One Of These Nights*, Elektra/Asylum Records, 1975) Fortunately, there are some really good masks available now. My favorite is the BYD CARE N-95 respirator, available from Amazon in a pack of 20 for $19.95. I advise this: Have one mask for each day of the week; at the end of the day put the mask in a paper bag, and set it aside for a week. If they don’t let them get soiled, you can safely use these 7 for 2 months. The virus will not remain viable, as long as the mask remains clean and dry. If you get COVID or the masks become wet or soiled, throw them away.

I hope that you have found some positive elements in this long piece. I plan next week to let you know about some very good things happening in our county. Any views expressed are my own, and do not represent any organization with which I am affiliated.

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