REQUEST FOR EMERGENCY USE AUTHORIZATION

On behalf of Dr, William W. O'Neill, Dr. John E. McKinnon, Dr. Dee Dee Wang and Dr. Marcus J. Zervos, an Emergency Use Authorization is requested for hydroxychloroquine in limited circumstances for disease prevention (pre or post exposure prophylaxis) and for treatment of EARLY COVID-19 infections pursuant to Section 564 of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3).

Background

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Act, subject to terms of any authorization issued under that section.

According to the requirements set out in Section 564(c) of the Act, namely;

(1) that COVID-19 can cause a serious or life threatening condition as reported by the Secretary in his public health emergency,

(2) that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, it is unreasonable to believe that the current HHS/NIH doctrine of individual case isolation until a patient requires hospitalization, and then the initiation of hospital-based anti-viral drug treatment in the LATE stages of infection, may have any practical effect in halting the epidemiological spread and significantly reducing the mortality rate associated with COVID-19, a viral disease caused by the SARS-CoV-2 Virus. This applies to the use of remdesivir, favipiravir lopinavir/ritonavir, hydroxychloroquine with and without Zinc and an added antibiotic, and arbidol.

(3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition with the exception being the correctly timed use of systemic steroids in hospitalized patients with lower respiratory tract disease involvement. No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.

Disease prevention (pre-exposure -PrEP or post exposure- PEP) prophylaxis and early outpatient illness are very different than interventions in later hospitalized florid disease and as numerous clinical trials have demonstrated, the treatments grossly differ. Based on the results of trials from numerous sources (see below), it is reasonable to believe that the current established procedure for the epidemiological management of COVID-19 be changed from a hospital-based doctrine, to a more focused, community-based approach that involves the prophylactic, outpatient and early disease use of Hydroxychloroquine with or without additional antibiotic and/or Zinc supplementation. This use

involves the known and potential benefits of early-use hydroxychloroquine which outweigh the known and potential risks of this drug, for the treatment of patients in the EARLY outpatient stage of COVID-19 infection while patients are still ambulatory and do not present with severe advanced disease requiring mechanical ventilation.

The doctrine of "Stay at Home" quarantines and population lockdown without testing, to wait for COVID-infected patients to develop dyspnea and the need for hospitalization as well as the attendant overwhelming of community medical facilities, is unrealistic. It is also not part of the National Pandemic Influenza Plan painstakingly developed by HHS as the prototype response for a large serious respiratory RNA virus infectious disease outbreak. This is a criticism applicable not only to the United States, but to many countries that refrained from implementing any form of early treatment, such as the UK, Canada, France, and others (Figure 1). The decision by HHS, NIH, and the CDC to recommend lockdown and quarantine while waiting for COVID victims to develop shortness of breath and the onset of the more severe second phase of COVID-19 disease pathogenesis is not supported by the progressively accumulating early-treatment data that began on 15 February 2020.

In contrast to the minimal results of anti-viral therapy in late-stage COVID patients, five published studies, including two controlled clinical trials and three more studies awaiting publication, have all demonstrated a significant major efficacy of hydroxychloroquine as a cheap, antiviral medication when used in the early outpatient stage of COVID-19 infection. This is in addition to over 30 smaller patient trials which demonstrate the same results. Early use hydroxychloroquine (HCQ) is a safe medication that appears to halt the progression of patients to the more severe and lethal second-stage of COVID-19 infection with the attending risk of hospitalization, possible ICU admission, invasive intubation and possible death (Figure 2). [1]

The last hope for some degree of COVID-19 control lies with pre-exposure prophylaxis, physician-directed hydroxychloroquine outpatient drug therapy (given within the first 7 days of patient symptoms), early stage hospitalization, as well as post-exposure prophylactic use of hydroxychloroquine in asymptomatic, uninfected, high-risk Health Care Workers (HCW) and individuals with a high number of inter-personal contacts during their normal daily activities. (Figure 2). Outside of this, there is only the future development of a vaccine for control and thousands of Americans are going to lose their lives during this "immunization gap" with further catastrophic economic damage to the Nation.

Product Description

This EUA request is for the outpatient use of hydroxychloroquine sulfate in the formulation of 200 milligram (mg) tablets. As with many of the drugs approved by the FDA for human use, the precise molecular mechanisms involved in the actions of hydroxychloroquine have not been fully elucidated, nor have the effective intracellular micromolar concentrations of these drugs been well established where the different and broad-range of physiological effects are taking place.

