

# White Paper References

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<https://www.rheumatology.org/Portals/0/Files/Hydroxychloroquine-Plaquenil-Fact-Sheet.pdf?ver=2020-04-30-154904-073>



## PATIENT FACT SHEET

## Hydroxychloroquine (Plaquenil)



### WHAT IS IT?

Hydroxychloroquine (Plaquenil) is considered a **disease-modifying anti-rheumatic drug (DMARD)**. It can decrease the pain and swelling of arthritis. It may prevent joint damage and reduce the risk of long-term disability. Hydroxychloroquine is in a class of medications that was first used to prevent and treat malaria. Today, it

is used to treat [rheumatoid arthritis](#), some symptoms of [lupus](#), childhood arthritis (or [juvenile idiopathic arthritis](#)) and other autoimmune diseases. It is not clear why hydroxychloroquine is effective at treating autoimmune diseases. It is believed that hydroxychloroquine interferes with the communication of cells in the immune system.



### HOW TO TAKE IT

Hydroxychloroquine comes in an **oral tablet**. Adult dosing for rheumatic diseases ranges from 200 mg to 400 mg per day (typically 5 mg/kg, maximum 400mg daily). In some cases, higher doses are used. It can be taken as a single daily dose or in 2

divided doses if taking more than one tablet. It is recommended to be taken with food. Symptoms can start to improve in one to two months, but it may take up to six months before the full benefits of this medication are experienced.



### SIDE EFFECTS

Hydroxychloroquine typically is very well tolerated. Serious side effects are rare. The most common side effects are nausea and diarrhea, which often improve with time. Less common side effects include rash, changes in skin pigment (such as darkening or dark spots), hair changes, and muscle weakness. Rarely, hydroxychloroquine can lead to anemia in some individuals. This can happen in individuals with a condition known as G6PD deficiency or porphyria. In rare cases, hydroxychloroquine can cause visual changes or loss of vision. Such vision problems are more likely to occur in individuals taking high doses for many years, in individuals 60 years or older, those

with significant kidney or liver disease, and those with underlying retinal disease. At the recommended dose, development of visual problems due to the medication is rare. It is recommended that you have an eye exam within the first year of use, then repeat every 1 to 5 years based on current guidelines.

Additional rare reports of changes in the heart rhythm have been reported with the use of hydroxychloroquine, particularly in combination with other medications. While monitoring for this risk is not typical in the office setting, it has been indicated in hospitalized and critically ill patients to evaluate for interactions with other medications.



### TELL YOUR DOCTOR

Although there are few drug interactions with hydroxychloroquine, to be safe, be sure to tell your doctor about all of the medications you are taking, including over-the-counter drugs and natural remedies. Be sure to notify your other physicians when taking this drug. This drug does not have a strong effect on the immune system, so vaccines recommended by other

physicians are generally acceptable. Notify your eye doctor when you are on this medication so regular visual screening tests can be performed. If you are pregnant, considering becoming pregnant, or lactating, please discuss this with your doctor before taking this medication. However, hydroxychloroquine has been shown to be safe during pregnancy and breast feeding.

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Why Lupus Patients May Hold The Key To Whether Hydroxychloroquine Could Work - Part 2

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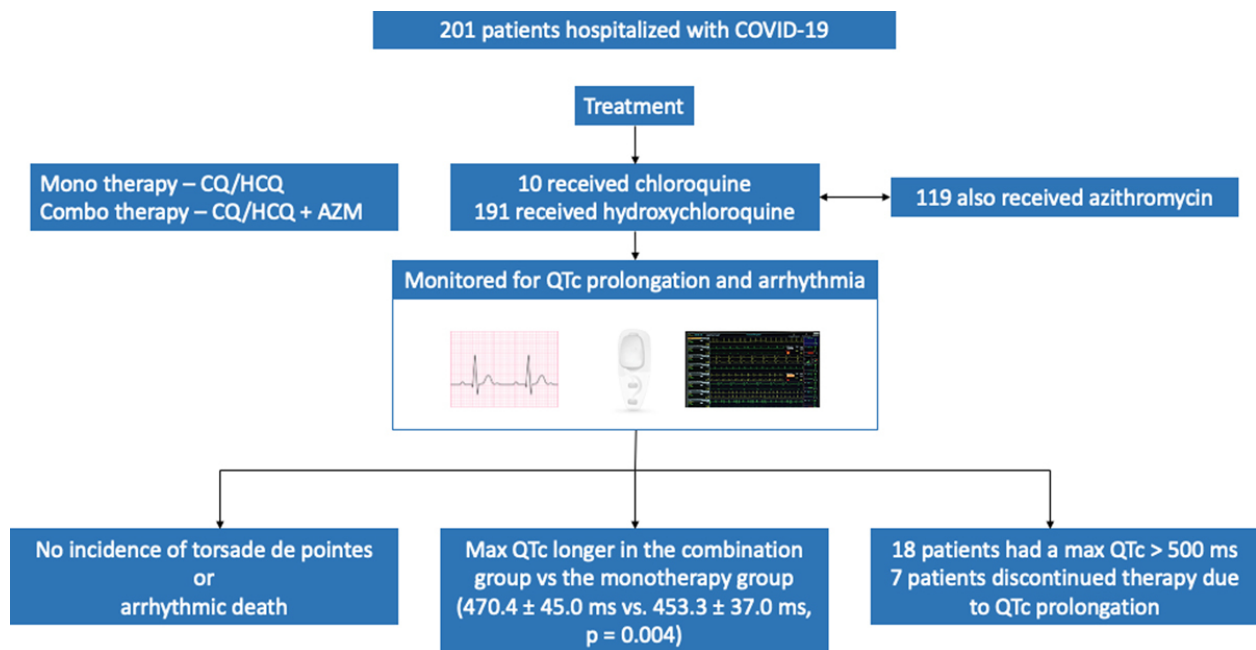
## Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection

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### Background:

The novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is responsible for the global coronavirus disease 2019 pandemic. Small studies have shown a potential benefit of chloroquine/hydroxychloroquine±azithromycin for the treatment of coronavirus disease 2019. Use of these medications alone, or in combination, can lead to a prolongation of the QT interval, possibly increasing the risk of Torsade de pointes and sudden cardiac death.

### Methods:

Hospitalized patients treated with chloroquine/hydroxychloroquine±azithromycin from March 1 to the 23 at 3 hospitals within the Northwell Health system were included in this prospective, observational study. Serial assessments of the QT interval were performed. The primary outcome was QT prolongation resulting in Torsade de pointes. Secondary outcomes included QT prolongation, the need to prematurely discontinue any of the medications due to QT prolongation, and arrhythmogenic death.

## Results:

Two hundred one patients were treated for coronavirus disease 2019 with chloroquine/hydroxychloroquine. Ten patients (5.0%) received chloroquine, 191 (95.0%) received hydroxychloroquine, and 119 (59.2%) also received azithromycin. The primary outcome of torsade de pointes was not observed in the entire population. Baseline corrected QT interval intervals did not differ between patients treated with chloroquine/hydroxychloroquine (monotherapy group) versus those treated with combination group (chloroquine/hydroxychloroquine and azithromycin;  $440.6 \pm 24.9$  versus  $439.9 \pm 24.7$  ms,  $P=0.834$ ). The maximum corrected QT interval during treatment was significantly longer in the combination group versus the monotherapy group ( $470.4 \pm 45.0$  ms versus  $453.3 \pm 37.0$  ms,  $P=0.004$ ). Seven patients (3.5%) required discontinuation of these medications due to corrected QT interval prolongation. No arrhythmogenic deaths were reported.

## Conclusions:

In the largest reported cohort of coronavirus disease 2019 patients to date treated with chloroquine/hydroxychloroquine±azithromycin, no instances of Torsade de pointes, or arrhythmogenic death were reported. Although use of these medications resulted in QT prolongation, clinicians seldomly needed to discontinue therapy. Further study of the need for QT interval monitoring is needed before final recommendations can be made.

## What Is Known?

- The antimalaria drugs chloroquine and hydroxychloroquine and the commonly used macrolide antibiotic azithromycin are all known to increase the corrected QT interval.
- A corrected QT interval >500 ms increases the risk of torsade de pointes by 2- to 3-fold. Other risk factors include drug interactions affecting drug serum levels, concomitant use of QT prolonging agents, female gender, structural heart disease, genetic polymorphisms, electrolyte disturbances, bradycardia, and hepatic disease.

## What the Study Adds?

- In hospitalized COVID-19 patients, the use of chloroquine/hydroxychloroquine and azithromycin resulted in a significantly greater increase in the corrected QT interval when compared with monotherapy with either chloroquine or hydroxychloroquine.
- Although patients experienced corrected QT interval prolongation, especially when combination therapy was used, the risk of arrhythmic death and torsade de pointes were not increased.
- Though the efficacy of chloroquine/hydroxychloroquine±azithromycin in patients with coronavirus disease 2019 (COVID-19) is unproven, the arrhythmic risk appears to be low and may not warrant monitoring in most hospitalized patients.

## Introduction

In December of 2019, reports of an unknown pneumonia not responsive to traditional treatments emerged in Wuhan, China. The pathogen, which came to be identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus that is now known to be responsible for the coronavirus disease 2019 (COVID-19) illness. Since then, the virus has spread internationally infecting  $\approx$ 1 million individuals and resulting in  $>50\,000$  deaths. COVID-19 was declared a public health emergency of international concern on January 30, 2020<sup>1</sup>. Although strong data supporting any specific therapy has been lacking, several pharmacological intervention strategies have been proposed for the management of COVID-19 in hopes of decreasing morbidity and mortality related to the illness. One such therapy currently under study in humans is the use of chloroquine or hydroxychloroquine. Chloroquine, a medication commonly used to treat malaria, has been shown to inhibit viral infection by changing the endosomal pH that is required for viral-cell fusion as well as interfering with the glycosylation of cellular receptors of SARS-CoV.<sup>2</sup> Compared with chloroquine, hydroxychloroquine has been shown in vitro to have higher inhibition against SARS-CoV-2.<sup>3</sup> These limited studies have resulted in a surge in the use of chloroquine or hydroxychloroquine with and without azithromycin in patients requiring inpatient care for COVID-19. Although many are hopeful that these inexpensive and readily available medications may be the key to decreasing mortality in this pandemic, as of the writing of this article, no such data exists. A notable concern is the association of QT prolongation and Torsade de pointes (TdP) with these medications when individually prescribed, and the increased risk when they are administered together, especially in patients with hepatic disease or renal failure. To evaluate the arrhythmic safety of chloroquine/hydroxychloroquine $\pm$ azithromycin, we conducted this prospective evaluation in adult patients hospitalized with COVID-19.

## Methods

To minimize the possibility of unintentionally sharing information that can be used to reidentify private information, a subset of the data generated, and the analytical methods used for this study are available from the corresponding author to other researchers upon reasonable request. This study was approved by the Institutional Review Board of Northwell Health, which waived the requirement for individual informed consent.

From the start of the outbreak until April 4, 2020, 3180 patients have received combination hydroxychloroquine and azithromycin, and 1181 patients received hydroxychloroquine alone for the treatment of COVID-19 in 14 hospitals of the New York State Northwell Health system. The present study is an in-depth prospective, observational study from 3 of the hospitals. All hospitalized patients  $>18$  years of age with polymerase chain reaction confirmed COVID-19 illness treated with chloroquine/hydroxychloroquine $\pm$ azithromycin were identified from March 1 to March 23. The decision to treat with chloroquine/hydroxychloroquine $\pm$ azithromycin was based on the clinical decision of the admitting physician and predescribed healthcare system guidelines. Healthcare system criteria for the use of chloroquine/hydroxychloroquine $\pm$ azithromycin therapy placed on March 1 were as follows: confirmed Covid-19 polymerase chain reaction testing or high suspicion of Covid-19 with test pending; acute respiratory distress syndrome or severe illness characterized by systemic inflammatory response syndrome criteria; or clinician's judgment that the patient is likely to progress to acute respiratory distress syndrome or severe illness in the next 6 hours. Patients not meeting the criteria for therapy were excluded from the study. Patients chronically on hydroxychloroquine for autoimmune diseases, such as lupus, those with a documented hypersensitivity to any of the agents, and any patient that refused the therapies were excluded from the study.

Demographics, inpatient medication lists, values from the baseline ECGs including QRS duration, QRS morphology, and QT interval duration were collected on all patients before initiation of therapy. Inpatient medication orders were reviewed daily and any concomitant QT-prolonging agent usage was identified. Twice daily ECGs, except for patients that received a Mobile Cardiac Outpatient Telemetry (MCOT) Patch (BioTelemetry, Malvern, PA), were obtained to assess the corrected QT interval (QTc). Given the large number of COVID-19 patients admitted throughout the health system and the limited amount of telemetry beds available, the MCOT patches were used to monitor for both QT prolongation and for arrhythmias in patients on nontelemetry units. MCOT patches were preprogrammed to transmit twice daily telemetry strips for QT interval measurements. Telemetry or MCOT Patch urgent alerts were reviewed for all patients and any cardiac arrhythmias were documented. Premature discontinuation of any of the medications due to QT prolongation was also noted. All QT intervals obtained from an ECG or MCOT patch were manually measured by a physician on the research team. Lead II was utilized for the measurement of the QT interval on ECG. If the T-wave could not easily be measured in lead II, leads V6, or I were alternatively used. The end of the T-wave was defined as the tangent drawn from the steepest last limb of the T-wave to its intersection with the baseline. If a baseline BBB was present, the J-T interval was measured and 120 ms was added to obtain the QT interval duration. Bazett formula was used to calculate the corrected QT interval. Baseline QT interval measurements obtained from the MCOT patch were compared with that of the baseline ECG utilizing lead I, as the MCOT patch provides a lead I strip, to ensure accuracy. Serial ECGs were not obtained on MCOT patients to decrease staff exposure. Given the observational nature of the study, members of the research team measuring the QT interval were not blinded to the patient information or course. All telemetry, ECG, and MCOT patch monitoring findings, and QT interval measurements were adjudicated by a senior board-certified cardiac electrophysiologist and a cardiac electrophysiology fellow board-certified in cardiovascular disease.

### **Outcome Measures**

The primary clinical outcome of the study was QT prolongation resulting in TdP. Secondary outcomes included QT prolongation and QT prolongation that resulted in the need to prematurely terminate chloroquine, hydroxychloroquine, or azithromycin as well as arrhythmogenic death.

### **Statistical Analysis**

As this was a prospective, observational study without a specific control population, only a basic statistical analysis was utilized. Continuous variables were reported as the mean $\pm$ SD and categorical variables were reported as numerical values and percentages. The Welch *t* test was used to compare ECG changes during treatment with the patients' baseline ECGs. A multivariable linear regression analysis was performed to test the impact of monotherapy versus combination therapy, and gender along with the interaction between the 2 on the outcome of change in QTc. Fisher exact test was used to compare the number of patients with a QTc >500 ms in the monotherapy versus combination groups. The SAS Version 9.4 (Cary, NC) statistical software was used for the analysis.

### **Results**

Between March 1st and March 23, there were 201 patients that were treated for COVID-19 with either chloroquine or hydroxychloroquine at 3 hospitals in the Northwell Health system. A minority of these patients (10, 5.0%) received chloroquine. Of the 201 patients on either chloroquine or hydroxychloroquine, 119 (59.2%) also received azithromycin. The treatment regimens for these

medications were as follows: chloroquine 500 mg by mouth twice daily for 1 day followed by 500 mg by mouth once daily for 4 days, hydroxychloroquine 400 mg by mouth twice daily for 1 day followed by 200 mg by mouth twice daily for 4 days, and azithromycin 500 mg by mouth or intravenous daily for 5 days. The average age of the cohort was 58.5±9.1 and 115 (57.2%) were male patients. Complete demographics are displayed in [Table 1](#), and details regarding inpatient medication usage are outlined in [Table 2](#).

A baseline ECG was performed before initiating therapy for COVID-19 for all patients. A majority of patients were in sinus rhythm (177, 88.1%) with baseline heart rate of 80.5±17.7 beats per minute. The mean QRS duration for the population at baseline was 92.8±19.0 ms with 46 patients (22.9%) having an intraventricular conduction delay, incomplete, or complete right bundle branch block, left bundle branch block, or a ventricular paced rhythm.

Serial ECGs were used to monitor QTc intervals for 84 patients, and 117 patients (58.2%) were monitored with an MCOT patch. The baseline QTc for the entire cohort was 439.5±24.8 ms and 8 patients (4.0%) had a baseline QTc >500 ms. The average maximum QTc during treatment for the entire cohort was 463.3±42.6 ms and the post-treatment QTc was 454.8±40.1 ms. The average increase in the QTc after the 5-day course treatment was 19.33±42.1 ms ([Table 3](#)).

The baseline QTc intervals for the monotherapy group were 438.9±25.0 ms and for the combination therapy group was 439.9±24.7 ms ( $P=0.79$ ). The maximum QTc during treatment was significantly shorter in patients treated with chloroquine/hydroxychloroquine monotherapy when compared with patients treated with a combination of either of these medications and azithromycin (453.3±37.0 versus 470.4±45.0 ms,  $P=0.004$ ; [Table 4](#)). Additionally, there were no statistically significant effects of gender ( $P=0.091$ ) or an interaction between the effects of gender and medications on the difference between the Maximum QTc and the baseline QTc ( $P=0.93$ ). The overall trajectory of QTc change is represented in [Figure 1](#). The number of patients with a peak QTc >500 ms was 7 (8.6%) in the monotherapy group versus 11 (9.2%) in the combination therapy group ( $P=1.00$ ) ([Figure 2](#)). Further details regarding these patients can be found in [Table 5](#).

In addition to QT prolongation, there were 17 instances of new-onset atrial fibrillation that were discovered either on telemetry or an MCOT patch. Seven patients had monomorphic nonsustained ventricular tachycardia, and 1 patient had sustained, hemodynamically stable, monomorphic ventricular tachycardia in the setting of likely viral myocarditis ([Table 6](#)). The primary outcome of QT prolongation leading to TdP was not observed in the entire population. Arrhythmogenic death was also not observed in the entire cohort. The secondary outcome involving the need to discontinue hydroxychloroquine due to QT prolongation occurred in 7 (3.5%) patients with average QTc of 504.4±39.5 ms. Details regarding these patients can be found in [Tables 7](#) and [8](#). The trajectory of their QTc change is represented in [Figure 3](#). A complete list of arrhythmic events and interventions is listed in [Table 9](#). Following the development and implementation of the Northwell flow chart to minimize TdP in COVID-19 inpatients on hydroxychloroquine/azithromycin, lidocaine was used to facilitate continuation of hydroxychloroquine in 2 other patients.<sup>4</sup> The first patient's QTc increased from baseline of 458 to 594 ms after receiving hydroxychloroquine 400 mg for 2 doses followed by 200 mg for 3 doses and 2 doses of intravenous azithromycin 500 mg. The patient was given a single dose of intravenous lidocaine 100 mg, which improved QTc to 479 ms. Azithromycin was discontinued at this time while hydroxychloroquine 200 mg twice daily was continued for the full 5-day course. Of note, this patient was given a dose of intravenous

amiodarone 150 mg 2 days before reaching the peak QTc during a rapid response for atrial fibrillation and acute hypoxic respiratory failure that required intubation. Two days after finishing the course of hydroxychloroquine, the QTc prolonged to 601 ms. Of note, the patient was receiving intravenous furosemide and pantoprazole, which may have contributed to the QTc prolongation. The patient appropriately responded to another dose of intravenous lidocaine. The subsequent QTc improved to 551 ms and normalized to <500 ms on subsequent ECGs. The second patient's QTc increased from 456 ms to 620 ms after receiving 1 dose of hydroxychloroquine. She was given a dose of intravenous lidocaine 100 mg, which improved the QTc to 550 ms. This patient went on to complete the 5-day course of hydroxychloroquine with no further prolongation of QTc.

## Discussion

The main findings of this study were (1) the use of chloroquine/hydroxychloroquine and azithromycin led to a significantly greater increase in the corrected QT interval when compared to monotherapy with either chloroquine or hydroxychloroquine, (2) prolongation of the QTc only led to premature discontinuation of these medications in 3.5% of patients, and (3) there were no instances of the primary end point of TdP in the entire cohort.

The SARS-CoV-2 virus is an enveloped  $\beta$  coronavirus that is thought to have transmitted to humans via zoonotic transfer.<sup>5,6</sup> Virus binding and cell entry are facilitated by a type I membrane spike glycoprotein on the surface of the SARS-CoV-2 virus that binds to ACE (angiotensin-converting enzyme)-2 receptors found in the upper and lower human respiratory tract.<sup>7,8</sup> The SARS-CoV-2 virus emerged from China in December of 2019 and has subsequently resulted in an explosion of proposed therapies for treating the virus. Among these therapies, chloroquine/hydroxychloroquine with and without azithromycin are now commonly being used, following studies that showed virus-cell fusion inhibition.<sup>2,3</sup> To date, there has been little actionable clinical data on the efficacy of using these medications in humans infected with the SARS-CoV-2 virus. In a 2005 cohort of 23 hospitalized patients with SARS-CoV, To et al<sup>9</sup> reported a direct correlation between viral load and increasing age, suggesting an increased expression of ACE-2 receptors with age may result in higher viral loads. The relationship between viral load and disease severity, however, was not addressed. Viral load was noted to peak during the first week of illness and steadily declined over the following week.<sup>10</sup> Subsequently, a 30-patient study in mildly symptomatic patients showed no benefit of chloroquine with regards to clearance of viral load, time to temperature normalization, and disease progression.<sup>11</sup> Major trials evaluating clinical efficacy of this combination therapy are currently underway globally.

A major concern with the use of this therapy has been the risk of QT prolongation and TdP. TdP is a form of polymorphic ventricular tachycardia that occurs in the setting of QT prolongation that is characterized by gradual twisting and amplitude change of the QRS complexes around an isoelectric line that either spontaneously terminates or degenerates to ventricular fibrillation in about 10% of cases.<sup>12,13</sup> Traditionally, QT-prolonging agents have been avoided in individuals with a QTc >500 ms due to a 2-fold to 3-fold increase in risk for TdP with such intervals.<sup>14-16</sup> Most drugs cause QT prolongation by blocking the human ether-a-go-go related gene (*hERG*) potassium channel, the voltage-gated ion channel that mediates the rapid component of the delayed rectifier potassium current,  $I_{Kr}$ , resulting in lengthening of both ventricular repolarizations, and the duration of the ventricular action potential.<sup>17</sup> In a similar fashion, this can result in the reactivation of calcium influx causing triggered early



afterdepolarization activity. A well-timed early afterdepolarization trigger, in the presence of a prolonged QT interval, can result in TdP.<sup>18</sup>

Other risk factors for TdP include drug interactions affecting drug serum levels, concomitant use of QT-prolonging agents, female sex, structural heart disease, genetic polymorphisms, electrolyte disturbances, bradycardia, and hepatic disease. Such risk factors result in repolarization reserve reduction.<sup>18,19</sup> Although the QTc is sensitive for predicting TdP, it is not specific. The relationship between QT prolongation and TdP is not linear as drugs that prolong the QT have not consistently been associated with cardiac arrhythmias. Incidences of sudden cardiac death occurring in the absence of QT prolongation on surface ECG have also been reported. Of all the QT prolonging drugs, antiarrhythmics have the highest risk of TdP with an incidence of 1% to 5%, whereas the risk from noncardiovascular drugs is much lower at 0.001%.<sup>13</sup>

Four hundred million courses of antimalarial drugs are annually used around the world.<sup>20</sup> Antimalarial drugs are well known for their potential cardiac toxicity and QT prolongation effects. Of the drugs used, quinidine and halofantrine are the most likely to cause QT prolongation and TdP.<sup>21-23</sup> Chloroquine's reported risk of sudden cardiac death is limited to cases of hypotension due to vasodilation and negative inotropy resulting from rapid parenteral administration of the medication or situations of self-inflicted overdose.<sup>24</sup> The risk of QT prolongation and TdP with hydroxychloroquine is limited to a series of case reports in patients with either chronic use or overdose.<sup>25-27</sup>

The reported effects of chloroquine and hydroxychloroquine on the QT interval may also be significantly affected by the course of acute malaria. Increased sympathetic tone due to fevers, anxiety, and anorexia at the onset of illness results in QT interval shortening. As patients recover with medical therapy, QT interval normalizes. QT interval normalization on day 3 of therapy, which coincides with peak drug level, may have been mistakenly attributed to the drugs.<sup>24</sup> Furthermore, the Bazett formula, used in malaria studies, overestimates the number of patients with QT prolongation and could have contributed to the reported QT prolonging effects of chloroquine and hydroxychloroquine.<sup>28</sup>

Azithromycin, a widely utilized macrolide antibiotic, has been reported to increase QT interval and incidence of TdP.<sup>29-35</sup> In a 2012 retrospective observational study, 5 days of therapy with azithromycin was found to have a small but statistically significant increase in cardiovascular death driven by sudden cardiac death. This effect did not persist after the treatment was stopped.<sup>36</sup> The proarrhythmic mechanism of azithromycin is thought to be due to the drug's ability to increase cardiac sodium current and promote intracellular sodium loading.<sup>37</sup> However, data are lacking to show that the increased risk of death with azithromycin is a result of QT prolongation and TdP. Moreover, azithromycin and chloroquine combination therapy has been used for the protection against malaria and sexually transmitted infections in pregnant women with no reports of syncope or sudden cardiac death.<sup>38</sup>

Our study revealed that in the entire cohort treated with chloroquine/hydroxychloroquine or azithromycin, the increase in QTc to its peak (max QTc), and post-treatment QTc (final QTc) were statistically significant ( $P < 0.05$ ; [Table 3](#)). When further broken down to 2 treatment cohorts as shown in [Table 4](#), the group treated with the combination therapy had longer Max and Final QTc intervals compared with the monotherapy group ( $P = 0.004$  and  $P = 0.002$ , respectively). However, it is important to highlight that no patient had QTc prolongation that resulted in TdP. Seven patients (3.5%) needed to discontinue the medications due to QTc prolongation. Two additional patients were treated with intravenous lidocaine that shortened the QTc allowing for continuation of hydroxychloroquine. The

decision to discontinue therapy was variable based on provider personal threshold and comfort. This explains why some patients with similarly prolonged QTc intervals continued therapy.

As the volume of hospitalized COVID-19 patients has increased throughout our health system, our ability to monitor every patient receiving combination therapy became limited due to the finite amount of telemetry beds available. The use of MCOT patch monitors allowed us to expand remote monitoring of cardiac arrhythmias and QT prolongation in patients not on traditional telemetry. The MCOT monitor is Food and Drug Administration–approved for the measurement, analysis, and reporting of QT intervals. The use of the monitor resulted in a reduction of exposures and personal protective equipment use by healthcare workers as the need for serial ECGs to monitor the QT interval was eliminated in this subset of patients.

Further investigation of this combination therapy is needed, especially given the lack of randomized controlled trials showing efficacy. Based on our experience, although patients experience QTc prolongation, especially when combination therapy is used, the risk of arrhythmic death or TdT were not increased. Furthermore, to date, a total of 3180 patients have received combination hydroxychloroquine and azithromycin, and 1181 patients received hydroxychloroquine alone for the treatment of COVID-19 in our healthcare system. There continues to be no reports of TdT in those patients. In short, the use of this combination therapy for a period of 5 days may not warrant monitoring for cardiac arrhythmias in most patients. Our Infection disease team is no longer recommending the addition of azithromycin. Coupled with the findings in this study, we have simplified our approach to monitoring patients on therapy. If the baseline QTc is  $\leq 500$  ms (550 if bundle branch block or QRS duration  $>120$  ms) no monitoring or serial ECGs will be required. If the baseline QTc is  $>500$  ms (550 if bundle branch block or QRS duration  $>120$  ms) on telemetry or MCOTs, no serial ECGs will be utilized for arrhythmia and QTc monitoring. We will be performing a prospective analysis of this approach.

### **Limitations**

The main limitation of this study is the absence of a control cohort of patients with COVID-19 infections that were not treated with any of these medications. Although this would have provided a stronger analysis, nearly every hospitalized patient with COVID-19 received  $\geq 1$  of these medications during the course of their admission during this study period. The number of patients with underlying cardiac disease in the study is small, potentially limiting generalizability to that population. The study is subject to the same limitations as other observational studies. Although baseline QT interval readings on MCOT were correlated to the baseline ECGs, subsequent QT intervals in the MCOT subset obtained while on therapy were not. This fact and the difference in filtering in MCOT patches versus traditional 12-lead ECG are a limitation. Over 4000 patients across the 17 hospitals in the Northwell Health system have received one or both therapies as of April 4, 2020 with no reported instances of TdT. This statistic, although very encouraging, may be subject to reporting bias. Lastly, our cohort of 201 patients, from the initial phases of this pandemic, represents a small fraction of the total patients we have treated. Further work is needed to confirm our findings in an even larger group of patients.

### **Conclusions**

This is the largest reported cohort to date of patients with COVID-19 that were treated with chloroquine/hydroxychloroquine with and without azithromycin. We observed a marked increase in the QT intervals of these patients during treatment, that was more pronounced in patients treated with

combination therapy. Despite this increase, very few patients had the medications discontinued prematurely due to QT prolongation. Most importantly, there were no cases of torsade de pointes or arrhythmic death in the entire population. Further study of the need for QT interval monitoring is needed before final recommendations can be made.

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## Physicians

**Daniel Wohlgelernter, M.D.**  
M.D., F.A.C.C.

**Expertise:** *Clinical & Preventive Cardiology*

Dr. Wohlgelernter earned his medical degree from the Yale University School of Medicine in New Haven, Connecticut. He completed his internship and residency in Internal Medicine, as well as a fourth year as chief medical resident, at the Yale Medical Center.

He trained in cardiology at Yale, and served on the Yale medical school faculty for two years before joining the UCLA faculty in 1985. He is Board Certified in Internal Medicine and Cardiology (Cardiovascular Disease). He is a Fellow of the American College of Cardiology.

Dr. Wohlgelernter has authored numerous medical journal articles and textbook chapters on a variety of topics pertaining to the diagnosis and treatment of heart disease. His special interests include preventive cardiology, management of lipid disorders and hypertension, and noninvasive management of arrhythmias.

Dr. Wohlgelernter was a recipient of The Thomas L. Stern, M.D. prize for excellence in teaching, awarded by the Santa Monica-UCLA Medical Center Family Practice Residency Program. He was listed as a member of Southern California Super Doctors from 2010 to 2016 as featured in Los Angeles Magazine. He was named one of US News and World Report's 'Top Doctors' in September 2012 and was named one of California's Top Doctors in January 2015 and January 2016 in Los Angeles magazine. Dr. Wohlgelernter has also appeared on The Discovery Channel as a cardiology commentator.

Dr Wohlgelernter offers a **concierge program** that allows him to provide in-depth medical services and extra time for his patients. Click **here** to learn more.



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## Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature

[Clotilde Chatre](#)<sup>1</sup>, [François Roubille](#)<sup>2,3</sup>, [Hélène Vernhet](#)<sup>4</sup>, [Christian Jorgensen](#)<sup>1,5</sup>, [Yves-Marie Pers](#)<sup>6,7</sup>

### Abstract

**Introduction:** Chloroquine and hydroxychloroquine are widely used in the long-term treatment of connective tissue disease and usually considered safe. However, chloroquine- or hydroxychloroquine-related cardiac disorder is a rare but severe adverse event, which can lead to death. This systematic review investigates cardiac complications attributed to chloroquine and hydroxychloroquine.

**Methods:** PubMed, EMBASE, and Cochrane database searches were conducted using keywords derived from MeSH terms. Reports published prior to 31 July, 2017 were eligible for inclusion, without restriction to study design. Searches were also conducted on reference lists of included studies.

**Results:** Eighty-six articles were identified, reporting individual cases or short series, providing information on 127 patients (65.4% female). A majority of patients were treated with chloroquine (58.3%), with the remaining treated with hydroxychloroquine (39.4%), or both in succession. Most patients had been treated for a long time (median 7 years, minimum 3 days; maximum 35 years) and with a high cumulative dose (median 1235 g for hydroxychloroquine and 803 g for chloroquine). Conduction disorders were the main side effect reported, affecting 85% of patients. Other non-specific adverse cardiac events included ventricular hypertrophy (22%), hypokinesia (9.4%), heart failure (26.8%), pulmonary arterial hypertension (3.9%), and valvular dysfunction (7.1%). For 78 patients reported to have been withdrawn from treatment, some recovered normal heart function (44.9%), while for others progression was unfavorable, resulting in irreversible damage (12.9%) or death (30.8%).

**Limitations:** The risk of cardiac complications attributed to chloroquine/hydroxychloroquine was not quantified because of the lack of randomized controlled trials and observational studies investigating the association.

**Conclusions:** Clinicians should be warned that chloroquine- or hydroxychloroquine-related cardiac manifestations, even conduction disorders without reperussion, may be initial manifestations of toxicity, and are potentially irreversible. Therefore, treatment withdrawal is required when cardiac manifestations are present.

fn6

<https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v2>

## **Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study**

### **Abstract**

Background: Hydroxychloroquine has recently received Emergency Use Authorization by the FDA and is currently prescribed in combination with azithromycin for COVID-19 pneumonia. We studied the safety of hydroxychloroquine, alone and in combination with azithromycin.

Methods: New user cohort studies were conducted including 16 severe adverse events (SAEs). Rheumatoid arthritis patients aged 18+ and initiating hydroxychloroquine were compared to those initiating sulfasalazine and followed up over 30 days. Self-controlled case series (SCCS) were conducted to further establish safety in wider populations. Separately, SAEs associated with hydroxychloroquine-azithromycin (compared to hydroxychloroquine-amoxicillin) were studied. Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate calibrated hazard ratios (CalHRs) according to drug use. Estimates were pooled where I<sup>2</sup><40%. Results: Overall, 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin were included. No excess risk of SAEs was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. SCCS confirmed these findings. However, when azithromycin was added to hydroxychloroquine, we observed an increased risk of 30-day cardiovascular mortality (CalHR 2.19 [1.22-3.94]), chest pain/angina (CalHR 1.15 [95% CI 1.05-1.26]), and heart failure (CalHR 1.22 [95% CI 1.02-1.45]) Conclusions: Short-term hydroxychloroquine treatment is safe, but addition of azithromycin may induce heart failure and cardiovascular mortality, potentially due to synergistic effects on QT length. We call for caution if such combination is to be used in the management of Covid-19.

fn7 and 8

[https://www.youtube.com/watch?v=htyCEeq\\_YVI](https://www.youtube.com/watch?v=htyCEeq_YVI)

Dr. Richard Urso, ophthalmologist on Laura Ingraham July 10, 2020.

