Hydroxychloroquine in Early Treatment of High-Risk COVID-19 Outpatients: Efficacy and Safety Evidence

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- Every one of the now 10 studies of high-risk outpatient hydroxychloroquine (HCQ) use has shown risk reduction for hospitalization or mortality. Meta-analysis demonstrates 44% reduction in hospitalization, $p=10^{-5.5}$, and 75% reduction in mortality, $p=10^{-19}$.
- The numerous systematic case-series studies have shown exceedingly good treatment benefit vs mortality. They have already saved many tens of thousands of lives.
- The "natural experiment" studies of population medication responses provide compelling evidence of temporal relations between medication use and mortality reduction.
- The RCT studies proclaimed supposedly as definitively showing no benefit of HCQ use in outpatients have all involved almost entirely low-risk subjects with virtually no hospitalization or mortality events and are uninformative and irrelevant for bearing upon risks according to HCQ use in high-risk outpatients.
- HCQ has been safely used for 65 years by hundreds of millions of people worldwide, in tens of billions of doses, in people with autoimmune and other chronic diseases, in children, in pregnant women etc. It is one of the safest medications known.
- The FDA has no systematic evidence of fatal adverse events from hydroxychloroquine prophylaxis or outpatient treatment use and has invalidly used evidence in hospitalized inpatients to create a false public warning by extrapolating to outpatient use.
- The totality of any or fatal cardiac arrhythmia events among more than 15,000 patients treated with hydroxychloroquine or hydroxychloroquine+azithromycin is zero.
- The large database study of more than 900,000 older patients taking hydroxychloroquine shows no excess all-cause mortality and no excess occurrence of fatal cardiac arrhythmia. The same study, of 320,000 older patients taking hydroxychloroquine + azithromycin, shows no excess all-cause mortality and minuscule excess fatal arrhythmia frequency, estimated 9/100,000 patients, compared to the large number of patients whose lives will be saved by outpatient use of these medications.
- A small percentage of high-risk COVID-19 patients, likely less than 5%, may have contraindications to use of hydroxychloroquine alone or combined with azithromycin. Clinical decisions about such use are part of standard physician workup and apply to most FDA-approved medications and do not detract from use.
- The need for outpatient use of hydroxychloroquine and other medications is crucial for saving the lives of tens of thousands of high-risk COVID-19 patients until the pandemic completely subsides. Even with widespread vaccination, cases of the disease are still occurring, and many of those patients need immediate treatment.

Introduction

Numerous studies by now have examined use of hydroxychloroquine (HCQ) with respect to a range of outcomes in COVID-19 disease, to the point that indiscriminate or "cherry-picked" selection from among the studies can support almost any assertion about these associations. However, given the pressing need to reduce disease mortality dramatically, that outcome, or its main predecessor, hospital admission, are the logical foci of research bearing upon therapeutic utility of HCQ. Further, the proposed mechanism of action of HCQ lies in its antiviral properties, either in parallel with or in support of zinc ions, which may be naturally sufficient in healthy younger people but may require supplementation in older people or those with chronic morbidities. In addition, current evidence suggests that low-risk people, i.e., people under age 60 years and not obese (BMI<30) and without chronic comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, COPD, asthma, kidney disease, immunocompromise etc., need only symptomatic management for COVID-19 and do not need to be treated, except in the infrequent circumstance of progression to dyspnea under light activity, typically PO_2<94%, at which point they become high-risk and active treatment is warranted. Thus, the intended application of HCQ is for use of HCQ and its companion medications (zinc, antibiotics azithromycin or doxycycline, ivermectin, anticlotting agents, vitamin D, and possibly prednisone or budesonide starting on symptoms day-6 or at dyspnea; these combinations denoted by "HCQ+" use) in high-risk patients as early as possible after clinical diagnosis of COVID-19 or true-positive SARS-CoV-2 test result (McCullough et al., 2020). For this reason, only studies of HCQ in this specific application contribute relevant evidence: early outpatient use, high-risk patients, hospitalization or mortality as endpoints.

Second, a long debate exists about types of studies upon which reliance can be placed for evidential reasoning and decisions about clinical utility. This debate may have originated with the recognition in the 1950s or 1960s that observational studies (case-control studies, cohort studies, large case-series studies etc.) are associational in nature and potentially subject to biased or confounded information and false-positive (or false-negative) results. Alternatively, well-conducted, large-enough, representative double-blinded randomized controlled trials (RCTs) can provide quasi-experimental evidence. In reductio ad absurdum, some licensing and approval bodies have made policies to include only evidence from RCTs. However, it is well known that RCTs are generally designed according to statistical power for detecting magnitude of association of the primary endpoint, not for limiting imbalanced proportions in the treatment arms residual to randomization, and that they are subject to many other potential flaws and are easily intentionally distorted or subverted in practice (Frieden, 2017; Deaton and Cartwright, 2018). Additionally, a massive amount of work has been carried out in empirically comparing the results of RCTs to their nonrandomized counterpart studies. The definitive Cochrane Library meta-analysis of what includes tens of thousands of individual studies demonstrates that standard adjusted modern nonrandomized trials show virtually identical results to their randomized counterparts (Anglemyer et al., 2014). For this reason, the sole

reliance on RCT evidence is *scientifically* unwarranted (Frieden, 2017), and while it may sometimes be challenging to summarize a more diverse body of scientific evidence, that is precisely how *scientific* conclusions are derived. This reasoning process most frequently follows the foundational schema of "aspects" of causal reasoning laid out by Sir Austin Bradford Hill more than 50 years ago (Hill, 1965) and is discussed at length in the "Reference Manual" (Committee on the Development of the Third Edition of the Reference Manual on Scientific Evidence, 2011). In consideration of conclusions of efficacy or harm, all relevant evidence needs to be evaluated.

In sum, this Brief will reason from epidemiologic studies and evidence pertaining to safety and efficacy in preventing hospitalization and mortality with early HCQ+ use in high-risk COVID-19 outpatients. The Brief comprises four sections: A. Outpatient studies non-compliant with the defining conditions of hospitalization or mortality with early HCQ+ use in high-risk COVID-19 outpatients, i.e., reasons for their non-consideration in this Brief; B. Outpatient studies bearing upon hospitalization or mortality risks with early HCQ+ use in high-risk COVID-19 outpatients; C. Population "natural experiments" bearing upon efficacy of population use of HCQ in mortality reduction; D. Studies of safety and adverse endpoints with outpatient HCQ+ use.

A. Outpatient studies non-compliant with the defining conditions of hospitalization or mortality with early HCQ+ use in high-risk COVID-19 outpatients

Seven studies not relevant for further discussion have been published or released to-date concerning HCQ use in outpatients, as follows.

1. The Boulware University of Minnesota prevention study (Boulware et al., 2020), in which 821 asymptomatic healthcare workers with presumed exposure to SARS-CoV-2-infected individuals were randomized to HCQ (n=414) or placebo (n=407) a few days after exposure and followed-up for confirmed or probable COVID-19 as well as for hospitalization. The paper stated a medication-start 4-day limit from symptom onset but was later clarified not to include medication shipping time which involved an additional 2-3 days in more than half of the subjects (Wiseman et al., 2020). The authors concluded that no benefit of HCQ was seen, however a 42% reduction in Covid-19 disease was found if the drug was taken starting within 3 days from exposure (p=.044) (Wiseman et al., 2020). This study is not informative about more-serious outcomes because its study subjects were mostly low-risk individuals, median age 40-41 years. The low risk is demonstrated by 1 COVID-19-related hospitalization among the 407 placebo patients (0.25%). This low a placebo-group risk limits how much better the HCQ arm can do, which was 1 hospitalization among the 414 treated subjects. Serious adverse reactions were reported in the study as zero.