Physiologically-Based Pharmacokinetic (PBPK) model simulations of the plasma drug levels and extracellular tissue spaces have been used to estimate the optimal HCQ dosing regimens. However, in reality, it is difficult to observe how these various simulations take into account the slow and accumulative intracellular concentrations of HCQ that varies with the length of time of drug administration, the prolonged ½ life of the drug in the human body, as well as the prolonged length of

time for various HCQ effects to physiologically appear and then disappear after the cessation of drug intake.[2]

Hydroxychloroquine (and chloroquine) have known in-vitro antiviral activity since 1969.[3] Activity against SARS-CoV with chloroquine was demonstrated in 2004 and evidence of in-vitro activity against other viruses has been shown.[4,5] to be able to change the pH at the surface of the cell membrane, affects endocytosis steps potentially affecting the bond between PICALM and clathrin, inhibit aspects of nucleic acid replication in some cases, interfere with the glycosylation of both receptor (ACE2 receptor) and some viral proteins/enzymes in some viruses, may affect phosphorylation of p38 mitogen-activated protein kinase (MAPK), broadly modify the new virus assembly of some viruses, modify new virus particle transport, release, and other processes.[6] In Dengue virus models, HCQ activates the innate immune signaling pathways of IFN-β, AP-1 and NFκB, and was shown to induced cellular production of reactive oxygen species (ROS), as host immune defense against viral infection.[7] Both hydroxychloroquine and its relative chloroquine, appear able to bind to the human ACE-2 protein that serves as the CoV-2 viral receptor and interfere with the viral S protein's ability to bind to gangliosides. Recent studies showed improved HCQ activity over CQ in-vitro with lower EC50 values for HCQ.[8,9]

First reports on the clinical use of HCQ outside of its anti-parasitic role, occurred in Systemic Lupus Erythematosus (SLE) patients more than 50 years ago. In this application, the dosage for the outpatient use of HCQ in SLE is a loading initial dose of 400 mg orally once or twice a day. The maintenance dose ranges between 200 and 400 mg per day with variable avocations for dosing based on actual or ideal body weight. One study on SLE use indicates that effective HCQ blood levels are similar regardless of height and body weight and that a dose of 6.5 mg/kg of actual body weight (max 400 mg daily) is appropriate.[10]

The Protocols for Rheumatoid Arthritis suggest an Initial Loading Dose of 400 to 600 mg salt (310 to 465 mg base)/day orally divided in 1 or 2 doses, with a Maintenance Dose of 200 to 400 mg salt (155 to 310 mg base)/day orally divided in 1 or 2 doses and a Maximum Dose of 600 mg salt (465 mg base)/day or 6.5 mg/kg salt (5 mg/kg base)/day, whichever is lower, should not be exceeded. Accordingly, the advice is to reduce the daily dose to below 400 mg per day for those weighing less than 61 kg. [5]

For COVID-19 treatment, the suggested dose of HCQ sulphate is 400mg BID on day 1, followed by 200mg BID on day 2-5. Because of the long elimination half-life of the drug (32–50 days), the duration of treatment should not exceed 5-10 days to avoid accumulation of hydroxychloroquine concentrations in plasma and tissues, and associated increased risk of toxicity, and because there is no in vitro evidence that longer courses improve drug activity on SARS-CoV-2.[11] Lower doses for longer duration are being used in pre-exposure prevention trials such at the WHIP COVID-19 Study (NCT04341441), with good safety profiles and no severe adverse events. [12]

Safety of Hydroxychloroquine

Hydroxychloroquine has an excellent safety profile. Led by Dr. Dani Prieto-Alhambra, Professor of Pharmaco-and Device Epidemiology at the University of Oxford, a team of researchers from around the world met to analyze the safety profile of hydroxychloroquine. From 26 – 29 March 300 researchers from 30 countries and six continents formed teams to examine the data from fourteen datasets, from six countries: Germany, Japan, the Netherlands, Spain, the UK, and the USA. The research was to provide

real-world evidence and inform healthcare decision-making in response to the current global pandemic.[13]

Over 300 international researchers from the Observational Health Data Sciences and Informatics (OHDSI) community described the safety profile and potential harms of Hydroxychloroquine and Azithromycin and found that Hydroxychloroquine had been shown to be a safe drug in over 130,000 patients.[6] When administered at the doses used for current indications like rheumatoid arthritis and lupus in the developed nations, and amoebic liver abscesses and malaria in the under-developed countries, there were no serious side effects. It should be noted that that some of the short-term amplified doses of Hydroxychloroquine used in Lupus patients with complications, are much higher than the doses proposed for use in early COVID-19 cases. This study did not find any consistent reason to make them think that the drug Hydroxychloroquine was anything other than a safe medication in general but urge caution in using it in combination with azithromycin.