Dr. Daniel Wallace, rheumatologist on Dr. Oz April 8, 2020

fn9

Dr. Richard Urso, ophthalmologist on Laura Ingraham July 10, 2020

fn10 (see fn6)

<https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v2>

fn11

<https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis>

FDA Adverse Events Reporting System (FAERS) Public Dashboard



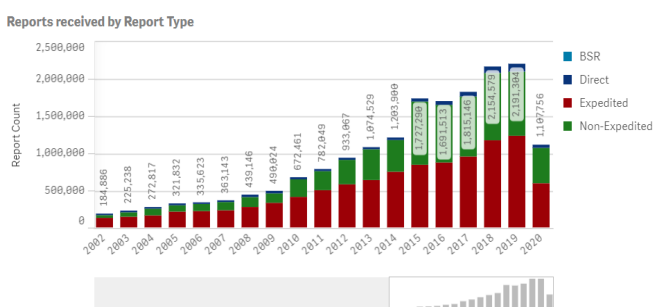
Home Search Disclaimer Site Feedback Report a Problem FAQ

Total Reports **20,292,362** Serious Reports (excluding death) **11,257,840** Death Reports **1,955,232** Reports by Report Type

Since 1968 Last 10 Years

Reports received by Report Type

Year	Total Reports	Expedited	Non-Expedited	Direct	BSR
Total Reports	20,292,362	10,816,472	8,476,580	998,447	863
2020	1,107,756	591,641	473,701	42,414	-
2019	2,191,304	1,226,972	858,964	105,368	-
2018	2,154,579	1,166,859	900,169	87,551	-
2017	1,815,146	949,669	803,447	62,030	-
2016	1,691,513	869,569	770,951	50,993	-
2015	1,727,290	838,968	846,659	41,663	-
2014	1,203,900	745,949	423,719	34,232	-
2013	1,074,529	634,745	411,395	28,389	-
2012	933,067	577,473	326,575	29,019	-



Data as of June 30, 2020

This page displays the number of adverse event reports received by FDA for drugs and therapeutic biologic products by the following Report Types.

- Direct Reports are voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals.
- Mandatory Reports are submitted by manufacturers and are categorized as:
  - Expedited reports that contain at least one adverse event that is not currently described in the product labeling and for which the patient outcome is serious, or

fn12

<https://www.cdc.gov/parasites/malaria/index.html>

## World Malaria Day 2020: CDC and partners continue the fight against a global killer

**Malaria** is a mosquito-borne disease caused by a parasite. People with malaria often experience fever, chills, and flu-like illness. Left untreated, they may develop severe complications and die. In 2018 an estimated 228 million cases of malaria occurred worldwide and 405,000 people died, mostly children in the African Region. About 2,000 cases of malaria are diagnosed in the United States each year. The vast majority of cases in the United States are in travelers and immigrants returning from countries where malaria transmission occurs, many from sub-Saharan Africa and South Asia.

[CDC's Malaria Program](#)



### About Malaria

FAQs, Malaria the Disease, Where Malaria Occurs, Transmission...



### Diagnosis

Guidelines for Clinicians, Microscopy, Rapid Diagnostic Tests...



### Treatment

Guidelines for Clinicians, Treatment with Artesunate, Drug Resistance Testing...



### Prevention and Control

Choosing a Drug to Prevent Malaria, Reducing Malaria's Impact...



### About Our Division

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### References and Resources

Education & Training, Fact Sheets, Brochures, Posters, MMWRs...

## Malaria

CDC



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Malaria and Travelers +

CDC and Malaria +

Faces of Malaria +

Glossary

References and Resources +

## Chloroquine and Hydroxychloroquine

Information on chloroquine, hydroxychloroquine, and COVID-19 can be found here: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>

Chloroquine and hydroxychloroquine are FDA-approved drugs used to prevent and treat certain types of malaria. They have a long elimination half-life of 30–45 days, allowing for weekly dosing when used in prevention of malaria, and a short 48-hour treatment course when used to treat malaria. These drugs are generally well tolerated at doses used for malaria but may cause pruritis and exacerbate psoriasis. With frequent dosing, rarely reported adverse events include retinopathy and cardiac arrhythmias (QT prolongation specifically) in those with liver or kidney dysfunction. Exceeding recommended doses of chloroquine and hydroxychloroquine can lead to death, and fatal overdoses have been reported. Hydroxychloroquine is also FDA approved for use in rheumatoid arthritis and systemic lupus erythematosus. These drugs are available by prescription only.



# Chloroquine and Hydroxychloroquine

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<https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>

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Page last reviewed: March 25, 2020

Content source: Global Health, Division of Parasitic Diseases and Malaria

fn13 (see fn3)

<https://www.ahajournals.org/doi/10.1161/CIRCEP.120.008662>

## Circulation: Arrhythmia and Electrophysiology

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### Effect of Chloroquine, Hydroxychloroquine, and Azithromycin on the Corrected QT Interval in Patients With SARS-CoV-2 Infection

Moussa Saleh, James Gabriels, David Chang, Beom Soo Kim, Amtul Mansoor, Eitezaz Mahmood, Parth Makker, Haisam Ismail, Bruce Goldner, Jonathan Willner, Stuart Beldner, Raman Mitra, Roy John, Jason Chinitz, Nicholas Skipitaris, Stavros Mountantonakis, Laurence M. Epstein

Originally published 29 Apr 2020 | <https://doi.org/10.1161/CIRCEP.120.008662> | Circulation: Arrhythmia and Electrophysiology. 2020;13

### Jump to

Abstract

What Is Known?

What the Study Adds?

Introduction

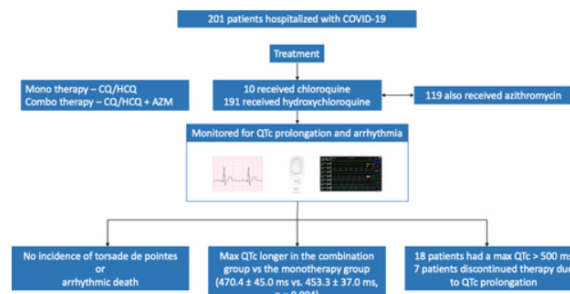
Methods

Outcome Measures

Statistical Analysis

Results

### Abstract



fn14

<https://www.aspph.org/yale-dr-harvey-risch-wins-50000-ruth-leff-siegel-award/>

August 9, 2018

### **Yale: Dr. Harvey Risch Wins \$50,000 Ruth Leff Siegel Award**

Dr. Harvey Risch from Yale School of Public Health is the recipient of the \$50,000 Ruth Leff Siegel Award. Dr. Risch has made novel, sustained and substantial contributions to understanding the etiology and early diagnosis of pancreatic cancer. To start with, in 2001, the second of two reports was published showing an association between colonization by *Helicobacter pylori* and risk of pancreatic cancer. Dr. Risch recognized that because *H. pylori* does not colonize the human pancreas, bacterial effects on gastric acidity, risk up or down according to organism CagA-negative or -positive strain type, respectively, should modulate pancreatic cancer risk. This hypothesis (Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of *N*-nitroso compounds and excess gastric acidity. *J Natl Cancer Inst.* 2003;95(13):948-60.) was directly confirmed by Dr. Risch in two population-based case control studies, one in Connecticut, where CagA-positive and -negative strains are both common (Risch HA et al., ABO blood group, *Helicobacter pylori* seropositivity, and risk of pancreatic cancer: a case-control study. *J Natl Cancer Inst* 2010;102(7):502-5) and a second in Shanghai, China, where CagA-positive strains predominate (Risch HA et al., *Helicobacter pylori* seropositivities and risk of pancreatic carcinoma. *Cancer Epidemiol Biomarkers Prev* 2014;23(1):172-8.). This theory has also been confirmed in recent studies in Poland and Australia.

More recently, Dr. Risch has been working on methods for earlier recognition and detection of pancreatic cancer. Various prodrome factors of pancreatic cancer are known, but are nonspecific and many are not confined to pancreatic origins. Dr. Risch recognized that models combining both risk factors and prodrome factors could achieve sufficient specificity to begin to be useful in predicting incipient pancreatic cancer diagnosis. To do this, he developed a novel analytic method to combine population-based case-control data with population cancer incidence data (from SEER) to enable the calculation of age- and gender-specific absolute risks of cancer development from case-control studies, which otherwise allow only the estimation of relative risks.

Dr. Risch then applied this model to data from his Connecticut pancreatic cancer study, to demonstrate that various combinations of risk and prodrome factors have 5-10 percent or greater 5-year risks of pancreatic cancer diagnosis. Over the entire population, he estimated that about 0.9 percent of individuals have 5-year risks this high. Because the prodrome factors that he evaluated in this model are easily observable (diagnosis of diabetes mellitus and how long ago it occurred; years in the past when pancreatitis was diagnosed; years in the past when cigarette smoking stopped; and years in the past when PPI medication use started), it is a simple statistical matter to estimate these risks and no laboratory testing is needed. This seminal paper (Risch HA et al., Detectable symptomatology preceding the diagnosis of pancreatic cancer and absolute risk of pancreatic cancer diagnosis. *Am J Epidemiol* 2015;182(1):26-34) was an "Editor's Choice" article and was featured with accompanying editorial commentaries.

Finally, Dr. Risch's work has clearly demonstrated that aspirin usage, both regular and low-dose, cuts risk of pancreatic cancer by about one-third (the seminal paper noted on the previous page). This paper was

the confirmation in an independent study of Dr. Risch's first paper on aspirin use and reduced risk of pancreatic cancer (Streicher SA, Yu H, Lu L, Kidd MS, Risch HA. Casecontrolstudy of aspirin use and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2014;23(7):1254-63). Both publications have received substantial media attention. Dr. Risch's 2017 seminal paper showed that as prophylactic aspirin use has become more popular in western countries, aspirin use has been associated with increasingly lower risks of pancreatic cancer. A paper by the Harvard cohorts in December 2017 noted that they observed no association with aspirin use, but those data were already included in Dr. Risch's 2017 seminal meta-analysis of 21 studies that indeed demonstrate this association. Dr. Risch has a response letter to the Harvard study (Risch HA. Re: Regular use of aspirin or non-aspirin nonsteroidal anti-inflammatory drugs is not associated with risk of incident pancreatic cancer in two large cohort studies. *Gastroenterology* 2018, accepted for publication) showing that the evidence supporting the aspirin association is quite strong. Dr. Risch's 2017 seminal paper has recently been awarded "Best of the AACR Journals".

Dr. Harvey Risch is professor of epidemiology in the department of epidemiology and public health at the Yale School of Public Health and Yale School of Medicine. Dr. Risch received his MD degree from the University of California San Diego and PhD from the University of Chicago. After serving as a postdoctoral fellow in epidemiology at the University of Washington, Dr. Risch was a faculty member in epidemiology and biostatistics at the University of Toronto before coming to Yale. Dr. Risch's research interests are in the areas of cancer etiology and prevention, and in epidemiology methods. He is especially interested in the effects of reproductive factors, diet, genetic predisposition, and histopathologic factors in the causation of ovarian cancer, and these factors as well as infection and immune functioning in the etiology of pancreatic cancer. His major research projects have included studies of ovarian cancer, pancreas cancer, lung cancer, bladder cancer, esophageal and stomach cancer, and of cancers related to usage of oral contraceptives and no contraceptive estrogens. Dr. Risch is associate editor of the *Journal of the National Cancer Institute*, Editor of the *International Journal of Cancer*, and Member of the Board of Editors, the *American Journal of Epidemiology*.

The recipient of the \$25,000 award is [Dr. John Chabot](#) for radically increasing patient survival and R0 resections in LAPC patients. His seminal paper was titled "Resection of Locally Advanced Pancreatic Cancer without Regression of Arterial Encasement After Modern-Era Neoadjuvant Therapy."

Dr. Chabot has spent the duration of his career at New York-Presbyterian/Columbia since 1983, when he began his internship in transplantation. He has dedicated his career with resolute focus on the prevention, treatment, and cure for pancreatic cancer. Having progressed from intern, resident, and fellow to professor, mentor, and executive director of the Pancreas Center at New York-Presbyterian/Columbia, Dr. Chabot intimately understands the culture and practice of medicine and surgery at the hospital. He is in a well-grounded position to lead Columbia Doctors in responding to the challenges associated with rapid innovation, advancing technology, and the highly informed patient. In addition to serving as executive director of the Pancreas Center, Dr. Chabot is Chief of GI/Endocrine Surgery at New York-Presbyterian Hospital and the David V. Habif Professor of Surgery at Columbia University College of Physicians and Surgeons.

fn15 (see fn6)

<https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v2>

fn16

[https://www.jstage.jst.go.jp/article/bst/14/1/14\\_2020.01047/article](https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/article)

**Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies**

[Jianjun Gao](#), [Zhenxue Tian](#), [Xu Yang](#)

2020 Volume 14 Issue 1 Pages 72-73

Abstract

The coronavirus disease 2019 (COVID-19) virus is spreading rapidly, and scientists are endeavoring to discover drugs for its efficacious treatment in China. Chloroquine phosphate, an old drug for treatment of malaria, is shown to have apparent efficacy and acceptable safety against COVID-19 associated pneumonia in multicenter clinical trials conducted in China. The drug is recommended to be included in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19 infection in larger populations in the future.

fn17

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7135139/>

[Int J Antimicrob Agents](#). 2020 Apr; 55(4): 105932.

Published online 2020 Mar 4. doi: [10.1016/j.ijantimicag.2020.105932](https://doi.org/10.1016/j.ijantimicag.2020.105932)

PMCID: PMC7135139

PMID: [32145363](https://pubmed.ncbi.nlm.nih.gov/32145363/)

**Chloroquine and hydroxychloroquine as available weapons to fight COVID-19**

Repositioning of drugs for use as antiviral treatments is a critical need <sup>[1]</sup>. It is commonly very badly perceived by virologists, as we experienced when reporting the effectiveness of azithromycin for Zika virus <sup>[2]</sup>. A response has come from China to the respiratory disease caused by the new coronavirus (SARS-CoV-2) that emerged in December 2019 in this country. Indeed, following the very recent publication of results showing the in vitro activity of chloroquine against SARS-CoV-2 <sup>[3]</sup>, data have been reported on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia (named COVID-19) at different levels of severity <sup>[4,5]</sup>. Thus, following the in vitro results, 20 clinical studies were launched in several Chinese hospitals. The first results obtained from more than 100 patients showed the superiority

of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects [\[4,5\]](#). This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia [\[4,6\]](#).

There is a strong rationality for the use of chloroquine to treat infections with intracellular microorganisms. Thus, malaria has been treated for several decades with this molecule [\[7\]](#). In addition, our team has used hydroxychloroquine for the first time for intracellular bacterial infections since 30 years to treat the intracellular bacterium *Coxiella burnetii*, the agent of Q fever, for which we have shown in vitro and then in patients that this compound is the only one efficient for killing these intracellular pathogens [\[8,9\]](#). Since then, we have also shown the activity of hydroxychloroquine on *Tropheryma whipplei*, the agent of Whipple's disease, which is another intracellular bacterium for which hydroxychloroquine has become a reference drug [\[10,11\]](#). Altogether, one of us (DR) has treated ~4000 cases of *C. burnetii* or *T. whipplei* infections over 30 years (personal data).

Regarding viruses, for reasons probably partly identical involving alkalinisation by chloroquine of the phagolysosome, several studies have shown the effectiveness of this molecule, including against coronaviruses among which is the severe acute respiratory syndrome (SARS)-associated coronavirus [\[1,12,13\]](#) ([Table 1](#)). We previously emphasised interest in chloroquine for the treatment of viral infections in this journal [\[1\]](#), predicting its use in viral infections lacking drugs. Following the discovery in China of the in vitro activity of chloroquine against SARS-CoV-2, discovered during culture tests on Vero E6 cells with 50% and 90% effective concentrations (EC<sub>50</sub> and EC<sub>90</sub> values) of 1.13 µM and 6.90 µM, respectively (antiviral activity being observed when addition of this drug was carried out before or after viral infection of the cells) [\[3\]](#), we awaited with great interest the clinical data [\[14\]](#). The subsequent in vivo data were communicated following the first results of clinical trials by Chinese teams [\[4\]](#) and also aroused great enthusiasm among us. They showed that chloroquine could reduce the length of hospital stay and improve the evolution of COVID-19 pneumonia [\[4,6\]](#), leading to recommend the administration of 500 mg of chloroquine twice a day in patients with mild, moderate and severe forms of COVID-19 pneumonia. At such a dosage, a therapeutic concentration of chloroquine might be reached. With our experience on 2000 dosages of hydroxychloroquine during the past 5 years in patients with long-term treatment (>1 year), we know that with a dosage of 600 mg/day we reach a concentration of 1 µg/mL [\[15\]](#). The optimal dosage for SARS-CoV-2 is an issue that will need to be assessed in the coming days. For us, the activity of hydroxychloroquine on viruses is probably the same as that of chloroquine since the mechanism of action of these two molecules is identical, and we are used to prescribe for long periods hydroxychloroquine, which would be therefore our first choice in the treatment of SARS-CoV-2. For optimal treatment, it may be necessary to administer a loading dose followed by a maintenance dose.

fn18

<https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa093/5847586>

**Opinion: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis**

[Harvey A Risch](#)

*American Journal of Epidemiology*, kwaa093, <https://doi.org/10.1093/aje/kwaa093>

**Published:** 27 May 2020

**Abstract**

More than 1.6 million Americans have been infected with SARS-CoV-2 and >10 times that number carry antibodies to it. High-risk patients presenting with progressing symptomatic disease have only hospitalization treatment with its high mortality. An outpatient treatment that prevents hospitalization is desperately needed. Two candidate medications have been widely discussed: remdesivir, and hydroxychloroquine+azithromycin. Remdesivir has shown mild effectiveness in hospitalized inpatients, but no trials have been registered in outpatients. Hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media, and outpatient trials results are not expected until September. Early outpatient illness is very different than later hospitalized florid disease and the treatments differ. Evidence about use of hydroxychloroquine alone, or of hydroxychloroquine+azithromycin in inpatients, is irrelevant concerning efficacy of the pair in early high-risk outpatient disease. Five studies, including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy. Hydroxychloroquine+azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20%, 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians to prescribe.

**Advisory on the use of hydroxy–chloroquine as prophylaxis for SARS-CoV-2 infection**

The **National Task force for COVID-19** constituted by Indian Council of Medical Research recommends the use of hydroxy– chloroquine for prophylaxis of SARS-CoV-2 infection for high risk population. Copy is annexed.

The Advisory provides for placing the following high risk population under chemoprophylaxis with hydroxy chloroquine:

- Asymptomatic Healthcare Workers involved in the care of suspected or confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory confirmed cases

The protocol recommended by the National Task force has been approved by the Drug Controller General of India for restricted use in emergency situations.

While following the above recommendations, States should take note of the following:

- 1) **The placing of healthcare workers under chemoprophylaxis should not instill a sense of false security.** They should follow all prescribed public health measures such as frequent washing of hands, respiratory etiquettes, keeping a distance of minimum 1m and use of Personal protective equipment (wherever applicable).
- 2) They should self-monitor their health and report to health authorities immediately in the event of them becoming symptomatic.
- 3) The high risk contacts of a positive case placed under chemo prophylaxis, **should remain in home quarantine while on prophylactic therapy.**
- 4) As recommended by the said Task Force, the drug should only be given on the prescription of a registered medical practitioner. The contraindications mentioned in the recommendations should strictly be followed.
- 5) Apart from the symptoms of COVID-19 (fever, cough, breathing difficulty), if the person on chemo-prophylaxis develops any other symptoms, he should immediately seek medical treatment of the medical practitioner who has prescribed the chemoprophylaxis.

It is reiterated that the intake of the above medicine should not in still sense of false security.



सत्यमेव जयते

**प्रोफेसर (डा.) बलराम भार्गव**, पद्म श्री

एमडी, डीएम, एफआरसीपी (जी), एफआरसीपी (ई), एफएसीसी,  
एफएएचए, एफएएमएस, एफएनएस, एफएएससी, एफएनए, डीएससी

**सचिव, भारत सरकार**

स्वास्थ्य अनुसंधान विभाग

स्वास्थ्य एवं परिवार कल्याण मंत्रालय एवं

महानिदेशक, आई सी एम आर

**Prof. (Dr.) Balram Bhargava**, Padma Shri

MD, DM, FRCP (Glasg.), FRCP (Edin.),  
FACC, FAHA, FAMS, FNAsc, FASc, FNA, DSc

**Secretary to the Government of India**

Department of Health Research  
Ministry of Health & Family Welfare &  
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भारत सरकार

वी. रामलिंगस्वामी भवन, अंसारि नगर

नई दिल्ली - 110 029

**Indian Council of Medical Research**

Department of Health Research

Ministry of Health & Family Welfare

Government of India

V. Ramalingaswami Bhawan, Ansari Nagar

New Delhi - 110 029

**D.O.No.VIR/4/2020/ECD-I**

22<sup>nd</sup> March, 2020

Dear Madam

Please find attached the final recommendation of the National Taskforce for COVID-19 for the use of hydroxychloroquine as prophylaxis. This recommendation supersedes the earlier recommendation dated 21.3.2020

With regards

Yours sincerely,

(Balram Bhargava)

**Encl: As above**

**Smt. Preeti Sudan,**  
Secretary (Health & Family Welfare)  
Ministry of Health & Family Welfare,  
Nirman Bhawan,  
New Delhi-110008.



## Recommendation for empiric use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection

### **Background:**

Hydroxy-chloroquine is found to be effective against coronavirus in laboratory studies and in-vivo studies. Its use in prophylaxis is derived from available evidence of benefit as treatment and supported by pre-clinical data. The following recommendation for the use of hydroxy-chloroquine as a prophylactic agent against SARS-CoV-2 infection is based on these considerations, as well as risk-benefit consideration, under exceptional circumstances that call for the protection of high-risk individuals.

The National Taskforce for COVID-19 recommends the use of hydroxy-chloroquine for prophylaxis of SARS-CoV-2 infection for selected individuals as follows:

### **Eligible individuals:**

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19
- Asymptomatic household contacts of laboratory confirmed cases

### **Dose:**

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals*
- Asymptomatic household contacts of laboratory confirmed cases: *400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals*

### **Exclusion/contraindications:**

- The drug is not recommended for prophylaxis in children under 15 years of age.
- The drug is contraindicated in persons with known case of retinopathy, known hypersensitivity to hydroxychloroquine, 4-aminoquinoline compounds

### **Key considerations:**

- The drug has to be given only on the prescription of a registered medical practitioner.
- Advised to consult with a physician for any adverse event or potential drug interaction before initiation of medication
- The prophylactic use of hydroxychloroquine to be coupled with the pharmacovigilance for adverse drug reactions through self-reporting using the Pharmacovigilance Program of India (PvPI) helpline/app.
- If anyone becomes symptomatic while on prophylaxis he/she should immediately contact the health facility, get tested as per national guidelines and follow the standard treatment protocol.
- All asymptomatic contacts of laboratory confirmed cases should remain in home quarantine as per the national guidelines, even if they are on prophylactic therapy.
- Simultaneously, proof of concept and pharmacokinetics studies be taken up expeditiously. Findings from these studies and other new evidence will guide any change in the recommendation.

fn20

<https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3>

## **Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial**

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**[This article is a preprint and has not been peer-reviewed \[what does this mean?\]. It reports new medical research that has yet to be evaluated and so should \*not\* be used to guide clinical practice.](#)**

### **Abstract**

**Aims:** Studies have indicated that chloroquine (CQ) shows antagonism against COVID-19 in vitro. However, evidence regarding its effects in patients is limited. This study aims to evaluate the efficacy of hydroxychloroquine (HCQ) in the treatment of patients with COVID-19. **Main methods:** From February 4 to February 28, 2020, 62 patients suffering from COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment, Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of HCQ. **Key findings:** For the 62 COVID-19 patients, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female, the mean age was 44.7 (15.3) years. No difference in the age and sex distribution between the control group and the HCQ group. But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31). Notably, all 4 patients progressed to severe illness that occurred in the control group. However, there were 2 patients with mild adverse reactions in the HCQ treatment group. **Significance:** Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia.

fn21

<https://www.sciencedirect.com/science/article/pii/S1477893920301319>

Volume 34, March–April 2020, 101663

## **Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study**

### **Abstract**

#### **Background**

We need an effective treatment to cure COVID-19 patients and to decrease virus carriage duration.

#### **Methods**

We conducted an uncontrolled, non-comparative, observational study in a cohort of 80 relatively mildly infected inpatients treated with a combination of hydroxychloroquine and azithromycin over a period of at least three days, with three main measurements: clinical outcome, contagiousness as assessed by PCR and culture, and length of stay in infectious disease unit (IDU).

#### **Results**

All patients improved clinically except one 86 year-old patient who died, and one 74 year-old patient still in intensive care. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day7, and 93% at Day8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day5. Consequently patients were able to be rapidly discharged from IDU with a mean length of stay of five days.

#### **Conclusion**

We believe there is urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients at an early stage before irreversible severe respiratory complications take hold and to decrease duration of carriage and avoid the spread of the disease. Furthermore, the cost of treatment is negligible.

fn22

<https://abc7ny.com/coronavirus-treatment-long-island-news-nassau-county/6093072/>

## **Coronavirus News: Long Island doctors embrace combination drug therapy in fighting COVID-19**

By Eyewitness News

Monday, April 13, 2020

PLAINVIEW, Nassau County (WABC) -- Doctors on Long Island are using some decades-old medication with promising results in fighting the novel coronavirus.

Dr. Ryan Saadi, of Quantaira Health, partnered with Dr. Muhammad Alam at Plainview Hospital and Dr. Imtiaz Ahmad, a Harvard-trained epidemiologist and pulmonologist in Florida, to use the much-talked-about hydroxychloroquine combined with the antibiotic doxycycline.

The combination therapy was administered to dozens of high-risk COVID-19 patients at three long term care facilities on Long Island. They say most of those patients have now fully recovered.

"I'll be honest with you, this was not something I was expecting to see," Dr. Saadi said.

Although impressive, not everyone completed the therapy with positive results.

Out of 54 patients with a median age of 67, nine of them did not complete the six-day therapy due to side effects, a hospital transfer, and three of them died.

The results of the small group study were submitted to a major medical journal for review. A total of 45 COVID-19 patients did complete the combination therapy successfully and clinically recovered.

"Forty-five patients, and these are high risk, and they completely recover?" Dr. Saadi said. "I mean, that number is powerful. We have to look into that."

The FDA has not approved the combination therapy for use against COVID-19 and urges the public to avoid using the drugs at home.

ABC News Chief Medical Correspondent Dr. Jen Ashton says the therapy still needs to undergo a clinical trial.

"When you do a clinical trial, we need to study a lot of patients," she said. "The smaller the number in a trial, the less valid the results are thought to be. So while we are always looking for promise and hope, it is really important to think critically."

Dr. Saadi agrees and said this is a situation of urgency, and a clinical trial can happen in two to three weeks.

It is a race to give suffering families some relief potentially.

fn23

<https://pubmed.ncbi.nlm.nih.gov/32418114/>

Sci China Life Sci. 2020 May 15;1-7.

doi: 10.1007/s11427-020-1732-2. Online ahead of print.

## **Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19**

### **Abstract**

Coronavirus disease 2019 (COVID-19) is a pandemic with no specific drugs and high fatality. The most urgent need is to find effective treatments. We sought to determine whether hydroxychloroquine (HCQ) application may reduce the death risk of critically ill COVID-19 patients. In this retrospective study, we included 550 critically ill COVID-19 patients who need mechanical ventilation in Tongji Hospital, Wuhan, from February 1, 2020 to April 4, 2020. All 550 patients received comparable basic treatments including antiviral drugs and antibiotics, and 48 of them were treated with oral HCQ treatment (200 mg twice a day for 7-10 days) in addition to the basic treatments. Primary endpoint is fatality of patients, and inflammatory cytokine levels were compared between HCQ and non-hydroxychloroquine (NHCQ) treatments. We found that fatalities are 18.8% (9/48) in HCQ group, which is significantly lower than 47.4% (238/502) in the NHCQ group ( $P < 0.001$ ). The time of hospital stay before patient death is 15 (10-21) days and 8 (4-14) days for the HCQ and NHCQ groups, respectively ( $P < 0.05$ ). The levels of inflammatory cytokine IL-6 were significantly reduced from 22.2 (8.3-118.9)  $\text{pg mL}^{-1}$  at the beginning of the treatment to 5.2 (3.0-23.4)  $\text{pg mL}^{-1}$  ( $P < 0.05$ ) at the end of the treatment in the HCQ group but there is no change in the NHCQ group. These data demonstrate that addition of HCQ on top of the basic treatments is highly effective in reducing the fatality of critically ill patients of COVID-19 through attenuation of inflammatory cytokine storm. Therefore, HCQ should be prescribed as a part of treatment for critically ill COVID-19 patients, with possible outcome of saving lives. hydroxychloroquine, IL-6, mortalities, COVID-19.

### **Conflict of interest statement**

The author(s) declare that they have no conflict of interest. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

fn24

<https://pgibertie.files.wordpress.com/2020/04/2020.04.15-journal-manuscript-final.pdf>

### **Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine**

Abstract Background: Telemedicine can facilitate patient's assessment with initial flu-like symptoms in the COVID-19 pandemic, moreover it promotes social isolation. Hydroxychloroquine and azithromycin are associated with reduction in COVID-19 patients' viral load. This study aims to assess whether empirical prescription of hydroxychloroquine and azithromycin for patients with suspected COVID-19 is associated with less need for hospitalization Methods: A telemedicine team evaluated suspected COVID-19 outpatients with flu-like symptoms, if no contraindications were detected, treatment with hydroxychloroquine and azithromycin was prescribed after consent from subjects. Patients were monitored daily by telemedicine appointments. Results: Of the 636 symptomatic outpatients, 412 started treatment with hydroxychloroquine and azithromycin and 224 refused medications (control group). Need for hospitalization was 1.9% in the treatment group and 5.4% in the control group (2.8 times greater) and number needed to treat was 28 (NNT = 28). In those who started treatment before versus after the seventh day of symptoms, the need for hospitalization was 1.17% and 3.2%, respectively. Conclusion: Empirical treatment with hydroxychloroquine associated with azithromycin for suspected cases of COVID-19 infection reduces the need for hospitalization ( $p < 0.001$ ).

Funding: this study does not have any type of funding

fn25

[https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3575899](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3575899)

## **Countries which Primarily Use Antimalarial Drugs As COVID-19 Treatment See Slower Dynamic of Daily Deaths**

16 Pages Posted: 21 Apr 2020

[Maxime Izoulet](#)

### **Abstract**

COVID-19 (Coronavirus Disease-2019) is an international public health problem with a high rate of severe clinical cases. Several treatments are currently being tested worldwide. This paper focuses on anti-malarial drugs such as chloroquine or hydroxychloroquine, which have been currently reviewed by a systematic study as a good potential candidate and that has been reported as the most used treatment by a recent survey of physicians. We compare the dynamics of COVID-19 daily deaths in countries using anti-malaria drugs as a treatment from the start of the epidemic versus countries that do not, the day of the 3rd death and the following 10 days. We show that the first group have a much slower dynamic in daily deaths than the second group. This univariate analysis is of course only one additional piece of evidence in the debate regarding the efficiency of anti-malaria drugs, and it is also limited as the two groups certainly have other systemic differences in the way they responded to the pandemic, in the way they report death or in their population that better explain differences in dynamics (systematic differences that may also explain their choice to rely on anti-malaria drugs in the first place). Nevertheless, the difference in dynamics of daily deaths is so striking that we believe that the urgency context commands presenting the univariate analysis before delving into further analysis. In the end, this data might ultimately be either a piece of evidence in favor of anti-malaria drugs or a stepping stone in understanding further what other ecological aspects play a role in the dynamics of COVID-19 deaths.

**Note:** Funding: None.

Conflict of Interest: None.

fn26

<https://www.medrxiv.org/content/10.1101/2020.04.18.20063875v2>

## **National Consumption of Antimalarial Drugs and COVID-19 Deaths Dynamics : an Ecological Study**

Maxime Izoulet

### **Abstract**

COVID-19 (Coronavirus Disease-2019) is an international public health problem with a high rate of severe clinical cases. Several treatments are currently being tested worldwide. This paper focuses on anti-malarial drugs such as chloroquine or hydroxychloroquine, which have been currently reviewed by a systematic study as a good potential candidate and that has been reported as the most used treatment by a recent survey of physicians. We compare the dynamics of COVID-19 death rates in countries using anti-malaria drugs as a treatment from the start of the epidemic versus countries that do not, the day of the 3rd death and the following 10 days. We show that the first group have a much slower dynamic in death rates than the second group. This univariate analysis is of course only one additional piece of evidence in the debate regarding the efficiency of anti-malaria drugs, and it is also limited as the two groups certainly have other systemic differences in the way they responded to the pandemic, in the way they report death or in their population that better explain differences in dynamics (systematic differences that may also explain their choice to rely on anti-malaria drugs in the first place). Nevertheless, the difference in dynamics is so striking that we believe that the urgency context commands presenting the univariate analysis before delving into further analysis. In the end, this data might ultimately be either a piece of evidence in favor of anti-malaria drugs or a stepping stone in understanding further what other ecological aspects place a role in the dynamics of COVID-19 deaths.