2. The Boulware University of Minnesota study (Skipper et al., 2020) in which symptomatic, non-hospitalized adults with laboratory-confirmed or probable COVID-19 and high-likelihood of exposure were randomized within 6 days of symptom onset to HCQ (n=212) or masked placebo (n=211). The paper stated a medication-start 4-day limit from symptom onset but like its companion study above (Boulware et al., 2020) was criticized for not including medication shipping time (Wiseman et al., 2020). This study is non-informative because its study subjects were mostly low-risk individuals, median age 40 years. The low risk is demonstrated by 8 COVID-19-related hospitalizations among the 211 placebo patients (3.8%). In spite of this flawed study design, hospitalizations in treated subjects (4/212 = 1.9%) were half of that in the placebo group. Though not statistically significant and thus possible to have occurred by chance, this 50% cut in risk of hospitalization (the outcome of relevance) is consistent with all of the informative studies to be considered herein. The author conclusion in this study, "Hydroxychloroquine did not substantially reduce symptom severity or prevalence over time in nonhospitalized persons with early COVID-19" is technically correct but misleading because symptom severity or prevalence is a minor issue compared to hospitalization and mortality, and the study did demonstrate a nonsignificant 50% reduction in hospitalization risk. The authors reported that there were no serious adverse events attributable to HCQ, even with the higher-than-recommended HCQ doses used in the study.

3. The Catalonia non-blinded randomized trial (Mitjà et al., 2020a) in which 136 COVID-19 patients were assigned to HCQ and 157 control patients to no treatment, i.e., no placebo. Median time from onset of symptoms to enrolment was 3 days in both groups. This study is noninformative because its subjects were mostly low-risk individuals, median age 42 years. The low risk is demonstrated by 11 COVID-19-related hospitalizations among the 157 control patients (7.0%). In spite of the composition of low-risk subjects in the study, the treated subjects had even lower risk of hospitalization (8/136 = 5.9%). There were no cardiac disorders observed among the treated subjects, and no serious adverse events adjudicated by the pharmacovigilance consultants in the study as related to HCQ.

4. The small non-randomized but controlled Marseille trial (Gautret et al., 2020). The Marseille COVID-19 research group conducted large, city-wide population screening for COVID-19 based out of the Institut Hospitalier Universitaire. This 60-bed hospital served as a clinic base for screening, work-up, day-patient medication provision, and where necessary, overnight hospital inpatient care. In this study, 42 tested-positive screenees were assigned to control (standard-of-care; n=16), HCQ (n=14) and HCQ+azithromycin (n=6) regimens; 6 patients started on medication but left the trial prior to completing the full course. Some of the controls were identified in other Marseille hospitals, making the comparison of HCQ vs control uncertain. The outcome of this study was day-6 test-positive viral carriage, not hospitalization or mortality, thus not relevant to hospitalization or mortality risks.

5. The Catalonia, Spain, cluster-randomized study (Mitjà et al., 2020b). Another randomized trial in predominantly low-risk patients. Mean patient age 49 years. Mortality in the control group 8/1300, 0.62%. Mortality reduced by HCQ monotherapy by 32%. This study incidentally included 293 nursing-home residents who are by definition high-risk. In them, the "primary outcome," new PCR-confirmed symptomatic COVID-19 infection within 14 days, was cut in half. This reduction was borderline statistically significant at p=.050. Aside from this result, for all of the low-risk subjects in this study, the results again do not bear upon hospitalization or mortality risks of high-risk outpatients.

6. The Health-Care Workers RCT (Abella et al., 2020). This trial randomized 132 hospital-based health-care workers to equal groups of 8 weeks of 600mg daily HCQ vs placebo. The primary outcome was nasal swab viral PCR positivity and seropositivity at 4 and 8 weeks of the study. Median age of study participants was 33 years. No hospitalizations occurred in this study and no serious adverse events were observed. The young age and obvious low risks of the study subjects makes this study uninformative about effect of HCQ on risks of hospitalization or mortality.

7. The US Multicenter PEP Study (Barnabas et al., 2020). Through advertising and social media, this study recruited households with likely COVID-19 cases. Seemingly unaffected household members were recruited to participate. Subjects were approximately equally randomized to HCQ vs vitamin C as control. I note that vitamin C has been considered as playing a role in outpatient COVID-19 treatment (Carr and Rowe, 2020). The dose of HCQ, 400 mg/d for 3 days, then 200 mg/d for an additional 11 days, takes 5 days to build up tissue levels sufficient to be preventative (Chatterjee et al., 2020; Goenka et al., 2020; Khurana et al., 2020; Yadav et al., 2020). Subjects provided daily nasal swabs for viral PCR testing for outcome determination by day-14. Subjects were considered positive for PCR positivity at cycle threshold (Ct) of 40 or less. It should be noted that positivity at Ct values of 35-40 reflects infections 3-6 weeks in the past and that half of PCR sample positivities at threshold Ct less than 40 reflect such old infections (Singanayagam et al., 2020). The median age of study subjects was 39 years. One treated and one control subject were each briefly hospitalized for COVID-19-related reasons. One person in each group was also briefly hospitalized for treatment-unrelated reasons. This is again a study of low-risk individuals and uninformative about effect of HCQ on hospitalization or mortality risks. No serious adverse events related to the HCQ treatment were observed.

B. Outpatient studies bearing upon hospitalization or mortality risks with early HCQ+ use in high-risk COVID-19 outpatients

1. São Paulo, Brazil study (Barbosa Esper et al., 2020). This study involved consecutive outpatients with two days of flu-like symptoms suspected to be COVID-19. Subjects were examined by a telemedicine team or emergency-room physicians and those without contraindications were offered treatment with HCQ+azithromycin. Of these, 224 declined treatment and served as the control group, and 412 accepted treatment. The study outcome was hospitalization, based upon worsening condition or PO_2 <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, reported P-value<.0001. The average age of the patients was 62.5 years, thus the majority were a priori classified as high-risk. 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.

2. A second study of mild-to-moderate newly symptomatic early stage COVID-19 outpatients in Brasilia, Brazil, recruited through social media referrals and various medical clinics and confirmed by rtPCR (Cadegiani et al., 2020a; Cadegiani et al., 2020b). Patients were recruited into parallel nonoverlapping treatment arms of HCQ (5 days), ivermectin (3 days) or nitazoxanide (6 days), according to clinical judgement of treating physicians. All patients received azithromycin for 5 days; roughly 80% of the patients also received vitamin D supplements, and 54% of the HCQ patients also received spironolactone. The control group comprised newly symptomatic outpatients identified in the same sources over the same time period, who declined or were not offered treatment with HCQ, ivermectin or nitazoxanide, but were provided standard medical care for COVID-19. In total, 159 patients were treated with HCQ and 137 controls participated. There were no hospitalizations or deaths among the HCQ patients, whereas 27 control patients were hospitalized and 2 died.