The major stated concern of the FDA and NIH advisories and the cardiology opinions restricting use of HCQ and HCQ+AZ, was for a prolongation of QT interval > 500msec leading into a fatal Torsades de Pointes, a rare type of ventricular arrhythmias, as well as for cardiac arrhythmias in general. In the inpatient population, this risk can be significantly mitigated by protocol driven EKG evaluations during the hospitalization. Multiple cohort studies have demonstrated the safety of HCQ in the lupus population, where it is routinely used even during pregnancy, with the only established contraindication for therapy being known retinopathy.[14,15] Furthermore, the American College of Rheumatology does not recommend routine universal EKG screening or even glucose-6-phosphate dehydrogenase for HCQ therapy, as clinical data have not demonstrated any significant risk of associated hemolysis in numerous cohort studies in both lupus and rheumatoid arthritis.[15] Baseline EKG is not recommended for Rheumatoid Arthritis, Scleroderma, or SLE patients starting hydroxychloroquine therapy, and HCQ is one of the few drugs not contraindicated in pregnancy and nursing mothers.[15]

One Oxford study examined cardiac arrhythmia outcomes and obtained for its random effects meta-analysis result, RR=1.08, P-value=0.36 for HCQ + Azithromycin (AZ) use vs HCQ + Amoxicillin use (another broad-spectrum antibiotic. The fixed-effects meta-analysis RR=1.04, P-value=0.41. This study clearly demonstrates that cardiac arrhythmia adverse events are not appreciably increased by combining HCQ with AZ.[13] The same study compared HCQ use to sulfasalazine use and again found no difference in cardiac arrhythmia risk: for HCQ, a slightly lower RR=0.89, P-value=.13. The subjects analyzed in the Oxford study were largely older adults with multiple comorbidities in addition to rheumatoid arthritis. Finally, the Oxford study allows for a direct estimate of the number of arrhythmia events attributable to HCQ+AZ use. Among 306,106 people taking sulfasalazine (which is known *not* to produce QT prolongation), 877 with cardiac arrhythmias were identified, representing 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% or 47/100,000 older multi-comorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. Fatalities according to FAERS comprise <20% of HCQ-related arrhythmia events. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger plasma drug levels as five days of HCQ at 400 mg/day, the recommended dose for outpatient Covid-19.

In another systemic review of published cardiac complications attributed to HCQ in the pre-COVID-19 era by a Cardiology team led by Dr. Fram and colleagues, identified only 69 articles where most cardiotoxicity events were reversable with standard of care with 2 fatalities identified, directly attributable to acute intentional overdoses.[16]

The June 15 withdrawal of the Emergency Use Authorization for HCQ came after review of several press releases and non-peer reviewed data indicating possible increased mortality in the HCQ treatment arms. Coincidentally, after peer-review of the data was performed, none of these studies demonstrated an increased cardiovascular risk or increased risk in mortality and the published Lancet study by Mehra et al, was retracted as the data had been fabricated.[17,18 19] Unfortunately, the released data did affect not just the FDA but also the WHO leading to initial stoppage of the SOLIDARITY trial HCQ arm and the RECOVERY trial in the UK trial doing the same. Both studies have now stopped their HCQ arms due to possible lack of efficacy without any safety signal but neither has published the data associated with their press releases. One key flaw in most of these treatment study designs was the introduction of HCQ and other therapies, or the bias selection of patients for treatment, once the patients had advanced end organ disease and were requiring high oxygen supplementation and/or where already in the critical care units. At this time in the clinical course, high mortality would be expected with any treatment regimen and potential benefits in COVID-19 may be difficult to discern as secondary end organ damage and associated deterioration would now be the predominant disease drivers. Data supporting early treatment for viral control in COVID-19 is emerging from multiple laboratories.[20]

Finally, the recently published randomized trial of HCQ as postexposure prophylaxis for COVID-19 by Dr. Boulware and colleagues, did not demonstrate significant benefit of the strategy but acknowledged that there were flaws with the study and that further research was needed. This study also did not demonstrate any increased in cardiovascular or severe events or mortality in the treatment arm.[21]

Together, these very small numbers of arrhythmias and cardiac events, as well as the null results in the very large empirical study, should therefore negate the worry about HCQ causing deaths for the drug itself or in combination with Azithromycin in early outpatient use.[1] The FDA, NIH and cardiology society warnings about cardiac arrhythmia adverse events, while appropriate for theoretical and physiological considerations about use of these medications, are not borne out in mortality in real-world use. Theoretical calculations about potential adverse events and from measured physiologic changes rather than from current real-world mortality experience with these medications suggest it would be incumbent upon all three organizations to reevaluate their positions as soon as possible.[1]

It is unclear why the FDA, NIH and cardiology societies made their recommendations about HCQ+AZ use now, when the Oxford study analyzed 323,122 users of HCQ+AZ compared to 351,956 users of HCQ + amoxicillin, i.e., that the combination of HCQ + AZ has been in widespread standard-of-care use in the US and elsewhere for decades, use comparable to HCQ + Amoxicillin as if it just involved an alternate antibiotic choice, this use predominantly in older adults with multiple comorbidities, with no such strident warnings about the use given during that time.[1]

It is also curious the recommendation for remdesivir use as early as possible was made without either FDA approval or RCT evidence of efficacy in the outpatient context at this time, or exactly how IV medication would be provided to hundreds of patients nationwide each day when other simpler strategies have faced significant logistical limitations (e.g., face masks). Additionally, the drug will now be available at a cost of approximately $3k dollars for a short course of treatment, which will limit its use and will put a significant financial strain on our healthcare systems. More affordable and equally efficacious regimens are needed and no options for early outpatient therapy are currently available.