### **Competing Interest Statement**

no competing interests to declare

### **Funding Statement**

no external funding



fn27

[https://www.researchgate.net/publication/341197843\\_COVID-19\\_in\\_Iran\\_a\\_comprehensive\\_investigation\\_from\\_exposure\\_to\\_treatment\\_outcomes](https://www.researchgate.net/publication/341197843_COVID-19_in_Iran_a_comprehensive_investigation_from_exposure_to_treatment_outcomes)

### **COVID-19 in Iran, a comprehensive investigation from exposure to treatment outcomes**

**Preprint (PDF Available)** · May 2020 *with* 896 Reads

#### Abstract

**Background** There is a growing need for information regarding the recent coronavirus disease of 2019 (Covid-19). We present a comprehensive report of Covid-19 patients in Iran. **Methods** One hundred hospitalized patients with Covid-19 were studied. Data on potential source of exposure, demographic, clinical, and paraclinical features, therapy outcome, and post-discharge follow-up were analyzed. **Results** The median age of the patients was 58 years, and the majority of the patients (72.7%) were above 50 years of age. Fever was present in 45.2% of the patients on admission. The most common clinical symptoms were shortness of breath (74%) and cough (68%). Most patients had elevated C-reactive protein (92.3%), elevated erythrocyte sedimentation rate (82.9%), lymphocytopenia (74.2 %) on admission. Lower lobes of the lung were most commonly involved, and ground-glass opacity (81.8%) was the most frequent finding in CT scans. The administration of hydroxychloroquine improved the clinical outcome of the patients. Lopinavir/ritonavir was efficacious at younger ages. Of the 70 discharged patients, 40% had symptom relapse, (8.6%) were readmitted to the hospital, and 3 patients (4.3%) died. **Conclusions** This report demonstrates a heterogeneous nature of clinical manifestations in patients affected with Covid-19. The most common presenting symptoms are non-specific, so attention should be made on broader testing, especially in age groups with the greatest risk and younger individuals who can serve as carriers of the disease. Hydroxychloroquine and lopinavir/ritonavir (in younger age group) can be potential treatment options. Finally, patients discharged from the hospital should be followed up because of potential symptom relapse.

fn28

<https://www.europeanreview.org/wp/wp-content/uploads/4539-4547.pdf>

European Review for Medical and Pharmacological Sciences 2020; 24: 4539-4547 S.A. MEO1 , D.C. KLONOFF2, J. AKRAM3

### **Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19**

**Abstract.** – **OBJECTIVE:** The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called COVID-19, has caused a pandemic which has swiftly involved the entire world and raised great public health concerns. The scientific community is actively exploring treatments that would potentially be effective in combating COVID-19. Hydroxychloroquine has been demonstrated to limit the replication of SARS-CoV-2 virus in vitro. In malarial pandemic countries, chloroquine is widely used to treat malaria. In malarial non-pandemic nations, chloroquine is not widely used. Chloroquine and hydroxychloroquine share similar chemical structures and mechanisms of action. The aim of this study was to indirectly

investigate the efficacy of chloroquine and hydroxychloroquine for the treatment of COVID-19 by determining the prevalence of COVID-19 in malaria pandemic and non-pandemic nations. We sought evidence to support or refute the hypothesis that these drugs could show efficacy in the treatment of COVID-19. MATERIALS AND METHODS: We reviewed in vitro studies, in vivo studies, original studies, clinical trials, and consensus reports, that were conducted to evaluate the antiviral activities of chloroquine and hydroxychloroquine. The studies on “COVID-19 and its allied treatment were found from World Health Organization (WHO), ISI-Web of Science, PubMed, EMBASE, Scopus, Google Scholar, and clinical trial registries. The search was based on keywords: antiviral drugs, chloroquine, hydroxychloroquine, COVID-19, COVID-19 treatment modalities, and coronavirus. In addition, we analyzed the prevalence of COVID-19 in malaria pandemic and non-pandemic countries. The review and analyses were performed on March 28, 2020. RESULTS: For this study, we identified a total of 09 published articles: 03 clinical trials with sample size 150; 03 in vitro studies and 03 expert consensus reports. These studies were all suggestive that chloroquine and hydroxychloroquine can successfully treat COVID-19 infections. We found that COVID-19 infections are highly pandemic in countries where malaria is least pandemic and are least pandemic in nations where malaria is highly pandemic. CONCLUSIONS: Chloroquine and hydroxychloroquine have antiviral characteristics in vitro. The findings support the hypothesis that these drugs have efficacy in the treatment of COVID-19. People are currently using these drugs for malaria. It is reasonable, given the hypothetical benefit of these two drugs, that they are now being tested in clinical trials to assess their effectiveness to combat this global health crisis.

**Introduction** The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called COVID-19 emerged in December 2019 and swiftly spread worldwide. As of March 28, 2020, it involved 197 countries and has infected 571,678 people with a mortality rate of 26494 (4.63%)<sup>1</sup>. Viral infections are the most contagious infectious diseases and are common triggers for constituting major biological, clinical and socioeconomic problems worldwide<sup>2</sup>. Human infections with COVID-19 have raised great public health concern globally<sup>2</sup>. The World Health Organization (WHO) has declared “COVID-19” outbreak as a global public health emergency<sup>1</sup>.

The COVID-19 virus strain belongs to the betacoronavirus genus which also includes SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) characteristics. This virus is transmitted from animal to animal, animal to human and human to human<sup>1,3</sup>. Currently more than one billion people are in lockdown in their homes, flights have been cancelled, and the global transportation system has become paralyzed worldwide in response to the highly contagious nature of the COVID-19. Presently, there is no acknowledged effective remedy for COVID-19 infection. Hydroxychloroquine and chloroquine have similar chemical structures and cellular mechanisms of action<sup>4</sup>. Recent literature has suggested the possibility that these drugs could be used as antiviral drugs to cure COVID-19 infections<sup>5</sup>. This study’s aim was to investigate indirect epidemiologic evidence of the antiviral characteristics of hydroxychloroquine and chloroquine in the treatment of COVID-19 infection and to analyze the prevalence trends of COVID-19 in malaria-pandemic countries. **Materials and Methods** We searched in vitro/in vivo studies, original studies, clinical trials, and expert consensus reports (that were written in English or contained an abstract written in English) about the antiviral activities of hydroxychloroquine and chloroquine and their efficacy as treatments of novel Coronavirus COVID-19 infections. We recorded the data on the prevalence trends of COVID-19 in malaria pandemic and non-pandemic countries. The data were obtained from the World Health Organization<sup>1,6</sup>, reports published in the

Institute of Scientific Information (ISI) Web of Knowledge, Thomson Reuter journals<sup>7</sup>, “PubMed, Medline”<sup>8</sup> and clinical trial registries<sup>9</sup>. The relevant studies were explored through keywords including antiviral drugs, chloroquine, hydroxychloroquine, COVID-19, COVID-19 treatment modalities, and coronavirus. In addition, we also recorded the prevalence trends of COVID-19 in malaria-pandemic countries. The malaria pandemic countries data was collected from the World Health Organization<sup>6</sup>. Each article was selected based on its title topic and its abstract. We included a total of 09 published articles: 03 clinical trials with sample size: 150; 03 in vitro studies; and 03 expert consensus reports. After the studies had been shortlisted, the appropriate characteristics, drug efficacy and prevalence findings were recorded and analyzed. Ethical Statement and Statistical Analysis In this study the information about the characteristics of hydroxychloroquine, chloroquine and prevalence of novel COVID-19 infection was obtained from the World Health Organization, ISI-Web of Knowledge, Thomson Reuter journals<sup>7</sup>, “Pub-Med, Medline<sup>8</sup>,” and clinical trial registries<sup>9</sup>. Hence, ethical approval was not required. The findings were recorded, tabulated and outcomes were expressed. Results In this study, we selected total 09 published articles: 03 clinical trials with sample size: 150; 03 in vitro studies; and 03 expert consensus. After the studies had been shortlisted, the appropriate characteristics, drug efficacy and prevalence findings were recorded and analyzed. The basic science in vitro data was suggestive (but not conclusive) that chloroquine and hydroxychloroquine can inhibit COVID-19 infections (Table I). The clinical and consensus data from the literature review was also suggestive (but not conclusive) that chloroquine and hydroxychloroquine can successfully treat COVID-19 infections (Tables II and III). We also established a link between COVID-19 and its spread in malaria pandemic nations. On March 28, 2020 there were 571678 confirmed cases worldwide, with a mortality rate of 26494 (4.63%). The most affected continents were the European Region 324343 (56.73% of the total deaths); Western Pacific Region 101462 (17.74%); American Region 100314 (17.54%); Eastern Mediterranean Region 38931 (6.80%); and South-East Asia Region 3085 (0.53%); the least affected region was Africa 2831 (0.49%) (Table IV, Figures 1, 2). The present outbreak of COVID-19 infection markedly affected countries which are malaria-free, such as Italy 86498 (15.13% of the total cases in malaria non-pandemic countries), United States 85228 (14.90%), China 82230 (14.38%), Spain 64059 (11.20%), Germany 48582 (8.49%), France 32542 (5.69%), Switzerland 12104 (2.11%), and United Kingdom 14547 (2.54%). The findings from WHO incidence data demonstrate that COVID-19 is highly pandemic in countries where malaria is least pan-demic, and COVID-19 is least pandemic in nations where malaria is highly pandemic (Figures 1-3). The findings were significantly correlated (Figure 3). Assuming that in malaria-endemic countries a significant fraction of the population uses chloroquine or hydroxychloroquine regularly, this international malaria incidence and COVID-19 incidence data, is consistent with (although not proof of) a beneficial effect of hydroxychloroquine and chloroquine in restraining the replication of SARS-CoV-2 virus causing COVID-19 (Table I). Discussion In this study, we tested the hypothesis that hydroxychloroquine and chloroquine could be useful for treating COVID-19. From the epidemiologic data we identified, we could not refute this hypothesis. In the current pandemic crisis of COVID-19, there is no proven recommended therapy for COVID-19 other than supportive care.

Chloroquine, a widely used anti-malarial has been reported as a potential broad-spectrum antiviral drug<sup>10,11</sup>. Chloroquine blocks viral infections by increasing endosomal pH which then interferes with virus/cell fusion. This drug also interferes with the glycosylation of cellular receptors for SARS-CoV and hence decreases virus-cell binding<sup>12</sup>. Wang et al<sup>13</sup> reported that chloroquine works at entry and post-entry phases of the 2019-nCoV infection in Vero E6 cells. It has an additional immune-modulating activity, which may enhance its antiviral effect in vivo if used collectively. Moreover, the concentration

of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90  $\mu$ M, which can be clinically achieved, as demonstrated in the plasma of rheumatoid arthritis patients who received administration of 500mg. Chen et al<sup>14</sup> investigated the effectiveness and safety of hydroxychloroquine in the treatment of COVID-19 patients. The authors enrolled total 30 subjects (15 with a COVID-19 infection and 15 controls). The subjects were randomized 1:1 to a hydroxychloroquine group and a control group. Subjects in the hydroxychloroquine group received hydroxychloroquine 400 mg per day for 5 days while those in the control group received only conventional treatment. The primary endpoint was a negative conversion rate of COVID-19 nucleic acid in a respiratory pharyngeal swab on day 7 after randomization. COVID-19 nucleic acid in throat swabs was negative in 13 (86.7%) cases in the hydroxychloroquine group and 14 (93.3%) cases in the control group. The median duration from hospitalization to virus nucleic acid negative conversion was 4 days in hydroxychloroquine group, which was comparable to that in the control group 1-4 days. The median time for body temperature normalization in the hydroxychloroquine group was 0-2 days after hospitalization, which was also comparable to that in the control group 0-3 days. Radiological progression was shown on CT images in 5 cases (33.3%) of the hydroxychloroquine group and 7 cases (46.7%) of the control group, and all subjects showed improvement in follow-up examinations. Four cases (26.7%) of the hydroxychloroquine group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function. A problem with interpreting whether hydroxychloroquine was beneficial in this study was the high conversion rate of the control subjects (14 of 15), leaving little room for a statistically significant better outcome to be achieved with any intervention. Gautret et al<sup>15</sup> performed a clinical trial study on subjects with COVID-19 infections who received 600 mg of hydroxychloroquine daily. The authors found that hydroxychloroquine was associated with viral load reduction and viral disappearance in these COVID-19 subjects. Moreover, its impact was magnified by the addition of azithromycin. This latter drug has been shown to block viral internalization into host cells<sup>16</sup>. Yao et al<sup>17</sup> and Liu et al<sup>18</sup> conducted in vitro studies on COVID-19. Cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019. The pharmacological properties of chloroquine and hydroxychloroquine were investigated by using SARS-CoV-2 infected Vero cells. It was found that chloroquine was highly effective in the control of 2019-nCoV infection in vitro. Hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 in vitro. Gao et al<sup>18</sup> conducted a clinical trial on 100 COVID-19-infected Chinese patients. The authors presented their findings in a scientific session with a team of experts from government and regulatory authorities, along with organizers of clinical trials. They noted that chloroquine had a significant effect both in terms of clinical outcome and viral clearance compared to control groups. Chloroquine was found to be useful in inhibiting the exacerbation of pneumonia, improving lung imaging, and bringing about virus-negative results, therefore shortening the disease's course. The experts group concluded that chloroquine phosphate has potent activity against COVID-19 and added the drug in the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19 under the National Health Commission of the People's Republic of China. Zhou et al<sup>19</sup> demonstrated that hydroxychloroquine could provide better outcomes than chloroquine for the treatment of SARS-CoV-2 infection. The authors highlighted three likely mechanisms for how these two drugs are beneficial for protecting from the development of and complications from COVID-19 virus infections: (1) inhibition of receptor binding by the virus; (2) inhibition of membrane fusion by the virus; and (3) immune modulation to decrease cytokine release. Hydroxychloroquine appears to decrease the dangerous progression of COVID-19 toward cytokine storm by reducing CD154 expression in T-cells. Moreover, the authors suggested that hydroxychloroquine, compared to chloroquine, has fewer side effects, and is more potent at maximum tolerated doses.

Finally, consensus reports were published by experts 2020-22 under multicenter collaboration by the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Consensus and State Council of China. These expert groups recommended chloroquine phosphate tablet, 500mg twice per day for 10 days, for patients diagnosed as mild, moderate, and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine. In the present study, besides reviewing evidence supporting the hypothesis that chloroquine and hydroxychloroquine might be useful for COVID-19 infections, we also established a possible correlation between the outbreak of COVID-19 and its spread in malaria pandemic nations. The present outbreak of COVID-19 infection has markedly spread to countries and continents which are Malaria-free such as China, Italy, United States, Spain, Germany, France, Switzerland, United Kingdom and Iran. However, its incidence is very low in south-east Asian and African countries where malaria is pandemic (Table IV, Figures 1-3), despite most of these countries' health infrastructure being quite fragile. A possible explanation behind this could be that these latter nations frequently suffer from malaria and the population frequently takes antimalarial drugs including hydroxychloroquine and chloroquine. These two drugs, which are malaria treatments might be linked to the lower reported incidence of COVID-19 infections in these malaria-endemic countries, compared to many malaria non-endemic countries, because chloroquine appears to have broad-spectrum antiviral properties<sup>22</sup>. The possible mechanism of antiviral intervention by chloroquine is a multi-targeted mechanism, depending on the time point at which the drug is added. When added during and shortly after the infection, chloroquine may raise intracellular pH and then inhibit the endosome-mediated fusion of the virus with human cells. When the drug is given after this first target, it can still act on later stages of the viral life cycle, as reported for other viruses<sup>23</sup>. We believe it is significant that on March 29, 2020 the United States Food and Drug Administration issued an emergency use authorization for hydroxychloroquine and chloroquine for COVID-19 infections<sup>24</sup>. This is the first systematic analysis article, to our knowledge, on the relationship between the incidence of COVID-19 infections and the incidence of malaria according to country. We looked at this relationship because we assumed that countries with a higher incidence of malaria also have a higher likelihood of widespread use of chloroquine and hydroxychloroquine. A strength of this study is its up-to-date data on the national incidences of COVID as of the day prior to journal submission. Another strength is that the study data was gathered using reliable sources including "World Health Organization, Web of Science, Pub-Med, Medline, EMBASE, and Scopus databases" and clinical trial registry. Three limitations of this study are as follows: (1) We assumed that the numbers of patients with COVID-19 have been correctly tabulated in countries where malaria is and is not endemic. Some malaria-endemic countries are resource-poor, and it is possible that they have not tested their citizens as widely as some malaria non-pandemic countries with more resources. (2) We assumed that in malaria-endemic countries a significant fraction of the population uses chloroquine or hydroxychloroquine regularly. However, there is no accurate data available as to what percentage of the population in malaria-endemic countries actually use these two drugs. A third limitation of this study is the limited number of studies that were available from our data sources as to the clinical benefits of using these two drugs for COVID-19 infections, and we could not identify any randomized controlled trials of these two drugs for this type of infection. Conclusions In this study, we tested the hypothesis that hydroxychloroquine and chloroquine could be useful for treating COVID-19. From the epidemiologic data that we assembled and the basic science and clinical literature about these drugs that we reviewed, we could not refute this hypothesis. We urge the global scientific community to organize large randomized controlled trials to test this hypothesis during this global health crisis.

fn29 (see fn23)

<https://pubmed.ncbi.nlm.nih.gov/32418114/>

fn30

<https://www.mediterranee-infection.com/wp-content/uploads/2020/04/MS.pdf>

**Full-length title: Early treatment of 1061 COVID-19 patients with hydroxychloroquine and azithromycin, Marseille, France Short title: Treatment of COVID-19**

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#### ABSTRACT

**BACKGROUND:** Hydroxychloroquine (HCQ) and azithromycin (AZ) are promising drugs against COVID-19.

**METHODS:** We conducted an uncontrolled non-comparative observational study in a cohort of 1061 unpublished infected patients treated with HCQ+AZ combination for at least three days. Endpoints were death, worsening and viral shedding persistence.

**RESULTS:** Good clinical outcome and virological cure were obtained in 973 patients within 10 days (91.7%). Prolonged viral carriage was observed in 47 patients (4.4%) and was associated to a higher viral load at diagnosis ( $p < 10^{-2}$ ) but viral culture was negative at day 10. All but one were PCR-cleared at day 15. A poor clinical outcome was observed for 46 patients (4.3%) and 8 died (0.75%) (74-95 years old). Mortality was lower than in patients treated with other regimens in all Marseille public hospitals ( $p < 10^{-2}$ ). Five patients are still hospitalized (98.7% of patients cured so far). Poor clinical outcome was associated to older age (OR 1.11), initial higher severity (OR 10.05) and low HCQ serum concentration. Poor clinical and virological outcomes were associated to the use of selective beta-blocking agents and angiotensin II receptor blockers ( $P < 0.05$ ). No cardiac toxicity was observed.

**CONCLUSION:** Early HCQ+AZ combination is a safe and efficient treatment for COVID19.

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<https://www.sciencedirect.com/science/article/pii/S2052297520300615?via%3Dihub>

### [New Microbes and New Infections](#)

Available online 6 June 2020, 100709

## **Clinical Efficacy of Chloroquine derivatives in COVID-19 Infection: Comparative meta-analysis between the Big data and the real world**

Author links open overlay

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### **Abstract**

In the context of the current COVID-19 pandemic, we conducted a meta-analysis on the effects of chloroquine derivatives in patients, based on unpublished and published reports available publicly on the internet as of May, 27, 2020. The keywords “hydroxychloroquine”, “chloroquine”, “coronavirus”, “COVID-19” and “SARS-Cov-2” were used in the PubMed, Google Scholar and Google search engines without any restrictions as to date or language. Twenty studies were identified involving 105,040 patients (19,270 treated patients) from nine countries (Brazil, China, France, Iran, Saudi Arabia, South Korea, Spain, and USA). Big data observational studies were associated with conflict of interest, lack of treatment dosage and duration, and absence of favorable outcome. Clinical studies were associated with favorable outcomes and details on therapy. Among clinical studies, three of four randomized controlled trials reported a significant favorable effect. Among clinical studies, a significant favorable summary effect was observed for duration of cough (Odds ratio (OR), 0.19,  $p = .00003$ ), duration of fever (0.11,  $p = .039$ ), clinical cure (0.21,  $p = .0495$ ), death (0.32,  $p = 4.1 \times 10^{-6}$ ) and viral shedding (0.43,  $p = .031$ ). A trend for a favorable effect was noted for the outcome “death and/or ICU transfer” (0.29,  $p = .069$ ) with a point estimate remarkably similar to that observed for death ( $\sim 0.3$ ). In conclusion, a meta-analysis of publicly available clinical reports demonstrates that chloroquine derivatives are effective to improve clinical and virological outcomes but, more importantly, it reduces mortality by a factor 3 in patients infected with COVID-19. Big data are lacking basic treatment definitions and are linked to conflict of interest.

## ORIGINAL ARTICLE

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### Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

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**Background & objectives:** Healthcare workers (HCWs) are at an elevated risk of contracting COVID-19. While intense occupational exposure associated with aerosol-generating procedures underlines the necessity of using personal protective equipment (PPE) by HCWs, high-transmission efficiency of the causative agent [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] could also lead to infections beyond such settings. Hydroxychloroquine (HCQ), a repurposed antimalarial drug, was empirically recommended as prophylaxis by the National COVID-19 Task Force in India to cover such added risk. Against this background, the current investigation was carried out to identify the factors associated with SARS-CoV-2 infection among HCWs in the country.

**Methods:** A case-control design was adopted and participants were randomly drawn from the countrywide COVID-19 testing data portal maintained by the ICMR. The test results and contact details of HCWs, diagnosed as positive (cases) or negative (controls) for SARS-CoV-2 using real-time reverse transcription-polymerase chain reaction (qRT-PCR), were available from this database. A 20-item brief-questionnaire elicited information on place of work, procedures conducted and use of PPE.

**Results:** Compared to controls, cases were slightly older (34.7 vs. 33.5 yr) and had more males (58 vs. 50%). In multivariate analyses, HCWs performing endotracheal intubation had higher odds of being SARS-CoV-2 infected [adjusted odds ratio (AOR): 4.33, 95% confidence interval (CI): 1.16-16.07]. Consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22-0.88); a dose-response relationship existed between frequency of exposure to HCQ and such reductions ( $\chi^2$  for trend=48.88;  $P < 0.001$ ). In addition, the use of PPE was independently associated with the reduction in odds of getting infected with SARS-CoV-2.

**Interpretations & conclusions:** Until results of clinical trials for HCQ prophylaxis become available, this study provides actionable information for policymakers to protect HCWs at the forefront of COVID-19 response. The public health message of sustained intake of HCQ prophylaxis as well as appropriate PPE use need to be considered in conjunction with risk homeostasis operating at individual levels.



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<https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/32611916>

**Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19.**

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Jul 3, 2020

Chatterjee, Pranab; Anand, Tanu; Singh, Kh Jitenkumar; Rasaily, Reeta; Singh, Ravinder; Das, Santasabuj; Singh, Harpreet; Praharaj, Ira; Gangakhedkar, Raman R; Bhargava, Balram; Panda, Samiran

Indian J Med Res

**Background & objectives:** Healthcare workers (HCWs) are at an elevated risk of contracting COVID-19. While intense occupational exposure associated with aerosol-generating procedures underlines the necessity of using personal protective equipment (PPE) by HCWs, high-transmission efficiency of the causative agent [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] could also lead to infections beyond such settings. Hydroxychloroquine (HCQ), a repurposed antimalarial drug, was empirically recommended as prophylaxis by the National COVID-19 Task Force in India to cover such added risk. Against this background, the current investigation was carried out to identify the factors associated with SARS-CoV-2 infection among HCWs in the country. **Methods:** A case-control design was adopted and participants were randomly drawn from the countrywide COVID-19 testing data portal maintained by the ICMR. The test results and contact details of HCWs, diagnosed as positive (cases) or negative (controls) for SARS-CoV-2 using real-time reverse transcription-polymerase chain reaction (qRT-PCR), were available from this database. A 20-item brief-questionnaire elicited information on place of work, procedures conducted and use of PPE. **Results:** Compared to controls, cases were slightly older (34.7 vs. 33.5 yr) and had more males (58 vs. 50%). In multivariate analyses, HCWs performing endotracheal intubation had higher odds of being SARS-CoV-2 infected [adjusted odds ratio (AOR): 4.33, 95% confidence interval (CI): 1.16-16.07]. Consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22-0.88); a dose-response relationship existed between frequency of exposure to HCQ and such reductions ( $\chi^2$  for trend=48.88;  $P < 0.001$ ). In addition, the use of PPE was independently associated with the reduction in odds of getting infected with SARS-CoV-2. **Interpretations & conclusions:** Until results of clinical trials for HCQ prophylaxis become available, this study provides actionable information for policymakers to protect HCWs at the forefront of COVID-19 response. The public health message of sustained intake of HCQ prophylaxis as well as appropriate PPE use need to be considered in conjunction with risk homeostasis operating at individual levels.

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<https://www.medrxiv.org/content/10.1101/2020.06.26.20056507v1>

### **Chronic treatment with hydroxychloroquine and SARS-CoV-2 infection.**

Antonio Ferreira, Antonio Oliveira-e-Silva, Paulo Bettencourt

#### **Abstract**

Background: Hydroxychloroquine sulphate (HCQ) is being scrutinized for repositioning in the treatment and prevention of SARS-Cov-2 infection. This antimalarial drug is also chronically used to treat patients with autoimmune diseases. Methods: By analyzing the Portuguese anonymized data on private and public based medical prescriptions we have identified all cases chronically receiving HCQ for the management of diseases such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Additionally, we have detected all laboratory confirmed cases of SARS-CoV-2 infection and all laboratory confirmed negative cases in the Portuguese population (mandatorily registered in a centrally managed database). Cross linking the two sets of data has allowed us to compare the proportion of HCQ chronic treatment (at least 2 grams per month) in laboratory confirmed cases of SARS-CoV-2 infection with laboratory confirmed negative cases. Results: Out of 26,815 SARS-CoV-2 positive patients, 77 (0.29%) were chronically treated with HCQ, while 1,215 (0.36%) out of 333,489 negative patients were receiving it chronically (P=0.04). After adjustment for age, sex, and chronic treatment with corticosteroids and/or immunosuppressants, the odds ratio of SARS-CoV-2 infection for chronic treatment with HCQ has been 0.51 (0.37-0.70). Conclusions: Our data suggest that chronic treatment with HCQ confer protection against SARS-CoV-2 infection.

#### **Competing Interest Statement**

The authors have declared no competing interest.

#### **Funding Statement**

No external funding was received.

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<https://www.ijidonline.com/action/showPdf?pii=S1201-9712%2820%2930534-8>

## **Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19**

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**Significance:** The United States is in an acceleration phase of the COVID-19 pandemic. Currently there is no known effective therapy or vaccine for treatment of SARS-CoV-2, highlighting urgency around identifying effective therapies. **Objective:** The purpose of this study was to evaluate the role of hydroxychloroquine therapy alone and in combination with azithromycin in hospitalized patients positive for COVID-19.

**Design:** Multi-center retrospective observational study. **Setting:** The Henry Ford Health System (HFHS) in Southeast Michigan: large six hospital integrated health system; the largest of hospitals is an 802-bed quaternary academic teaching hospital in urban Detroit, Michigan. **Participants:** Consecutive patients hospitalized with a COVID-related admission in the health system from March 10, 2020 to May 2, 2020 were included. Only the first admission was included for patients with multiple admissions. All patients evaluated were 18 years of age and older and were treated as inpatients for at least 48 h unless expired within 24 h. **Exposure:** Receipt of hydroxychloroquine alone, hydroxychloroquine in combination with azithromycin, azithromycin alone, or neither.

**Main outcome:** The primary outcome was in-hospital mortality. **Results:** Of 2,541 patients, with a median total hospitalization time of 6 days (IQR: 4–10 days), median age was 64 years (IQR: 53–76 years), 51% male, 56% African American, with median time to follow-up of 28.5 days (IQR: 3–53). Overall in-hospital mortality was 18.1% (95% CI: 16.6%–19.7%); by treatment: hydroxychloroquine + azithromycin, 157/783 (20.1% [95% CI: 17.3%–23.0%]), hydroxychloroquine alone, 162/1202 (13.5% [95% CI: 11.6%–15.5%]), azithromycin alone, 33/147 (22.4% [95% CI: 16.0%–30.1%]), and neither drug, 108/409 (26.4% [95% CI: 22.2%–31.0%]). Primary cause of mortality was respiratory failure (88%); no patient had documented torsades de pointes. From Cox regression modeling, predictors of mortality were age > 65 years (HR: 2.6 [95% CI: 1.9–3.3]), white race (HR: 1.7 [95% CI: 1.4–2.1]), CKD (HR: 1.7 [95% CI: 1.4–2.1]), reduced O<sub>2</sub> saturation level on admission (HR: 1.5 [95% CI: 1.1–2.1]), and ventilator use during admission (HR: 2.2 [95% CI: 1.4–3.3]). Hydroxychloroquine provided a 66% hazard ratio reduction, and hydroxychloroquine + azithromycin 71% compared to neither treatment (p < 0.001).

**Conclusions and relevance:** In this multi-hospital assessment, when controlling for COVID-19 risk factors, treatment with hydroxychloroquine alone and in combination with azithromycin was associated with reduction in COVID-19 associated mortality. Prospective trials are needed to examine this impact. © 2020 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-ncnd/4.0/>).

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<https://link.springer.com/article/10.1007/s11606-020-05983-z>

- Original Research
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### **Risk Factors for Mortality in Patients with COVID-19 in New York City**

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[Journal of General Internal Medicine](#) (2020)

Abstract

Background

New York City emerged as an epicenter of the coronavirus disease 2019 (COVID-19) pandemic.

Objective

To describe the clinical characteristics and risk factors associated with mortality in a large patient population in the USA.

Design

Retrospective cohort study.

Participants

6493 patients who had laboratory-confirmed COVID-19 with clinical outcomes between March 13 and April 17, 2020, who were seen in one of the 8 hospitals and/or over 400 ambulatory practices in the New York City metropolitan area

Main Measures

Clinical characteristics and risk factors associated with in-hospital mortality.

Key Results

A total of 858 of 6493 (13.2%) patients in our total cohort died: 52/2785 (1.9%) ambulatory patients and 806/3708 (21.7%) hospitalized patients. Cox proportional hazard regression modeling showed an

increased risk of in-hospital mortality associated with age older than 50 years (hazard ratio [HR] 2.34, CI 1.47–3.71), systolic blood pressure less than 90 mmHg (HR 1.38, CI 1.06–1.80), a respiratory rate greater than 24 per min (HR 1.43, CI 1.13–1.83), peripheral oxygen saturation less than 92% (HR 2.12, CI 1.56–2.88), estimated glomerular filtration rate less than 60 mL/min/1.73m<sup>2</sup> (HR 1.80, CI 1.60–2.02), IL-6 greater than 100 pg/mL (HR 1.50, CI 1.12–2.03), D-dimer greater than 2 mcg/mL (HR 1.19, CI 1.02–1.39), and troponin greater than 0.03 ng/mL (HR 1.40, CI 1.23–1.62). Decreased risk of in-hospital mortality was associated with female sex (HR 0.84, CI 0.77–0.90), African American race (HR 0.78 CI 0.65–0.95), and hydroxychloroquine use (HR 0.53, CI 0.41–0.67).

## Conclusions

Among patients with COVID-19, older age, male sex, hypotension, tachypnea, hypoxia, impaired renal function, elevated D-dimer, and elevated troponin were associated with increased in-hospital mortality and hydroxychloroquine use was associated with decreased in-hospital mortality.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a pandemic that has impacted medical systems, societies, and economies worldwide. The first case of COVID-19, caused by severe acute respiratory syndrome 2 virus (SARS-CoV-2)<sup>1</sup>, was reported in China in December 2019<sup>2</sup>. The virus has spread globally at a rapid pace, resulting in more than 2 million confirmed cases as of April 17, 2020<sup>3</sup>. In recent weeks, New York City has emerged as an epicenter of the pandemic, with over 120,000 confirmed cases and over 13,000 deaths due to confirmed or probable COVID-19 death as of April 17, 2020<sup>4</sup>. Studies of the clinical characteristics and epidemiologic characteristics of COVID-19 have been conducted in countries experiencing outbreaks earlier than the USA<sup>5,6,7,8,9,10,11</sup>. Large-scale observational data of the clinical characteristics and outcomes of COVID-19 in the population of the USA are scarce. In this study, we describe the clinical characteristics of COVID-19 in ambulatory and inpatient settings and identify risk factors associated with mortality in hospitalized patients.

## Study Design and Participants

A multicenter retrospective cohort study of patients with COVID-19 patients was conducted using the medical records of the Mount Sinai Health System, a large urban health system of 8 hospitals and more than four hundred ambulatory practices in the New York City metropolitan area. Patients with a positive SARS-CoV-2 test result and an encounter with a healthcare provider for COVID-19 between March 12 and April 17, 2020, were included in this study. A confirmed case of COVID-19 was defined as a positive result on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab specimens. The study population was dichotomized into ambulatory and hospitalized groups. The former included patients whose encounter was an office visit, emergency department (ED) visit, or telehealth/telemedicine. Inpatients and ambulatory patients who were subsequently admitted to the hospital were included in the hospitalized group.

Both groups were further subdivided into survivors and non-survivors. Ambulatory non-survivors were patients who had expired prior to presentation to the ED, who had expired in the ED prior to admission to the hospital units, or who had an office or telemedicine encounter and were later found out to be deceased. Ambulatory survivors included all other ambulatory patients. Hospitalized non-survivors were

patients who had expired as of April 17, 2020. Hospitalized survivors were patients who had been discharged home or to other facilities as of April 17, 2020.

Icahn School of Medicine at Mount Sinai has waived informed consent and Institutional Review Board approval because the study used a de-identified database.

### Definitions

The following covariates were extracted from the database: patients' age, sex, ethnicity, race, smoking status, vital signs including temperature, peripheral oxygen saturation (SpO<sub>2</sub>), heart rate, respiratory rate (RR), blood pressure (BP), body mass index (BMI), and laboratory results including white blood cell count (WBC), D-dimer, interleukin-6 (IL-6), hemoglobin, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), procalcitonin, ferritin, lactate dehydrogenase (LDH), fibrinogen (FBG), interleukin-6 (IL-6), comorbidities, and treatments.

### Statistical Analysis

Continuous variables were reported as median with interquartile range. Categorical variables were expressed as proportions. Temporary changes of vital signs and laboratory values in survivors and non-survivors for the first 14 days after admission were assessed. To illustrate the risk associated with changes in the continuous variables, including vital signs and laboratory values, multivariate generalized additive models were used to calculate the odds ratio (OR) for mortality, with each median value set as a reference (i.e., OR = 1). The hazard ratio (HR) of each variable for mortality risk was assessed using univariate Cox proportional hazard regression model. To account for missing data values for laboratory results, we introduced multiple imputation, which is a procedure used to replace missing values with other plausible values by creating multiple filling-in patterns to avert bias caused by missing data. Using the dataset with imputed values, univariate and multivariate Cox model were fit to calculate HR.

The multivariate Cox model was adjusted for the following variables assessed in the univariate Cox model: patients' age, sex, race, cigarette use history, past medical history of asthma, hypertension, diabetes, or cancer, systolic BP, RR, SpO<sub>2</sub>, BMI, initial laboratory values (lymphocyte proportion, D-dimer, IL-6), and hydroxychloroquine use. For this Cox regression analysis, we excluded variables from the univariable analysis if their between-group differences were not significant, if the number of events was too small to calculate hazard ratios, or if they had collinearity with other significant values. Each hospital was considered by the clustering term in the Cox proportional hazard model analysis where the clustering effect associated with hospitals was accounted for by the robust sandwich estimator. Preliminary confirmation of predictability of the Cox proportional hazard model demonstrated the area under the curve (AUC) to be 0.808 (95% CI, 0.790–0.825, Supplementary Figure [1](#)). To investigate the effect of hydroxychloroquine while addressing the imbalance among treatment groups, we introduced inverse probability weighting (IPTW) based on propensity scoring to control for observed differences in baseline characteristics between treatment group and control group. IPTW was calculated based on the same variables as used in the Cox regression models, except for hydroxychloroquine use. We then fitted an IPTW-adjusted Cox with doubly robust methods. Survival curves with stratification for hydroxychloroquine were constructed using the Kaplan-Meier method. All statistical analyses were performed using version 3.6.2 of the R programming language (R Project for Statistical Computing; R Foundation).

## Demographic and Clinical Characteristics

Between March 13 and April 17, there were 6493 confirmed COVID-19 cases, including 2785 (42.9 %) ambulatory patients and 3708 (57.1%) hospitalized patients. The demographics, clinical characteristics, and laboratory findings are shown in Table [1](#). The median age of the group was 59 (interquartile range [IQR] 43 to 72) with 66.6% of the patients older than 50 years of age. 45.5% of the patients were female. Based on patients' self-reported race, 26.9% were white, 24.1% were African American, 4.4% were Asian, and 44.7% were other. Based on self-reported ethnicity, 57.5% were Non-Hispanic, 25.4% were Hispanic, and the rest were unknown or not reported.