3. The Marseille screening and treatment study (Million et al., 2021). The Marseille investigators report on their cohort of 10,429 COVID-19 patients treated with HCQ, azithromycin and other medications. In the pertinent analysis, patients age 60 and older, 1,495 patients treated with HCQ+azithromycin for 3+ days were compared to 520 patients given the medications for less than 3 days, or given only the individual medications, or not given either one. An appreciable fraction of patients had comorbidities, thus at a priori high-risk. The age, sex and time-period adjusted-regression analysis showed a mortality odds ratio of 0.17 (95% CI 0.06-0.48), p=.0007, for this comparison. It should be noted that the "unexposed" group included an appreciable number of patients that had used HCQ+azithromycin but for shorter duration, or had used HCQ alone, thus likely biasing the

observed hazard ratio nullward.

4. The Hapvida Brazil outpatient treatment study (Szente Fonseca et al., 2020). This study involved 717 consecutively numbered tested-positive symptomatic patients over age 40 presenting at the 42 outpatient clinics and emergency rooms of the 6-million-member Hapvida HMO in Brazil between May 11 and June 3, 2020. The mean age of included patients was 51 years. Hapvida services a number of Brazil states with large indigenous populations and higher frequencies of diabetes, heart disease and other chronic conditions, thus the HMO defines age 40 to be the threshold of high-risk at which to consider actively treating COVID-19 outpatients. In the new protocol initiated by the HMO, treatment specifics were chosen ad lib from 7 medications by the attending physician and monitored for quality assurance. The COVID-19 protocol included (all as oral medications): HCQ as first-line treatment, if used (400 mg bid day 1, 400 mg qd days 2-5), prednisone (1 mg/kg qd x 5 days, started on symptom day-6, no taper), azithromycin (500 mg qd x 5 days), ivermectin (12 mg qd x 2 days), plus symptom relievers. Zinc sulfate, oseltamivir and nitazoxanide were also available to be prescribed but were used infrequently. Doctors quickly found that most of the prescribed HCQ was not available at common drugstores, thus if prescribed it was offered free of charge to all patients who only had to sign informed consent to receive it. The study showed, adjusted for age, gender, dyspnea at presentation, obesity, diabetes, and heart disease, that use of both HCQ and prednisone together was associated with an odds ratio for hospitalization of 0.40 (95% CI 0.21-0.75), p=.0042; use of HCQ only, odds ratio=0.45 (95% CI 0.25-0.80), p=.0065; and use of prednisone only, odds ratio=0.51 (95% CI 0.26-0.99), p=.049. In this model, use of azithromycin conveyed a small additional though not significant benefit, odds ratio=0.85 (95% CI 0.54-1.34), p=.48, and ivermectin offered no additional benefit. Similar magnitudes of association as these were seen for the medications among the 717 subjects with death as the outcome, but the small numbers of deaths (n=11) precluded statistical significance of these associations. No cardiac arrhythmia events requiring medication termination for any of the medications used in the 717 patients were observed, and thus there were no deaths attributable to such arrhythmias.

5. A matched retrospective cohort study was carried out among outpatients within the Hackensack Meridian Health Network, New Jersey (Ip et al., 2021). Between March 1 and April 22, 2020, 1,274 patients with non-admission ER visits were identified and confirmed infected with SARS-CoV-2 by PCR testing. Of these, 97 received prescriptions for or had started taking HCQ, and from the remaining 1,177, 970 were propensity-score matched by age, demographic variables and a host of comorbidity factors, presenting symptoms, indicators of disease severity, baseline laboratory tests, and ER-visit and follow-up times. After the matching, HCQ-treated subjects were slightly older and had more frequent cancer histories than untreated subjects. More than three-quarters of the subjects had comorbidities or were over age 60, making them high-risk. In the matched multivariate analysis, treatment with HCQ significantly cut the risk of hospitalization by 46% (p=.038).

6. A study was conducted in 23 nursing homes in Marseille (Ly et al., 2020), in which of 226 infected residents, 37 were detected because of COVID-19 symptoms and 189 through mass screening. In multivariate analysis adjusted for sex, age, use of oxygen therapy and detection modality (symptoms vs screening), receipt of HCQ+azithromycin for at least three days was associated with 63% reduced mortality risk (p=.02).

7. A study in Andorra was carried out at a public nursing home from March 15 to June 5, 2020 (Heras et al., 2020). This study identified 100 PCR-confirmed COVID-19 patients during this interval. Patients received HCQ+azithromycin, HCQ with other antibiotics such as beta-lactam or quinolone types, or other antibiotics alone. Median age was 85 years. In multivariate analysis of mortality risk adjusted for sex, Barthel's index of activities of daily living, and fact of lymphocytopenia, treatment with HCQ+azithromycin vs only other antibiotics had OR=0.044 (95%CI 0.006-0.35), p=.004. Treatment with HCQ+other antibiotics vs other antibiotics alone had OR=0.32, p=.37.

8. A study of COVID-19 mortality was performed in a nursing home in Milan, Italy (Cangiano et al., 2020). Ninety-eight of the 157 residents tested positive for SARS-CoV-2 by nasal swab PCR or serology and were followed over time. The average age of study patients was 90 years. Subjects who have been receiving vitamin D in their usual health care had reduced mortality. In logistic regression models adjusted for age, sex, Barthel's index and BMI, regular vitamin D supplementation was associated with 5-fold reduced mortality risk, p=0.04. In addition, in the adjusted model, receipt of HCQ was associated with 7-fold reduced mortality, p=.03. These authors noted that "Hydroxychloroquine was prescribed only in patients with better ECG tracings and those receiving less drugs that might induce QT interval prolongation, such as antipsychotic and antidepressant agents, thus being probably fitter than those who did not receive this therapy." However, antipsychotic and antidepressant medications have not been shown to provide 7-fold mortality reduction in treatment of COVID-19 outpatients, thus these medications cannot fully explain the large reduction in mortality risk seen with HCQ use. It is also unclear whether patients receiving such medications would be likely to have physiologically higher risks of mortality.

9. The national Saudi Arabia Study (Sulaiman et al., 2020). In this study, all mild-moderate cases of PCR-positive COVID-19 presenting at national outpatient treatment clinics between 5-26 June were recruited for enrollment. Treated patients received 400 mg HCQ bid on day-1 and 200 mg bid for an additional four days. Both treated (n=3,320) and control (n=4,572) patients received zinc sulfate 60 mg qd for five days, cetirizine 10 mg qd for 10 days, and paracetamol as-needed. Treated and control patients were comparable in distributions of age, sex and nine comorbidities reported. In multivariate modeling adjusted for age, gender and comorbidities, HCQ receipt cut mortality some 3-fold, OR= 0.36 (95%CI 0.16-0.80). However, the Saudi health-care system involves unique national personal identifiers and all of the almost 8,000 study subjects were followed for occurrence of hospitalization and mortality. Thus, the 7

deaths of patients in the HCQ group and 54 in the standard-of-care control group represent a more than 5-fold reduction in mortality with HCQ+zinc treatment vs zinc only. It should be noted that a major fraction of the patients in the Saudi study were of low-risk, however the 61 deaths and 788 hospital admissions make the study informative for those risks.