In a French COVID treatment study, 3,119 patients were treated with a higher dose of HCQ-AZ (200 mg of oral HCQ, three times daily for ten days and 500 mg of oral AZ on day 1 followed by

250 mg daily for the next four days, respectively) for at least three days and 618 (16.5%) patients treated with other regimen ("others"). Outcomes were death, transfer to the intensive care unit (ICU), ≥10 days of hospitalization and viral shedding.[22]

Treatment with HCQ-AZ was associated with a decreased risk of transfer to ICU or death (Hazard ratio (HR) 0.18 0.11–0.27), decreased risk of hospitalization ≥10 days (odds ratios 95% CI 0.38 0.27–0.54). QTc prolongation (>60 msec) was observed in 25 patients (0.67%) leading to the cessation of treatment in 12 cases including 3 cases with QTc> 500 msec. No cases of *torsade de pointe* or sudden death were observed. Overall, the case fatality rate among the 3,737 patients was 1.1%. This can be contrasted with the hospital-level case fatality rates of roughly 25%, in the Oxford University RECOVERY clinical trials.[22]

Recently a French Medical Panel petitioned their national government to allow HCQ+AZ and HCQ + Doxycycline for outpatient use in early COVID cases. Their assessment was that this medication was generally safe for short-term use in the early treatment of most symptomatic high-risk COVID outpatients, where not contraindicated, and that they are effective in preventing hospitalization for the overwhelming majority of such patients. Their assessment was that if these HCQ-combined medications become the standard-of-care, they would save an enormous number of lives that would otherwise be lost to this Pandemic disease.[23] Similarly, in recent days countries like Spain, Morocco, Nigeria, India, Brazil and others, have reported their continued use and evaluate the use of HCQ in both prophylaxis and early treatment.

Supporting Documentation and Clinical Trials

Symptomatic outpatient infection is a pathologically and clinically different disease than the life-threatening inpatient acute respiratory distress syndrome seen in some hospitalized patients experiencing manifestations of cytokine storm caused by SARS-CoV-2, thus there is little reason to think that the same treatment would be useful for both early and late COVID-19 disease where different pathophysiological processes are involved[24,25]. Intervention in stabilizing US and global health without further detriment to global economic recovery requires very careful analysis of the available literature. It would be difficult to comprehend that Hydroxychloroquine, a medication that has been used by more than 2 billion people in treatment, in 2020, has acutely become a toxic medication[26].

Prophylaxis prevention with hydroxychloroquine:

There have been multiple publications on use of HCQ in prevention and post-exposure prophylaxis for COVID-19. South Korea was the first to publish an observational study demonstrating post-exposure use of HCQ in 211 individuals exposed to known COVID-19 patients, prevented SARS-CoV-2 infection. Subsequent peer-reviewed and in-print studies in India have prompted the Indian Council of Medical Research to state that the low-dose pre-exposure prophylactic administration of HCQ in healthcare workers, combined with the use of PPE, may provide a greater than 80% reduced chance of contracting COVID-19. [27-29] Indian Sawai Man Singh Hospital reported on June 19th, that in their trial of 4300 high risk healthcare workers who are receiving HCQ prophylaxis only 45 have tested positive so far. These healthcare workers were managing up to 500 COVID-19 patients in the hospital including ICU patients during the peak of their epidemic. The results have been shared with ICMR for

this study.[29] Plans are now underway for the mass prophylaxis of 100,000 residents in the slum areas of Mumbai.

In Portugal, Ferreira et al demonstrated chronic treatment with HCQ for management of diseases autoimmune diseases confers a degree of protection against SARS-CoV-2 infection and COVID-19 disease. In this cohort of 26,815 COVID-19 patients, only 77 had been on chronic HCQ. The odds ratio for protection was 0.51 ((0.37-70), which correlates to almost a 50% reduction in cases.[30] Similar studies are underway looking at these populations on chronic HCQ in India, Brazil and Detroit, MI.

Outpatient hydroxychloroquine intervention:

A total of 4.6 billion people live in countries where hydroxychloroquine is recommended for COVID-19[26]. Countries with limited financial infrastructure and limited access to clinical trials have become early adopters of hydroxychloroquine in outpatient intervention to prevent overloading an already fragile healthcare infrastructure. In Brazil, where the numbers of COVID-19 cases have continued to increase, expanded use of HCQ on May 20,2020 was associated with a deflection in the country's overall case fatality rate as compared to Mexico, a country that has not adopted early hydroxychloroquine intervention (Figure 3). This same trend in lowering of case fatality rate can be observed in Italy, Turkey, and other countries who use HCQ for early intervention in COVID-19 (Figure 3).