## Ambulatory and Hospitalized Comparison

The median age was 47 years old in the ambulatory group (IQR 34 to 60) and 66 years old in the hospitalized group (IQR 55 to 78). 858 patients died (13.2%): 52 patients in the ambulatory group (1.9%) and 806 patients in the hospitalized group (21.7%). Among ambulatory patients, 69% were emergency room encounters without hospital admission, 18.2% were office-based encounters, and 1.4% were telemedicine encounters.

Compared with that of ambulatory patients, a higher proportion of hospitalized patients were older, were male, or had a history of cigarette use. Hospitalized patients were more likely to have coexisting medical conditions including asthma, chronic obstructive pulmonary disease (COPD), hypertension, obesity, diabetes mellitus (DM), chronic kidney disease (CKD), and cancer. Hospitalized patients were more likely to have abnormal vital signs and abnormal laboratory values including higher WBC count, lymphocyte, and neutrophil counts, higher levels of AST, CRP, procalcitonin, ferritin, IL-6, LDH, D-dimer, and troponin, and lower levels of eGFR and hemoglobin. Clinical characteristics of hospitalized patients stratified by age group, gender, race, and hydroxychloroquine use are shown in Supplementary Tables [2](#), [3](#), [4](#), and [5](#), respectively.

## Survivors and Non-Survivors

Clinical characteristics of the 2014 survivors and 806 non-survivors in the hospitalized group are shown in Table [2](#) (Supplementary Table [1](#) for the ambulatory group). The median number of days to discharge for survivors was 5 days (IQR, 3 to 9 days). The median number of days to death for non-survivors was also 5 days (IQR, 3 to 9 days). Compared with survivors, non-survivors were older and the higher proportion were male. Non-survivors were more likely to have a history of cigarette use and coexisting medical conditions including COPD, hypertension, DM, and CKD.

Temporal changes of vital signs and laboratory values in survivors and non-survivors during hospitalization are shown in Figure [1](#). Throughout hospitalization, non-survivors had higher heart rate and respiratory rate and lower oxygen saturation compared with survivors. Initial laboratory findings of non-survivors demonstrated higher WBC count and higher levels of D-dimer, IL-6, AST, CRP, procalcitonin, ferritin, LDH, fibrinogen, and troponin. Throughout hospitalization, non-survivors had higher WBC count, neutrophil proportion, LDH, and ferritin levels, and lower eGFR and lymphocyte proportion. Non-survivors also had higher levels of CRP, D-dimer, and IL-6 in the first week of hospitalization. Non-survivors showed a marked increase in LDH, CRP, D-dimer, AST, ALT, and procalcitonin on day 1 after admission. Both groups had a trend of decreasing hemoglobin levels and increasing platelet counts during hospitalization; however, a more pronounced decrease in hemoglobin

levels was seen in non-survivors, while an increase in platelet counts was greater for survivors. The generalized additive models demonstrated correlations between laboratory values and increased odds of in-hospital mortality which are similar to the difference observed between hospitalized survivors and non-survivors (Supplementary Figure 3).

## Treatment

The majority of hospitalized patients received hydroxychloroquine (74.6% of survivors and 71.3% of non-survivors) and azithromycin (67.4% of survivors and 71.3% of non-survivors). Fewer hospitalized patients received other medications such as remdesivir, anakinra, tocilizumab, or sarilumab (Table 2). The majority of ambulatory patients did not receive hydroxychloroquine or azithromycin. Kaplan-Meier estimate showed lower mortality in hospitalized patients who received hydroxychloroquine (log rank  $P$  value < 0.001) (Supplementary Figure 4).

## Risk Factors Associated with Mortality in Hospitalized Patients

The results of multivariate Cox proportional hazard regression models are shown in Table 3 (univariate models are shown in Supplementary Table 6). Of 3708 hospitalized patients, 888 patients remained hospitalized as of April 7 and were not included in the analysis. In the multivariate analysis, factors associated with a higher risk of in-hospital mortality included age over 50, systolic blood pressure less than 90 mmHg, a respiratory rate greater than 24 per min, SpO<sub>2</sub> less than 92%, eGFR less than 60 mL/min/1.73m<sup>2</sup>, IL-6 greater than 100 pg/mL (6.5 times upper limit of normal [ULN]), D-dimer greater than 2 mcg/mL (4 times ULN), and troponin greater than 0.03 ng/mL. Factors associated with a lower risk of in-hospital mortality included female sex, African American race, and hydroxychloroquine use. The adjustment with IPTW did not lead to a significant change in the HR of hydroxychloroquine (without IPTW: HR 0.53, CI 0.41–0.67; with IPTW: HR 0.53, CI 0.41–0.68).

We report a large retrospective cohort study of both ambulatory and hospitalized patients with COVID-19 from across the New York City metropolitan area. The clinical characteristics described here represent the first large retrospective cohort study from the US population in a city at the epicenter of the pandemic.

Early reports showed that COVID-19 had a mortality rate among all confirmed cases of 2%<sup>12</sup> which is significantly lower compared with that of 34% with MERS<sup>13</sup> and 10% with SARS<sup>14</sup>. The mortality rate in hospitalized patients reported previously ranged from 4 to 28%<sup>2, 7, 8, 9, 11</sup>. The mortality rate of 25.9% among hospitalized patients in our study may be explained by more severe disease in our total cohort, by a different reporting method, or by geographic variation.

We identified several risk factors associated with mortality in hospitalized patients with COVID-19 that have been previously reported including older age and male sex. We report additional risk factors associated with in-hospital mortality including low SBP, tachypnea, low SpO<sub>2</sub>, low eGFR, and higher levels of IL-6, D-dimer, and troponin levels.

The severity of coronavirus infection in humans has been previously described to increase during viral clearance suggesting pathogenicity arising from host immune response<sup>15</sup>. Our study confirmed again that older patients with COVID-19 hospitalization are at significantly higher risk of mortality. We did not observe any independent association between in-hospital mortality and some of the common coexisting medical conditions including hypertension, diabetes, or cancer. However, using calculated GFR as a



surrogate for CKD, we observed that decreased renal function was a risk factor for in-hospital mortality, a finding that is consistent with previous studies<sup>16</sup>.

IL-6 and other pro-inflammatory cytokines production are felt to be due to immune dysregulation rather than normal response to SARS-CoV infection<sup>17, 18</sup>. Our findings are consistent with this theory, and we observed elevated IL-6 as an independent prognostic risk factor, with higher levels in non-survivors. In hospitalized patients, we saw fluctuating IL-6 levels, with a significant increase seen on day 1 of admission and an increasing level trend that was more pronounced in non-survivors.

Thrombocytosis was associated with disease activity in SARS and was thought to be secondary to the direct effect of the virus or effect of inflammatory cytokines<sup>19</sup>. We observed a greater thrombocytosis during hospitalization in survivors than in non-survivors. A previous study of IL-6 in primates revealed that there is a dose-dependent response of thrombocytosis induced by IL-6<sup>20</sup>. The discrepancy between high IL-6 levels and lack of thrombocytosis in non-survivors could be explained by endothelial damage and subsequent platelet consumption from viral infection, impaired platelet release from megakaryocytes in the lung, or direct impairment of hematopoiesis<sup>21</sup>. This may suggest that the absence of reactive thrombocytosis may portend a poor response to SARS-CoV-2 infection.

Elevated D-dimer in COVID-19 patients has been described previously<sup>22, 23</sup>. We report in this study its independent association with an increased risk of in-hospital mortality. Abnormal D-dimer alone is non-specific; however, the higher elevation in non-survivors suggests that coagulopathy, particularly disseminated intravascular coagulation (DIC), may contribute to mortality in COVID-19.

One of the functional receptors for pathogenic human coronavirus such as SARS-CoV is angiotensin-converting enzyme 2 (ACE2)<sup>24</sup>, and these receptors are expressed in heart tissues<sup>25</sup>. This suggests that SARS-CoV-2 virus could directly affect the heart. Similar to the previous finding that showed an association of cardiac injury and a higher risk of in-hospital mortality<sup>26</sup>, we observed elevated troponin levels in hospitalized patients as a risk factor for increased mortality.

Hydroxychloroquine is an analog of chloroquine, a widely used anti-malarial with immunomodulatory effects<sup>27</sup>. In vitro studies have shown that hydroxychloroquine has activity against SARS-CoV-2<sup>28</sup>. The clinical data of hydroxychloroquine in patients with COVID-19 come from small studies that have shown mixed results. Chen et al. randomized 30 hospitalized patients with COVID-19 to receive hydroxychloroquine 400 mg daily for 5 days or placebo and found that 86.7% of the hydroxychloroquine group and 93.3% of the control group had negative throat swabs<sup>29</sup>. Chen et al. randomized 62 patients to hydroxychloroquine or placebo and reported shortened time to clinical recovery, fever resolution, and cough improvement in the hydroxychloroquine group<sup>30</sup>. Mahevas et al. reviewed 181 hospitalized patients with COVID-19 data who received hydroxychloroquine 600 mg daily and reported no difference in outcomes, including in ICU admission and/or death at 7 days follow-up<sup>31</sup>. Another randomized trial of 150 hospitalized patients by Tang et al. did not show symptomatic improvement at 28 days or clearance of SARS-CoV-2 with hydroxychloroquine use<sup>32</sup>. We attempted to adjust for all known confounders between the groups who did and did not receive hydroxychloroquine using multivariate regression analyses and the IPTW method, which revealed that hydroxychloroquine use was associated with decreased risk of in-hospital mortality. Due to the inherent limitations of our retrospective study design, there was no conclusive determination on the efficacy of hydroxychloroquine in patients with COVID-19. More robust studies such as randomized clinical trials are needed.

Our study has several limitations. First, we have no long-term follow up data for ambulatory and discharged patients; hence, the clinical outcome observed may not be reflective of the true eventual outcome, particularly in the ambulatory group. Second, we have patients who remained hospitalized at the time of our analyses and did not have our outcomes, such as discharge or mortality, and were excluded for our comparison of survivors and non-survivors. Third, due to limitations and local testing policy during the study duration, there are an unknown number of patients who were not diagnosed with COVID-19 because of a lack of severe symptoms and/or hospitalization. Fourth, we are not able to adjust for unknown confounders that may affect the true treatment effect. These limitations prevent any definitive conclusions on the efficacy of any treatment.

## CONCLUSIONS

In this retrospective study of over 6000 ambulatory and hospitalized patients with COVID-19 in the New York City metropolitan area, age, male sex, tachypnea, low systolic blood pressure, low peripheral oxygen saturation, impaired renal function, elevated IL-6, elevated D-dimer, and elevated troponin were found to be risk factors for mortality. Hydroxychloroquine use was associated with decreased mortality.

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## COVID-19 Outpatients – Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study

[Martin Scholz](#)\*, [Roland Derwand](#), [Vladimir Zelenko](#)

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### Abstract

*Objective:* To describe outcomes of patients with coronavirus disease 2019 (COVID-19) in the outpatient setting after early treatment with zinc, low dose hydroxychloroquine, and azithromycin (the triple therapy) dependent on risk stratification. *Design:* Retrospective case series study. *Setting:* General practice. *Participants:* 141 COVID-19 patients with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the year 2020. *Main Outcome Measures:* Risk-stratified treatment decision, rate of hospitalization and all-cause death. *Results:* Of 335 positively PCR-tested COVID-19 patients, 127 were treated with the triple therapy. 104 of 127 met the defined risk stratification criteria and were included in the analysis. In addition, 37 treated and eligible patients who were confirmed by IgG tests were included in the treatment group (total N=141). 208 of the 335 patients did not meet the risk stratification criteria and were not treated. After 4 days (median, IQR 3-6, available for N=66/141) of onset of symptoms, 141 patients (median age 58 years, IQR 40-67; 73% male) got a prescription for the triple therapy for 5 days. Independent public reference data from 377 confirmed COVID-19 patients of the same community were used as untreated control. 4 of 141 treated patients (2.8%) were hospitalized, which was significantly less ( $p<0.001$ ) compared with 58 of 377 untreated patients (15.4%) (odds ratio 0.16, 95% CI 0.06-0.5). Therefore, the odds of hospitalization of treated patients were 84% less than in the untreated group. One patient (0.7%) died in the treatment group versus 13 patients (3.5%) in the untreated group (odds ratio 0.2, 95% CI 0.03-1.5;  $p=0.16$ ). There were no cardiac side effects. *Conclusions:* Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset with the used triple therapy, including the combination of zinc with low dose hydroxychloroquine, was associated with significantly less hospitalizations and 5 times less all-cause deaths.

fn38

<https://www.medrxiv.org/content/10.1101/2020.08.20.20178772v1.full.pdf>

Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: A multi-center observational study Andrew Ip, M.D. M.S., Jaeil Ahn, Ph.D., Yizhao Zhou, M.S., Andre H. Goy, M.D., Eric Hansen, B.S. M.S., Andrew L Pecora, M.D., Brittany A Sinclair, M.S., Urszula Bednarz, B.S CCRP, Michael Marafelias, B.S., Shivam Mathura, B.A., Ihor S Sawczuk, M.D., Joseph P. Underwood, M.D., David M. Walker, M.D., Rajiv Prasad, M.D., Robert L. Sweeney, D.O., Marie G. Ponce, M.D., Samuel La Capra, M.D., Frank J. Cunningham, MD, Arthur G. Calise, D.O., Bradley L. Pulver, M.D., Dominic Ruocco, M.D., Gregory E. Mojares, D.O., Michael P. Eagan, M.D., Kristy L. Ziontz, D.O., Paul Mastrokyriakos, D.O., and Stuart L Goldberg, M.D. Division of Outcomes and Value Research, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack NJ, USA (A.I, S.L.G) Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University, Washington, D.C. , USA (J.A., Y.Z.) John Theurer Cancer Center at Hackensack University Medical Center, Hackensack NJ, USA (A.H.G., A.L.P., B.A.S., U.B., M.M.) COTA, Boston MA, USA (E.H., S.M.) Hackensack Meridian Health, Hackensack NJ and Hackensack Meridian School of Medicine at Seton Hall University, Nutley NJ, USA (I.S.S.) Hackensack University Medical Center, Hackensack NJ , USA (J.P.U., D.M.W.) Bayshore Medical Center, Holmdel NJ, USA (R.P.) Jersey Shore University Medical Center, Neptune City NJ, USA (R.L.S., M.G.P.) JFK Medical Center, Edison NJ, USA (S.L., F.J.C.) Hackensack Meridian Mountainside Medical Center, Montclair NJ, USA (A.G.C.) All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 2 Ocean Medical Center, Brick NJ, USA (B.L.P.) Palisades Medical Center, North Bergen NJ, USA (D.R) Pascack Valley Medical Center, Westwood NJ, USA (G.E.M) Raritan Bay Medical Center, Old Bridge NJ, USA (M.P.E) Riverview Medical Center, Red Bank NJ, USA (K.L.Z.) Southern Ocean Medical Center, Manahawkin NJ, USA (P.M.) Corresponding Author: Stuart L Goldberg MD John Theurer Cancer Center at Hackensack University Medical Center 92 Second Street, Hackensack NJ 07601 Email: [stuart.goldberg@hackensackmeridian.org](mailto:stuart.goldberg@hackensackmeridian.org) Key words: Hydroxychloroquine, COVID-19, Outpatient Lay Summary: In this observational study of 1,274 COVID-19 patients, hydroxychloroquine given as an outpatient treatment was associated with a 47% reduction in the hazard of hospitalization. Adverse events were not increased (2% QTc prolongation events, 0% arrhythmias). Further validation is required. Use of hydroxychloroquine to treat COVID-19 in the outpatient setting should be reserved for a clinical trial or after discussion with a physician regarding risks and benefits. All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 3 Abstract Background: Hydroxychloroquine has not been associated with improved survival among hospitalized COVID-19 patients in the majority of observational studies and similarly was not identified as an effective prophylaxis following exposure in a prospective randomized trial. We aimed to explore the role of hydroxychloroquine therapy in mildly symptomatic patients diagnosed in the outpatient setting. Methods: We examined the association between outpatient hydroxychloroquine exposure and the subsequent progression of disease among mildly symptomatic non-hospitalized patients with documented SARS-CoV-2 infection. The primary outcome assessed was requirement of hospitalization. Data was obtained from a retrospective review of

electronic health records within a New Jersey USA multi-hospital network. We compared outcomes in patients who received hydroxychloroquine with those who did not applying a multivariable logistic model with propensity matching. Results: Among 1274 outpatients with documented SARS-CoV-2 infection 7.6% were prescribed hydroxychloroquine. In a 1067 patient propensity matched cohort, 21.6% with outpatient exposure to hydroxychloroquine were hospitalized, and 31.4% without exposure were hospitalized. In the primary multivariable logistic regression analysis with propensity matching there was an association between exposure to hydroxychloroquine and a decreased rate of hospitalization from COVID-19 (OR 0.53; 95% CI, 0.29, 0.95). Sensitivity analyses revealed similar associations. QTc prolongation events occurred in 2% of patients prescribed hydroxychloroquine with no reported arrhythmia events among those with data available. All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 4 Conclusions: In this retrospective observational study of SARS-CoV-2 infected non-hospitalized patients hydroxychloroquine exposure was associated with a decreased rate of subsequent hospitalization. Additional exploration of hydroxychloroquine in this mildly symptomatic outpatient population is warranted. All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 5 Introduction The majority of infections with SARS-CoV-2 result in mildly symptomatic or asymptomatic illnesses that can be managed in outpatient settings. However, progression of the COVID-19 illness may result in significant morbidity and mortality requiring hospitalization and consumption of healthcare resources. In New Jersey, an early COVID-19 epicenter in the United States, approximately 11% of positive cases required hospitalization (216 per 100,000 population).<sup>1</sup> As testing availability has increased and testing practices have broadened to include mildly symptomatic and asymptomatic individuals the Centers for Disease Control and Prevention has reported a United States national cumulative COVID-19 hospitalization rate of 94.5 per 100,000 individuals.<sup>2</sup> Hydroxychloroquine, an antimalarial agent with antiviral and anti-inflammatory properties, has been touted as a potential therapy for COVID-19.<sup>3</sup> Among hospitalized COVID-19 patients, observational studies have noted that hydroxychloroquine exposure has not been associated with a reduction in the risk of death.<sup>4-7</sup> A recent observational study from Michigan, however, reported improved survival when hydroxychloroquine was administered within 2 days of hospitalization.<sup>8</sup> When used as post-exposure prophylaxis within 4 days after moderate or high risk exposure, a prospective randomized trial found that hydroxychloroquine failed to prevent illness compatible with Covid-19 or confirmed infection.<sup>9</sup> Given that the majority of SARS-CoV-2 infected patients are mildly symptomatic and are managed in the outpatient setting, it remains important to explore whether early administration of hydroxychloroquine could delay progression to more severe illness requiring hospitalization. A trial from Spain randomized younger (mean age 41.6 years) mildly symptomatic outpatients to a 7-day course of hydroxychloroquine or observation, reporting no significant reductions in mean All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 6 viral load or reduction in hospitalization rate (7.1% control versus 5.9% hydroxychloroquine).<sup>10</sup> A second randomized study enrolled 491 USA and

Canadian subjects via the internet, of whom 34% had virology confirmed infection. Although the overall hospitalization rate was only 3.2% within the population participating in the study (median age 40), more patients receiving placebo (4.7%) compared to hydroxychloroquine (1.9%) required hospitalization.<sup>11</sup> A Brazilian study of 636 symptomatic, but virology unconfirmed patients treated by telemedicine at home, also noted a reduction in hospitalization rate (5.4% vs 1.9%), with the greatest reductions occurring among the patients who started hydroxychloroquine therapy within the first 7 days of symptoms.<sup>12</sup> A small French report noted a reduction in symptoms with early therapy compared to observation.<sup>13</sup> Finally, a German report of 141 outpatients, when compared to cases in the community, noted a decrease in hospitalization rate (2.8% vs 15.4%) with a combination of hydroxychloroquine, azithromycin and zinc.<sup>14</sup> In summary, the majority of studies, although underpowered to show differences, are all directionally in favor of a reduced hospitalization rate with early outpatient treatment. Understanding the limitations of observational studies, but with the urgency for evaluating potential therapeutic approaches during the current COVID-19 pandemic, our hospital spanning New Jersey USA established an observational database utilizing an integrated electronic health record (EHR) system (EPIC; Verona, WI).<sup>15-18</sup> In this multi-center observational cohort study we report progression from mildly symptomatic SARS-CoV-2 infection diagnosed as an outpatient progressing to subsequent need for in-patient hospitalization according to outpatient exposure to hydroxychloroquine. All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 7

**Methods: Study Design and Cohort Selection** This retrospective, observational, multicenter cohort study within the Hackensack Meridian Health network (HMH) utilized EHR-derived data of patients with documented SARS-CoV-2 infection who received care initially within an outpatient setting. Our primary objective was to evaluate the association between hydroxychloroquine exposure and subsequent need for hospitalization in a population of patients with documented SARS-CoV-2 infection diagnosed in the outpatient setting. Database inclusion and exclusion criteria for this review: 1) Positive SARS-CoV-2 diagnosis by reverse-transcriptase polymerase chain reaction, 2) Outpatient status (includes emergency room diagnosis without immediate hospitalization on the same day) at an HMH outpatient facility between March 1, 2020 until April 22, 2020. Follow-up continued through May 22, 2020. Institutional Review Board (IRB) approval was obtained for access to the prospective observational database. The requirement for patient informed consent was waived by the IRB as this project represented a non-interventional study utilizing routinely collected data for secondary research purposes. Data Sources We collected data from HMH's EHR (Epic) which is utilized throughout the network. Outpatients treated at a network related facility were flagged by the EHR if SARS-CoV-2 polymerase chain reaction tests were positive. These EHR-generated reports served as our eligible cohort sample. Demographic, clinical characteristics, treatments, and outcomes were manually abstracted by research nurses and physicians from the John Theurer Cancer Center at All rights reserved. No reuse allowed without permission. (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: <https://doi.org/10.1101/2020.08.20.20178772>.this version posted August 25, 2020. The copyright holder for this preprint 8

Hackensack University Medical Center. Assignment of patients to our data team occurred in real-time but was not randomized. To reduce sampling bias the final cohort included 100% of outpatients by April 22, 2020 as noted on the EHR-generated reports. Data abstracted by the team were entered utilizing Research Electronic Data Capture (REDCap). Quality control was

performed by physicians (AI, SLG) overseeing nurse or physician abstraction. Demographic information was collected by an electronic face-sheet. Comorbidities were defined as diagnosed prior to hospitalization for COVID-19. If not listed in the patient's record comorbidities were recorded as absent. Exposure For hydroxychloroquine, exposure was defined as a prescription written for the drug as found in the EHR, by documentation in a provider note or in the medication section of the chart. No confirmation of prescription fill or adherence to the medication regimen was attempted. If no evidence of administration of the drug was found, this was recorded as not having received the drug. Hydroxychloroquine exposure, for the purpose of this study, was limited to initiation of treatment in the outpatient setting. Patients who did not have a prehospital exposure, subsequently admitted to a hospital, and then received hydroxychloroquine started in the inpatient setting were counted as having no outpatient exposure to hydroxychloroquine. Outcome Measures The primary outcome measurement was subsequent need for hospitalization with follow-up until May 22, 2020. Hospitalization was identified on EHR review which includes the 13-hospitals within the Hackensack Meridian Health network. The EPIC system also notifies a limited number of participating hospitals outside the network (Epic Care-Everywhere). No attempt to contact the patient to confirm hospitalization outside the network was permitted or performed. Among patients who were hospitalized, the time from date of diagnosis to hospitalization and the requirement for intensive unit care level support or death was also collected. Safety events including discontinuation due to QTc prolongation or arrhythmia incidence after hydroxychloroquine exposure were recorded as per chart review. Exploratory outcomes included the effect of outpatient hydroxychloroquine exposure on elderly patients over age 65, on patients with more than 2 days of self-reported symptoms, and on patients with at least one reported symptom of fever, shortness of breath, or cough. Statistical Analysis Demographic and clinical parameters of hydroxychloroquine treatment were summarized using median (Q1-Q3) for continuous variables and frequency (percentages) for categorical variables. The differences in the median/distributions of demographic and clinical parameters between the hydroxychloroquine treated and untreated (no hydroxychloroquine) groups were compared using Mood's median test for continuous variables and Fisher's exact test or Pearson's chi-squared test for categorical variables. The comparator group in both the unmatched and propensity matched cohorts included only patients who did not receive hydroxychloroquine. Multivariable adjusted logistic regression models were fitted to estimate the association between hydroxychloroquine exposure and the need for subsequent hospitalization using clinically likely confounders including age, gender, cancer, hypertension, COPD/asthma, diabetes, fever, cough, shortness of breath, and qSOFA score. When the model goodness-of-fit was not satisfied, we further reduced the aforementioned confounders using the stepwise variable selection and the lasso variable selection.<sup>20</sup> The hazard ratios (OR) and their 95% confidence intervals were summarized. To reduce the confounding effects secondary to imbalances in receiving hydroxychloroquine treatment inherent to a retrospective cohort study, we employed propensity-score matching. First, we calculated a propensity score (PS) of receiving hydroxychloroquine treatment for each patient using multivariable logistic regression via adjusting for the aforementioned set of confounder variables except time to hydroxychloroquine treatment. Goodness-of-fit of the multivariable logistic model was examined using the Hosmer-Lemeshow test. We then employed a nonparametric nearest neighbor matching of propensity scores to generate a matched cohort in a 1:10 ratio to pair a patient with hydroxychloroquine treatment to ten patients without hydroxychloroquine treatment (MatchIt Package in R)<sup>19, 20</sup> With the propensity matched cohort, we repeated the adjusted logistic model with the propensity matched set similar to the unmatched analyses. Sensitivity analyses for confounders were

conducted by including the propensity score as a covariate in the unmatched model and by including informative confounders chosen by stepwise selection. Missing data in categorical covariates were coded as a missing data category and were included in the all analyses. Completely observed data by excluding patients with missing covariates were also examined summarized in Supplementary Table. The Kaplan-Meier method and log-rank test were performed to evaluate and compare the median time from date of diagnosis to hospitalization between the hydroxychloroquine treated and untreated groups. Furthermore, we performed an exploratory analysis from time of symptom onset to date of first dose of hydroxychloroquine. A cut-off of less than 2 days from time of symptom onset was used for a logistic regression analysis comparing those with early disease versus later as there appeared to be a stronger benefit to early administration of hydroxychloroquine.<sup>21</sup> Statistical significance was determined when two-sided  $p$ -value $<0.05$ . Subgroup analyses were performed exploratory and thus multipletest correction was not applied. All statistical analyses were conducted using R software (ver. 3.4., R Project for Statistical Computing).

**Results: Characterization of the study cohort** There were 4302 patients flagged in the EHR with polymerase chain reaction confirmed infection with SARS-CoV-2. 1274 (30%) patients were evaluated and treated in the outpatient setting prior to any COVID-19 related hospitalization. 97 patients (7.6%) received prescriptions for hydroxychloroquine or had notation of an outpatient exposure to hydroxychloroquine. (Figure 1) Given potential imbalances in treatment allocation due to the observational nature of the study a propensity matched sample was constructed consisting of 1067 patients in total (97 with hydroxychloroquine exposure and 970 without). The distribution of baseline characteristics is shown in Table 1. In the unmatched cohort patients exposed to hydroxychloroquine were more likely to have comorbid conditions. The propensity matched cohorts were well balanced except for an excess of cancer history and a trend towards older age in the hydroxychloroquine cohort. In the propensity matched cohort 3 (3.1%) patients with outpatient exposure to hydroxychloroquine subsequently required ICU level support and 42 (4.3%) patients without exposure required ICU care. Ultimately, 2 (2.1%) patients with outpatient exposure to hydroxychloroquine died from COVID-19 related disease and 44 (4.5%) of patients without exposure died (Table 1). Primary study endpoints Among the 1067 outpatients in the propensity matched cohort, with a median of 39 days (IQR 6,46) follow-up, a total of 326 (30.6%) patients required subsequent hospitalization. Three hundred and five (31.4%) patients with no outpatient exposure to hydroxychloroquine were hospitalized and 21 (21.6%) of patients with exposure to hydroxychloroquine were hospitalized. Figure 2 shows the cumulative prevalence of hospitalization from date of diagnosis according to outpatient hydroxychloroquine exposure (log-rank  $p=0.045$ ). The cumulative prevalence of hospitalization from the self-reported date of onset of symptoms is shown in Supplementary Figure 1 (log-rank  $p=0.036$ ). 46 (4%) patients with no outpatient exposure required ICU care compared to 3 (3.1%) patients who had outpatient exposure to hydroxychloroquine. 47 (4%) patients with no outpatient exposure died compared to 2 (2%) patients with outpatient exposure to hydroxychloroquine. In patients prescribed hydroxychloroquine as an outpatient for whom follow-up electrocardiographic data were available, QTc prolongation events, defined as discontinuation due to physician discretion, occurred in 2 (2%) of patients, and arrhythmia events after hydroxychloroquine exposure were noted in no patients. (Table 1) In the primary multivariable logistic regression analysis with propensity matching there was an association between exposure to hydroxychloroquine and a reduced rate of hospitalization related to progressive COVID-19 illness (OR 0.53; 95% CI, 0.29, 0.95) (Table 2). Sensitivity analyses using stepwise (AIC based) variable and Lasso selection yielded similar results in the propensity matched cohorts (Supplementary tables 1-



2), and the significant association was also identified in the unmatched cohort (Supplementary tables 3-6). Exploratory study endpoints In an exploratory analysis we examined a subgroup of 749 outpatients in the propensity matched cohort who self-reported at least one major symptom of fever, cough or shortness of breath at the time of their time of SARS-CoV-2 diagnosis. In this subgroup 69 (9.2%) patients received hydroxychloroquine prescriptions and 680 (90.8%) patients did not. There were fewer hospitalizations in the hydroxychloroquine cohort (19 patients, 27.5%) compared to individuals with no exposure (259 patients, 38.1%). In the multivariable logistic regression analysis of these symptomatic patients, there was no significant association between hydroxychloroquine exposure and subsequent need for hospitalization (OR 0.74, 95% CI, 0.39, 1.37) (Supplementary table 7, Supplementary figure 2). Given the strong association between advanced age and subsequent hospitalization requirement in both the unmatched and propensity matched analyses, an additional analysis was conducted on the interaction between age and hydroxychloroquine exposure. Restricting the multivariable logistic regression model to the 282 persons age 65 years or greater resulted in a non-significant odds reduction of hospitalization (OR 0.49, 95% CI 0.17, 1.32). Similar directional trends were seen on sensitivity analyses in this elderly cohort. (Supplementary table 8) A final subgroup analysis was conducted in patients who were exposed to outpatient hydroxychloroquine according to duration of symptoms, more than 2 days of self-reported symptoms compared to 2 days or less. A univariate logistic regression analysis did not show a significant association with hospitalization, although a directional trend of increased hospitalization was noted when outpatient hydroxychloroquine was administered after more than 2 days of symptoms (OR 3.43, 95% CI 0.57, 66) (Supplementary table 9).

Discussion: In this multicenter retrospective observational cohort study of mildly symptomatic outpatients with polymerase chain reaction documented SARS-CoV-2 infection, we noted an association (OR 0.53; 95% CI, 0.29, 0.95) between outpatient exposure to hydroxychloroquine and a reduction in subsequent need for hospitalization. Safety events, defined as QT prolongation or arrhythmia occurrence, were minimal, occurring in 2% and 0% of patients. As the majority of COVID-19 patients are mildly symptomatic and treated in outpatient settings, our findings justify further exploration of hydroxychloroquine during this pandemic in this population. If the findings are confirmed, early hydroxychloroquine therapy to a broad outpatient population could have important implications for reducing limited healthcare resources. The economic impact on healthcare might also be significant as the financial cost of a short course of hydroxychloroquine to a large population would be easily recouped by even a modest reduction in hospitalizations. Our findings in the outpatient setting are in conflict with prior observational studies conducted among hospitalized patients potentially highlighting differences in effect based on the severity of disease.<sup>22</sup> Following an initial infection by SARS-CoV-2 resulting in attack of alveolar epithelial cells patients may develop a hyper-inflammatory state characterized by activation of the innate immune system and release of pro-inflammatory cytokines and chemokines. Patients who experience this 'cytokine storm' progress rapidly to respiratory failure and multi-organ failure.<sup>23- 26</sup> In these hospitalized patients the weak anti-inflammatory effects of hydroxychloroquine may be insufficient to block the cytokine cascade whereas more potent immunosuppressive agents such as dexamethasone and tocilizumab have been associated with beneficial effects.<sup>27-29</sup> By contrast, hydroxychloroquine has anti-viral effects, decreasing SARS-CoV-2 viral load, and thus may be more suited in preventing the significant tissue damage needed to incite the hyper-inflammatory state.<sup>3,30</sup> This would position hydroxychloroquine earlier in the clinical course, at the time of early infection, prior to hospitalization need.<sup>31</sup> As noted above, several recent studies have attempted to explore the role of hydroxychloroquine earlier in the clinical course of COVID-19.<sup>10-14</sup>

However, given enrollment of generally younger patients with low baseline rates of hospitalization, these studies appear under-powered to demonstrate meaningful effects. For example, the recent Spanish randomized trial explored early hydroxychloroquine use, at a median time from symptom onset of 3 days, in the outpatient setting.<sup>10</sup> While the study did not find a significant decrease in mean viral load up to 7 days after treatment, the investigators reported lower hospitalization rates in the population treated with hydroxychloroquine. Similar non-statistical directional reductions were noted in the other studies. Thus, the potential benefit of hydroxychloroquine in the early management of outpatients should be considered unanswered but of greater interest. We defined exposure to hydroxychloroquine based on documentation of a prescription being written, but confirmation of prescription fill or full adherence to the complete course was not ascertained, thus mimicking an intention-to-treat model. This limitation biased against finding a difference between cohorts, as non-adherent patients would be categorized within the hydroxychloroquine cohort even though in actuality they did not have drug exposure. Thus, our reduction in hospitalization association may be an underestimate of the effect size. Conversely, it is possible that some outpatients received prescriptions for hydroxychloroquine outside the HMM network and were misclassified in the opposite direction, although this is less likely as patients underwent initial testing within our hospital network and would have been contacted by HMM personnel to discuss testing results and/or had notation of a prescription fill in the EPIC pharmacy section.