10. The national Iran study (Mokhtari et al., 2021). This study comprised a multicenter, population-based national retrospective-cohort investigation of 28,759 adults with mild COVID-19 seen within 7 days of symptom onset at a network of Comprehensive Healthcare Centers throughout the country between March and September 2020. Patients were diagnosed by nasal swab RT-PCR (79%) or by clinical parameters and chest imaging (21%). Treated patients (n=7,295) received free of charge HCQ 400mg bid on day 1 and 200mg bid over days 2-5. Control subjects were treated with supportive care only. Treated and control patients were comparable in distributions of age and sex, but treated subjects had slightly higher frequencies of comorbidities. Adjusted for age, sex, BMI, hypertension, respiratory diseases, diabetes mellitus and cardiovascular diseases other than hypertension, treatment with HCQ was associated with a 38% reduction in risk of hospitalization (95%CI 31-44%) and a 70% reduction in mortality risk (95%CI 55-80%). Both of these risk reductions were highly statistically significant, and were equally so in patients diagnosed by PCR vs by clinical factors and chest imaging.

11. Case-series studies of high-risk outpatients. Case reports comprise truly anecdotal information because of lack of information about the representativeness of the subject for a particular disease or exposure group. On the other hand, organized systematic collections of sequentially eligible patients can be representative of their disease status, just as well-collected case subjects are in a case-control study. Thus, a common characteristic of a representative case series, such as hospitalization or mortality proportion, is a valid estimate of that characteristic for the disease as represented by the particular cases. In a case-control study, such an estimate would be compared to a parallel estimate in its control sample of individuals chosen to be representative of both a relevant underlying population and of the other characteristics of the cases, such as age, gender, race, etc. However, a case series by definition has no control sample, thus does not seemingly allow for estimation of a quantitative relative measure of the case characteristic to the control or population characteristic. This is the situation in general, when a numerical relative measure is needed. It is a different question however when a large discrepancy exists between the frequency of the case characteristic and the known population characteristic, and the goal is to determine evidence for the fact of the discrepancy rather than to estimate the numerical amount or ratio of the discrepancy. In this instance, systematic case-series data can indeed provide evidence.

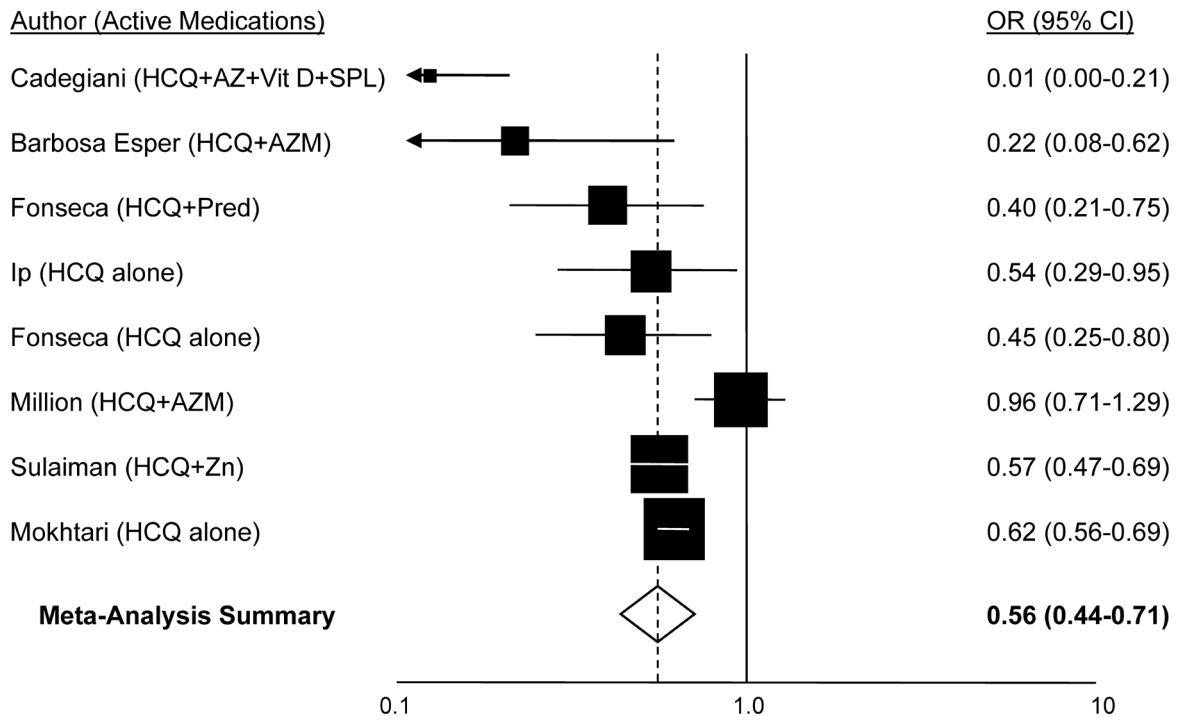
As a point of reference, mortality risk in Connecticut residents age 60 and older who have tested positive for carriage of SARS-CoV-2, through December 30, 2020, is 12.8% (5,577 deaths out of 43,506 patients) (Connecticut Department of Public Health). Other states may have

risks higher or lower than this, but this risk is still substantial. In comparison: the initial cohort of 405 high-risk outpatients treated with HCQ+azithromycin+zinc sulfate by Dr. Vladimir Zelenko, patients resident in the Village of Kiryas Joel, NY, had 2 deaths (Zelenko, 2020). Dr. Zelenko's second series of 400 high-risk outpatients from the same village and treated with the same regimen had zero deaths (Risch, 2020a). Dr. Lawrence Kacmar, in Aurora IL, has treated 68 high-risk outpatients with HCQ+azithromycin and observed zero deaths (Risch, 2020a). Dr. Brian Procter, in McKinney, TX, has treated 50 high-risk outpatients with HCQ+ azithromycin+ zinc sulfate+losartan+aspirin and observed zero deaths in his first series, and another 320 with one death in his second series (Procter et al., 2020). Dr. Steven Crawford, in a Festus, MO nursing home, has treated 52 high-risk outpatients with HCQ+rehydration and observed zero deaths (Risch, 2020a). Dr. Brian Tyson, in El Centro CA, has treated approximately 2,000 high-risk outpatients with HCQ+azithromycin and observed zero deaths (Risch, 2020a; Tyson B, personal communication, 2020). In total, these physicians have reported in the literature or to me, treatment of 3,300 high-risk outpatients with HCQ+azithromycin etc. and observed among them 3 COVID-19-related deaths, for mortality of 0.09%. This low mortality can only be described as stupendous and a tribute to the clinical engagement of these physicians, and completely distinguishable from the CT 12.8% mortality or similar risks of untreated high-risk outpatients in other US states. None of the physicians reported any cardiac arrhythmias either necessitating stopping the medications or fatal.

A theoretical counterargument to these substantial series of successfully treated outpatients is that they were self-selected and came to my attention because of their outstanding results and not because they were typical or representative of doctors treating COVID-19 patients across the US. However, two of these doctors were specifically asked to provide updates of their clinical experiences, Drs. Zelenko and Procter. Statistical evidence for benefit is in these replications. Even if the untreated mortality risk in high-risk tested-positive patients were as low as 1% (it is probably at least 10%), the likelihood that only one or fewer of these 400+320 patients would have died if left untreated is p=.0052. That is the p-value for the hypothesis that these two series had at most one death by chance with an unrealistically low 1% mortality risk untreated.

