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Senators and colleagues: thank you for convening this hearing. We all understand the endemic disease that we are facing, that we have to face it head-on and not hide from it hoping that it will go away. I want to give you my perspective.

In May of this year I observed that results of studies of a drug suggested to treat Covid, hydroxychloroquine, were being misrepresented by what I thought at the time was sloppy reporting. We have heard from Dr. McCullough how Covid disease progresses in phases, from viral replication, to florid pneumonia to multi-organ attack. Viral replication is an outpatient condition, but the pneumonia that fills the lungs with immune-system debris is hospitalizable and potentially life-threatening. We have also heard how each phase, each pathologic aspect of the disease, has to have its own specific treatments that apply to its own biologic mechanisms. Thus, I was frankly astounded that studies of hospital treatments were being represented as applying to outpatients, in violation of what I learned in medical school about how to treat patients.

We are now finally coming to address why over the last six months, our government research institutions have invested billions of dollars in expensive patent medication and vaccine development but almost nothing in early outpatient treatment, the first line of response to managing the pandemic. It is not that we lacked candidate medications to study, we have had a number of promising agents. But I believe that the early-on conflation of hospital with outpatient disease served to imply that treatment of outpatient disease had been studied and found ineffective. This illogical premise motivated me to look at the evidence for outpatient treatment.

I reiterate: we are considering the evidence for early treatment of high-risk outpatients to prevent hospitalization and mortality. That is it. Treatment starting in the first five days or so after the onset of symptoms. Treatment of older patients or patients with chronic conditions such as diabetes, obesity, heart diseases, lung diseases, kidney diseases, immune-system diseases, survivors of cancer etc. These are the people most likely to die from Covid, and they are the people most needing protection. I have sought to obtain reports of every study of every medication pertaining to early treatment of high-risk outpatients. I monitor the literature daily. And what I have found is actually quite remarkable. What I have observed is that while there have been positive reports about a number of drugs, every study of outpatient use of one drug, hydroxychloroquine, with or without accompanying agents, has shown substantial benefit in reducing risks of hospitalization and mortality.

These studies break down into two major types. The first is double-blinded, randomized controlled trials, and the second is non-randomized but still controlled trials. You have heard from various government and scientific personalities that randomized controlled trials provide the strongest form of evidence. Many of these people have also claimed that randomized trials

provide the only trustworthy form of evidence. There is some truth in these assertions, but there is also lots of falsehood. We know for example that the great majority of drugs used to treat heart diseases were established with non-randomized trials. Cholesterol-lowering drugs were in widespread use before randomized trials were ever done. Azithromycin, the most commonly used antibiotic in children, was not established by randomized trials. The idea that only randomized trials provide trustworthy evidence is a simplistic notion that may sound good in theory, but the comparison between randomized and non-randomized trials is something that has actually been extensively studied in the medical literature. I am an epidemiologist because even though I love biological theories, I develop them all the time to study how nature works, but it is from the human empirical data that we learn how indeed nature works.

And we have huge amounts of empirical data to show that randomized trials and their corresponding non-randomized trials give the same answers. Dr. Tom Frieden, previously Director of the CDC, in 2017 wrote an extensive essay in the New England Journal of Medicine showing that non-randomized trials can provide fully compelling evidence, especially when they are done carefully to account for reasons why patients received the drugs, and importantly, when circumstances are such that the cost of waiting for randomized trials involves major sickness and mortality as we have been experiencing this year. But Dr. Frieden's essay, as authoritative as it is, provides only snapshots of the empirical evidence for his observations. The real evidence comes from a meta-analysis of meta-analyses done by the Cochrane Library Consortium, a British international organization formed to organize medical research findings to facilitate evidence-based choices about health interventions. The Cochrane investigators examined what involve tens of thousands of comparisons between randomized trials and their non-randomized counterparts and found that the two types of studies arrived at virtually identical conclusions. This is the real evidence about why good non-randomized trials comprise evidence every bit as important as randomized trials. Large amounts of consistent empirical data are the evidence, not plausible but simplistic assumptions, no matter who says them.

So what did I find about hydroxychloroquine in early use among high-risk outpatients? The first thing is that hydroxychloroquine is exceedingly safe. Common sense tells us this, that a medication safely used for 65 years by hundreds of millions of people in tens of billions of doses worldwide, prescribed without routine screening EKGs, given to adults, children, pregnant women and nursing mothers, must be safe when used in the initial viral-replication phase of an illness that is similar at that point to colds or flu. In fact, a study by researchers at the University of Oxford showed that in 14 large international medical-records databases of older rheumatoid arthritis patients, no significant differences were seen in all-cause mortality for patients who did or did not use hydroxychloroquine. The Oxford investigators also looked at cardiac arrhythmias and found no increase for hydroxychloroquine users. This was in more than 900,000 hydroxychloroquine users. This is examined at length in my paper in the American Journal of Epidemiology in May. Now, the FDA posted a warning on July 1 on its website about hydroxychloroquine used in outpatients, but we can discuss this later; the FDA

has had no systematic evidence in outpatients and erroneously extrapolated from hospital inpatients to outpatients, what I said earlier was invalid.