Our study was conducted early in the United States pandemic during a timeframe when testing for COVID-19 was largely limited to individuals with symptomatic disease. Thus, we suspect that those included in our observational cohort represent a bias towards more advanced disease with a higher likelihood of hospitalization. Indeed 30.6% of our cohort subsequently required hospital based care, which is higher than current state and national hospitalization rates.<sup>1,2</sup> Our findings need to be taken into context of current testing availability. This observational study has several additional limitations. We recorded hospitalizations based on EHR documentation, but we have not accounted for hospitalizations outside the HMM network. Since the patients in our series received outpatient care at an HMM facility we believe that subsequent hospitalizations outside the network were minimal. Observational studies also cannot draw causal inferences given inherent known and unknown confounders. We attempted to adjust for known confounders using our propensity model approach but acknowledge we may not have captured all possible confounders. Misclassifications of the data are possible due to manual abstraction of EHR structured and unstructured data. Missing data, laboratory studies not obtained, and symptoms not reported or documented also limited our analyses. Our study also focused on patients in New Jersey USA, limiting the applicability to other geographic regions with differing treatment and hospitalization algorithms. In conclusion, hydroxychloroquine exposure among outpatients with mildly symptomatic COVID-19 was associated with a reduction in hospitalization rates from disease progression in this multi-center observational cohort. Further external validation of this finding is required. Although use of hydroxychloroquine in this outpatient population outside the context of a clinical trial cannot be recommended, our study suggests that additional evaluations of hydroxychloroquine are needed in this mildly symptomatic SARS-CoV-2 infected population.

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## **Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial**

[Philippe Gautret<sup>1</sup>](#), [Jean-Christophe Lagier<sup>2</sup>](#), [Philippe Parola<sup>1</sup>](#), [Van Thuan Hoang<sup>3</sup>](#), [Line Meddeb<sup>4</sup>](#), [Morgane Mailhe<sup>4</sup>](#), [Barbara Doudier<sup>4</sup>](#), [Johan Courjon<sup>5</sup>](#), [Valérie Giordanengo<sup>6</sup>](#), [Vera Esteves Vieira<sup>4</sup>](#), [Hervé Tissot Dupont<sup>2</sup>](#), [Stéphane Honoré<sup>7</sup>](#), [Philippe Colson<sup>2</sup>](#), [Eric Chabrière<sup>2</sup>](#), [Bernard La Scola<sup>2</sup>](#), [Jean-Marc Rolain<sup>2</sup>](#), [Philippe Brouqui<sup>2</sup>](#), [Didier Raoult<sup>8</sup>](#)

### **Abstract**

**Background:** Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COV-19 patients. We evaluate the effect of hydroxychloroquine on respiratory viral loads.

**Patients and methods:** French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16<sup>th</sup>, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point.

**Results:** Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the literature for untreated patients. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

**Conclusion:** Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

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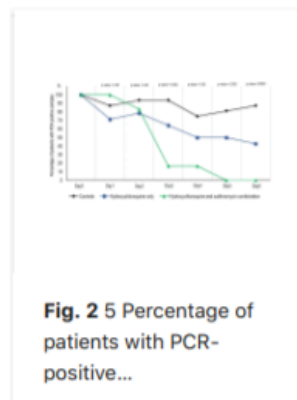
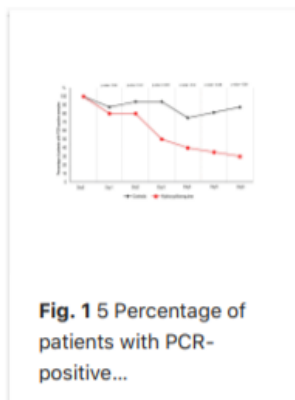
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## Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

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Abstract Background: Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV2, and reported to be efficient in Chinese COV-19 patients. We evaluate the effect of hydroxychloroquine on respiratory viral loads. Patients and methods: French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16 , to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point. Results: Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported in the literature for untreated patients. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination. Conclusion: Despite its small sample size, our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin. Keywords: 2019-nCoV; Azithromycin; COVID-19; Clinical trial; Hydroxychloroquine; SARS-CoV-2.

### Figures



Covid-19 Etude rétrospective chez 88 sujets avec 3 approches thérapeutiques différentes (traitement symptomatique / azithromycine / azithromycine + hydroxychloroquine)

INTRODUCTION Le collectif « Laissons les médecins prescrire » a été créé suite à la parution du décret n°2020-293 du 23 mars 2020 modifié par les décrets 2020-314 du 25 mars et 2020-337 du 26 mars 2020. Ces textes qui limitent la liberté de prescription, pour les médecins libéraux, de l'hydroxychloroquine (PLAQUENIL®) ont été émis par les autorités françaises sans autre justification scientifique dûment documentée que l'avis relatif aux recommandations thérapeutiques du Haut Conseil de la Santé Publique (HCSP) rendu le 23 mars 2020. Cette interdiction est intervenue après publication par le Professeur Didier Raoult (IHU Méditerranée, Marseille) d'une étude proposant un traitement précoce de l'infection COVID-19 par l'association hydroxychloroquine (HCQ)/azithromycine (AZM) (1). L'avis du HCSP du 23 mars 2020 considère que les résultats de cette étude doivent être pris avec prudence notamment pour des raisons méthodologiques et demandent à être confirmés ou infirmés. Il encourage l'analyse des effets éventuels de l'hydroxychloroquine et d'autres molécules à effet anti-viral dans le cadre de l'essai européen Discovery, qui ne reprend pas, pour sa part, les conditions du protocole proposé par l'équipe du Pr Raoult. La mise à l'écart et d'une façon si brutale d'une molécule préconisée par une équipe française de renommée mondiale suscitait dès lors les plus vives interrogations. Pourquoi empêcher par une contrainte réglementaire forte, la prescription d'un traitement connu pour ses effets antiviraux et immuno-modulateurs et présenté par son promoteur comme étant de nature à : - faire chuter rapidement la charge virale chez les patients infectés traités précocement, - réduire ainsi leur contagiosité et contribuer à limiter la progression de l'épidémie, - diminuer le risque d'évolution vers une forme grave de la maladie ? Les décrets pris par le Premier ministre restreignaient au contraire l'usage de cette molécule aux formes évoluées oxygène-requérantes voire à celles présentant une défaillance d'organe, justifiant alors une prise en charge en réanimation, alors que la plupart s'accorde pour dire que la deuxième phase de la maladie n'est plus virale mais réactionnelle inflammatoire. Les médecins de terrain qui connaissent parfaitement cette molécule utilisée depuis de nombreuses années dans le traitement de certaines polyarthrites rhumatoïdes, du lupus érythémateux disséminé ou dans la chimioprophylaxie du paludisme, ont commencé dans le cadre du Covid-19, à traiter certains de leurs patients voire à s'auto-traiter tant que le médicament était encore disponible. Dans un contexte de fortes tensions polémiques, le collectif a souhaité mettre en place une évaluation compassionnelle (hors AMM1), dont l'objectif était de pouvoir infirmer ou confirmer les résultats de cette première étude française qui laissait envisager une efficacité de l'association en usage précoce, ce qui est précisément le rôle des médecins généralistes, très attentifs au soin et à la prévention des complications pour éviter les passages en réanimation souvent délétères pour le patient et coûteux pour l'Assurance Maladie. Les retours d'information du terrain semblaient intéressants, il était important voire fondamental, dans cette phase d'urgence sanitaire, de collecter les observations et de les analyser afin de pouvoir proposer une recommandation d'usage, tout en évaluant la tolérance des molécules testées dans un contexte de Dès lors, en tant que professionnels, et hors de toute polémique, le collectif s'est proposé de travailler objectivement sur les problématiques suivantes : x COVID-19 : quels éléments diagnostiques ? x Comment comprendre les résultats des études sur l'hydroxychloroquine et sur l'azithromycine ? x Quelle est la toxicité réelle de l'hydroxychloroquine ? x Etat des lieux des expériences terrain déjà acquises x En phase épidémique, quels éléments tirer de cette expérience ? x Comment aborder le

déconfinement ? QUELLE EST LA TOXICITE REELLE DE L'HYDROXYCHLOROQUINE ? Nous nous sommes penchés en priorité sur le sujet, tant cette préoccupation conditionnait le reste. Rapidement après le début de la polémique sont apparus dans les médias puis dans des publications relayées par différentes instances, des alertes informant du caractère devenu brutalement toxique de l'hydroxychloroquine, médicaments pourtant largement utilisés depuis plusieurs décennies. Il convient de rappeler que l'hydroxychloroquine, commercialisée sous le nom de PLAQUENIL<sup>®</sup>, était en vente au prix de 4,26 euros, hors ordonnance, jusqu'au 15 janvier 2020. Aucune alerte n'ayant été émise jusqu'en janvier 2020 sur ce produit, il paraissait important de vérifier les données de pharmacovigilance<sup>2</sup> de ce médicament pointé subitement du doigt comme un « poison » par les Agences Régionales de Santé. 30/03/2020 – 11h45 : le Docteur Martine Wonner, députée du Bas-Rhin, adresse une demande officielle à Monsieur Dominique Martin, directeur général de l'ANSM et à Madame Christelle Carbonnell, directrice générale adjointe pour obtenir les données de pharmacovigilance du PLAQUENIL<sup>®</sup>. 01/04/2020 – 20h28 : le Docteur Martine Wonner relance en absence de réponse. 03/04/2020 – 09h35 : Monsieur Dominique Martin envoie une note générale sur l'hydroxychloroquine, sans données de pharmacovigilance, et précise que ses services n'ont pas le temps de travailler sur ce sujet en ce moment. 03/04/2020 – 12h30 : 2e relance du Docteur Martine Wonner priant de fournir les données de pharmacovigilance, à savoir le nombre de boîtes vendues, le nombre d'événements indésirables déclarés, le nombre d'EIG (événements indésirables graves) et l'imputabilité. 09/04/2020 : les données de pharmacovigilance 2017, 2018, 2019 sont transmises au Docteur Wonner qui en fait réaliser une analyse par des médecins spécialistes de ce type de données. La synthèse de cette analyse est présentée dans le tableau ci-dessous. phase précoce de la maladie.

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HYDROXYCHLOROQUINE DONNÉES 2017-2019 EXPOSITION : 3 863 852 boîtes de 30 comprimés à 200 mg (Total : 115 915 560 comprimés) Les données de pharmacovigilance comportent 312 cas rapportant spontanément au moins un effet indésirable. La grande majorité des effets indésirables rapportés sont des effets oculaires et cutanéomuqueux, ceux qui sont décrits habituellement lors des traitements au long cours de l'hydroxychloroquine. Sur ces 312 effets indésirables, 21 (soit 6,7 %) sont des effets cardiovasculaires. En 3 ans, 2 décès ont été rapportés, dont un cas dans le cadre d'une intoxication médicamenteuse volontaire chez un sujet prenant 6 psychotropes en plus de l'hydroxychloroquine.

Courant mars 2020, l'ANSM<sup>3</sup> publie une mise en garde à la suite de trois décès suspects sous HCQ en Nouvelle-Aquitaine, une des régions les moins exposées au COVID-19. Plusieurs questions se posent donc : ☐ sur quels critères a-t-on imputé la responsabilité de l'hydroxychloroquine ? et en si peu de temps ? ☐ s'est-on assuré que ces personnes n'avaient pas une atteinte cardiaque liée au virus (myocardite, myopéricardite, péricardite ou des antécédents cardiaques) ? ☐ à quel stade de la maladie étaient les patients ? ☐ les contre-indications d'emploi de l'hydroxychloroquine ont-elles été respectées ? ☐ les patients souffraient-ils de comorbidité ? La surprise est grande en médecine générale, chez les cardiologues, les dermatologues<sup>4</sup> mais aussi les rhumatologues qui connaissent le mieux ce médicament. « Il faut être factuel, simple. On a des données de tolérance depuis 30 ans, qui montrent que ce n'est pas un produit hautement toxique. Il faut le manier avec la prudence mais ce n'est pas hautement toxique. C'est un médicament utilisé en première ligne dans de nombreuses maladies inflammatoires. » Pr Jean Sibilia, chef de service de rhumatologie, CHU de Strasbourg Il convient d'ajouter que le protocole thérapeutique proposé avec le PLAQUENIL® dure 7 à 10 jours, contrairement au traitement chronique des pathologies rhumatologiques, administré pendant des mois et le plus souvent des années. Les médecins traitants connaissent les précautions à suivre sur le plan cardiaque, ce d'autant plus que l'HCQ est associée à l'AZM : ☐ respect des contre-indications cardiologiques à l'inclusion et des troubles ioniques ☐ surveillance ECG avec arrêt de la prise si allongement du QT (trouble de la conduction) Le collectif « Laissons les médecins prescrire » ne pouvant conduire l'étude compassionnelle souhaitée auprès de 1 000 médecins touchés par le COVID-19 et dont le protocole avait été transmis à la Direction Générale de la Santé, a recueilli des informations rétrospectives disponibles. C'est la synthèse de ces données qui est communiquée dans le présent document et fait l'objet de conclusions que nous souhaitons partager avec l'ensemble des médecins. Car il y bien toujours URGENCE - à soigner ! x 24 087 décès (à l'hôpital et en structures médico-sociales) annoncés par la Direction Générale de la Santé le 29/04/2020 au soir (sous déclaration), auxquels s'ajoutent les 9 000 décès à domicile (chiffre estimé par les médecins libéraux) x plus de 4 000 médecins enregistrés comme malades par le site de la CARMF (sous déclaration) - à prévenir une 2e vague de contamination lors du déconfinement prévu pour débuter progressivement en date du 11 mai

- I. COVID-19 : poser un diagnostic avec certitude L'agent du COVID-19 est le SARS-CoV-2. C'est une équipe chinoise qui l'a identifié et a publié sa séquence génomique en janvier 2020. Ce virus a été classé par les taxonomistes dans la famille des coronaviridae, virus à ARN, dont la majorité des souches contaminent les animaux. La plupart du temps les infections qui touchent les êtres humains sont responsables d'épidémies hivernales résolutives en quelques semaines. Depuis quelques années,

des infections graves à Coronavirus ont émergé. Le SARS-CoV-2 est classé dans le même sous-genre que le SARS-COV qui a été responsable de l'épidémie de SRAS en 2002-2003. A ce jour, le diagnostic virologique repose sur deux grandes classes de tests, qui, en France, ne sont toujours pas disponibles à large échelle, ce qui entrave le suivi de l'épidémie. ☒ La détection du virus par PCR avec dosage semi-quantitatif (réponse + ou -) ou quantitatif (mesure de la charge virale) x La technique par écouvillonnage naso-pharyngé a été la première accessible en médecine libérale mais en nombre très limité et à retardement. x Cet examen doit être bien réalisé +++ , au niveau du cavum, et il convient de « racler » les cellules et non de recueillir de simples sécrétions sinon s'ensuivent de nombreux tests faux négatifs. La plupart des médecins ont dû asseoir leur diagnostic sur l'examen clinique, lequel, réalisé finement, peut être considéré comme fiable ce d'autant plus que l'on a pu identifier la personne contaminante et que celle-ci a été testée positive en milieu hospitalier. ☒ Tests sérologiques Ils commencent à peine à être disponibles en laboratoire de ville mais ne sont pas toujours validés par la Direction Générale de la Santé, même si certains de ces tests ont été validés dans d'autres pays, voire par certains services d'immuno-virologie de CHU, et sont largement utilisés. On rappelle toute l'importance de disposer de tests à la fois en phase diagnostique précoce et en suivi de l'acquisition de l'immunité d'un patient infecté, sous forme a- ou paucisymptomatique, et a fortiori symptomatique. Notre système immunitaire nous défend, en particulier en fabriquant des immunoglobulines (Ig), communément appelées anticorps. Dans un premier temps, il synthétise des IgM puis des IgA et des IgG. Les IgM témoignent d'une infection récente et les IgG d'une infection plus ancienne, voire très ancienne. Si l'on a des IgM négatives avec des IgG positives on est bien immunisé et protégé et, en général, on n'est plus contagieux à ce stade.

En matière de COVID-19, la recommandation de nombreux biologistes est de réaliser les tests sérologiques 3 semaines après la fin des symptômes. En effet, il semblerait que l'on assiste à une montée tardive des anticorps chez de nombreux patients, ce qui a fait écrire à certains qu'une immunité pourrait ne pas être acquise. Les connaissances de l'infection sont à approfondir, mais cette précision est utile pour limiter au maximum ce type de faux négatifs.

- II. COVID-19, pathologie multiforme : réaliser une étude sémiologique fine pour préconiser une attitude thérapeutique cohérente Comprendre la physiopathologie d'une maladie, c'est se donner les moyens de soigner de façon éclairée. Les taxonomistes ont classé le SARS-CoV-2 dans la même catégorie que l'agent du SRAS, il est déjà intéressant de regarder si des analogies cliniques existent. Si l'on réalise une analyse sémiologique fine, c'est bien le cas, même si tout n'est pas comparable, et cette analyse sera à refaire une fois l'urgence sanitaire passée puisque le COVID-19 est surtout décrit dans la littérature sous ses formes graves (publications hospitalières) et que les médecins français qui sont souvent de bons cliniciens ont rapporté des événements jusqu'ici non enregistrés dans la littérature. La maladie évolue en deux phases : une première phase d'infection virale assez caractéristique pour les personnes symptomatiques, et une seconde phase avec atteinte fréquente



pulmonaire et systémique, pouvant conduire les patients en réanimation. Il convient de noter que les symptômes sont souvent labiles. Plusieurs hypothèses physiopathologiques ont été évoquées pour expliquer cette 2e phase qui ne font pas encore consensus. De nouvelles informations sont publiées tous les jours comme celles de l'équipe strasbourgeoise alertant sur des signes neurologiques (2). Le travail du médecin de ville étant d'identifier précocement les malades afin de les soigner et de les isoler pour éviter la transmission de l'infection, un recueil sémiologique précis a été réalisé sur les dossiers analysés par nos soins et sont présentés au chapitre IV.

- III. COVID-19 : traiter de façon pertinente La préoccupation des médecins traitants n'est pas la phase du parcours de soin en réanimation des patients souffrant de COVID-19, celle-ci relève des centres hospitaliers publics ou privés. La préoccupation des médecins de ville est de traiter le plus précocement possible les patients afin que ceux-ci n'aient justement pas à effectuer de séjour en réanimation. Il est donc important de diminuer voire réduire à zéro la charge virale de toute urgence pour bloquer l'évolution de la maladie. Les virologues testent régulièrement in vitro l'efficacité de différentes molécules de la pharmacopée sur les virus existants ou émergents. C'est ainsi que hydroxychloroquine et azithromycine ont été testées in vitro comme des centaines d'autres molécules. ☒ Données in vitro à la base d'un rationnel physiopathologique Action anti-virale Plusieurs études réalisées in vitro indiquent que la chloroquine exerce des effets antiviraux directs sur plusieurs virus, y compris les coronavirus, et notamment le SARS-CoV-2, agent responsable de la pandémie COVID-19 (3,4,5). Elle agit en inhibant l'entrée du virus dans les cellules par augmentation du pH endosomal requis pour la fusion du virus avec les cellules, mais aussi en inhibant la réplication (c'est-à-dire la multiplication intracellulaire du virus) en interférant avec la glycosylation des récepteurs cellulaires pour le virus. Il s'agit de données obtenues sur des cultures cellulaires en tube, mais les concentrations inhibitrices sont du même ordre que celles obtenues dans le plasma des patients traités pour paludisme ou polyarthrite rhumatoïde (5,6). L'hydroxychloroquine (HCQ) possède également des effets antiviraux démontrés in vitro sur des cellules humaines mises en culture et infectées par plusieurs virus, y compris les coronavirus. Ces effets ont été confirmés récemment pour le SARS-CoV-2, sur des cellules de primate, les concentrations inhibitrices étant du même ordre que celles observées en thérapeutique (7,8). Le choix de l'azithromycine (AZM) pour être associée à l'HCQ, n'est pas seulement dû à l'utilisation très large de cet antibiotique dans les infections pulmonaires, mais aussi parce qu'il possède aussi une activité antivirale in vitro. Elle a été démontrée sur des cellules bronchiques humaines en culture provenant de patients atteints de bronchite chronique ; sur ce modèle, AZM réduit la charge virale et augmente la sécrétion de l'interféron (facteur libéré par les cellules infectées pour inhiber la prolifération du virus dans les cellules voisines) (9). L'équipe du professeur Raoult, qui a montré que l'association HCQ/AZM faisait rapidement disparaître la charge virale des patients infectés par le COVID-19, a également mis en évidence une action synergique de ces deux

médicaments pour inhiber in vitro la prolifération du virus dans des cellules infectées en culture, à des concentrations identiques à celles observées chez les patients traités (1). Action immunomodulatrice et anti-inflammatoire Outre son activité antivirale, la chloroquine et son dérivé hydroxylé, l'hydroxychloroquine, possèdent une activité immunomodulatrice et anti-inflammatoire, mise à profit dans le traitement des maladies auto-immunes. Le mode d'action est complexe, différent de celui des glucocorticoïdes et des immunosuppresseurs (10).

Dans le débat qui oppose les experts à propos de l'utilisation de la chloroquine et de l'hydroxychloroquine, certains craignent que ces médicaments puissent inhiber la réponse immunitaire du patient et favoriser les complications pulmonaires. Les données d'une étude effectuée chez l'animal semblent éloigner cette crainte. En effet, chez des souris infectées par le virus de la grippe aviaire A H5N1, il a été montré que la chloroquine, donnée à titre thérapeutique, augmentait le taux de survie des animaux et que l'analyse histologique de leur poumon mettait en évidence une diminution de l'inflammation et de l'œdème (11). La même équipe a montré que la chloroquine augmentait in vitro la vitalité de cellules pulmonaires humaines mises en culture et infectées par le virus de la grippe aviaire A H5N1. ¶ De l'in vitro vers l'in vivo Les espoirs que font naître les tests in vitro sont souvent suivis d'échecs in vivo. La raison en est que les taux thérapeutiques efficaces in vivo sont souvent inatteignables à des doses tolérables par les patients, qui peuvent alors être victimes d'effets indésirables voire toxiques du médicament administré. C'est par exemple l'inquiétude soulevée dans SciencesetAvenir.fr du 24/04/2020 par le Professeur Molimard, qui, se fondant sur la concentration minimale d'hydroxychloroquine (HCQ) efficace pour inhiber in vitro la croissance du COVID-19 sur des cultures cellulaires (au moins 1 micromolaire ou 1µM), a utilisé un modèle pharmacocinétique pour en déduire que l'HCQ devait être prise à des doses mortelles pour espérer une efficacité thérapeutique. Néanmoins, plutôt que de faire un calcul théorique, il eût été plus simple de consulter les données publiées qui indiquent que les taux plasmatiques observés chez les patients traités pour lupus ou en prévention du paludisme atteignent, voire dépassent, le seuil de 1µM, comme le montre le tableau ci-dessous :

Dans l'étude préliminaire publiée par l'équipe du Professeur Raoult, le taux plasmatique moyen a été trouvé à 0,46 µg/ml (soit 1,37 µM) chez 20 patients traités par 600 mg d'HCQ par jour pendant 10 jours (1). Une étude américaine, intégrant les données pharmacologiques, cliniques et virologiques obtenues chez 116 patients infectés par le COVID-19 et traités par HCQ, a conclu que les taux plasmatiques étaient comparables aux concentrations efficaces in vitro et que la dose thérapeutique devait être comprise entre 400 et 600 mg/jour (15). Enfin, la posologie de 600 mg/j a été confirmée par une étude chinoise utilisant un modèle pharmacologique à partir des données in vitro (16). Le Professeur Molimard tempère ses conclusions alarmistes en affirmant que les modèles de calcul qu'il a utilisés « prédisent que la concentration de l'HCQ serait 700 fois plus forte dans les poumons que dans le plasma sanguin », ce qui ne l'empêche pas de conclure à

l'inefficacité et au risque de survenue de troubles potentiellement mortels du traitement par HCQ. Ces conclusions bien entendu questionnent eu égard aux données antérieurement publiées dans un contexte moins passionnel.

Données in vivo accessibles Dans un premier temps, c'est la chloroquine, substitut synthétique de la quinine, vieux médicament commercialisé en France depuis 1949 pour faire le traitement et la prévention du paludisme, qui a été remise au premier plan par les médecins chinois qui ont écrit l'avoir utilisée avec une certaine efficacité chez les patients infectés par le COVID-19, même si leurs publications n'apportent pas de données précises et objectives. L'hydroxychloroquine, son dérivé hydroxylé, indiquée pour traiter les maladies articulaires d'origine inflammatoire, a également été utilisée, seule, par de nombreux centres hospitaliers chinois. Cette approche thérapeutique est percutante puisqu'elle permet d'agir au stade le plus précoce possible de l'infection, à savoir au niveau de la porte d'entrée intracellulaire du virus, alors les autres thérapeutiques proposées et testées interviennent à une étape postérieure de l'infestation virale. L'objectif du Professeur Raoult, en ajoutant l'azithromycine, était avant tout d'après son intervention référencée ci-dessous (28/04/2020), d'effectuer la prévention des surinfections bactériennes, ce qui est parfaitement pertinent.

<https://www.youtube.com/watch?v=FcvDi6tjldk&feature=youtu.be> Ce qui est clair, c'est qu'en associant deux molécules ayant une action antivirale performante in vitro, une synergie d'action a sans doute pu permettre d'obtenir une efficacité in vivo, qui plus est avec des doses thérapeutiques courantes pour les deux médicaments considérés.

Première communication IHU Méditerranée : essai ouvert et non randomisé Les résultats détaillés de cette étude (1) ont été publiés et il est donc possible de les analyser. Vingt-six patients ont été inclus pour recevoir l'hydroxychloroquine (600 mg/j pendant 7 jours) associée chez six d'entre eux à l'azithromycine pendant 5 jours (500 mg le premier jour et 250 mg les 4 jours suivants). Il est important de noter que les doses utilisées d'HCQ et d'AZM sont celles préconisées dans le traitement des maladies rhumatologiques précitées et sur une durée de temps très courte. La négativation du test PCR détectant le virus sur un écouvillon pharyngé réalisé au 6ème jour a été observée chez 70 % des patients, contre seulement chez 20 % des témoins ; cependant la comparaison est historique, la comparabilité des deux groupes n'étant pas assurée par la méthodologie. De plus, comme l'indique le tableau, sur les 16 témoins, 7 n'ont pas été testés au 5ème jour et 5 au 6ème jour, d'où une possible sous-estimation des tests négatifs à la fin de l'étude dans ce groupe. Dans le groupe de 26 patients inclus pour être traités, 6 patients sont déclarés perdus de vue, alors qu'il s'agit d'arrêts prématurés, puisqu'on connaît leur devenir ; quatre d'entre eux sont sortis de l'étude pour aggravation de leur état (3 passages en soins intensifs et 1 décès) ; ils n'ont pas été pris en compte dans l'analyse et ceci a peut-être surestimé le pourcentage de négativation sous traitement. Il aurait fallu réaliser une analyse dite « en intention de traiter » prenant en compte tous les patients inclus pour être traités.

Deuxième étude IHU Méditerranée S'appuyant sur les résultats de l'étude clinique préliminaire ayant suggéré une supériorité de l'association hydroxychloroquine/azithromycine ainsi que de ceux d'une étude in vitro ayant démontré une action antivirale synergique des deux produits, l'équipe marseillaise a publié les résultats du traitement combiné administré à 80 patients (incluant les 6 patients traités par l'association dans l'étude préliminaire) (17). Quatre des patients étaient des porteurs sains et les 76 autres étaient symptomatiques, 33 atteints d'une infection des voies respiratoires supérieures et les 43 autres d'une broncho-pneumopathie. Le diagnostic était confirmé par un test PCR positif sur prélèvement naso-pharyngé à l'inclusion ; le prélèvement a été répété quotidiennement durant le traitement, permettant de montrer la négativation du portage viral dans 83 % des cas à J7 et à 93 % à J8. La mise en culture des prélèvements s'est révélée négative chez 97,5% des patients à J5 et à J8 un seul patient restait contagieux. Sur le plan clinique, 65 patients ont quitté l'hôpital au bout de 4,6 jours en moyenne, les 15 autres ont eu recours à une oxygénothérapie ; 3 d'entre eux ont dû être admis en soins intensifs (temporairement pour 2 de ces patients) ; un seul patient, âgé de 86 ans est décédé. Troisième étude IHU Méditerranée (18) Du 3 mars au 9 avril 2020, 59 655 échantillons provenant de 38 617 patients ont été testés pour le diagnostic du COVID-19 par PCR. Sur les 3 165 patients positifs, 1 061 patients (non publiés précédemment) répondaient aux critères d'inclusion. Cette cohorte a été traitée pendant au moins 3 jours par l'association HCQ/AZM avec suivi minimal de 9 jours. La description de la population et son évolution sous traitement sont présentées dans le tableau ci-dessous. Pour l'équipe soignante, un bon résultat clinique et une guérison virologique ont été obtenus chez 973 patients en 10 jours (91,7%). La présence du virus a été constatée chez 47% des patients (4,4%) en fin de traitement, elle était associée à une charge virale plus élevée au moment du diagnostic ( $p < 0,01$ ) ; tous les patients ont été testés négatifs à J15. Une évolution défavorable a été constatée chez 46 patients (4,3 %) : 10 ont été transférés dans des unités de soins intensifs, 5 patients sont décédés (0,47%) (74-95 ans) et 31 ont été hospitalisés au moins 10 jours ou plus. Dans ce groupe, 25 patients sont désormais guéris et 16 étaient toujours hospitalisés, ce qui portait le taux total de guérison à 98% au moment de la publication des résultats sur le site de l'IHU. Les mauvais résultats cliniques étaient significativement associés à un âge avancé (OR 1.11), à une gravité initiale plus élevée (OR 10.05) et à des concentrations sériques d'hydroxychloroquine basses. Ils ont également été notés chez des patients traités par bêta-bloquants ou par des inhibiteurs de l'angiotensine II ( $p < 0,05$ ). La mortalité a été significativement plus faible chez les patients qui avaient reçu 3 jours ou plus l'association HCQ/AZM que ceux ayant été traités par d'autres types de soins que ce soit à l'IHU ou dans les hôpitaux publics de Marseille ( $p < 0,01$ ). Aucune toxicité cardiaque n'a été observée. La conclusion de l'équipe a été : la combinaison HCQ/AZM, utilisée en phase précoce de la maladie est un traitement sûr et efficace pour le traitement du COVID-19, avec un taux de mortalité de 0,5%, chez les patients âgés. Outre la prévention de l'aggravation de la maladie, le traitement élimine le virus et de ce fait la contagiosité, dans l'immense majorité des cas.

Etudes en cours au niveau mondial Une centaine d'essais dans le monde se penche actuellement sur l'action de l'hydroxychloroquine dans le COVID-19. ☒ De façon peu compréhensible, la plupart sont réalisés à un stade tardif de la maladie, là où AUCUNE ACTION de l'HCQ n'est attendue, eu égard à la physiopathologie de la maladie. C'est par exemple le cas de l'étude européenne « DISCOVERY » qui devait inclure 3 200 patients dont 800 en France (160 testant l'hydroxychloroquine seule sans association avec l'azithromycine) chez des patients ayant une atteinte pulmonaire. Il semblerait que cette étude conduite, en ouvert, aurait déjà vu l'arrêt de deux bras testés dont le bras HCQ, pour inefficacité. ☒ Des études chez des personnes COVID+ au stade précoce de la maladie ont cours, mais avec l'HCQ seule et donc se privant de la synergie avec l'AZM [Chine, Corée, Thaïlande, USA, Canada]. C'est le cas de l'étude de Levantovsky et al. (19) réalisée en double aveugle versus placebo chez 62 patients pour évaluer l'efficacité de l'hydroxychloroquine seule, à une dose de 400 mg par jour pendant 5 jours. Fièvre et toux ont disparu en moyenne 1 jour plus tôt dans le groupe traité par HCQ à un stade précoce de la maladie. Aucun patient recevant l'HCQ ne s'est aggravé, alors que 4 des 31 patients du bras contrôle ont vu la maladie progresser. ☒ Très peu d'études ont été/sont conduites chez des personnes COVID+ au stade précoce de la maladie avec l'association HCQ/AZM : elles sont en cours aux USA, Brésil, Pakistan et dans plusieurs pays d'Afrique comme le Sénégal. Il convient de préciser que l'étude COVIDOC menée à Montpellier, recrute des patients hospitalisés avec un tableau respiratoire, en faisant, à notre sens, une prescription encore trop tardive. Les résultats de ces études commencent à émerger comme celle Barbosa et al. (20) au Brésil et qui nous intéresse particulièrement puisque réalisée en ambulatoire dans des conditions de terrain proches de celles que connaissent les médecins libéraux français actuellement, à savoir : carence de tests, carence de protection nécessitant de fréquentes consultations en télémédecine, mauvaises conditions de suivi clinique. Cette étude, conduite chez 636 patients symptomatiques, à la méthodologie imparfaite en raison de toutes ces carences, montre que l'association HCQ/AZM a permis une réduction drastique du nombre d'hospitalisations par rapport au groupe témoin ( $p < 0,001$ ).

Plusieurs études ont été citées par les autorités de santé françaises pour soutenir ☒ une inefficacité de l'hydroxychloroquine Outre le fait qu'aucune n'a testé le protocole préconisé par le Professeur Raoult, ces études ont favorisé la mise en échec de l'hydroxychloroquine : prescription en 2e phase de maladie, dose non respectée, non association avec l'azithromycine, prescription chez des patients avec atteinte sévère nécessitant une hospitalisation et bien souvent une réanimation. Dans la presse ou les réseaux sociaux on a même également assisté à des conclusions totalement aberrantes sur des méthodologies très discutables. A titre d'exemple, la mise en avant de l'étude chinoise de Chen et al. (21) réalisée du 6 au 25 février. Dans cette étude, trente patients ont été inclus dans un essai en 2 groupes de 15 patients, l'un traité par hydroxychloroquine 400 mg/j pendant 5 jours (HCQ) et l'autre sans HCQ (groupe annoncé comme témoin). L'étude de montre pas de différence entre les 2 groupes : 13 négativations du portage viral au 7ème jour

dans le groupe HCQ et 14 dans le groupe « témoin ». MAIS "Tous les patients ont reçu une nébulisation d'interféron alpha, tandis que dans le groupe expérimental (HCQ) 12 patients (80%) ont reçu de l'Abidol® (umifénovir, antiviral) ; 10 patients (66,7%) du groupe témoin ont reçu de l'Abidol® et 2 (13,3%) un traitement par lopinavir/ritonavir" précisent les auteurs. Comment peut-on accorder du crédit à une étude comparative qui teste les effets de l'HCQ et donne en même temps à tous les patients (y compris les témoins) un antiviral (interféron alpha) et chez 80 % d'entre eux un second antiviral. Ce n'est pas sérieux ! ☹ voire une dangerosité, avec communication d'une avalanche d'événements indésirables graves par les différentes ARS5 du pays depuis courant mars. Il convient de rappeler que, dans le cadre d'un usage compassionnel, l'hydroxychloroquine doit être utilisée correctement, sur prescription médicale, et dans l'habituelle évaluation de la balance bénéfice/risque. L'hydroxychloroquine doit être prescrite dans le respect des contre-indications (grossesse, allaitement, insuffisance rénale sévère, insuffisance hépato-cellulaire, cardiomyopathie, troubles de la conduction ou du rythme ventriculaire). - Avant traitement, il est nécessaire de disposer d'un ECG 12 dérivations (l'espace QT doit être  $\leq 440$  ms) et de vérifier que la kaliémie est normale. Un examen ophtalmologique est inutile car le traitement est de courte durée. - Il est essentiel de connaître les traitements pris par le patient pour éviter les interactions médicamenteuses potentiellement dangereuses, notamment les médicaments connus pour allonger l'espace QT, les diurétiques hypokaliémiants, les psychotropes abaissant le seuil épileptogène. - La dose quotidienne de 600 mg ne doit pas être dépassée ; elle sera abaissée à 400 mg en cas d'insuffisance légère rénale ou hépatique et, par précaution, chez les patients de plus de 70 ans. - Lorsque l'azithromycine est co-prescrite, une surveillance cardiovasculaire s'impose avec mesure de la fréquence cardiaque au moins 2 fois par jour. La réalisation d'un ECG est souhaitable 48 heures après le début du traitement : elle s'impose à tout moment si le pouls diminue de 15 % par rapport à la valeur avant traitement (moyenne du pouls mesuré à 4 reprises). - Les effets secondaires les plus fréquemment rapportés sont les céphalées et les troubles digestifs (douleurs abdominales, nausées, vomissements, diarrhées). Ils disparaissent en général dès la réduction de la dose ou à l'arrêt du traitement. - S'agissant d'un traitement de courte durée, il est peu probable d'observer les effets secondaires oculaires, cutanéomuqueux, musculo-squelettiques ou neuropsychiatriques, parfois signalés lors du traitement au long court. Toute auto-médication est à PROSCRIRE. Enfin, il est important de ne pas prendre des signes de la maladie COVID-19 pour des effets secondaires.