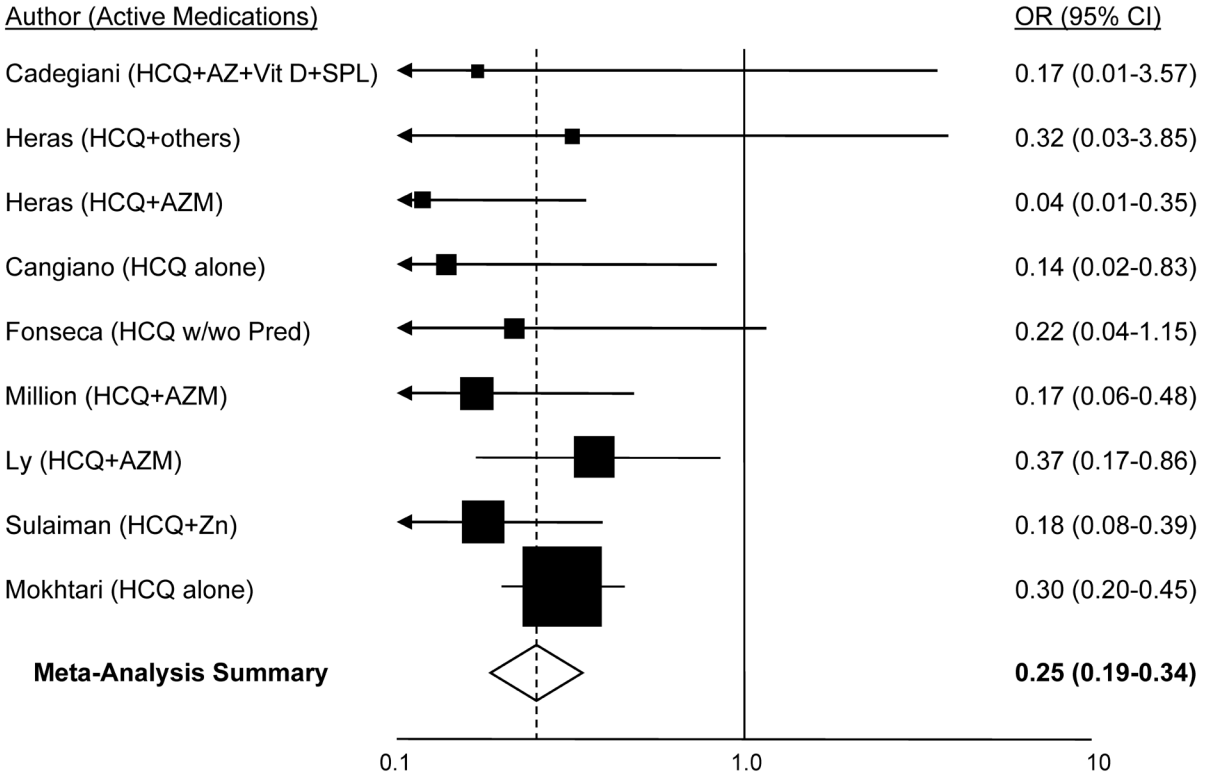
In total, these numerous case series reports provide overwhelming evidence of the efficacy of HCQ in early outpatient treatment of high-risk COVID-19 disease. These are not anecdotal numbers but multiple systematic samples of real-world effective usage of these medications.

Random-effects meta-analysis of the ten studies' results for HCQ use and risks of hospitalization (Figure 1) and mortality (Figure 2) are shown on the next page. The heterogeneity I^2=71% (p=.0011) for hospitalization, mostly due to the Million et al. study which was carried out in a day-hospital that may have had lower standards for short-term admissions than the other studies. The heterogeneity I^2=0% (p=.52) for mortality.



Outpatient hydroxychloroquine-based treatments and risk of Covid-19 hospitalization

Figure 1



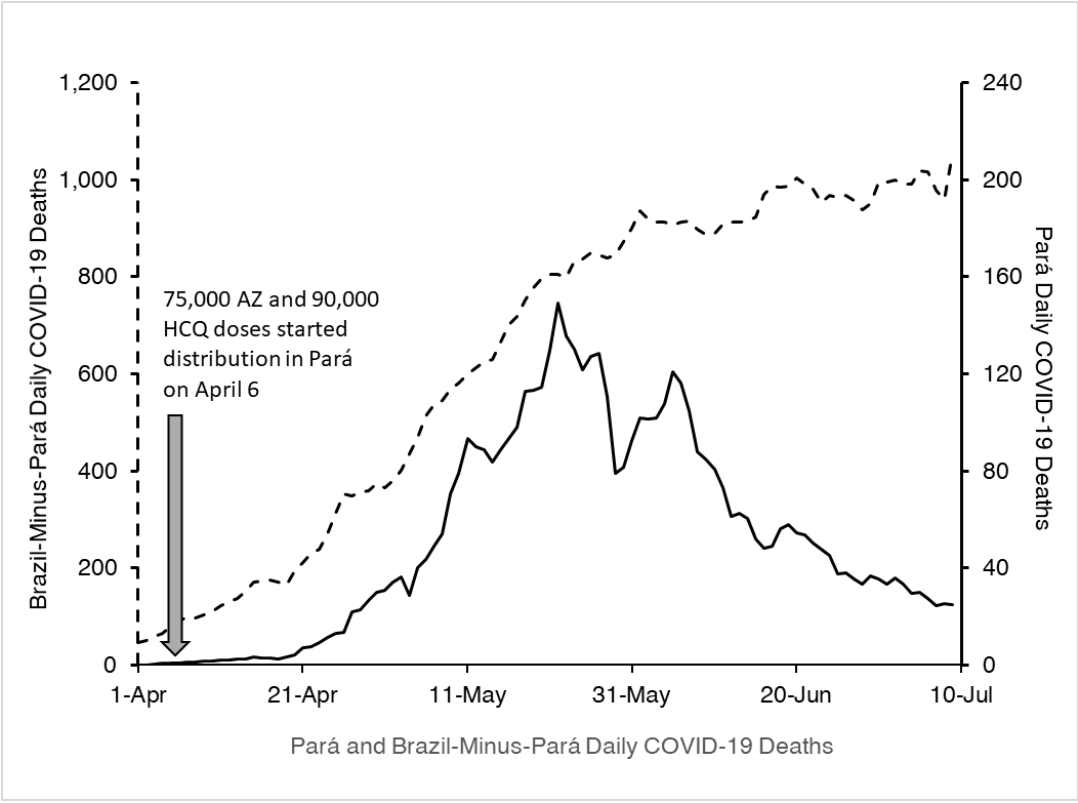
Outpatient hydroxychloroquine-based treatments and risk of Covid-19 mortality

Figure 2

C. Population "natural experiments" bearing upon efficacy of population use of HCQ in mortality reduction

1. The Vadodara, India study (Raja, 2020). In this study, public health authorities administered HCQ to 342,000 residents of the western India city of Vadodara, including health workers and other frontline personnel. Each person completed a full course of HCQ, 400mg bid for the first dose and 400 mg per week for at least three weeks. The investigators sampled 100,000 persons in the city, including 48,873 close contacts of positive patients, contacts who had taken one dose of HCQ, among whom 102 afterward became COVID-19 positive and 12 died from the infection; 17,776 close contacts of positive patients among which contacts 48 took two doses of HCQ, turned positive and one died; and 33,563 close contacts of patients among which contacts took three HCQ doses, 43 tested positive and one died. Aside from the 39% reduction in case occurrence with three doses, among these tested-positive individuals, there is an inverse trend in mortality risk with number of doses of HCQ taken, odds ratio = 0.32 (95% CI 0.11-0.94), p=.011, for each successive dose after the first, i.e., odds ratio = 0.32^2 = 0.10 for two doses after the first. This study is not yet fully described, so details about its methods are not available, and is small (but statistically significant), limiting its evidential weight, though dose-response trends in risk can be particularly informative.