Most important is the trend in Case Fatality Rate (CFR) by country. Using readily available data from the European CDC, the website "Our World in Data" allows real time analysis of case fatality rate by countries with more than 100 confirmed COVID-19 cases. Costa Rica, an early adopter of hydroxychloroquine use remains with very low case fatality rate. Brazil's health system Unimed on 4/23 established a hydroxychloroquine early intervention protocol, which is reflected with the stabilization and subsequent deflection of CFR with expanded usage of HCQ on May 20th, 2020. Following publication of the falsified data in the Lancet paper on May 25th, 2020, the use of HCQ in the US decreased, with ultimate revocation of the EUA on June 15, 2020. During this time course, June 1-June 28th, the United States' Case Fatality Rate surpassed that of Brazil, a country with more daily COVID-19 cases than the US, and remains with a higher CFR than Brazil (Figure 3). [19]

Another supportive study by Barbosa Esper R, et al., using empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine.[31] The study was a controlled non-randomized trial of HCQ+AZ in 636 symptomatic high-risk outpatients in São Paulo, Brazil. All consecutive patients were informed about the utility and safety profile of the medications and offered the treatment, and those who declined (n=224) comprised the control group. Patients were monitored daily by telemedicine. The study outcome was need for hospitalization, defined as clinically worsening condition or significant shortness of breath (blood oxygen saturation <90%). Even though the severities of all of the recorded flu-like signs and symptoms and of important comorbidities (diabetes, hypertension, asthma, stroke) were substantially greater in the treated patients than the controls, the need for hospitalization was significantly lower, 1.2% in patients starting treatment before day 7 of symptoms, 3.2% for patients starting treatment after day 7, and 5.4% for controls, P-value<.0001. No cardiac arrhythmias were reported in the 412 treated patients. The most common side effect of treatment was diarrhea (16.5%), but 12.9% of treated patients presented with diarrhea before treatment began.

Early Stage Hospitalization hydroxychloroquine intervention:

In this respect, the first Western study of HCQ+AZ (24) was controlled but not randomized or blinded, and involved 42 patients hospitalized in Marseilles, France. The first study, Gautret P, et al performed an early hydroxychloroquine and azithromycin as a treatment of COVID- 19. [32] This study showed that the sooner these medications are used, the better their effectiveness, as would be expected for viral early respiratory disease. The average start date of medication use in this study was day-4 of symptoms. This study has been criticized on various grounds that are not germane to the science, but the most salient criticism is the lack of randomization into the control and treatment groups. This is a valid general scientific criticism but does not represent epidemiologic experience in this instance.

If the study had shown a 2-fold or perhaps 3-fold benefit, that magnitude of result could be postulated to have occurred because of subject-group differences from lack of randomization. However, the 25-fold or 50-fold benefit found in this study is not amenable to lack of randomization as the sole reason for such a huge magnitude of benefit. Further, the study showed a significant, 7-fold benefit of taking HCQ+AZ over HCQ alone, P-value=0.035, which cannot be explained by differential characteristics of the controls, since it compares one treatment group to the other, and the treated subjects who received AZ had more progressed pneumonia than the treated subjects receiving HCQ alone, which should otherwise have led to worse outcomes.

The study size has been described as "small," but that criticism only applies to studies not finding statistical significance. Once a result has exceeded plausible chance finding, greater statistical significance does not contribute to evidence for causation.[1] No different conclusion would have resulted had a study with 1000 patients found the same 50-fold benefit but with a P-value of 10-10. Study size limitation only applies to studies having findings within the play of chance. That is not the case here.

A second study by the Marseilles group involved 1061 patients tested positive for SARS-CoV-2 treated with HCQ+AZ for at least 3 days and followed for at least 9 days. The authors state "No cardiac toxicity was observed." Good clinical outcome and virological cure were seen in 973 patients (92%). Five patients died, and the remainder were in various stages of recovery.[33]

A small study is ongoing in a long-term care facility in Long Island, NY by Dr. M. Alam and colleagues.[22] This study has been employing HCQ + doxycycline rather than HCQ+AZ for treatment of high-risk Covid-19 patients. Doxycycline itself has antiviral activity against SARS-CoV-2 at in vitro concentrations 5.6μM median, activity against other viruses and known anti-inflammatory effects.[34] Among the first 54 residents treated in the Long Island study, 6 were hospitalized and 3 (5.6%) died. An unofficial update of these data indicates that of about 200 high-risk patients treated with HCQ + doxycycline, 9 (4.5%) have died. A similar study is evaluating hydroxychloroquine plus zinc with either azithromycin or doxycycline for the treatment of COVID-19 in the outpatient setting (NCT04370782).