☹ Analyse rétrospective du collectif de médecins : les data in vivo accessibles « Primum non nocere » est bien conscient à l'esprit de la grande majorité des médecins ! C'est donc dans cet état d'esprit que les médecins libéraux avaient commencé à s'approprier le traitement préconisé par le Professeur Raoult. L'objet de ce rapport est donc de partager l'expérience terrain acquise, même si elle est beaucoup plus limitée que ce qu'elle aurait pu être, en raison de la mise en indisponibilité du PLAQUENIL® par les autorités de santé. Cette étude rétrospective

est méthodologiquement très critiquable puisque les médecins libéraux se sont vus amputés 1/ de moyens de protection pour eux-mêmes et leurs patients, 2/ d'outils diagnostiques, 3/ d'outils thérapeutiques. Les résultats sont présentés au chapitre IV. A ce stade, il nous paraît utile de préciser que les experts des essais cliniques parmi les médecins du collectif savent parfaitement ce qu'est une étude bien construite.

- IV. Résultats de l'étude rétrospective conduite en médecine libérale Cette étude rétrospective a été conduite dans le cadre d'une urgence sanitaire avec des contraintes et des carences qui la rendent forcément imparfaite. Nous soulignerons donc au fur et à mesure tout ce qui eut pu être évalué dans une situation idéale. Aux critiques qui pourraient également survenir sur le fait que cette virose peut être asymptomatique et évoluer par elle-même de façon très favorable, il convient de rappeler que le rôle du médecin est de soigner des personnes symptomatiques, de leur apporter réconfort et de faire en sorte que l'impact d'une maladie donnée soit le plus limité possible, pour leur santé mais également pour leur vie quotidienne (capacité de travail, de vie familiale, sociale, ...).
- IV.1. Méthodologie Il s'agit d'une étude observationnelle rétrospective, qui a consisté à recueillir les données cliniques, thérapeutiques et évolutives de patients, parmi lesquels figurent essentiellement des soignants ou des membres de leur famille, atteints d'une infection par le COVID-19. Tous les patients étaient symptomatiques, suivis en ambulatoire durant les mois de mars et avril 2020, et avaient donné leur consentement pour que les données les concernant soient réunies. Quand c'était possible, le diagnostic était confirmé par un test PCR positif sur un prélèvement naso-pharyngé ; dans le cas contraire, le patient devait avoir une symptomatologie évocatrice et avoir été en contact avec des patients pour lesquels un diagnostic virologique d'infection à COVID-19 avait été porté. Tous les sujets avaient été interrogés au préalable sur leurs antécédents, en particulier cardio-vasculaires, et sur les traitements en cours. Ils ont bénéficié d'un examen clinique, comportant la mesure de la pression artérielle, de la fréquence cardiaque et de la fréquence respiratoire. Pour chaque patient, a été recueillie la présence des symptômes en rapport avec l'infection et notamment ceux de la liste suivante : fièvre, hypersudation, frissons, fatigue, céphalées, toux, obstruction nasale, douleur pharyngée, dyspnée, anosmie, agueusie, nausées, diarrhée, vomissements et vertiges. Quand c'était possible, les autres éléments disponibles pour le diagnostic ont été recueillis : température corporelle, saturation en oxygène, résultat du scanner pulmonaire quand il avait été réalisé. Les patients ont été classés en 3 groupes selon le traitement administré : - patients traités par l'association hydroxychloroquine (400 à 600 mg/j pendant une période pouvant aller jusqu'à dix jours) et azithromycine (500 mg le premier jour et 250 mg les 4 jours suivants) ; - patients traités par azithromycine seule à la posologie indiquée ci-dessus ; - patient recevant un autre traitement, le plus souvent paracétamol à la demande, associé ou non à d'autres traitements à visée symptomatique (groupe témoin). Le choix des traitements a parfois été dicté par les éventuelles contre-indications existantes chez certains patients et surtout par la disponibilité des médicaments :

l'hydroxychloroquine a été prescrite avant la parution du décret restreignant son utilisation aux hôpitaux, et dans deux cas l'azithromycine a été remplacée par un autre macrolide, la clarithromycine, en raison des ruptures d'approvisionnement. Dans tous les cas, le médecin a pris la responsabilité de la prescription après avoir informé le patient des risques éventuels et obtenu son accord, quand le médecin n'était pas lui-même son propre patient. Tous les sujets traités par hydroxychloroquine ont bénéficié d'un électrocardiogramme avant traitement et 48 heures après son début.

Dans les jours qui ont suivi le traitement, les patients ont à nouveau été interrogés sur la symptomatologie présente et sur les éventuels effets indésirables survenus sous traitement ; ils ont bénéficié à nouveau d'un examen clinique, et, dans la mesure du possible, d'un second écouvillonnage naso-pharyngé pour test PCR. L'évolution clinique a fait l'objet d'une évaluation qualitative selon 3 items (amélioration, stabilité, aggravation) et quantitative, mesurée par le délai de résolution des symptômes, exprimé en jours. Le suivi a été en moyenne d'un mois pour l'ensemble des patients, après la date des symptômes initiaux. Finalement le médecin et le patient ont évalué globalement l'efficacité et la tolérance du traitement selon 4 items (excellente, bonne, moyenne, médiocre) Analyse statistique L'analyse a été réalisée en intention de traitement sur Statview 5.0. Les comparaisons entre groupes ont été effectuées par des tests non paramétriques (test de Kruskal-Wallis et test de Mann-Whitney avec correction de Bonferroni). Les résultats de cette analyse confirment ceux obtenus sur l'ensemble des 88 patients, montrant une différence significative entre les 3 groupes ( $p = 0,001$ ). L'analyse des groupes 2 à 2 donne également des résultats identiques : comparativement à celui des patients sous traitement symptomatique, le temps de résolution des symptômes est significativement plus court chez les patients traités par azithromycine donnée seule ( $p = 0,0149$ ) ou en association avec l'hydroxychloroquine ( $p = 0,0002$ ), mais il n'y a pas de différence significative entre le groupe azithromycine seule et le groupe azithromycine plus hydroxychloroquine ( $p = 0,3321$ ). Décès Un homme du groupe témoin, âgé de 82 ans, en bon état général, avec un très léger surpoids (IMC6 = 26,12) et sans comorbidité, est décédé après que son état clinique se soit brutalement aggravé à J29 du cours évolutif de la maladie. Il avait été vu par le SAMU en stade précoce, et avait reçu pour instruction de rester confiné à domicile « en l'absence de signes de gravité ». Hospitalisations Cinq hospitalisations ont été enregistrées : 3 dans le groupe PLQ/AZM et 2 dans le groupe témoin. Groupe PLQ/AZM : ☐ Une patiente de 53 ans, sans antécédent médical majeur, avec un IMC élevé (40,57), a débuté le traitement à J6 de l'évolution de la maladie, avec du PLAQUENIL® seulement le premier jour, puis de la clarithromycine a été ajoutée au 2e jour du traitement (et non de l'azithromycine en raison de la rupture d'approvisionnement). Elle a été hospitalisée au 5e jour du traitement en service de pneumologie en raison d'une dyspnée et d'expectorations hémoptoïques. Le scanner thoracique montrait des lésions en verre dépoli, avec une atteinte chiffrée à 12%. Le PLAQUENIL® a été arrêté ; curieusement, elle n'a été



placée sous oxygénothérapie que 48h après, et ce malgré une désaturation qui est apparue quelques heures après son entrée. Une antibiothérapie IV par céphalosporine de 3e génération a été mise en place. Sa sortie a eu lieu au 5e jour. La guérison totale est survenue au 24e jour. ☒ Un patient de 70 ans, a été hospitalisé pendant 6 jours en réanimation où il a été intubé et ventilé. Le traitement PLQ/AZM a été instauré en hospitalisation à J12 de l'évolution de la maladie. La guérison a été obtenue en 40 jours.

☒ Le 3e dossier concerne une patiente qui a demandé à être hospitalisée pour pouvoir bénéficier du traitement PLQ/AZM, disponible seulement en milieu hospitalier à cette date. Cette dame est la conjointe du patient décédé quelques jours avant et elle a dû insister auprès du service qui avait pris en charge son conjoint et n'était pas favorable au traitement par hydroxychloroquine, pour qu'on administre le médicament. L'hospitalisation ne relève donc ni d'un rationnel clinique, ni de complications, mais d'une obligation administrative. Son évolution clinique a été spectaculaire en 48 heures sous traitement, elle a été traitée 5 jours et est rentrée à son domicile à cette issue. Groupe Témoin : ☒ Un médecin de 50 ans, sans aucun antécédent médical particulier, grand sportif, a vu son état se dégrader et nécessiter une hospitalisation de 10 jours. Travaillant en Alsace, région extrêmement touchée par l'épidémie, il a dû reprendre son exercice en cabinet avant la guérison totale. ☒ Le 2e patient est le patient décédé, son séjour hospitalier a duré 48 heures (cf supra).

En plus du patient décédé (groupe témoin) et décrit ci-dessus, cinq patients ont rapporté au moins un effet secondaire : 1 dans le groupe des patients sous traitement symptomatique (2,9 %) et 4 sous traitement par l'association hydroxychloroquine-azithromycine (20 %). Dans ce groupe, les effets secondaires les plus fréquents ont été des troubles digestifs et des céphalées, rapportées chez 3 des 4 patients. Ils sont présentés dans le tableau ci-dessous, et ont été analysés selon les bonnes pratiques de pharmacovigilance. Aucun événement indésirable cardiologique n'a été signalé dans les 3 groupes.

IV.3. Discussion Sémiologie Concernant la clinique, cette étude rétrospective nous a enseigné les points majeurs suivants : - le questionnement « Dyspnée » doit être affiné dans les études futures car une dyspnée de repos est rarement présente alors qu'une dyspnée d'effort, même minime est fréquemment retrouvée, ce qui a fait recommander à l'un de nos confrères le test « 1 étage » = évaluation de l'apparition d'un essoufflement soit en montant un étage, soit en faisant, au cabinet, monter un patient à plusieurs reprises sur un support surélevé de type marche de step, - des signes d'oppression/pesanteur thoracique et des troubles cutanés doivent être recherchés de façon systématique car souvent non signalés spontanément, - la mesure de la fréquence respiratoire est indispensable, au même titre que le serait la mesure de la SaO<sub>2</sub> ; mais tous les médecins ne sont pas équipés d'oxymètre, ce qui nous semble être une recommandation importante pour l'avenir l'évaluation des répercussions psychologiques et psychiatriques est également à réaliser, étant donné le tropisme neurologique du virus. Elles n'avaient pas été initialement questionnées par les médecins, mais des situations d'angoisse, de

labilité émotionnelle, de troubles de la concentration voire de confusion ont été rapportées. IV.4 Conclusion On ne peut pas dire qu'il n'existe pas de traitement du COVID-19 pris à un stade précoce. Cette étude souligne tout l'intérêt d'approfondir la connaissance de la maladie et d'affiner les indications thérapeutiques des deux protocoles étudiés : traitement par l'azithromycine seule et traitement par l'association hydroxychloroquine/azithromycine. En effet, une étude conduite chez un très grand nombre de patients, en double aveugle, permettrait sans doute, vu le polymorphisme de la maladie, de dégager des indications précises et plus subtiles. Il serait par exemple intéressant d'évaluer l'efficacité de ces protocoles chez les patients à présentation dominante pulmonaire / neurologique / vasculaire / cutanée. L'étude rétrospective du Collectif « Laissons les médecins prescrire » fera l'objet d'une publication en anglais dans les jours à venir.

- V. En phase épidémique, quels éléments tirer de cette expérience ? V.1. Recommandations cliniques L'analyse sémiologique doit être fine, la recherche d'une dyspnée d'effort doit être systématique ainsi que le questionnement sur les atteintes cutanées, l'oppression thoracique, le retentissement psychologique et équilibre émotionnel (cf supra). A notre sens, un scanner thoracique doit obligatoirement faire partie du diagnostic clinique. Ce scanner doit être réalisé immédiatement si des signes fonctionnels respiratoires initiaux existent, et, en leur absence, à J7/J8 en raison de la fréquence de lésions « en verre dépoli » caractéristiques des deux infections SARS-CoV (SRAS et COVID-19) chez des patients totalement asymptomatiques sur le plan respiratoire. La recherche du virus doit être réalisée par test PCR, à un stade précoce de la maladie. Tant que la pandémie est en cours la réalisation d'une sérologie est nécessaire, dans un délai d'environ trois semaines après les derniers signes fonctionnels afin d'éviter les faux négatifs liés à la montée tardive des anticorps. ☐ Femmes enceintes Des sages-femmes ont signalé des accouchements compliqués avec transfert en réanimation et nécessité d'intubation de patientes COVID+. Une alerte a été adressée au Ministre de la santé afin que des recommandations soient établies pour les femmes enceintes, sans suite. Sans vouloir engendrer de panique à un moment où les femmes sont en situation de fragilité, il convient à notre sens : 1/ d'équiper les femmes enceintes de masques chirurgicaux dès le début de la grossesse tant que la pandémie est en cours, 2/ de dépister systématiquement en début de 9e mois de grossesse les femmes potentiellement infectées, qu'elles soient symptomatiques ou pas, par un test PCR, 3/ de réaliser une sérologie chez toutes les femmes enceintes dont l'histoire médicale pourrait évoquer une infection COVID+ récente, 4/ de faire accoucher les femmes COVID+ non guéries en maternité de niveau 2 ou 3 pour anticiper la prise en charge d'un accouchement complexe et de discuter de l'opportunité d'une césarienne programmée, en particulier pour les patientes présentant des comorbidités. ☐ Enfants et jeunes majeurs Contrairement à ce qui a été annoncé, les enfants ne sont pas épargnés par le COVID-19. Statistiquement, en France, la population des mineurs est inférieure en nombre à la population des majeurs et il faut donc bien avoir cette donnée en tête quand on parle des chiffres de contamination des moins de 18 ans. Le jeune public est également moins exposé

à des comorbidités et le fait que les enfants, pour ceux qui sont suivis par des pédiatres, reçoivent souvent une dose de vitamine D avant l'entrée dans l'hiver, sont assurément deux éléments importants à prendre en compte dans la présentation clinique de la maladie. Il semblerait que la catégorie des jeunes majeurs et des mineurs soit particulièrement celle exposée aux atteintes dermatologiques (rashes de différente nature mais également lésions de type acrosyndrome) et aux anosmies et agueusies rapportées qui peuvent souvent être les seuls symptômes de la maladie, ce que les médecins du collectif ont également constaté dans de nombreux cas.

Les dermatologues ont également signalé des lésions qui sembleraient spécifiques du COVID-19, à type d'engelures. Photo : source Société Française de Dermatologie Il faut également suivre de près les alertes des médecins anglais, et plus récemment celles des médecins de l'hôpital Necker-Enfants-Malades (Paris) qui ont été lancées sur des cas de grands syndromes inflammatoires avec défaillance cardiaque, proches de ceux observés dans la maladie de Kawasaki chez de jeunes enfants. Les médecins anglais qui avaient les premiers sonné l'alerte, avaient des doutes sur l'origine de ces syndromes, en période de pénurie de tests permettant d'affirmer une infection COVID-19, les cas de Necker semblent confirmer cette hypothèse, ainsi que ceux rapportés par des médecins belges. Ces enfants en réanimation présentent, entre autres, des atteintes myocardiques et pulmonaires qu'il faudra sans doute remettre en perspective avec certaines lésions mal expliquées chez l'adulte dont le grand nombre de péricardites et myopéricardites, lorsque recherchées de façon systématique devant des oppressions thoraciques importantes. Il est important que les médecins partagent leurs observations et les publient pour accélérer la compréhension de cette infection virale. L'épidémie de SRAS a donné lieu à des publications a posteriori de sémiologies extra-pulmonaires, il va être fondamental de revoir tous ces dossiers, une fois l'urgence passée, pour comparer ces deux types d'infections générées par des virus à la même classification taxonomique.

V.2. Recommandations thérapeutiques On ne peut pas dire qu'il n'existe pas de proposition thérapeutique pour le COVID-19 Même si méthodologiquement elles sont imparfaites, les études de l'IHU Méditerranée (1,17,18), l'étude chinoise publiée par Levantovsky et al. (19), celle de Barbosa et al. (20), ainsi que la présente conduite par le collectif des médecins français vont toutes dans le même sens. Le traitement combinant hydroxychloroquine et azithromycine fait mieux que le seul traitement symptomatique en matière d'efficacité et sans créer de dommages graves lorsque la prescription est encadrée. Il est terrible de constater qu'à ce jour, nous aurions pu avoir une réponse encore plus précise et mieux documentée si le collectif « Laissons les médecins prescrire » avait pu conduire l'étude programmée auprès de 1 000 médecins COVID+ qui se seraient auto-traités et auto-surveillés consciencieusement. Mieux encore, il eut été possible d'évaluer en parallèle différentes propositions thérapeutiques émanant des médecins libéraux, en première ligne sur le front du COVID-19 et avec des problématiques totalement différentes de celles des services de réanimation.

A la lumière des résultats de l'étude que nous avons conduite, et dans l'attente des études que nous trouverions légitimes et intelligent de conduire en urgence, et que nous détaillerons ci-dessous, nos recommandations aux médecins généralistes et spécialistes de terrain pourraient être : Patient symptomatique ayant bénéficié des recommandations cliniques énoncées en V.1. Absence de contre-indication à HCQ et AZM + surveillance cardiologique possible

- prescription de l'association HCQ/AZM PLAQUENIL® 600 mg/jour pendant 10 jours + azithromycine (500 mg le premier jour et 250 mg les 4 jours suivants)
- surveillance : kaliémie et ECG avant inclusion, évolution des signes cliniques, ECG 48h après la première prise de traitement
- prise en charge : ambulatoire / HAD7 / hospitalisation publique ou privée pendant 48 heures si patient dont les comorbidités nécessitent une surveillance cardiologique rapprochée en début de traitement
- si prise en charge ambulatoire, l'idéal serait la remise par le médecin d'un kit patient récupéré en fin de suivi : masque chirurgical, thermomètre, oxymètre, tableau pour auto-relevé par le patient des signes de pancarte à transmettre quotidiennement à son médecin (T°, pouls, fréquence respiratoire, oxymétrie, notice d'information numéros d'urgence)

Contre-indication à l'HCQ

- prescription de l'azithromycine : x en absence de signe/s fonctionnel/s ou radiologique/s pulmonaire/s : 500 mg le premier jour et 250 mg les 4 jours suivants
- x en présence de signe/s fonctionnel/s ou radiologique/s pulmonaire/s : 500 mg le premier jour et 250 mg pendant 10 à 14 jours
- surveillance : évolution des signes cliniques
- prise en charge : ambulatoire avec remise d'un kit patient si possible

Contre-indication à l'AZM

- prescription de l'hydroxychloroquine PLAQUENIL® 600 mg/jour pendant 10 jours
- surveillance : kaliémie et ECG avant inclusion, évolution des signes cliniques, ECG 48h après la première prise de traitement
- prise en charge identique à celle préconisée pour l'association HCQ/AZM

Contre-indication à l'HCQ et à l'AZM et patientes enceintes

- traitement symptomatique
- surveillance : évolution des signes cliniques avec évaluation biquotidienne
- prise en charge : ambulatoire avec kit patient si possible et instructions précises en cas d'aggravation

Il est important d'ajouter que des cas de micro-embols pulmonaires ayant été soulignés dans plusieurs publications, la réalisation d'un angioscanner peut avoir sa pertinence dans des situations cliniques inexpliquées par une tomодensitométrie normale ou subnormale. La prévention des thromboses est de ce fait indispensable chez les personnes à risque et/ou avec des signes d'atteinte pulmonaire.

Dans tous les cas il fait pertinence d'ajouter une substitution en vitamine D qui est importante au niveau de la défense immunitaire anti-virale et qui vient d'être rappelée, en particulier au sujet du COVID-19 par Grant et al. (22), si le patient n'est pas substitué régulièrement et n'a pas de contre-indication à cette prescription. Ce point est d'autant plus important que nous sommes en fin de période hivernale, où les stocks de vitamine D sont bas et que le confinement empêchant l'exposition UV a aggravé cette situation.

☒ Personne contact asymptomatique Les personnes contact doivent être testées, suivre le même protocole de soins si positives ; toutes doivent être équipées de masques chirurgicaux pendant 15 jours et faire l'objet d'une surveillance clinique, voire d'une chimioprophylaxie si celle-ci est disponible

(cf infra). V.3. Etudes cliniques qu'il nous semble urgent de conduire Etude à visée thérapeutique N°1 : ETUDE RANDOMISEE EN DOUBLE AVEUGLE HCQ/AZM versus AZM seule EN PHASE PRECOCE DE MALADIE COVID-19 QUELLE QUE SOIT LA SYMPTOMATOLOGIE FONCTIONNELLE Objectif : affiner les résultats d'efficacité et de tolérance, en fonction de l'état clinique initial des patients, de leur âge et de leurs facteurs de risque Les critères majeurs d'évaluation devant être : la durée d'évolution des signes fonctionnels, la nécessité d'un transfert en réanimation, une évolution fatale, la survenue d'autres événements indésirables. Etudes à visée de prévention de la maladie N°2 : ETUDE RANDOMISEE EN DOUBLE AVEUGLE HCQ versus PLACEBO EN CHIMIOPROPHYLAXIE8 CHEZ DES PATIENTS EN CONTACT UNIQUE AVEC UN PATIENT INFECTE Deux bras PLAQUENIL® : dose de 400 mg pendant 10 jours / dose de 600 mg pendant 7 jours. Les critères majeurs d'évaluation devant être : la survenue de la maladie et la tolérance du traitement. N°3 : ETUDE RANDOMISEE EN DOUBLE AVEUGLE HCQ versus PLACEBO EN CHIMIOPROPHYLAXIE CHEZ DES SUJETS EN CONTACT PERMANENT AVEC DES PATIENTS INFECTES (les soignants notamment) PLAQUENIL® : dose de 200 mg/jour pendant la durée d'exposition. Les critères majeurs d'évaluation devant être : la survenue de la maladie et la tolérance du traitement. Pour mémoire, plusieurs études sont actuellement en cours dans cette optique, elles sont présentées dans le tableau page suivante. Etudes de suivi épidémiologique et médico-économique N°3 : ETUDE DE SUIVI DES SEQUELLES PULMONAIRES et autres, CHEZ LES PATIENTS NON TRAITES N°4 : ETUDE COUT/EFFICACITE

VI. Comment aborder le déconfinement ? Prévenir : une dimension fondamentale dans une stratégie de déconfinement L'Institut Pasteur estime le taux d'immunisation de la population française à 5,7%. Dans certains territoires particulièrement touchés, ce taux est évalué aux alentours de 12%. Il va être important d'éviter cette « deuxième vague » épidémique au moment du déconfinement. PROTÉGER – TESTER – ISOLER est la stratégie proposée par le Premier ministre dans son allocution du 28/04/2020. 1- PROTÉGER toute la population par le port de masques et les gestes barrière. 2- TESTER en masse et en premier lieu les personnes symptomatiques et leur entourage. 3- ISOLER les malades COVID + et les personnes ayant été en contact avec eux. Il est clair que ces mesures doivent être appliquées, à condition de disposer des moyens pour le faire, moyens qui eussent dus être à disposition au premier jour de l'épidémie. Mais cela est INSUFFISANT ! En effet, SANS traitement précoce, l'état de santé des patients malades reste susceptible de s'aggraver et de les conduire à l'hôpital ; il est URGENT de CHANGER la stratégie thérapeutique et il est du devoir et de la responsabilité médicale de permettre le même accès aux soins pour toutes et tous. Un point est donc essentiel 4- TRAITER La stratégie peut reposer sur trois axes ☐ Traitement précoce des malades selon les recommandations précisées au chapitre V.2. avec recueil des paramètres de suivi, à visée épidémiologique. Ceci passe par la remise à disposition en médecine de ville du PLAQUENIL® et par une gestion adaptée des stocks de cette molécule ainsi que de ceux d'azithromycine qui sont au plus bas à ce jour dans certaines régions. ☐ Prévenir en favorisant le bon fonctionnement du système immunitaire Recharge des

stocks de Vitamine D ☐ Mise en place d'une chimioprophylaxie, en s'appuyant dans un premier temps, sur les données des études rhumatologiques faisant état des contaminations moindres chez les patients lupiques et souffrant de polyarthrite rhumatoïde, en attendant les résultats des études préconisées (chapitre V.3.)

**CONCLUSION** Le Plan de déconfinement progressif à compter du 11 mai a été présenté le 28 avril 2020 par le gouvernement. Nous souhaitons sa pleine réussite dans l'intérêt de toutes les concitoyennes et tous les concitoyens de ce pays. Forts des enjeux humains individuels et collectifs, de l'impact économique et social de cette crise inédite, l'expérience de terrain objectivée et les résultats présentés dans ce rapport, autorisent les auteurs à quelques recommandations. C'est dans ce cadre clairement défini que les soignants de première ligne pourront contribuer à la réussite de la sortie de crise, la prévention d'une seconde vague et le retour à la normalisation de l'accès aux soins pour tous, et notamment pour toutes celles et ceux qui y ont renoncé depuis plusieurs semaines. Partant de l'annonce que les tests seront proposés et organisés sur les territoires de santé à destination des personnes symptomatiques et de l'entourage des personnes positives, et avant un déploiement des tests à plus grande échelle, trois scénarii pourraient être expérimentés. Les médecins traitants seront mis à contribution pour pratiquer les tests virologiques PCR, la conduite à tenir proposée au moment de la mise en quarantaine de la personne et sous couvert de son accord est : 1- En l'état actuel de la réglementation, le patient est orienté vers un établissement de santé du territoire pour une hospitalisation de très courte durée permettant après un bilan sanguin, et un examen cardiovasculaire la mise en route immédiate d'un traitement (ce type de suivi a été proposé à l'ARS Alsace sous l'intitulé « Etude compassionnelle Alsace » par le collectif). Le patient peut rentrer à domicile avec un kit de surveillance afin d'assurer un suivi clinique qualitatif jusqu'à résolution des symptômes et contrôle de la virologie. 2- Si la réglementation quant à la libre prescription des médecins était amenée à changer dans cette phase de déconfinement ou si le patient refuse l'orientation en établissement de santé, le maintien en confinement à l'hôtel ou à domicile devra s'accompagner au minimum de la prescription d'un traitement antibiotique. 3- Dans les territoires où la circulation du virus sera considérée comme active, zone rouge sur la cartographie qui sera présentée, il convient de proposer une chimioprophylaxie par hydroxychloroquine à une grande partie de la population afin de la protéger. Il sera bien entendu important, une fois l'épidémie terminée, d'analyser les complications et les séquelles des patients qui ont été hospitalisés en réanimation, en fonction des traitements reçus mais également d'être vigilant sur le dépistage et la prise en charge des syndromes de stress post traumatique engendrés par cette pandémie et sa gestion. Enfin, il sera crucial de définir une stratégie de santé publique percutante pour prévenir une prochaine pandémie, qui ne risquera pas de survenir, afin que le corps médical soit armé pour y faire face, à l'hôpital comme en ville.

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<https://www.theguardian.com/commentisfree/2020/jun/05/lancet-had-to-do-one-of-the-biggest-retractions-in-modern-history-how-could-this-happen>

### **The Lancet has made one of the biggest retractions in modern history. How could this happen?**

The Lancet is one of the oldest and most respected medical journals in the world. Recently, they published an article on Covid patients receiving hydroxychloroquine with a dire conclusion: the drug increases heartbeat irregularities and decreases hospital survival rates. This result was treated as authoritative, and major drug trials were immediately halted – because why treat anyone with an unsafe drug?

Now, that Lancet study has been retracted, withdrawn from the literature entirely, at the request of three of its authors who “can no longer vouch for the veracity of the primary data sources”. Given the seriousness of the topic and the consequences of the paper, this is one of the most consequential retractions in modern history.



### **Covid-19: Lancet retracts paper that halted hydroxychloroquine trials**

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It is natural to ask how this is possible. How did a paper of such consequence get discarded like a used tissue by some of its authors only days after publication? If the authors don't trust it now, how did it get published in the first place?

The answer is quite simple. It happened because peer review, the formal process of reviewing scientific work before it is accepted for publication, is not designed to detect anomalous data. It makes no difference if the anomalies are due to inaccuracies, miscalculations, or outright fraud. This is not what peer review is *for*. While it is the internationally recognised badge of “settled science”, its value is far more complicated.

At its best, peer review is a slow and careful evaluation of new research by appropriate experts. It involves multiple rounds of revision that removes errors, strengthens analyses, and noticeably improves manuscripts.

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At its worst, it is merely window dressing that gives the unwarranted appearance of authority, a cursory process which confers no real value, enforces orthodoxy, and overlooks both obvious analytical problems and outright fraud entirely.

Regardless of how any individual paper is reviewed – and the experience is usually somewhere between the above extremes – the sad truth is peer review in its entirety is struggling, and retractions like this drag its flaws into an incredibly bright spotlight.

The ballistics of this problem are well known. To start with, the vast majority of peer review is entirely unrewarded. The internal currency of science consists entirely of producing new papers, which form the cornerstone of your scientific reputation. There is no emphasis on reviewing the work of others. If you spend several days in a continuous back-and-forth technical exchange with authors, trying to improve their manuscript, adding new analyses, shoring up conclusions, no one will ever know your name. Neither are you paid. Peer review originally fitted under an amorphous idea of academic “service” – the tasks that scientists were supposed to perform as members of their community. This is a nice idea, but is almost invariably maintained by researchers with excellent job security. Some senior scientists are notorious for peer reviewing manuscripts rarely or even never – because it interferes with the task of producing more of their own research.

However, even if reliable volunteers for peer review can be found, it is increasingly clear that it is insufficient. The vast majority of peer-reviewed articles are never checked for any form of analytical consistency, nor can they be – journals do not require manuscripts to have accompanying data or analytical code and often will not help you obtain them from authors if you wish to see them. Authors usually have zero formal, moral, or legal requirements to share the data and analytical methods behind their experiments. Finally, if you locate a problem in a published paper and bring it to either of these parties, often the median response is no response at all – silence.

This is usually not because authors or editors are negligent or uncaring. Usually, it is because they are trying to keep up with the component difficulties of keeping their scientific careers and journals respectively afloat. Unfortunately, those goals are directly in opposition – authors publishing as much as possible means back-breaking amounts of submissions for journals. Increasingly time-poor researchers, busy with their own publications, often decline invitations to review. Subsequently, peer review is then cursory or non-analytical.

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And even still, we often muddle through. Until we encounter extraordinary circumstances.





## Unreliable data: how doubt snowballed over Covid-19 drug research that swept the world

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Peer review during a pandemic faces a brutal dilemma – the moral importance of releasing important information with planetary consequences quickly, versus the scientific importance of evaluating the presented work fully – while trying to recruit scientists, already busier than usual due to their disrupted lives, to review work for free. And, after this process is complete, publications face immediate scrutiny by a much larger group of engaged scientific readers than usual, who treat publications which affect the health of every living human being with the scrutiny they deserve.

The consequences are extreme. The consequences for any of us, on discovering a persistent cough and respiratory difficulties, are directly determined by this research. Papers like today's retraction determine how people live or die tomorrow. They affect what drugs are recommended, what treatments are available, and how we get them sooner.

The immediate solution to this problem of extreme opacity, which allows flawed papers to hide in plain sight, has been advocated for years: require more transparency, mandate more scrutiny. Prioritise publishing papers which present data and analytical code alongside a manuscript. Re-analyse papers for their accuracy before publication, instead of just assessing their potential importance. Engage expert statistical reviewers where necessary, pay them if you must. Be immediately responsive to criticism, and enforce this same standard on authors. The alternative is more retractions, more missteps, more wasted time, more loss of public trust ... and more death.


- James Heathers is a research scientist at Northeastern University in Boston MA. He studies biosignal methodology and metascience.

- This article was amended on 12 June 2020 to clarify that not all peer review is unrewarded, as an earlier version had said.

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[https://www.youtube.com/watch?v=4HYK5pL2Z\\_s](https://www.youtube.com/watch?v=4HYK5pL2Z_s)

YouTube Search




The video player shows a CBSN news segment. The main frame features a man in a white lab coat, James Todaro, MD, speaking. Two smaller inset frames show a woman and another man, both with CBSN logos. A text overlay at the bottom of the video reads: "CORONAVIRUS CRISIS MAJOR COVID-19 STUDY RETRACTED THE LANCET ISSUES CORRECTION AFTER MISREPORTING ON ANTIMALARIAL DRUGS TO TREAT COVID-19 CBSN". The video progress bar shows 0:03 / 55:49 and the title "The origin of the #LancetGate scandal".

The Man Behind [#LancetGate](#): A Breaking Science Scandal with Global Ramifications · James Todaro, MD

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13 days after publishing a paper on hydroxychloroquine (a potential drug for coronavirus treatment), The Lancet retracted the study due to faulty data.

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<https://www.usatoday.com/story/news/health/2020/05/22/covid-19-study-links-hydroxychloroquine-higher-risk-death/5244664002/>

## Coronavirus patients who took hydroxychloroquine had higher risk of death, study shows

[Adrianna Rodriguez](#)

USA TODAY

Published 1:48 p.m. ET May 22, 2020 | Updated 2:43 p.m. ET May 22, 2020

A new study shows coronavirus patients who took [hydroxychloroquine to treat COVID-19](#) had a higher risk of death than those who weren't given the drug.