2. In the northern Brazil state of Pará, COVID-19 deaths were increasing exponentially (Ministério da Saúde Brasil). On April 6, 2020, the public-hospital network purchased 75,000 doses of azithromycin and 90,000 doses of hydroxychloroquine (Alexandre Wolkoff, Hapvida Saúde HMO, Fortaleza, Brazil, personal communication, 2020). Over the next few weeks,



authorities began distributing these medications to infected individuals. Even though new cases continued to occur, on May 22 the death rate started to plummet and dropped to about one-eighth what it was at the peak. This is shown in the figure on the previous page. Pará daily mortality is the solid line, Brazil-minus-Pará daily mortality is the dashed line.

D. Studies of safety and adverse endpoints with outpatient HCQ+ use.

There is ample evidence that HCQ, especially in high doses over the short term, can cause nausea, vomiting, abdominal discomfort and diarrhea. While unpleasant, these complaints are not life-threatening and can generally be managed medically or with dose reduction. HCQ also has a spectrum of very rare adverse events that have little practical ramification except as suggested in cases such as G6PD deficiency, though a study of chronic HCQ use in such individuals shows no reported episodes of hemolysis during more than 700 months of HCQ usage among G6PD-deficient patients (Mohammad et al., 2018).

The major issue raised by the FDA and others concerns risks of cardiac arrhythmia, especially when HCQ is given in combination with azithromycin. Both HCQ and AZ can produce QTc prolongation, rare instances of fatal Torsades de Pointes and long QT-interval syndrome. Numerous studies have demonstrated QTc prolongation in hospitalized COVID-19 patients treated with HCQ and azithromycin (Bessière et al., 2020; Chorin et al., 2020; Mercuro et al., 2020; Ramireddy et al., 2020; Sridhar et al., 2020). Such physiologic QTc prolongation is typically 18-55ms and QTc can exceed 500ms in some individuals. Based on a large elevated *relative* risk of Torsades de Pointes for QTc>500ms, cardiologists generally regard exceeding this threshold as a contraindication for using HCQ or HCQ+azithromycin. However, large relative risks in the context of rare baseline *absolute* risks are not necessarily actionable, depending upon the absolute risk among the exposed, which can be estimated by multiplying the exposure relative risk times the baseline absolute risk. If the baseline absolute risk is many orders of magnitude smaller than the exposure relative risk is large, the absolute risk among the exposed will still be small. This is the reason why 10-fold or 20-fold relative risks of Torsades de Pointes for QTc>500ms, that seem very large as associations in observational studies, are still essentially unimportant for HCQ and HCQ+azithromycin treatment in general, except in patients who have additional comorbidity, medicine interaction or rare genetic contraindications. These contraindications, for example personal or family history of cardiac arrhythmia, are well documented and part of the standard workup physicians routinely perform when considering use of these medications.

Thus, the question of the frequency of occurrence of fatal Torsades de Pointes and long QT-interval syndrome must be evaluated by empirical data rather than by theoretical reasoning from physiologic observations. Even if these events were to occur with large-scale HCQ

monotherapy or HCQ+ treatment of high-risk COVID-19 outpatients, the sole issue concerning the application proposed herein is whether they would occur in frequency as great as or greater than mortality in such patients not treated. It is in fact obvious that such would not be the case: there is no epidemic of fatal arrhythmias occurring among the millions of older, multicomorbid individuals chronically treated with HCQ for lupus erythematosus, rheumatoid arthritis and other autoimmune diseases. The FDA long ago approved HCQ on-label as indicated for these diseases and that approval has been borne out in the long safety record of this drug. While it has been observed that sporadic individual cases of COVID-19-associated myocarditis have occurred, these have been in hospitalized patients and thus does not provide a rationale for an increased arrhythmia risk in early outpatient medication use.

There are three useful ways to evaluate arrhythmia occurrence and mortality in COVID-19 patients treated with HCQ or HCQ+: treated case-series reports, adverse events database analyses, and observational studies of these outcomes.

1. Treated case-series reports. As described earlier, in the totality of 3,300 high-risk outpatients treated early with HCQ, most with azithromycin as well, no cardiac arrhythmias were reported. In 202 high-risk outpatients treated early with HCQ+doxycycline, no cardiac arrhythmias were reported. In the Marseille cohort study (Lagier et al., 2020), among 3,737 treated outpatients, QTc prolongation (>60 ms) was observed in 25 (0.67%), including 2 treated with HCQ, 3 with azithromycin and 20 with HCQ+azithromycin (0.54%). Those investigators chose to terminate treatment for 3 cases with QTc of 500ms or longer (2 treated with azithromycin and 1 with HCQ+azithromycin). No cases of sudden death or Torsades de Pointes were observed in the 3,737. In the first Brazil study (Barbosa Esper et al., 2020), among 412 patients treated with HCQ+azithromycin, no arrhythmias were reported; two treated patients subsequently died, one from “acute coronary syndrome” and another from metastatic cancer. In the new Brazil study (Szente Fonseca et al., 2020), 521 high-risk outpatients were treated early with HCQ, azithromycin or both and no arrhythmias were reported among them. In the Hackensack Meridian Health Network study, 2 of the 97 treated subjects showed prolonged QTc intervals; neither had their medications stopped; and there were no arrhythmias. In total, these 3,300+202+3,737+412+521+97 = 8,269 early treated outpatients had no occurring or fatal arrhythmia events.

2. Adverse events database analyses. A search of the FDA Adverse Event Reporting System (FAERS) public dashboard for cardiac rhythm or cardiac sudden-death adverse events related to hydroxychloroquine (all forms named) and Plaquenil from 1968 through January 31, 2021 demonstrates 1,064 serious events including 200 deaths attributed to the hydroxychloroquine use. Of these, 57 events including 10 deaths were attributed to Torsades de Pointes and long QT-interval syndrome combined. This concerns the entirety of HCQ use over more than 50 years of data, over 1 billion uses and of longer-term use than the 5 days recommended for COVID-19 high-risk outpatient treatment. Since the MedWatch reporting system requires