In the US, the Henry Ford Hospital system examined 2,662 patients entering its five-hospital system in southeast Michigan from March 10, 2020 to May 2, 2020. This patient universe was sub-divided into four groups: a control group, a hydroxychloroquine group, a hydroxychloroquine with azithromycin group and an azithromycin-only group.[35] A key feature of this study is that it provides the best "early treatment" study to date. Median time from hospital admission to receipt of hydroxychloroquine and other medicines was just a single day. As the study notes: "The postulated pathophysiology of Covid-19 of the initial viral infection phase followed by the hyperimmune response

suggests potential benefit of *early administration* of hydroxychloroquine for its antiviral and antithrombotic properties."

This Ford study initially found at a statistically significant level that the hydroxychloroquine alone group was associated with a significantly lower mortality rate compared to patients not receiving hydroxychloroquine. While the mortality rate for the 487 patients in the control group receiving no medicine was 23.0%, it was 13.5% for the 1,234 patients receiving hydroxychloroquine alone

This compared to a rate of 19.9% for the HCQ/Azithromycin group and 21.7% for the azithromycin only group. This finding translates into a 40% reduction in the mortality rate for patients receiving early treatment of hydroxychloroquine. Later data and statistics equate the administration of HCQ with a 51% improvement in mortality in treated patients. This study has been accepted for publication but because of the expected media problems, it will be published soon.

These results, in turn, suggest that of the more than 100,000 Americans who have lost their lives to the SARS-CoV-2 virus, tens of thousands of them might have survived with an early treatment regime of hydroxychloroquine.

As a note, an accompanying safety study has been submitted for publication and further evidence to the safety of HCQ comes from the recent data from Wang and McKinnon, et.al. 2020 North American Consortium of Hydroxychloroquine Randomized Clinical Trials for Prevention of COVID-19: Release of Data Safety Monitoring Board Data. *Submitted for peer review.*[12]

"Since March 17, 2020, a total of 1966 participants have been enrolled across the 7 RCTs. DSMB and independent review events were collected from these RCTs. To date, there have been no SAE, no deaths related to hydroxychloroquine. No study participant has required hospitalization due to the drug. There have been no significant adverse cardiovascular events".

Finally, a recent meta-analysis by Million M, et al., of 20 available reports, including 105,040 patients has demonstrated that in clinical studies, chloroquine and its derivatives improve clinical and biological outcomes and reduce mortality by a factor 3 in COVID-19 patients. [36]

This is not simply anecdotal evidence and continuing accumulating data on HCQ continues to demonstrate its efficacy in improving clinical status in observational or randomized clinical trials for COVID-19 treatment modalities.

This also suggests that an even greater benefit might be obtained by using hydroxychloroquine as both a post-exposure and a pre-exposure prophylactic therapy for health care workers and other at-risk populations. Because of the uncertainties of the time of infection of secondary cases, the post-exposure individuals placed on hydroxychloroquine treatment may still become ill with COVID-19, but in the majority they should only require quarantine and general outpatient care.

This is while further **Early** use data continues to appear. On 23 June 2020, Nigerian authorities in the National Capitol released a statement concerning their preliminary trials on the use of chloroquine and hydroxychloroquine for prophylaxis for COVID-19. Their studies will be expanded to encompass pre-exposure prophylaxis, post-exposure prophylaxis, ambulatory and inpatient care.[20]

Non-randomized but controlled trials provide important evidence, if not "proof," for the major efficacy of early use of HCQ+AZ against SARS-CoV-2 infection in symptomatic high-risk outpatients. What can be said about the uncontrolled large case series of treated patients? Standard published case reports provide clinical evidence of the possibility of an exposure-outcome relationship, but not of the regularity, magnitude or representativeness of such a relationship. The same can be said of case series reports, meaning that subject entry into the series is not necessarily well-defined and no denominator information is provided from which to gauge what the series represents. However, a large series in the context of known risks of mortality or adverse events can allow for ballpark estimates of the denominator and thus provide a reasonable frame of reference for whether the outcomes likely represent beneficial or harmfull.[1]

Summary

Given the scope of the potential of lives possibly being saved, it is critical that this nation move forward with emergency use of the hydroxychloroquine under the sanctity of the doctor-patient relationship. It is equally important that the medical community move briskly forward with the conduct of robust randomized, blinded, and controlled early treatment clinical studies.

Here's the last thought, one from Dr. Harvey Risch of Yale University: *"We have a solution, imperfect, to attempt to deal with the disease. We have to let physicians employing good clinical judgment use it and informed patients choose it. There is a small chance that it may not work. But the urgency demands that we at least start to take that risk and evaluate what happens, and if our situation does not improve we can stop it, but we will know that we did everything that we could instead of sitting by and letting hundreds of thousands die because we did not have the courage to act according to our rational calculations."* [i]

Scope of Authorization Requested

- It is essential that Physicians be allowed to prescribe HCQ, with or without antibiotic additions, after assessment of indications, contraindications and under reasonable dosages based on their clinical judgement.