The study, [published Friday in the medical journal \*The Lancet\*](#), also found that COVID-19 patients were more likely to develop serious heart arrhythmias if treated with hydroxychloroquine, or its closely related cousin chloroquine.

Arrhythmias can lead to a sudden cardiac death, the report said, but researchers did not associate the study's fatalities with adverse cardiac affects.

Even though it's only an observational study – not the gold standard double-blind, randomized, controlled trials – experts say the enormous sample size makes it compelling.

The study comprises of 96,000 coronavirus patients from six different countries who were hospitalized between Dec. 20, 2019 and April 14, 2020. Nearly 15,000 patients were treated with hydroxychloroquine or chloroquine alone or in combination with an antibiotic – similar to the cocktail President Donald Trump said he was taking Monday.

“This is a much, much larger sample size than has ever been reported in regards to hydroxychloroquine and chloroquine,” said Dr. Matthew Heinz, hospitalist at Tucson Medical Center in Arizona. “The results are pretty compelling and fairly consistent.”

In all, 1,868 took chloroquine alone, 3,783 took that plus an antibiotic, 3,016 took hydroxychloroquine alone and 6,221 took that plus an antibiotic.

About 9% of patients taking none of the drugs died in the hospital, versus 16% on chloroquine, 18% on hydroxychloroquine, 22% on chloroquine plus an antibiotic, and 24% on hydroxychloroquine plus an antibiotic.

After taking into account age, smoking, various health conditions and other factors that affect survival, researchers estimate that use of the drugs may have contributed to 34% to 45% of the excess risk of death they observed.

“It really does give us some degree of confidence that we are unlikely to see major benefits from these drugs in the treatment of COVID-19 and possibly harm,” said Dr. David Aronoff, infectious diseases chief at Vanderbilt University Medical Center, who was not involved in the research.

About 8% of those taking hydroxychloroquine and an antibiotic developed a heart rhythm problem vs. 0.3% of the patients not taking any of the drugs in the study. More of these problems were seen with the other drugs, too.

“When you add azithromycin, it’s always worse,” Heinz said. “Cardiac death is something you can’t monitor for, you can’t detect.”

Hydroxychloroquine is an arthritis medicine that can also be used as a prevention or treatment of malaria, a red blood cell infection transmitted by a mosquito bite, according to the Mayo Clinic. It’s available in the U.S. under prescription only. It can also be used to treat discoid lupus erythematosus and systemic lupus erythematosus.

President Trump told reporters [during a roundtable discussion with restaurant executives at the White House on Monday](#) that he’s been taking the drug for the past week and a half, along with zinc and an initial dose of the antibiotic azithromycin.

He tweeted his praise for the drug combination Thursday saying it has “a real chance to be one for the biggest game changers in the history of medicine.”

[The Food and Drug Administration](#) has warned against taking hydroxychloroquine with antibiotics and has said the malaria drug should only be used for coronavirus in formal studies.

The long list of common side effects hydroxychloroquine, [also sold under the brand name Plaquenil](#), include nausea, vomiting, stomach pain or cramps, loss of appetite, weight loss, diarrhea, dizziness, spinning sensation, headache, ringing in your ears, nervousness, irritability, skin rash, itching or hair loss.

Despite the *Lancet* study, Heinz doesn’t believe ongoing studies that continue to use the drug in clinical trials should be halted as they have safety monitor boards that can pull the plug if things go awry.

“This is science. COVID-19 isn’t Democrat or Republican. It doesn’t get upset with tweets,” Heinz said. “We’re going to science our way through this (pandemic).”

fn45

<https://www.reuters.com/article/us-health-coronavirus-indonesia-chloroqu/exclusive-indonesia-major-advocate-of-hydroxychloroquine-told-by-who-to-stop-using-it-idUSKBN23227L>

## WORLD NEWS

MAY 26, 2020 / 9:39 AM / 3 MONTHS AGO

### **Exclusive: Indonesia, major advocate of hydroxychloroquine, told by WHO to stop using it**

[Kate Lamb](#), [Tom Allard](#)

(Reuters) - The World Health Organization has urged Indonesia, one of the world's biggest advocates of two malaria drugs to treat the coronavirus, to suspend such treatment over safety concerns, a source familiar with the advice told Reuters on Tuesday.

Any decision by Indonesia to halt use of the drugs, chloroquine and hydroxychloroquine, in coronavirus patients would mark a major global shift away from a treatment which has been touted for months by U.S. President Donald Trump.

Indonesia, the world's fourth most populous nation, had told doctors to use the drugs to treat all COVID-19 patients with symptoms from mild to severe. The country has ramped up production since March, granting two dozen licenses to local manufacturers who have churned out millions of doses.

The source, who spoke on condition of anonymity to discuss a recommendation not yet made public, said the WHO had sent a notice to Indonesia's health ministry advising that use of the drugs should be suspended.

Erlina Burhan, a doctor who helped draft coronavirus treatment guidelines as a member of the Indonesian Association of Pulmonologists, confirmed that the association had also received new advice from the WHO to suspend use of the drugs.

"We discussed the issues and there are still some disputes. We have no conclusion yet," she told Reuters.

A spokesperson for the WHO mission in Indonesia did not immediately respond to a request for comment. Indonesia's health ministry, Food and Drug Monitoring Agency (BPOM) and the spokesman for Indonesia's COVID-19 taskforce were not immediately available to comment.

Last week, the Lancet medical journal published the most comprehensive study to date on the drugs, which found that coronavirus patients prescribed them were more likely to experience heart rhythm disturbances and more likely to die.

### **"GAMECHANGER"**

On Monday, the WHO announced it was suspending the use of hydroxychloroquine for COVID-19 patients in a global clinical trial. It has advised against using the malaria drugs for the coronavirus outside such trials.

Trump has touted hydroxychloroquine for months as a potential cure or preventive treatment for the coronavirus, and has said he was taking it himself to prevent infection.

On March 21, Trump described hydroxychloroquine as a “gamechanger”. Days later, Indonesia’s President Joko Widodo said the drug, while not a cure, could help patients recover.

According to a report from the ministry of health prepared for parliament, Indonesian companies were on course to produce 15.4 million doses of the two drugs between April and May.

Indonesia’s food and drug agency published a COVID-19 “Informatorium” which included detailed dosage guidelines for the use of the drugs for adolescent and adult coronavirus patients suffering from moderate to severe symptoms.

The guidelines, which include warnings about potential heart complications, recommend they be used in tandem with the antibiotic azithromycin, a combination some studies show elevates the risk of heart rhythm disturbances.

Burhan said chloroquine and azithromycin have been routinely used. Earlier this month she told Reuters it was “hard to tell” if chloroquine was increasing the death rate of coronavirus patients, as any links were yet to be investigated.

Stephen Nissen, a cardiologist and chief academic officer of the Miller Family Heart, Vascular & Thoracic Institute at the Cleveland Clinic, said he was surprised Indonesian authorities had ever recommended widespread use of the drugs.

“We know these drugs produce a rare, but very serious and potentially lethal cardiovascular side effects, which is a heart rhythm disturbance that is very difficult to treat,” he said.

“So the idea of giving them routinely on the basis of the flimsiest of evidence of benefit makes absolutely no sense.”

Jane Quinn, a pharmacology researcher at Australia’s Charles Sturt University, said the anti-malaria drugs could be more dangerous for Indonesians than for other groups, because of the enzyme profile of Indonesia’s population.

“The evidence from looking at those enzymes globally is that populations in Indonesia are actually much less effective at breaking chloroquine and hydroxychloroquine down,” she said, adding this could make the drugs less effective and more toxic.

fn46

<https://medicalxpress.com/news/2020-05-trial-hydroxychloroquine-covid-treatment.html>

MAY 25, 2020

### **WHO suspends hydroxychloroquine trial as COVID-19 treatment**

The World Health Organization said Monday it had temporarily suspended clinical trials of hydroxychloroquine as a potential treatment for COVID-19 being carried out across a range of countries as a precautionary measure.

The decision came after publication last week of a study in *The Lancet* which indicated that using the drug on COVID-19 patients could increase their chances of dying, WHO chief Tedros Adhanom Ghebreyesus told a virtual press conference.

Tedros said that the executive group of the so-called Solidarity Trial, in which hundreds of hospitals across several countries have enrolled patients to test several possible treatments for the novel coronavirus, had as a precaution suspended trials using that drug.

"The Executive Group has implemented a temporary pause of the hydroxychloroquine arm within the Solidarity Trial while the safety data is reviewed by the Data Safety Monitoring Board," Tedros said.

"The other arms of the trial are continuing," he stressed.

Hydroxychloroquine is normally used to treat arthritis but pronouncement from public figures including US President Donald Trump—who announced last week he is taking the drug—has prompted governments to bulk buy the medicine.

Brazil's health minister also recommended last week using hydroxychloroquine, as well as the anti-malarial chloroquine, to treat even mild COVID-19 cases.

The *Lancet* study found that both drugs can produce potentially serious side effects, particularly heart arrhythmia.

And neither drug benefitted patients hospitalised with COVID-19, according to a *Lancet* study, which looked at the records of 96,000 patients across hundreds of hospitals.

Tedros stressed Monday that the two drugs "are accepted as generally safe for use in patients with autoimmune diseases or malaria."

WHO chief scientist Soumya Swaminathan told Monday's briefing that the WHO-backed Solidarity Trial had been looking only at the effects of hydroxychloroquine and not chloroquine.

The decision on suspending enrolment for trials using hydroxychloroquine was "a temporary measure", she said.

"We're just acting by precaution," WHO emergencies chief Michael Ryan agreed.

**'Dangerous assumption'?**

The COVID-19 pandemic, which began late last year in China, has killed nearly 350,000 people worldwide and infected almost 5.5 million, according to an AFP tally using official sources.

While there is still no approved treatment or vaccine for the novel coronavirus, drastic measures that at one point saw half of humanity under lockdown have pushed down transmission rates in a number of countries.

As many nations begin to gradually lift restrictions, the WHO on Monday stressed the need to keep up with physical distancing measures and to scale up efforts to test and detect cases.

"All countries need to remain on high alert," WHO expert Maria Van Kerkhove said, stressing that "even countries that have seen a decline in cases must remain ready."

She warned that studies using antibody tests to determine how many people have been infected and might have some level of immunity "indicate that a large proportion of the population remains susceptible."

"The virus will take the opportunity to amplify if it can," she said.

Ryan agreed, urging countries to "continue to put in place ... a comprehensive strategy to ensure that we continue on a downward trajectory and that we don't have an immediate second peak."

He warned against the idea that the pandemic might move in natural seasonal waves, stressing that the reason transmission is going down in a number of countries was the drastic measures put in place.

"My concern right now is that people might be assuming that the current rapid infections represents a natural seasonality," he said.

"Making an assumption that it is on a downward trajectory, and the next danger point is sometime in October or November, I think that would be a dangerous assumption."

"If we take the pressure off the virus then the virus can bounce back," he said.



fn47

<https://www.reuters.com/article/health-coronavirus-hydroxychloroquine-fr/eu-governments-ban-malaria-drug-for-covid-19-trial-paused-as-safety-fears-grow-idUSKBN2340A6>

MAY 27, 2020 / 10:48 PM / 3 MONTHS AGO

## **EU governments ban malaria drug for COVID-19, trial paused as safety fears grow**

[Matthias Blamont](#), [Alistair Smout](#), [Emilio Parodi](#)

PARIS/LONDON/MILAN (Reuters) - European governments moved on Wednesday to halt the use of anti-malaria drug hydroxychloroquine to treat COVID-19 patients, and a second global trial was suspended, further blows to hopes for a treatment promoted by U.S. President Donald Trump.

The moves by France, Italy and Belgium followed a World Health Organization decision on Monday to pause a large trial of hydroxychloroquine due to safety concerns.

A UK regulator said on Wednesday that a separate trial was also being put on hold, less than a week after it started. The study, being led by the University of Oxford and partly funded by the Bill and Melinda Gates Foundation, was expected to involve as many as 40,000 healthcare workers.

“All hydroxychloroquine trials in COVID-19 remain under close review” while investigators assess any further risks, the Medicines and Healthcare products Regulatory Agency (MHRA) said in an email to Reuters.

The swift moves by authorities in countries hit hardest by the pandemic highlighted the challenge for governments scrambling to find ways to treat patients and control the novel coronavirus.

After early reports that it might help some patients, regulators in several countries had allowed hydroxychloroquine to be used as a potential COVID-19 treatment.

Trump was a particularly strong supporter, describing the drug as a “gamechanger.” He later announced he was taking it to prevent infection.

However, more recent studies have raised serious safety issues. British medical journal The Lancet has reported coronavirus patients receiving hydroxychloroquine were more likely to die and experience dangerous irregular heartbeats.

On Wednesday, France’s health ministry cancelled a decree in place for nearly two months that had allowed hospital doctors to dispense it in specific situations for COVID-19.

Medicines agencies in France and Italy said the drug should not be used for COVID-19 outside clinical trials. Belgium’s regulator said trials aiming to evaluate the drug should also take potential risks into consideration.

Swiss drugmaker Novartis is pushing ahead with its U.S. study involving 440 patients, while French company Sanofi declined to comment on the future of its two trials.

Italian health authorities concluded that the risks, coupled with little evidence hydroxychloroquine was beneficial against COVID-19, merited a ban outside of clinical trials.

“New clinical evidence on the use of hydroxychloroquine in subjects with SARS-CoV-2 infection ... indicates an increased risk for adverse reactions with little or no benefit,” medicines agency AIFA said.

The WHO said a safety panel would evaluate by mid-June the drug’s use in its multi-country trial of potential COVID-19 treatments.

Germany is looking at The Lancet study and the WHO’s decision but has not made any decision about new guidance on hydroxychloroquine, a spokeswoman for its drugs regulator said.

The U.S. Food and Drug Administration has allowed healthcare providers to use hydroxychloroquine for COVID-19 through an emergency-use authorization, but has not approved them to treat it. It also warned in April, that for safety reasons, the drug should be used only for hospitalized COVID-19 patients or those in clinical trials.

The agency did not respond to queries asking whether it was reconsidering the emergency-use authorization.

fn48

<https://www.nytimes.com/2020/05/18/us/politics/trump-hydroxychloroquine-covid-coronavirus.html>

### **Malaria Drug Taken by Trump Is Tied to Increased Risk of Heart Problems and Death in New Study**

The drugs did not help coronavirus patients, and should not be used outside clinical trials, researchers said.

By Denise Grady Published May 22, 2020 Updated June 6, 2020 Update, June 4: Since initial reporting on this study, concerns were raised about the data used by the researchers, and on June 4 The Lancet retracted the study. Read our coverage here. The malaria drugs hydroxychloroquine and chloroquine did not help coronavirus patients and may have done harm, according to a new study based on the records of nearly 15,000 patients who received the drugs and 81,000 who did not. Some were also given the antibiotic azithromycin, or a related medicine. Hydroxychloroquine is the drug that President Trump has advocated, and that he said he has been taking in hopes of preventing coronavirus infection. People who received the drugs were more likely to have abnormal heart rhythms, according to the study in The Lancet. They were also more likely to die. But the findings were not definitive, because the study was observational, meaning that the patients were not picked at random to receive the drug or not, and may have had underlying differences that affected their outcomes. The findings match those of several earlier observational studies that also found no benefit and possible harm from the drugs, and that have led some medical centers to stop recommending their use. The new study is based on data from 96,032 coronavirus patients from 671 hospitals around the world. The authors say it is the most comprehensive study to date. While acknowledging the limitations of observational studies, they write, “our findings suggest not only an absence of Malaria Drug Taken by Trump Is Tied to Increased Risk of Heart Problems and Death in New Study therapeutic benefit but also potential harm with the use of hydroxychloroquine or chloroquine drug regimens,” with or without antibiotics, in hospitalized patients with Covid-19.

Because of possible underlying differences between treated and untreated patients, this type of study cannot provide definitive evidence about drug safety and effectiveness. Even so, the authors recommended that the drugs not be used outside clinical trials, and they said carefully controlled trials were urgently needed. Several clinical trials are underway around the world. Hydroxychloroquine and chloroquine are approved to treat malaria and the autoimmune diseases lupus and rheumatoid arthritis. They have long been considered safe for those conditions — except for people known to have underlying disorders affecting their heart rhythm.

The drugs, sometimes combined with the antibiotic azithromycin, have been widely used to treat coronavirus patients in hospitals around the world, despite the lack of evidence that they help. Anecdotal reports of patients who seemed to improve and laboratory findings of a possible antiviral effect spurred use of the drugs, because there is no proven treatment for Covid-19 and doctors have been desperate to give severely ill patients some kind of therapy. One month ago, the Food and Drug Administration issued a safety warning about both hydroxychloroquine and chloroquine, saying the drugs could cause dangerous abnormalities in heart rhythm in coronavirus patients, and should be used only in clinical trials or hospitals where patients can be closely monitored for heart problems. The National Institute of Allergy and Infectious Diseases made a similar warning, and also advised against combining the drugs with azithromycin outside clinical trials. › • • • CORONAVIRUS SCHOOLS BRIEFING: The pandemic is upending education. Get the latest news and tips as students go back to school. Sign Up

The findings of the new study did not suggest that the disturbances in heart rhythm caused the increased deaths that the authors observed, according to an editorial in *The Lancet*. The editorial said that some other property of the drugs might, in theory, worsen the illness, or that cardiac damage and low blood oxygen caused by the infection could make patients more vulnerable to dangerous rhythm abnormalities caused by the drugs. Mr. Trump revealed on Monday that he had been taking hydroxychloroquine and continued to test negative for the virus. Later this week, he said the regimen would end within a day or two and he would stop taking it.

fn49

<https://www.nytimes.com/2020/05/22/health/malaria-drug-trump-coronavirus.html>

### **Trump Says He's Taking Hydroxychloroquine, Prompting Warning From Health Experts**

His announcement drew immediate criticism from a range of medical experts, who warned not just of the dangers it posed for the president's health but also of the example it set. By Annie Karni and Katie Thomas May 18, 2020 WASHINGTON — President Trump said on Monday that he had been taking hydroxychloroquine, an antimalarial drug the Food and Drug Administration warned could cause serious heart problems for coronavirus patients. He said he was taking the drug as a preventive measure and continued to test negative for the coronavirus. "All I can tell you is so far I seem to be OK," Mr. Trump said, adding that he had been taking the drug for about a week and a half, with the approval of the White House physician. "I get a lot of tremendously positive news on the hydroxy," Mr. Trump continued, explaining that his decision to try the drug was based on one of his favorite refrains: "What do you have to lose?" But Mr. Trump's announcement surprised many of his aides and drew immediate criticism from a range of medical experts, who warned not just of the dangers it posed for the president's health but also of the example it set. "My concern would be that the public not hear comments about the use of hydroxychloroquine and believe that taking this drug to prevent Covid-19 infection is without hazards. In fact, there are serious hazards," said Dr. Steven E. Nissen, the chief academic officer of the Miller Family Heart, Vascular & Thoracic Institute at the Cleveland Clinic. Dr. Scott Solomon, a professor of medicine at Harvard Medical School, said Mr. Trump's decision to try the drug was up to him and his physician. "But what is irresponsible is the example he is setting," Dr. Solomon said. Trump Says He's Taking Hydroxychloroquine, Prompting Warning From Health Experts Mr. Trump publicly embraced hydroxychloroquine as a "game changer" in the fight against the virus in March, and his endorsement, amplified by Fox News hosts like Laura Ingraham and Sean Hannity, caused a run on the drug, making it scarce for those who took it for lupus and rheumatoid arthritis, for which it is regularly prescribed. But on Monday night, Dr. Manny Alvarez, the senior managing editor for Fox News's health news, said on air that the president's statement was "highly irresponsible" and asked what had changed since studies showed the drug had no benefits.

Mr. Trump first said he was considering taking the drug himself in April. But in recent weeks he had notably stopped promoting it, as did the Fox News hosts. But he then suggested at a news conference that injecting disinfectants into the human body could help combat the virus, causing confused callers to

flood state health hotlines and the makers of Clorox and Lysol to plead with Americans not to inject or ingest their products. His announcement on Monday came less than a month after the F.D.A. issued a safety warning about the drug, noting that it could cause dangerous abnormalities in heart rhythm in coronavirus patients and should not be used outside clinical trials or in hospitals where patients were closely monitored for heart problems. But by that time hydroxychloroquine had become a divisive issue within the Trump administration. Dr. Rick Bright, who led the federal agency involved in developing a coronavirus vaccine, said he was removed from his post after he pressed for rigorous vetting of the drug.

Dr. Bright said he was pressured to direct money toward hydroxychloroquine, one of several “potentially dangerous drugs promoted by those with political connections.” On Monday, the president not only promoted the drug but also said he was taking it. And he made it clear that his decision was based on trusting anecdotal evidence, and his own gut, over the warnings of the government, or any data.


In that sense his position was consistent with his view of other expert medical advice — he has also refused to follow the guidelines of the Centers for Disease Control and Prevention and wear a face mask. And before becoming president he had alleged that there was a link between the number of vaccines children got in early infancy and the development of autism. “I take it because I think I hear very good things,” Mr. Trump said, citing a letter he received from an unnamed doctor in Westchester, N.Y., promoting the use of hydroxychloroquine. “I want the people of this nation to feel good. I don’t want them being sick,” Mr. Trump said at the end of a round table with restaurant executives at the White House. “And there is a very good chance that this has an impact, especially early on.” The F.D.A. has warned hydroxychloroquine can cause serious heart problems for coronavirus patients. John Locher/Associated Press CORONAVIRUS SCHOOLS BRIEFING: The pandemic is upending education. Get the latest news and tips as students go back to school. Sign Up Mr. Trump said he started taking the drug about 10 days ago, around the same time two White House aides tested positive for the coronavirus, prompting the fears of the president and other top officials that the virus would spread rapidly through the West Wing.

As for taking hydroxychloroquine, “I’m not going to get hurt by it,” Mr. Trump said, adding that he was sharing the news to be transparent with Americans and appearing to enjoy the shock value of his announcement. “It has been around for 40 years for malaria, for lupus, for other things.” Later on Monday night, the White House physician, Dr. Sean P. Conley, released a statement that linked Mr. Trump’s decision to take the drug to the “support staff” who tested positive for the virus, an apparent reference to the president’s personal valet. “After numerous discussions he and I had regarding the evidence for and against the use of hydroxychloroquine, we concluded the potential benefit from treatment outweighed the relative risks,” Dr. Conley said. He also said the president “is in very good health and has remained symptom free.” Early studies of hydroxychloroquine in the laboratory suggesting that the drug could block the coronavirus from attacking cells prompted initial enthusiasm. But the studies of the drug in humans so far have pointed to serious side effects. “I think it’s a very bad idea to be taking hydroxychloroquine as a preventive medication,” said Dr. Eric Topol, a cardiologist and the director of the Scripps Research Translational Institute in La Jolla, Calif. “There are no data to support that, there’s no evidence and in fact there is no compelling evidence to support its use at all at this point.”

As for taking hydroxychloroquine, "I'm not going to get hurt by it," Mr. Trump said, adding that he was sharing the news to be transparent with Americans and appearing to enjoy the shock value of his announcement. "It has been around for 40 years for malaria, for lupus, for other things." Later on Monday night, the White House physician, Dr. Sean P. Conley, released a statement that linked Mr. Trump's decision to take the drug to the "support staff" who tested positive for the virus, an apparent reference to the president's personal valet. "After numerous discussions he and I had regarding the evidence for and against the use of hydroxychloroquine, we concluded the potential benefit from treatment outweighed the relative risks," Dr. Conley said. He also said the president "is in very good health and has remained symptom free." Early studies of hydroxychloroquine in the laboratory suggesting that the drug could block the coronavirus from attacking cells prompted initial enthusiasm. But the studies of the drug in humans so far have pointed to serious side effects. "I think it's a very bad idea to be taking hydroxychloroquine as a preventive medication," said Dr. Eric Topol, a cardiologist and the director of the Scripps Research Translational Institute in La Jolla, Calif. "There are no data to support that, there's no evidence and in fact there is no compelling evidence to support its use at all at this point."

fn50

<https://www.youtube.com/watch?v=ZYgiCALEdpE>



BFM TV. 17:12 DIRECT

That the great question we are all asking ourselves,

0:08 / 2:15

(Eng Subs) Hydroxychloroquine Lancet Study: Former France Health Minister blows the whistle

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fn51

<https://jamanetwork.com/journals/jamacardiology/fullarticle/2765631>

May 1, 2020

**Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)**

[Nicholas J. Mercuro, PharmD, BCIDP<sup>1</sup>](#); [Christina F. Yen, MD<sup>2</sup>](#); [David J. Shim, MD, PhD<sup>3</sup>](#); et al

**Key Points**

**Question** In hospitalized patients with coronavirus disease 2019 (COVID-19), what is the risk of corrected QT (QTc) prolongation when taking hydroxychloroquine with or without azithromycin?

**Findings** In a cohort study of 90 hospitalized patients with coronavirus disease 2019, use of hydroxychloroquine with or without azithromycin for treatment of COVID-19 was associated with

frequent QTc prolongation, and those taking hydroxychloroquine and azithromycin had greater QT prolongation than those taking hydroxychloroquine alone. One patient developed torsades de pointes.

**Meaning** Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.

#### Abstract

**Importance** Administration of hydroxychloroquine with or without azithromycin for the treatment of coronavirus disease 2019 (COVID-19)-associated pneumonia carries increased risk of corrected QT (QTc) prolongation and cardiac arrhythmias.

**Objective** To characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their use of hydroxychloroquine with or without concomitant azithromycin.

**Design, Setting, and Participants** This was a cohort study performed at an academic tertiary care center in Boston, Massachusetts, of patients hospitalized with at least 1 positive COVID-19 nasopharyngeal polymerase chain reaction test result and clinical findings consistent with pneumonia who received at least 1 day of hydroxychloroquine from March 1, 2020, through April 7, 2020.

**Main Outcomes and Measures** Change in QT interval after receiving hydroxychloroquine with or without azithromycin; occurrence of other potential adverse drug events.

**Results** Among 90 patients given hydroxychloroquine, 53 received concomitant azithromycin; 44 (48.9%) were female, and the mean (SD) body mass index was 31.5 (6.6). Hypertension (in 48 patients [53.3%]) and diabetes mellitus (in 26 patients [28.9%]) were the most common comorbid conditions. The overall median (interquartile range) baseline QTc was 455 (430-474) milliseconds (hydroxychloroquine, 473 [454-487] milliseconds vs hydroxychloroquine and azithromycin, 442 [427-461] milliseconds;  $P < .001$ ). Those receiving concomitant azithromycin had a greater median (interquartile range) change in QT interval (23 [10-40] milliseconds) compared with those receiving hydroxychloroquine alone (5.5 [-15.5 to 34.25] milliseconds;  $P = .03$ ). Seven patients (19%) who received hydroxychloroquine monotherapy developed prolonged QTc of 500 milliseconds or more, and 3 patients (8%) had a change in QTc of 60 milliseconds or more. Of those who received concomitant azithromycin, 11 of 53 (21%) had prolonged QTc of 500 milliseconds or more and 7 of 53 (13 %) had a change in QTc of 60 milliseconds or more. The likelihood of prolonged QTc was greater in those who received concomitant loop diuretics (adjusted odds ratio, 3.38 [95% CI, 1.03-11.08]) or had a baseline QTc of 450 milliseconds or more (adjusted odds ratio, 7.11 [95% CI, 1.75-28.87]). Ten patients had hydroxychloroquine discontinued early because of potential adverse drug events, including intractable nausea, hypoglycemia, and 1 case of torsades de pointes.

**Conclusions and Relevance** In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc. Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.

#### Introduction



As of April 10, 2020, more than 500 000 cases of coronavirus disease 2019 (COVID-19) have been reported in the United States, with no US Food and Drug Administration–approved treatments to date.<sup>1</sup> Against this backdrop, the use of hydroxychloroquine for COVID-19 treatment has gained traction, appearing in international and domestic therapeutic guidelines.<sup>2</sup> The presumed efficacy and widespread use of hydroxychloroquine stemmed from in vitro evaluations of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2 and a small prospective study claiming virologic clearance in 6 patients taking hydroxychloroquine with azithromycin.<sup>3,4</sup> The combination gained further attention after coverage by the lay press; however, subsequent studies have failed to replicate these findings.<sup>5</sup>

Although hydroxychloroquine and azithromycin are generally well-tolerated medications used in clinical practice, both can cause corrected QT (QTc) prolongation.<sup>6,7</sup> With sweeping usage and perhaps insufficient consideration for comorbidities or concomitant QT-prolonging therapies, the frequency of adverse drug events (ADEs) will likely increase. Furthermore, evidence suggests that patients with underlying cardiac comorbidities are disproportionately affected by COVID-19 and the virus itself provokes myocardial injury.<sup>8,9</sup> In this study, we aimed to characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their usage of hydroxychloroquine with or without concomitant azithromycin.

## Methods

The study was conducted according to Beth Israel Deaconess Medical Center institutional review board standards; informed consent was waived based on the board’s standards. This was a single-center, retrospective, observational study evaluating adults with COVID-19 who were hospitalized at Beth Israel Deaconess Medical Center in Boston, Massachusetts. We included patients admitted between March 1 and April 7, 2020, who received at least 1 day of hydroxychloroquine while inpatients and at least 1 positive COVID-19 nasopharyngeal polymerase chain reaction test result via the Pan Degenerate Amplification and Adaptation (PANDAA) qDx SARS-CoV-2 kit (Aldatu Biosciences). The antimicrobial stewardship team reviewed all hydroxychloroquine orders placed for patients with COVID-19 per internal treatment criteria, which included clinical and radiographic findings, laboratory results, and an electrocardiogram. The standard regimen was 400 mg of hydroxychloroquine twice on day 1, then 400 mg daily on days 2 through 5.

Data were extracted from the electronic medical records and deidentified. Medication administrations, ADEs, and treatment response were reviewed by an infectious disease-specialized pharmacist (N.J.M.) and physician (C.F.Y.). Electrocardiograms were manually evaluated by cardiologists (D.J.S. and T.R.M.) to calculate QTc intervals using the Bazett formula and so-called excess correction method for QRS values greater than 120 milliseconds. The Tisdale score, used to prognosticate QT prolongation in hospitalized patients, was applied retrospectively to evaluate QTc prolongation risk.<sup>10</sup> End points of interest were changes in QTc ( $\Delta$ QTc) in the cohort and between groups receiving hydroxychloroquine and hydroxychloroquine plus azithromycin, development of prolonged QTc interval to 500 milliseconds or more, and documented ADEs.

## Statistical Analysis

Nominal data were described using proportions. Normally distributed discrete data were described with means and SDs, and medians and interquartile ranges (IQRs) were used to represent data that were not normally distributed. Categorical variables were compared with a  $\chi^2$  or Fisher exact test and described

using odds ratios (ORs) and 95% CIs. The Mann-Whitney *U* test evaluated continuous variables, with a *P* value of less than .05 to represent the statistical significance threshold. The QTc prolongation risk ( $\geq 500$  milliseconds) was evaluated in a logistic regression model. Covariates evaluated in the Tisdale score and associated with QTc prolongation in univariate analysis ( $P < .10$ ) were included in the multivariable analysis. Statistical analyses were performed using SPSS version 25.0 (IBM).

## Results

Ninety patients were diagnosed with COVID-19 at a median (IQR) of 8 (5-12) days from the time of symptom onset. The mean (SD) age was 60.1 (16.7) years, 44 (48.9%) were women, and the mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 31.5 (6.6). The most common comorbidities were hypertension (48 patients [53%]) and diabetes mellitus (26 patients [28.9%]) ([Table 1](#)). Thirty patients (33%) were critically ill at the time of testing, and 23 (26%) were mechanically ventilated. All patients received hydroxychloroquine, and 53 (59%) received hydroxychloroquine plus azithromycin; most patients had at least 1 cardiovascular comorbidity and were taking 2 or more QTc-prolonging medications, and 46 (51%) had a high-risk baseline cumulative Tisdale score of 11 or more points.

The median (IQR) baseline QTc was 455 (430-474) milliseconds. With treatment, 10 of 90 patients (11%) had  $\Delta$ QTc of 60 milliseconds or more; 18 (20%) had posttreatment QTc intervals of 500 milliseconds or more. Of 37 patients receiving hydroxychloroquine monotherapy, 7 (19%) developed prolonged QTc of 500 milliseconds or more, and 3 (8%) had  $\Delta$ QTc of 60 milliseconds or more. With concomitant azithromycin, 11 of 53 patients (21%) had prolonged QTc and 7 (13%) had a  $\Delta$ QTc of 60 milliseconds or more ([Figure](#); eFigure 1 in the [Supplement](#)). Although the baseline QTc was shorter in patients receiving concomitant azithromycin compared with those taking hydroxychloroquine alone (median [IQR], 442 [427-461] milliseconds vs 473 [454-487] milliseconds;  $P < .001$ ), hydroxychloroquine and azithromycin was associated with a greater change in QTc compared with hydroxychloroquine alone (median [IQR] change, 23 [10-40] milliseconds vs 5.5 [-15.5 to 34.3] milliseconds;  $P = .03$ ) ([Figure](#)). Patients who were critically ill also had a nonsignificantly greater  $\Delta$ QTc than those who were not (median [IQR] change, 26.5 [11-51] milliseconds vs 16 [-8 to 35] milliseconds;  $P = .05$ ).

The likelihood of prolonged QTc ( $\geq 500$  milliseconds) was greater with concomitant loop diuretic administration (12 of 39 patients [31%] vs 6 of 51 patients [12%];  $P = .03$ ), or a baseline QTc of 450 milliseconds or more (15 of 50 patients [30%] vs 3 of 40 patients [8%];  $P = .008$ ). Both remained independently associated after controlling for 2 or more Systemic Inflammatory Response Syndrome criteria ([Table 2](#)). Age, sex, concomitant QT-prolonging medications administration, and comorbidities did not correlate with a QTc of 500 milliseconds or more. Forty-one patients were discharged, 4 died, and 45 remained hospitalized, with a median follow-up of 9 days. Twenty-one patients had repeated nasopharyngeal polymerase chain reaction testing after a median (IQR) of 3.0 (1.0-6.5) days after starting treatment; 0 of 8 (0%) in the hydroxychloroquine group and 1 of 13 (7.7%) in the hydroxychloroquine and azithromycin group had negative results.

Ten patients (11%) stopped taking hydroxychloroquine prior to day 5 of treatment for QTc prolongation. Possible hydroxychloroquine-associated ADEs included intractable nausea, resolving with medication discontinuation; development of new premature ventricular contractions and right bundle branch block; and a suspected case of hydroxychloroquine-associated hypoglycemia on day 2 of therapy, which was also in the context of poor oral intake. One patient who had hydroxychloroquine and azithromycin

discontinued because of QTc prolongation (499 milliseconds) developed torsades de pointes 3 days later (eFigures 2 and 3 in the [Supplement](#)) and subsequently developed other ventricular arrhythmias that were treated with lidocaine.