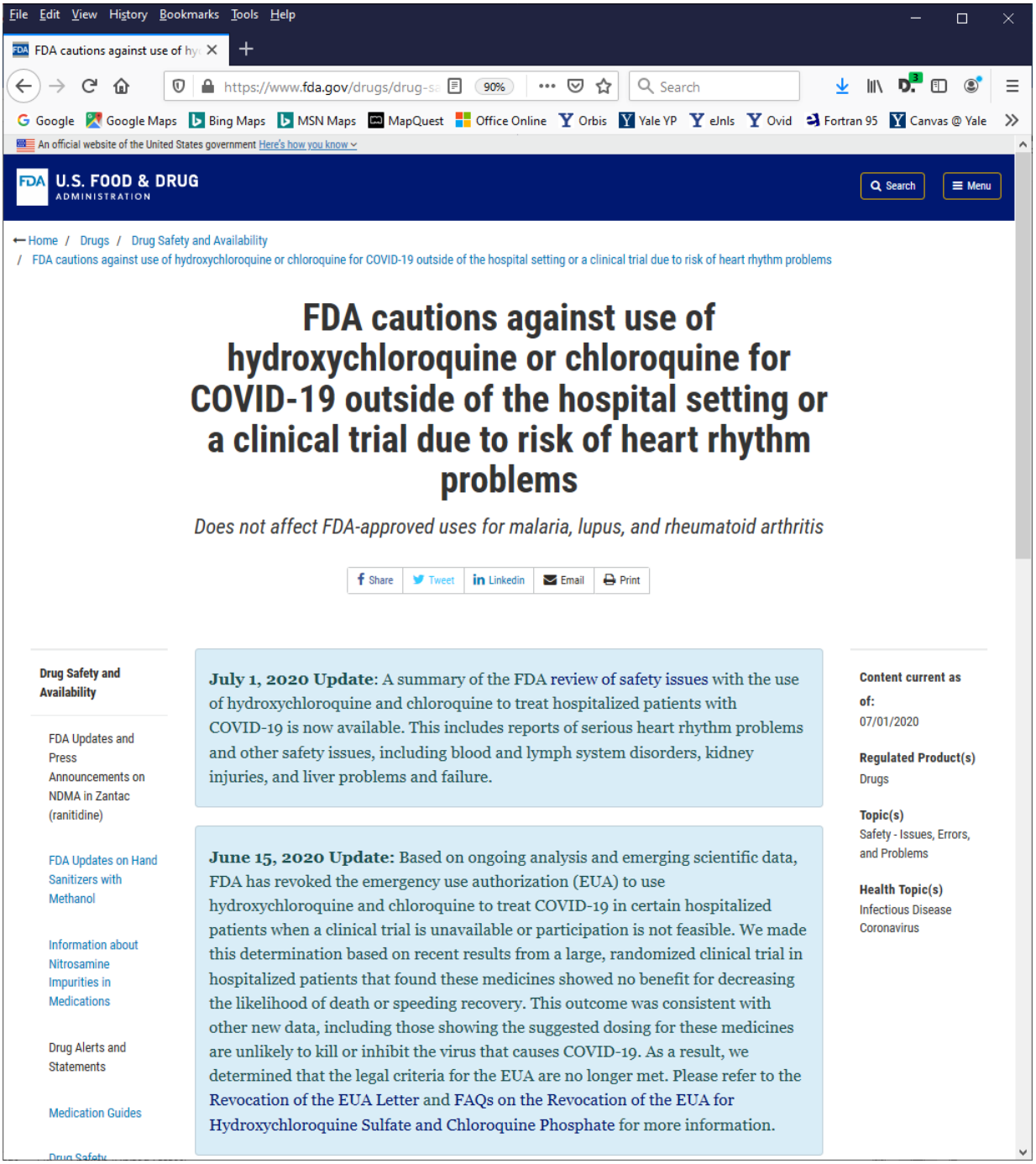
physicians, pharmacists or patients to initiate contact with the FDA, it appreciably undercounts drug side-effects. This undercounting may be 10- or 20-fold, and the FDA has stated that FAERS data cannot be used to calculate the incidence of adverse events in the US population, nor are internal odds-ratio calculation studies in the database meaningful (Swank et al., 2020). Nevertheless, even if the true numbers were 20-fold larger, they would still be minuscule compared to the amounts of medication usage, and minuscule compared to the numbers of deaths that have been and are continuing to occur among untreated high-risk outpatients.

The FDA has presented information on serious adverse events in the FAERS data combined with other sources in the FDA Pre-decisional, Deliberative, Internal Draft 16 July 2020 (FDA). The numbers given in the Draft do not give the dates over which they apply, nor whether the patients were inpatients or outpatients, nor whether the patients were in the US or other countries, nor whether they pertained to HCQ or chloroquine use, nor whether azithromycin was also used. However, the Draft states, "On July 1st, 2020, FDA posted a summary of the agency's review review [duplication in the original] of safety issues with the use of hydroxychloroquine and chloroquine to treat *hospitalized patients* [my italics] with COVID-19."

The fda.gov website (https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or) (see image next page) is titled "FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 *outside of the hospital setting* [my italics] or a clinical trial due to risk of heart rhythm problems" and includes directly underneath the title a text box saying, "July 1, 2020 Update: A summary of the FDA review of safety issues with the use of hydroxychloroquine and chloroquine to treat *hospitalized patients* [my italics] with COVID-19 is now available. This includes reports of serious heart rhythm problems and other safety issues, including blood and lymph system disorders, kidney injuries, and liver problems and failure." The text box on the FDA website plainly says that the FDA review concerned medication usage in *hospitalized* patients. This Brief concerns application of medication use in high-risk *outpatients*, therefore as I have discussed in depth, efficacy and adverse events in *hospitalized* patients do not apply to and cannot be extrapolated to outpatient use (Risch, 2020b). It is patently obvious that had the FDA had systematic adverse events data for outpatients, the subject of the warning, it would have said so as the justification of the warning. This alone is proof that FDA has no systematic adverse events data in outpatients treated with HCQ.

I now turn to the FDA Pharmacovigilance Memorandum May 19, 2020 (Swank et al., 2020) that appears to comprise the principal information upon which FDA relied for its HCQ EUA decisions prior to July 1. On the bottom of page 5, it says that in total 97 adverse events were identified between December 2019 and May 6, 2020 in the US as pertaining to COVID-19 disease. There is no description as to the severity of these events. The EUA restricting HCQ use was instituted on March 28, at which point the FDA's position was that all HCQ use was to be for severely sick hospitalized patients, or RCTs (which at the time were largely hospital-based). Between

December 1, 2019 and May 6, 2020, 1,268,819 COVID-19 cases were registered in the US (https://www.worldometers.info/coronavirus/country/us/). However, between December 1, 2019 and March 28, 2020, the date of the EUA, 125,250 cases had been registered. This means that of the COVID-19 cases that the FDA examined for adverse events through May 6, 1,143,569/1,268,819=90.1% occurred during the time of the EUA, i.e., at a time when HCQ would have only been officially available in hospital inpatient settings. This leaves 9.9% of the described 97 US adverse events, 10 events, as possibly pertaining to outpatient HCQ use. The FDA memo states that 5 of the 97 US events were reported through the EUA. However, this



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July 1, 2020 Update: A summary of the FDA review of safety issues with the use of hydroxychloroquine and chloroquine to treat hospitalized patients with COVID-19 is now available. This includes reports of serious heart rhythm problems and other safety issues, including blood and lymph system disorders, kidney injuries, and liver problems and failure.