- It is essential that studies evaluating HCQ for pre, post and early treatment, (including early hospital treatment) of HCQ be supported without the need for IND requirement limiting potential for studies to be initiated.

- A program of prophylactic HCQ based on the Indian and/or Henry Ford dosing rates should be initiated for all Health Care Workers that wish this and that do not have contraindications.

- Physicians or nurse practioners / physician assistants, should be added to case-contact tracing teams and allowed to administer a post exposure treatment dose of Hydroxychloroquine with or without antibiotic supplementation to close contacts of infected patients.

- Hydroxychloroquine prophylaxis should be offered to all individuals who are in close contact with others during their normal daily activities, to include bus drivers, police, fire, EMS, first responders and other high-risk groups.

For the reasons listed above, an Emergency Use Authorization is respectfully requested.

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Dr. William W. O'Neill MD

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Dr. John E. McKinnon

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Dr. Dee Dee Wang

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Dr. Marcus J. Zervos

June 30, 2020

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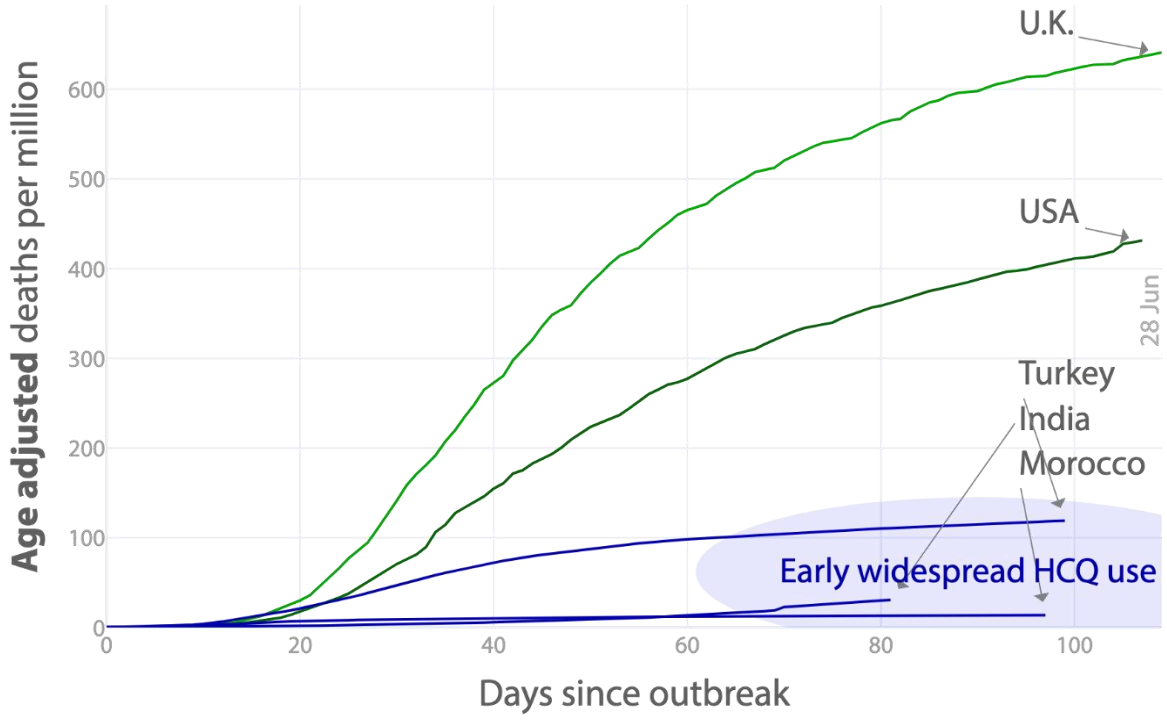

Figure 1. Comparison of quarantine and wait for late symptoms with hospitalization, or ambulatory HCQ treatment before supplemental oxygen is required. https://c19study.com/