About studies of hydroxychloroquine early use in high-risk outpatients, every one of them, and there are now seven studies, has shown significant benefit: 636 outpatients in São Paulo, Brazil; 199 clinic patients in Marseille, France; 717 patients across a large HMO network in Brazil; 226 nursing-home patients in Marseille; 1,247 outpatients in New Jersey; 100 long-term care institution patients in Andorra (between France and Spain); and 7,892 patients across Saudi Arabia. All these studies pertain to the early treatment of high-risk outpatients—and all showed about 50 percent or greater reductions in hospitalization or death. The Saudi study was a national study and showed 5-fold reduction in mortality for hydroxychloroquine plus zinc vs zinc alone. Not a single fatal cardiac arrhythmia was reported among these thousands of patients attributable to the hydroxychloroquine. These are the non-randomized but controlled trials that have been published.

Now we also know that all of the outpatient randomized controlled trials this year also together show statistically significant benefit. These six studies comprised generally much younger patients, only a fraction of whom were at high risk, so they individually had too few hospitalizations or deaths to be statistically significant. But they all suggested lower risks with hydroxychloroquine use, and when they were analyzed together in meta-analysis as my colleagues and I found, this lower risk was statistically significant across the studies.

We have spent the last six months with formal government policies and warnings against early outpatient treatment, with large government investments in vaccines and expensive new treatments yet to be proven and almost no support of inexpensive but useful medications, and a quarter of a million Americans have died from this mismanaged approach. Even with newly promising vaccines, we have almost no information about how they will perform in older and high-risk patients, in whom respiratory virus vaccines are known to have weak efficacy; it will be a number of months before they become widely available; and we don't know how long vaccine immunity will last, or even if the vaccines will work for the newly increasing mutant strains of the virus. As I have said on many occasions, the evidence for benefit of hydroxychloroquine used early in high-risk outpatients is extremely strong, and the evidence against harm is also equally strong. This body of evidence dramatically outweighs the risk/benefit evidence for remdesivir, monoclonal antibodies or the difficult to use bamlanivimab that the FDA has approved for emergency use authorizations while denying the emergency use authorization for hydroxychloroquine. This egregious double standard for hydroxychloroquine needs to be overturned immediately and its emergency use authorization application approved. This is how we will get on the road to early outpatient treatment and the major curtailment of mortality. Thank you.

References

Barbosa Esper R, Souza da Silva R, Teiichi Costa Oikawa F, et al. Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. April 15, 2020. Accessed April 30, 2020. https://pgibertie.files.wordpress.com/2020/04/2020.04.15-journal-manuscript-final.pdf

Heras E, Garibaldi P, Boix M, et al. COVID-19 mortality risk factors in older people in a long-term care center. Preprints September 9, 2020. https://doi.org/10.21203/rs.3.rs-70219/v2

Ip A, Ahn J, Zhou Y, et al. Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study. Preprints August 25, 2020. https://doi.org/10.1101/2020.08.20.20178772

Ladapo JA, McKinnon JE, McCullough PA, Risch HA. Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19 Infection, Hospitalization, and Death: Meta-Analysis. Preprints September 30, 2020. https://doi.org/10.1101/2020.09.30.20204693

Lagier JC, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. Travel Med Infect Dis 2020 Jun 25:101791. https://www.sciencedirect.com/science/article/pii/S1477893920302817

Ly TDA, Zanini D, Laforge V, Arlotto S, Gentile S, Mendizabal H, Finaud M, Morel D, Quenette O, Malfuson-Clot-Faybesse P, Midejean A, Le-Dinh P, Daher G, Labarriere B, Morel-Roux AM, Coquet A, Augier P, Parola P, Chabriere E, Raoult D, Gautret P. Pattern of SARS-CoV-2 infection among dependant elderly residents living in long-term care facilities in Marseille, France, March-June 2020. Int J Antimicrob Agents. 2020 Nov 6:106219. https://www.sciencedirect.com/science/article/pii/S0924857920304301

Risch HA. Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients That Should Be Ramped Up Immediately as Key to the Pandemic Crisis. Am J Epidemiol. 2020 Nov 2;189(11):1218-1226. https://academic.oup.com/aje/article/189/11/1218/5847586

Sulaiman T, Mohana A, Alawdah L, et al. The effect of early hydroxychloroquine-based therapy in COVID-19 patients in ambulatory care settings: A nationwide prospective cohort study. Preprints September 13, 2020. https://doi.org/10.1101/2020.09.09.20184143

Szente Fonseca SN, de Queiroz Sousa A, Wolkoff AG, Moreira MS, Pinto BC, Valente Takeda CF, Rebouças E, Vasconcellos Abdon AP, Nascimento ALA, Risch HA. Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis. Travel Med Infect Dis. 2020 Oct 31;38:101906. https://www.sciencedirect.com/science/article/pii/S1477893920304026