June 15, 2020 Update: Based on ongoing analysis and emerging scientific data, FDA has revoked the emergency use authorization (EUA) to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients when a clinical trial is unavailable or participation is not feasible. We made this determination based on recent results from a large, randomized clinical trial in hospitalized patients that found these medicines showed no benefit for decreasing the likelihood of death or speeding recovery. This outcome was consistent with other new data, including those showing the suggested dosing for these medicines are unlikely to kill or inhibit the virus that causes COVID-19. As a result, we determined that the legal criteria for the EUA are no longer met. Please refer to the Revocation of the EUA Letter and FAQs on the Revocation of the EUA for Hydroxychloroquine Sulfate and Chloroquine Phosphate for more information.

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number cannot be taken as indicative of patient hospitalization status, because the MedWatch consumer form has no questions related to application of the EUA, and data provided by physicians on MedWatch health professionals forms are frequently incomplete. It seems highly unlikely that at a time when the FDA EUA restriction of HCQ use to hospitalized patients was in force, that physicians would have prescribed 92/97 = 95% of HCQ use to outpatients. Thus, the 97 US adverse events described in the FDA memo can be reasonably assumed to apply largely to hospitalized patients. How many of these adverse events were fatalities is unstated, but likely around 20%. Regardless, the fact that the FDA repeatedly described its adverse events data as pertaining to hospitalized inpatients, first in its internal memo, FDA Pre-decisional, Deliberative, Internal Draft 16 July 2020, and second on the official FDA website of July 1, confirms that all or essentially all of US adverse events data used by the FDA to declare HCQ unsafe for outpatient use (including the 97 US events in the May 19 Memo) were inappropriate as based on hospital inpatient data. This invalid and outrageous conclusion has been the publicly stated position by the FDA since at least July 1 of 2020.

As well, the FDA states in its June 15, 2020 EUA revocation letter to Dr. Gary L. Disbrow PhD, Deputy Assistant Secretary, BARDA (Hinton, 2020), that it reviewed outcome data reported to BARDA for 1,762 patients as of May 26, 2020. In the description of clinical characteristics of these patients, "68.3% of patients were discharged," implying that the data concerned hospitalized inpatients only. The revocation letter also says that the FDA conducted a literature search and review at the CDC Stephen B. Thacker Library of COVID-19 research articles. The search identified 11 studies. The report of the search says, "All 11 studies were cohort studies conducted in hospitalized COVID-19 populations."

3. Observational studies of adverse outcomes. Three studies have examined adverse event outcomes associated with use of HCQ and HCQ+azithromycin. I have discussed the Oxford University study of 14 large medical records databases (Lane et al., 2020) in depth elsewhere (Risch, 2020b). That analysis shows that in more than 320,000 older rheumatoid arthritis patients with various comorbidities and who took HCQ+azithromycin, cardiac arrhythmia events were at no significant increase (relative risk 1.08, p=.36) vs similar numbers of patients who took HCQ+amoxicillin, demonstrating that the addition of azithromycin to HCQ does not enhance arrhythmia risk. The same study compared HCQ monotherapy to sulfasalazine use and again found no difference in cardiac arrhythmia risk: for HCQ, a slightly lower RR=0.89, P-value=.13. Further, among 306,106 people taking sulfasalazine (which is known not to produce QT prolongation), 877 with cardiac arrhythmias were identified, 0.287%. In 320,589 people taking HCQ+AZ, 1,068 had arrhythmias, 0.333%. The difference, 0.047% (95%CI 0.019%-0.074%) or 47/100,000 older multicomorbidity patients taking HCQ+AZ, is attributable to the HCQ+AZ use. These are events, not fatalities. As I have shown above (200/1,064), fatalities according to the FAERS comprise <20% of HCQ-related arrhythmia events, 9/100,000 (95%CI 4-15)/100,000. The maintenance HCQ dose in the Oxford study patients, 200 mg/day, gives as large or larger average circulating drug levels as five days of HCQ at 400 mg/day, the

recommended dose for outpatient COVID-19. These very small numbers of arrhythmias, as well as the null relative-risk results in this very large empirical study, should therefore put to rest the anxieties about population excess mortality of HCQ+AZ outpatient use.

The second study of HCQ adverse events, in outpatients, comprises the Boulware studies (Lofgren et al., 2020). This analysis included data from 2,795 outpatient participants, of whom 2,324 reported data on medication side-effects. The most common side effects were gastrointestinal disturbances. Two individuals were hospitalized for atrial arrhythmias, one on placebo and one on twice weekly HCQ. The patient taking HCQ recovered. No sudden deaths occurred. The medication use in this study caused no arrhythmia-related deaths.

The third study describes clinical characteristics of almost 8,000 COVID-19 patients treated in the Yale-New Haven Health System between March 1 and April 30, 2020 (McPadden et al., 2020). Median age of these patients was 52 years. Of these patients, 1,633 were hospitalized and of those, 227 (13.9%) died. 95.8% of hospitalized patients received HCQ and 32.7% azithromycin. There was no association between cardiac arrhythmia and mortality: odds ratio = 0.86 (95% CI 0.58-1.28), p=.46.

Conclusions

It is readily apparent that every one of the studies of high-risk outpatient HCQ use has shown risk reduction for hospitalization or mortality, averaging 44% for the former and 75% for the latter, and that the numerous systematic case-series studies have shown exceedingly good treatment benefit vs mortality. The "natural experiment" studies of population responses provide compelling evidence of temporal relations between medication use and mortality. The RCT studies proclaimed as definitively showing no benefit of HCQ use in outpatients have all involved almost entirely low-risk subjects with virtually no information about risks of hospitalization and mortality and are irrelevant for bearing upon HCQ use in high-risk outpatients. The totality of fatal cardiac arrhythmia events among more than 8,000 patients treated with HCQ and HCQ+azithromycin is zero. The large database study of more than 320,000 older patients taking HCQ+azithromycin shows no excess all-cause mortality (Risch 2020b) and minuscule excess fatal arrhythmia frequency, 9/100,000 patients, compared to the large number of patients whose lives will be saved by outpatient use of these medications. I have not discussed all of the other even lesser-frequent adverse events than the arrhythmias, but these are equally minuscule, and the FDA did not invoke them for its warning about outpatient use in the title statement of the warning. The FDA has stated publicly that it relied upon adverse event data from hospital inpatients to make policy applying to outpatient use. There are no systematic adverse event arrhythmia data of US outpatients from the beginning of 2020 through the present. The FDA website also publicly cautions that only (i.e., "due to")

arrhythmia data are relevant to its warning, by omitting from the title any assertions that other potential adverse events were important or frequent enough to be determinative. The FDA's extrapolation from adverse events in hospitalized patients to supposed risks in outpatients is flagrantly unwarranted. Outpatient viral replication is an entirely different disease than inpatient florid cytokine-driven pneumonia (Park et al., 2020) and the treatments are different. The need for outpatient use of HCQ is crucial for saving the lives of high-risk COVID-19 patients. The most recent published recommendations for early treatment of COVID-19 outpatients (McCullough et al., 2020) consider HCQ use and related medications of critical importance and is authored by some 50 clinicians providing this treatment. There is no comparison between the number of lives to be saved with early outpatient treatment and the minuscule numbers addressed in the analyses of adverse events, even what would be postulated to occur with widespread outpatient use. All of these data have been available to the FDA for some time. The improper warning on the FDA website must be removed immediately, and widespread early outpatient treatment must start immediately.

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