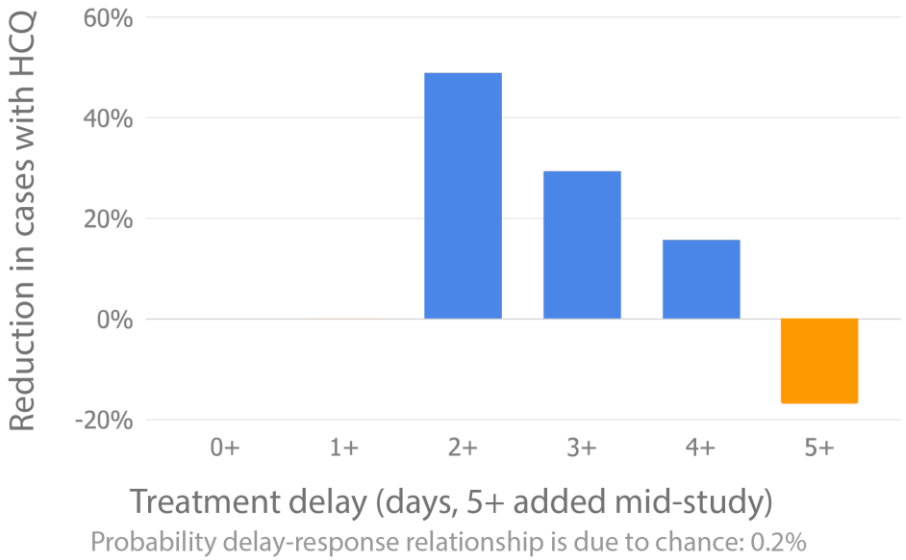

Figure 2. Delay in HCQ treatment from time of symptom onset and hospitalization. https://c19study.com/

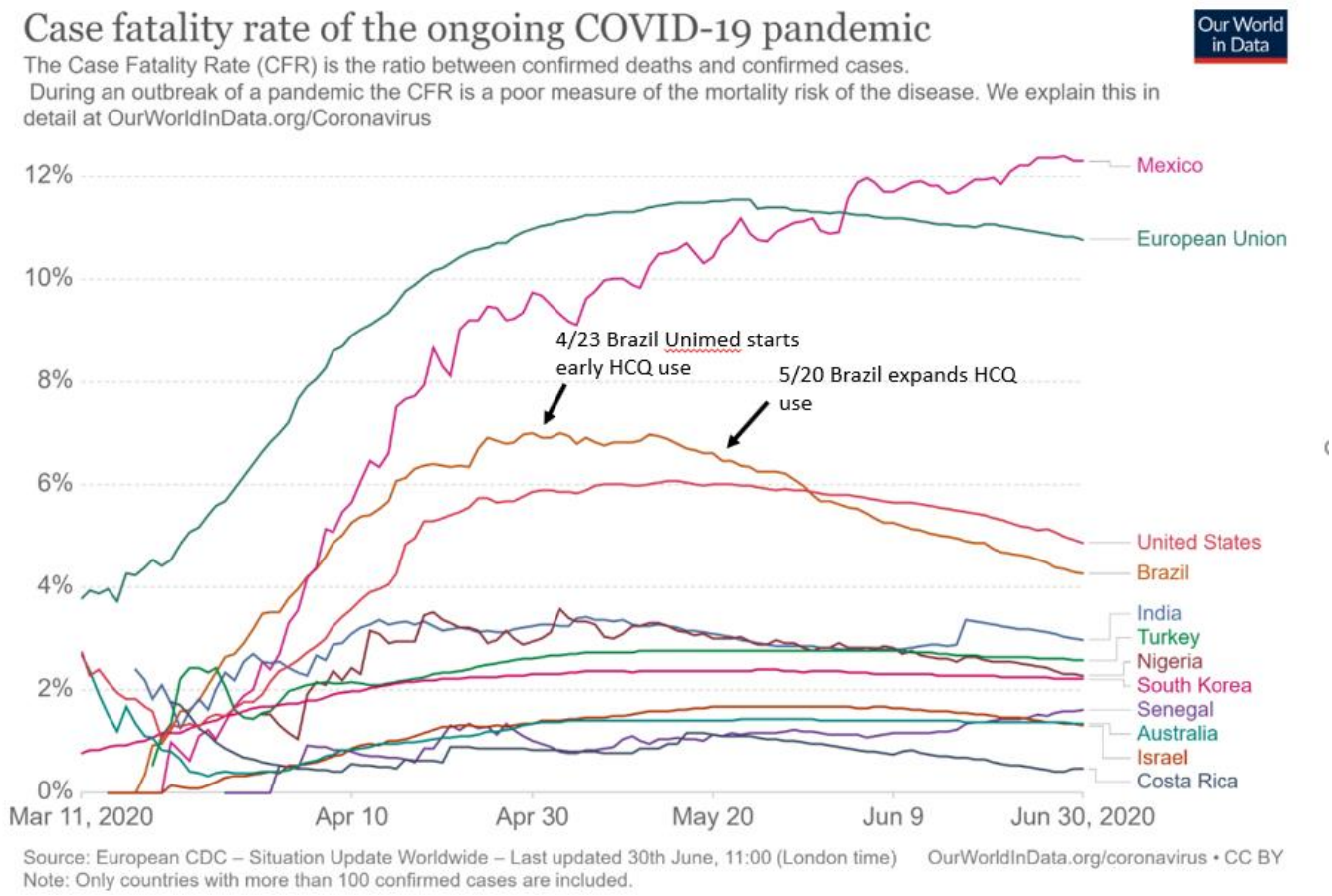

Figure 3. Case fatality rate of the ongoing COVID-19 pandemic by countries

Case fatality rate difference in countries making hydroxychloroquine available for early treatment, versus not (ie Mexico and European Union).