## Discussion

Proponents of hydroxychloroquine and chloroquine for COVID-19 treatment cite established safety in patients with autoimmune disorders, in vitro studies, and small nonrandomized clinical trials. However, the patients in these studies are clinically different from patients who were critically ill, infected with COVID-19, and receiving multiple QTc-prolonging medications with extended half-lives, which augment cardiotoxic risks. This was illustrated in a case of torsades de pointes from our cohort. Although hydroxychloroquine and azithromycin administration was discontinued 3 days prior to the event, the patient also had severe acute respiratory distress syndrome, bradycardia, hypothermia, propofol coadministration, and a new cardiomyopathy, raising concerns that the risk of QTc prolongation likely persisted, given the prolonged terminal half-life of each agent (eFigures 2 and 3 in the [Supplement](#)).<sup>11</sup>

Hydroxychloroquine is structurally and mechanistically similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of torsades de pointes and sudden cardiac death.<sup>6</sup> Azithromycin also has been implicated in QTc prolongation and proarrhythmic events; its Food and Drug Administration label highlights the dose-dependent elevation in QTc when combined with chloroquine.<sup>8,12</sup> Furthermore, enrollment was halted in a treatment arm for high-dose chloroquine plus azithromycin in a randomized clinical trial for patients hospitalized with severe COVID-19 pneumonia because of preliminary safety concerns about excessive cardiotoxicity.<sup>13</sup> Loop diuretics, which were independently associated with prolonged QTc in this study, are also frequently used for severe COVID-19 infection to manage volume and acute respiratory distress syndrome, which should necessitate careful electrolyte management.<sup>10</sup>

Within a 4-week observation period, 21 of 90 patients (23%) treated with hydroxychloroquine or hydroxychloroquine plus azithromycin had either significant QTc prolongation or  $\Delta$ QTc of 60 milliseconds or greater. This underscores the American College of Cardiology's recommendation for baseline risk assessment, frequent QTc monitoring, and strict cutoffs for therapy cessation; the Infectious Diseases Society of America voices similar concerns, recommending targeted antiviral therapeutics be limited to clinical trials.<sup>14,15</sup> Ultimately, curtailing hydroxychloroquine-associated ADEs would require a multidisciplinary effort across medicine, infectious diseases, pharmacy, cardiology, critical care, and health care quality.

## Limitations

While hydroxychloroquine and azithromycin administration likely contributed to the observed ADEs, we cannot exclude COVID-19-associated stress cardiomyopathy or myocarditis. Without a control arm, we cannot conclude that hydroxychloroquine and azithromycin conferred increased cardiotoxic risk; however, compared with hydroxychloroquine alone,  $\Delta$ QTc differences were likely associated with the addition of azithromycin. It remains possible that the true degree of QTc prolongation was underestimated, given clinical practice variation and a limited follow-up period: 45 patients remained hospitalized, and 19 patients had no follow-up electrocardiograms. However, for the observed duration,  $\Delta$ QTc and prolongation findings aligned with preliminary reports of significant QTc prolongation in 11% to 25% of patients.<sup>8,13</sup> Higher-risk groups may not have been represented, because institutional guidance

recommended against hydroxychloroquine for individuals with prolonged baseline QTc intervals. Numerous factors in this small cohort of adults who had complex, often critical illness could also have confounded clinical and safety end points.

## Conclusions

Patients who were hospitalized and receiving hydroxychloroquine for COVID-19 frequently experienced QTc prolongation and ADEs, including a case of torsades de pointes with administration of hydroxychloroquine and azithromycin, which to our knowledge has yet to be reported elsewhere in the literature. There is a critical need for rigorous, large-scale studies and risk-benefit assessment prior to initiating COVID-19 therapeutics, with careful attention to medication interactions, cardiac manifestations, routine electrocardiograms, and electrolyte monitoring.

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<http://www.ijmr.org.in/article.asp?issn=0971-5916;year=2020;volume=151;issue=5;spage=459;epage=467;aulast=Chatterjee>

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## Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

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**Background & objectives:** Healthcare workers (HCWs) are at an elevated risk of contracting COVID-19. While intense occupational exposure associated with aerosol-generating procedures underlines the necessity of using personal protective equipment (PPE) by HCWs, high-transmission efficiency of the causative agent [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] could also lead to infections beyond such settings. Hydroxychloroquine (HCQ), a repurposed antimalarial drug, was empirically recommended as prophylaxis by the National COVID-19 Task Force in India to cover such added risk. Against this background, the current investigation was carried out to identify the factors associated with SARS-CoV-2 infection among HCWs in the country.

**Methods:** A case-control design was adopted and participants were randomly drawn from the countrywide COVID-19 testing data portal maintained by the ICMR. The test results and contact details of HCWs, diagnosed as positive (cases) or negative (controls) for SARS-CoV-2 using real-time reverse transcription-polymerase chain reaction (qRT-PCR), were available from this database. A 20-item brief-questionnaire elicited information on place of work, procedures conducted and use of PPE.

**Results:** Compared to controls, cases were slightly older (34.7 vs. 33.5 yr) and had more males (58 vs. 50%). In multivariate analyses, HCWs performing endotracheal intubation had higher odds of being SARS-CoV-2 infected [adjusted odds ratio (AOR): 4.33, 95% confidence interval (CI): 1.16-16.07]. Consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI: 0.22-0.88); a dose-response relationship existed between

frequency of exposure to HCQ and such reductions ( $\chi^2$  for trend=48.88;  $P < 0.001$ ). In addition, the use of PPE was independently associated with the reduction in odds of getting infected with SARS-CoV-2.

**Interpretations & conclusions:** Until results of clinical trials for HCQ prophylaxis become available, this study provides actionable information for policymakers to protect HCWs at the forefront of COVID-19 response. The public health message of sustained intake of HCQ prophylaxis as well as appropriate PPE use need to be considered in conjunction with risk homeostasis operating at individual levels.

Since its global recognition in December 2019, the novel coronavirus disease (COVID-19) pandemic has spread to over 200 countries in less than five months. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of this disease, was noted to spread efficiently through respiratory droplets and contact routes<sup>[1],[2],[3],[4]</sup>. While common presenting symptoms are fever, fatigue, dry cough, myalgia and dyspnoea, a few patients have reported having diarrhoea, nausea, vomiting and new-onset anosmia or ageusia. A considerable proportion of the SARS-CoV-2-infected individuals (around 80%) did not have any noticeable symptoms and yet were able to transmit the infection<sup>[5]</sup>. Such unique transmission potentials of SARS-CoV-2 and lack of definitive antiviral therapy were the reasons behind its wide-scale spread. Evidence indicates that healthcare workers (HCWs) are particularly at risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure<sup>[6]</sup>.

In the absence of specific treatments against COVID-19, social distancing<sup>[7]</sup>, use of face masks<sup>[8]</sup> and frequent hand washing with alcohol rubs or soap constituted the infection prevention measures targeting general population<sup>[9]</sup>. However, HCWs, being exposed to a higher quantum of risk, needed additional intervention approaches for protection<sup>[10]</sup>. Aprons, gowns, gloves, masks, face shields and goggles addressed such needs. These protective gears serve useful purpose in settings where procedures such as nasopharyngeal swab collection, endotracheal intubation or respiratory suctioning are performed on suspected or confirmed patients of COVID-19, potentially generating aerosols from the respiratory tract<sup>[11]</sup>. However, caregiving in a pandemic situation would also entail the risks of transmission of SARS-CoV-2 infection to HCWs from asymptomatic individuals who are not necessarily undergoing invasive procedures<sup>[2],[12],[13]</sup>. Chemoprophylaxis for HCWs could potentially have add-on advantages to cover this additional risk.

Prophylaxis in the present context refers to the use of a short-term therapy to prevent acquisition of SARS-CoV-2 infection. Currently, there are no approved vaccines against SARS-CoV-2, which makes the alternative of using chemotherapeutic agents an attractive proposition. However, no antiviral medicines proved efficacious during the previous coronavirus outbreaks (SARS 2003; Middle East respiratory syndrome coronavirus 2012) and therefore, did not leave the therapeutic community with any viable options during the present COVID-19 pandemic<sup>[14],[15]</sup>. Hydroxychloroquine (HCQ) came into discussion against this background<sup>[16]</sup>. Ability of this compound to inhibit the infection by SARS-CoV-2, as well as viral replication in cell cultures in a time- and dose-dependent manner made it a primary choice<sup>[17]</sup>. Furthermore, HCQ elevates the  $pH$  of endosomes and inhibits SARS-CoV-2 RNA-mediated inflammatory response<sup>[18]</sup>. These laboratory findings encouraged researchers to consider HCQ, originally used for malaria, as a repurposed agent for prophylaxis against SARS-CoV-2<sup>[19]</sup>.

The National Task Force for COVID-19 in India took cognizance of this evidence and empirically recommended the use of HCQ as prophylaxis against SARS-CoV-2 infection in asymptomatic HCWs treating suspected or confirmed COVID-19 cases. Asymptomatic household contacts of confirmed

COVID-19 cases were also covered by this advisory released on March 22, 2020<sup>[20]</sup>. Around the same time, in South Korea, HCQ prophylaxis was used successfully to avert new infections after a large COVID-19 exposure event in a long-term care facility<sup>[21]</sup>. Scientific communications further underlined the necessity of examining the utility of such approaches in the context of high-burden, high-income countries such as Italy<sup>[22]</sup>. Against this backdrop, a case-control investigation was conducted to compare the risks of and protective factors against SARS-CoV-2 infection among HCWs in India.

## Material & Methods

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The ICMR COVID-19 Research Team developed the study proposal, which was approved by the ICMR Central Ethics Committee. Data collection for this investigation was done during May 8-23, 2020. Each participant was informed about the study purpose, and verbal consent was obtained before proceeding with telephonic interview. A data portal developed to capture the information regarding individuals undergoing testing for SARS-CoV-2 infection across India was used to identify the study participants. HCWs tested between the first week of April 2020 and the end of first week of May 2020 formed the sample pool, from which cases and controls were drawn. Symptomatic HCWs testing positive on real-time reverse transcription-polymerase chain reaction (qRT-PCR) for SARS-CoV-2 were defined as cases. Controls were symptomatic HCWs who tested negative on qRT-PCR for SARS-CoV-2 under similar considerations.

*Measures:* A brief 20-item interview schedule was developed to elicit the information on key issues, such as department, designation and length of employment, and use of personal protective equipment (PPE). Among exposure variables, the HCW was asked about contact with suspected or confirmed COVID-19 patients on ventilator and involvement in aerosol-generating procedures (AGPs) such as nasopharyngeal swab collection, endotracheal intubation and respiratory suction. To minimize recall bias, this enquiry was restricted to seven days before SARS-CoV-2 testing. A history of prophylactic HCQ intake with dosing details was also obtained.

*Telephonic interviews:* Participants were telephonically contacted by the researchers to introduce themselves, verify identities, describe the study purpose and check availability for interviews. If a participant's contact phone number in the ICMR data portal actually belonged to a treatment supporter or caregiver or relative, we reached out to the individual who was tested for COVID-19 through the primary contact. Following verbal consent, telephonic interviews, which took 5-11 min, were conducted. At the close of the interviews, participants' queries related to COVID-19 were addressed.

*Sample size:* It was intended to enrol cases and controls in a 1:1 ratio and match them for location (testing centre) and temporality (test date). Assuming that 50 per cent of the controls were on HCQ prophylaxis (exposure) and correlation coefficient for exposure between matched cases and controls would be 0.2, it was estimated that 484 cases would be required to detect an odds ratio of 1.50 with 80 per cent power at five per cent significance level<sup>[23]</sup>. These calculations were undertaken using Power Analysis Sample Size (PASS) software version 11.0<sup>[24]</sup>.

*Statistical analysis:* The data captured in hard copies during the telephonic interviews were checked for quality and computerized following the necessary corrections. The association of key risk factors with

SARS-CoV-2 infection was examined by comparing distributions of cases and controls across different exposures. Variables which had biologically plausible association with the outcome and were relevant for planning strategies for the prevention of SARS-CoV-2 infection in HCWs were entered into a standard logistic regression model<sup>[25]</sup>. STATA version 13.1 (StataCorp LP, College Station, TX, USA) was used for data analysis including trend analysis by Chi-square test.

## Results



The ICMR data portal contained the results and contact details of 23,898 symptomatic HCWs who were tested for SARS-CoV-2 infection. After excluding non-Indian nationals and missing or wrong contact details from this database, 21,402 records were obtained, with 1,073 (5%) confirmed SARS-CoV-2-infected HCWs. Although it was initially decided to contact 650 cases and controls each (accounting for 25% loss over the calculated sample size of 484), only 624 and 549 individuals could be contacted in the case and control groups, respectively. Completed interview schedules of 60.58 per cent of cases (378/624) and 67.94 per cent of controls (373/549) were available for analysis. The reasons for not being able to reach out to some of the participants were: calls not picked up, wrong numbers, ineligible candidates (not HCWs), consent refusal to name a few.

Fifty eight per cent of the cases and about half of the controls were males. While the mean age of the cases was 34.73 yr [ $\pm$ standard deviation (SD): 9.64; median: 33.0; interquartile range (IQR): 27-40], the mean age of the controls was 33.47 yr ( $\pm$ SD: 9.77; median: 31.0; IQR: 26-38). Age distribution did not follow Gaussian distribution in either group. [\[Table 1\]](#) presents details of the study participants.

*Vulnerability of HCWs:* Vulnerability of the study participants to SARS-CoV-2 infection was ascertained through a history of (i) placement in intensive care unit (ICU) catering to suspected or confirmed COVID-19 cases, (ii) procedures such as nasopharyngeal swab collection, intubation, respiratory suctioning and clinical specimen handling by HCWs and (iii) use of PPE. Endotracheal intubation was associated with higher odds of SARS-CoV-2 infection. Respondents who reported never using PPEs were also at a higher risk. On the other hand, when the participants were asked about individual components of PPE, usage of masks, caps, gowns and gloves was associated with reduced odds of acquiring SARS-CoV-2 infection [\[Table 2\]](#).

*Hydroxychloroquine prophylaxis:* Distribution of cases and controls across exposures in univariate analysis indicated the association of risk ( $P=0.087$ ) of SARS-CoV-2 infection with the lack of HCQ prophylaxis [\[Table 3\]](#). However, the number of maintenance doses taken by HCWs following the intake of a loading dose revealed a protective dose-response relationship. Consumption of four or more maintenance doses was associated with a significant decline in the risk of SARS-CoV-2 infection among the study participants [\[Figure 1\]](#). The significant declining trend had an overall  $\chi^2$  value of 48.88 ( $P < 0.001$ ).

Of the 172 cases and 193 controls reporting HCQ intake, no significant difference in the occurrence of adverse drug reactions was noted. The three most common side effects of HCQ as reported by the cases

and controls were nausea (5 vs. 8%), headache (6 vs. 5%) and diarrhoea (5 vs. 4%). While none of the controls on HCQ complained of palpitations, only one case (1/172, 0.6%) reported the same. Gastrointestinal symptoms such as acidity and vomiting following HCQ intake ranged from 0.6 per cent in cases to about two per cent in controls. Very few cases (0.6%) and controls (1.4%) had skin rashes after consuming HCQ.

*Multivariate analysis:* Factors found associated ( $P < 0.1$ ) with SARS-CoV-2 infection among HCWs in univariate analysis and having biological plausibility were entered into multivariate model. In case of conceivable similarity between explanatory variables, one was chosen over another to avoid collinearity. For example, PPE rather than individual items (cap, mask, gown, glove, etc.) of PPE was included in the model. Adjusted for <sup>[25]</sup> gender, use of PPE, endotracheal intubation, different intensity of exposure to prophylactic HCQ and testing place with date, intake of 4-5 maintenance doses of HCQ [adjusted odds ratio (AOR): 0.44; 95% confidence interval (CI): 0.22-0.88;  $P=0.02$ ] was found to independently impart the protective effect against SARS-CoV-2 infection among HCWs <sup>[Table 4]</sup>. Notwithstanding this effect, the advantage of PPE usage was also independently indicated by the multivariate model. Noticeably, six or more prophylactic doses of HCQ used by HCWs had a remarkably high (>80%) protective effect against SARS-CoV-2 infection.

## Discussion



Research to inform public health responses during infectious disease emergencies is gradually gaining importance worldwide. For example, Ebola virus disease in West Africa and Nipah virus outbreak in the Indian sub-continent required quick research responses to help mitigate human sufferings in the recent past <sup>[26],[27]</sup>. The current investigation can be considered as an example of this emerging trend. We leveraged a nationwide COVID-19 testing database to rapidly generate evidence to inform public health action.

The pivotal finding of our study was the noteworthy benefits of HCQ prophylaxis. It was identified that simply initiating HCQ prophylaxis did not reduce the odds of acquiring SARS-CoV-2 infection among HCWs. However, with the intake of four or more maintenance doses of HCQ, the protective effect started emerging, and in the adjusted multivariate model, a significant reduction (>80%) in the odds of SARS-CoV-2 infection in the HCWs was identified with the intake of six or more doses of HCQ prophylaxis. This dose-response relationship (Figure) added strength to the study outcomes. Worth noting in this context was that the National Task Force for COVID-19 in India recommended once a week maintenance dose for seven weeks (400 mg once weekly), following the loading dose (400 mg bd). Adherence to this recommended regimen is underlined by the findings of the present study. The potential antiviral and anti-inflammatory properties of HCQ <sup>[28]</sup>, together with the low cost of therapy, excellent oral bioavailability <sup>[29]</sup>, high tissue concentrations in the lungs relative to the plasma levels and acceptable safety profile lend support to this assertion <sup>[17]</sup>. However, HCQ prophylaxis should be taken in tandem with PPE use as indicated by the multivariate model (Table IV).

A recent registry-based analysis highlighted that HCQ did not offer therapeutic benefits to severe COVID-19 cases, and was associated with increased mortality <sup>[30]</sup>. This apparent disparity with the



findings of the current investigation could be explained by the two different application contexts. While the observational study involving registry-analysis focussed on the treatment of hospitalized COVID-19 patients, our emphasis was on the prevention of infections among HCWs. In treatment settings, severe COVID-19 patients are likely to have a very high viral load and cytokine levels, which may not be improved by HCQ therapy<sup>[31]</sup>. The registry-based analysis further recorded higher frequencies of ventricular arrhythmias in patients receiving HCQ. The toxicities of HCQ are likely to be infrequent in healthy groups undergoing prophylactic therapy as observed in our study participants. Biologically, it appears plausible that HCQ prophylaxis, before onset of infection, may inhibit the virus from gaining a foothold.

While the strength of the present analysis was the involvement of a countrywide database that drew upon more than 70 COVID-19 testing laboratories spread all over India, its limitations were rooted in its observational design. However, in the absence of clinical trial results<sup>[32]</sup> on safety and efficacy of HCQ chemoprophylaxis in the HCWs, this study offers evidence of public health importance. Higher prevalence of SARS-CoV-2 infection in the HCWs has been a global concern, including in countries such as Spain, Italy and the USA<sup>[33],[34],[35]</sup>, which further underscores the importance of the present findings.

The first part of the dose-response relationship curve showed an apparent increase in the odds of acquiring SARS-CoV-2 infection in HCWs who had taken 2-3 doses of HCQ prophylaxis. While this phenomenon cannot be fully explained by the data collected through the present study, lessons from other areas of public health could be of some help. The parallels<sup>[36]</sup> include (i) seat-belt legislations *vis-à-vis* speeding and road traffic casualties, and (ii) condom use promotion with unintended effects linked to greater sexual activities. Adams<sup>[37]</sup> and Wilde<sup>[38]</sup> allude to models of individual risk management which have the potential to explain such apparent paradoxes. They described that the introduction of a safety device could disrupt the balance between perceived hazards and rewards of risk-taking behaviours. Within the ambit of the present discussion, we consider (i) HCQ prophylaxis as a newly identified safety device, (ii) getting infected with SARS-CoV-2 as the perceived hazard, and (iii) not adhering to conventional respiratory infection prevention measures, such as PPE use, personal hygiene and social distancing as risk-taking behaviours.

In conclusion, public health message on the role of HCQ prophylaxis for the prevention of SARS-CoV-2 infection among HCWs emerging from this study should be considered with the existing understanding of risk homeostasis operating at individual levels.

fn53 (see fn35)

<https://www.ijdonline.com/action/showPdf?pii=S1201-9712%2820%2930534-8>

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Surgisphere/Lancet study James Todaro, MD On Friday, May 22, 2020, a study of 96,032 hospitalized COVID-19 patients was published in The Lancet showing that hydroxychloroquine was not only ineffective in the treatment of COVID-19, but actually increased mortality and incidence of lethal arrhythmias. By Monday, May 25, the WHO suspended all of its clinical trials on hydroxychloroquine because of safety concerns based on this study. While the WHO, Dr. Fauci and many other proclaimed COVID-19 experts all praised the study as evidence confirming their suspicion that hydroxychloroquine was harmful, independent researchers were not as convinced. For anyone looking, red flags were abundant. The study was impossibly large, claiming to capture detailed patient information on nearly every COVID-19 patient in North America. The study went so far as to even report more COVID-19 deaths than had actually occurred in the continent of Australia. Data from COVID-19 patients in Africa was good...Too good. The authors reported detailed cardiac monitoring in patients from electronic medical records when in reality, this quality of data is not readily available in Africa. Lastly, the corporation Surgisphere who was responsible for providing this data lacked a history of research and dedicated staff--instead appearing promotional with hires including a science fiction writer and erotic model posing as the Director of Sales. Only after facing mounting accusations of fraud from independent researchers did the study authors decide it was prudent to validate Surgisphere's dataset. Surgisphere refused, however, and the study was retracted less than two weeks from its publication. The study authors to this day still refuse to admit the study was fabricated and instead claim that it was retracted simply because they were unable to validate the data due to privacy agreements. Perhaps even more disappointing than the behavior of the authors is the way science and proclaimed experts failed to detect scientific fraud at the highest level. The study was approved by peer-review at one of the most prestigious medical journals in the world. Almost immediately after publication, news outlets including MSNBC and CNN along with the WHO and Dr. Fauci began to cite the study as evidence that hydroxychloroquine was harmful. The Lancet study is just another example during this pandemic where experts and global organizations failed to provide the American people with the truth. In this case, they presented us with just the exact opposite.

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391/>

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Ten Common Questions (and Their Answers) About Off-label Drug Use

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Abstract

The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education exercises, and the media. Yet, we propose that many health care professionals have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities. Off-label drug use involves prescribing medications for indications, or using a dosage or dosage form, that have not been approved by the US Food and Drug Administration. Since the Food and Drug Administration does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric, pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has led to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient. In addition, health care professionals should educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

**Abbreviations and Acronyms:** CME, Continuing Medical Education; FDA, Food and Drug Administration; OLDU, off-label drug use

The term *off-label drug use* (OLDU) is used extensively in the medical literature, continuing medical education (CME) exercises, and the media. It is a polarizing term because it can be associated with great benefit or harm to patients.<sup>1</sup> In addition, OLDU, along with allegations of pharmaceutical company promotion of OLDU, has been the cause of major lawsuits and historically large out-of-court legal settlements.<sup>2-7</sup> Therefore, all health care professionals have likely heard the term *OLDU* used, yet we propose that many have an underappreciation of its definition, prevalence, and implications. This article introduces and answers 10 questions regarding OLDU in an effort to clarify the practice's meaning, breadth of application, acceptance, and liabilities.

Question 1: What is the Definition of OLDU?

The most common form of OLDU involves prescribing currently available and marketed medications but for an indication (eg, a disease or a symptom) that has never received Food and Drug Administration (FDA) approval.<sup>8,9</sup> Hence, the specific use is “off-label” (ie, not approved by the FDA and not listed in

FDA-required drug-labeling information). The term *OLDU* can also apply to the use of a marketed medication in a patient population (eg, pediatric), dosage, or dosage form that does not have FDA approval.

The current role of the FDA is to control which medications are available commercially. Historically, the Food, Drug, and Cosmetic Act of 1938 required only that a new medication be safe.<sup>9</sup> In 1962, the Kefauver-Harris Amendment mandated that FDA-approved new drugs also must have evidence that they are effective.<sup>9</sup> Therefore, the FDA approves new medications that have been shown to be safe and effective for specific indications (ie, “on-label” prescribing). The FDA does not limit or control how the medications are prescribed by physicians once the medications are available on the market. By definition, OLDU is prescribing for an indication, or employing a dosage or dosage form, that has not been approved through the FDA process.

Off-label drug use can be motivated by several factors. First, a medication may not have been studied and approved for a specific population (eg, pediatric, geriatric, or pregnant patients).<sup>10</sup> Second, a life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved by the FDA or not. Third, if one medication from a class of drugs has FDA approval, physicians commonly use other medications in the same class without specific FDA approval for that use for the same indication.<sup>8,9</sup> In addition, if the pathologic or physiologic features of 2 conditions are similar, a physician may use a medication approved for 1 of these conditions for both (eg, diabetes and metabolic syndrome; psychiatric diseases such as anxiety and posttraumatic stress disorder).<sup>8</sup>

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Question 2: Is OLDU Common?

Indeed, OLDU is common. Radley et al<sup>1</sup> reported in 2006 that in a group of commonly used medications, 21% of prescriptions were for an off-label use. In certain subpopulations of patients, this rate may be even higher. For example, a study by Shah et al<sup>11</sup> found that 78.9% of children discharged from pediatric hospitals were taking at least 1 off-label medication. In addition, in a pediatric emergency department, the rate of OLDU was estimated to be 26.2%.<sup>2</sup> The off-label use of antidepressant, anticonvulsant, and antipsychotic medications is high and is more prevalent with increasing patient age.<sup>12</sup> In an intensive care unit, Lat et al<sup>13</sup> reported that 36.2% of medication orders were for an off-label use. In addition,  $\beta$ -adrenergic blocking agents are commonly prescribed for an off-label indication, and specialists may more commonly prescribe for off-label  $\beta$ -blocker use than primary care physicians.<sup>10</sup> In a headache specialty practice, Loder and Biondi<sup>14</sup> reported that off-label use accounted for 47% of prescriptions written.

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Question 3: Can an OLDU for a Given Drug Become a Widely Accepted Practice or Even a Standard of Care?

Off-label drug uses can become widely entrenched in clinical practice and become predominant treatments for a given clinical condition. For example, tricyclic antidepressants do not have FDA approval as a treatment for neuropathic pain, yet this class of drugs is considered a first-line treatment option.<sup>15</sup> The use of aspirin provides another interesting example of OLDU. Aspirin was widely used

before the introduction of the Food, Drug, and Cosmetic Act of 1938. Therefore, aspirin was grandfathered and approved as an existing drug without the rigorous testing that modern medications undergo. Currently, aspirin is FDA approved for use in patients with pain, fever, rheumatic diseases, cardiovascular diseases (eg, acute myocardial infarction, previous myocardial infarction, angina pectoris, and previous cerebrovascular disease), and a history of a revascularization procedure (eg, coronary artery bypass grafting and carotid endarterectomy).<sup>16</sup> However, aspirin does not have an indication for coronary disease prophylaxis in diabetic patients, yet guidelines recommend its use in these patients.<sup>8</sup> Therefore, aspirin prophylaxis for coronary disease in high-risk patients is an off-label use.

Elsewhere, medications are often prescribed for OLDU with poor or absent clinical evidence. Radley et al<sup>1</sup> reported that 73% of medications prescribed for an off-label use had poor or no scientific support. In critical care patients, OLDU was without adequate evidence 48.3% of the time.<sup>13</sup> Because OLDU is typically less critically evaluated than is on-label drug use, OLDU may be associated with an increase in medication errors.<sup>17</sup> Rinke et al<sup>17</sup> studied pediatric antidepressant drug use in a national error-reporting database and found that 77% involved off-label prescribing.

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Question 4: What are Some Examples of Widely Practiced OLDUs?

There are examples of widely practiced OLDUs in every specialty of medicine ([Table](#)). Since the patient population in pediatrics is often excluded from clinical drug studies, examples of OLDU are especially abundant. For example, morphine has never received an FDA indication for pain treatment in children, but it is extensively used for this indication in hospitalized pediatric patients.<sup>11</sup> In another example, researchers discovered in the 1970s that the nonsteroidal anti-inflammatory agent indomethacin was efficacious as a medical therapy for closing a persistent, symptomatic patent ductus arteriosus in newborns.<sup>18</sup> Thus, a trial of indomethacin became the treatment of choice for many affected newborns in an attempt to avoid curative surgery. Indomethacin has never been approved for this indication and, as such, this use remains an OLDU. In addition, many inhaled bronchodilators, antimicrobials, anticonvulsants, and proton pump inhibitors are often used in the pediatric population without formal FDA approval.<sup>30</sup>

The FDA has attempted to lessen the gap between FDA approval and contemporary drug-prescribing practices in pediatrics through the FDA Modernization Act of 1997. This Act created incentives, including exclusive marketing and patent extension, for pharmaceutical companies to test medications on children.<sup>31</sup>

Medications for psychiatric disorders are also frequently used for unapproved indications.<sup>12,32</sup> Patients with psychiatric disorders are often excluded from clinical trials, and these disorders are inherently difficult to study. Moreover, there is often crossover in symptoms from disease state to disease state, which has lead physicians to use psychiatric medications approved for one psychiatric condition for additional unapproved indications. For example, selective serotonin reuptake inhibitors have been used off-label for rare or difficult-to-study disorders, such as borderline personality disorder, stuttering, pathologic gambling, and alcoholism.<sup>16</sup> Moreover, selective serotonin reuptake inhibitors (eg, paroxetine, sertraline, and fluoxetine) are considered first-line treatments for premature ejaculation, another off-label use.<sup>33</sup> In recent years, antipsychotic drug use for unapproved FDA indications has

increased. Alexander et al<sup>32</sup> estimated that the cost of off-label antipsychotic drug use in 2008 was \$6.0 billion.

During the 1970s and 1980s, there was a proliferation of cardiac surgery to repair or replace diseased heart valves. Disease in many of these patients was the result of rheumatic abnormalities in patient populations with inadequate or no antibiotic drug treatment of infections earlier in their lives. In these patient populations, hemodynamic stability was of utmost concern during anesthesia, surgery, and the immediate postoperative course. Lowenstein<sup>34</sup> reported that high-dose morphine, combined with amnestic agents, could provide the type of stable anesthetic required for these patients and that the beneficial effects of the anesthetic would continue into the postoperative intensive care period. With the later introduction of the short-acting opioid fentanyl, it was infused in doses much greater than approved by the FDA, thus converting a short-acting drug into a long-acting drug. High-dose morphine- and fentanyl-based anesthetics, highly favored therapy for valve replacement surgery, were retained as core anesthetics with the introduction of coronary artery bypass graft surgery. Today, patients are typically brought to surgery much earlier in the disease course (hence, they tend to be more stable hemodynamically), and there is a focus on shortening stays in the intensive care unit after cardiac surgery. In addition, improvements in surgical technique have shortened operation times. For these reasons, high-dose opioid anesthesia is less common than in the past, although it is still used. These high doses of morphine and fentanyl have never been approved by the FDA, and, therefore, their use has always been off-label.

Postoperative nausea and vomiting in surgical patients can add to patient morbidity and the cost of health care. Postoperative nausea is common, occurring in nearly 70% to 80% of high-risk patients.<sup>35</sup> Because of this, practitioners have empirically explored a variety of antiemetic therapies. In patients at high risk for postoperative nausea and vomiting, bolus or infused propofol and bolus dexamethasone have gained favor as antiemetic regimens. However, these treatments have never been approved by the FDA for this indication. As such, they represent OLDUs.

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Question 5: If Efficacious, Why is Government Approval not Obtained to Convert Off-label Uses of Drugs to On-label Uses?

Obtaining a new FDA approval for a medication can be costly and time-consuming. To add additional indications for an already approved medication requires the proprietor to file a supplemental drug application, and, even if eventually approved, revenues for the new indication may not offset the expense and effort of obtaining approval.<sup>8</sup> Finally, generic medications may not have the requisite funding foundations needed to pursue FDA-approval studies.<sup>8</sup> For these financial reasons, drug proprietors may never seek FDA approval for a new drug indication.

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Question 6: Do Physicians Expose Themselves to Legal Vulnerability for Including OLDUs in Their Clinical Practices, Particularly if the Patient Experiences an Adverse Reaction Related to an OLDU?

Physicians have been involved in legal claims due to an adverse reaction related to a medication prescribed for an off-label use.<sup>8,36</sup> The legal theories used in these lawsuits include unregulated use of a research drug, failure to provide adequate informed consent for an OLDU, and medical

negligence.<sup>37</sup> In developing legal precedents for off-label therapies, the courts have typically treated drugs and devices as coequals. As such, many of the courts' views on OLDU have evolved from decisions regarding off-label uses of medical devices.

### Research vs Practice

The FDA makes it clear that it does not regulate the practice of medicine and that the federal Food, Drug, and Cosmetic Act of 1938 will not play a role in creating physician liability for OLDU.<sup>38</sup> However, the FDA requires stringent review before drugs and medical devices are involved in research to ensure that steps are taken to properly protect human study participants. When not classified as tools involved in research, medications can be prescribed and medical devices can be used in an off-label manner without FDA regulatory oversight. Regarding this point, during its evaluation of possible harm arising from placement of an orthopedic spine medical device, an Ohio appellate court stated that “the off-label use of a medical device is merely a matter of medical judgment and, as such, subjects a physician to professional liability for exercising professional medical judgment, but off-label use of a medical device is not barred by the U.S. Food and Drug Administration.”<sup>38,39</sup> By way of legal precedent and similar FDA regulatory processes, the same standard would apply to OLDU.

Drawing a clear line of demarcation between a drug's use in research vs practice can often be difficult. Prescribing a drug in a new and yet untested manner does not alone brand it as an interest of research.<sup>38</sup> The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research has attempted to define whether a drug's use might be classified as a practice or research tool, and their definitions follow. The goal of medical practice is to “provide diagnosis, preventative treatment or therapy.”<sup>38</sup> Research, on the other hand, is “designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.”<sup>38</sup> When not deemed research, legal claims brought solely on the basis of failure to gain adequate FDA approval before prescribing an off-label drug will likely be struck down. However, physicians may not be sheltered from other forms of liability theories.

### Medical Malpractice: Informed Consent

No court decision to date has mandated that a physician must disclose, through an informed consent process, the off-label use of a drug.<sup>40</sup> Two arguments are often voiced by those who oppose any routine requirement for disclosure: (1) disclosure may unduly frighten patients and (2) the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information may divert attention away from other more important patient care issues.<sup>40</sup>

Perhaps the most cited modern legal case involving the medical informed consent process is *Canterbury v Spence*.<sup>41</sup> The Canterbury court held that “the test for determining whether a particular peril must be divulged is its *materiality* to the patient's decision.”<sup>41</sup> A material risk is one in which “a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy.”<sup>41</sup>

Many courts have not considered OLDU to be an independent material issue requiring disclosure during the consent process.<sup>38</sup> A 1996 Ohio court held that off-label use of medical devices was a “matter of

medical judgment.”[38,42](#) According to the court, physicians may be subject to professional liability for medical negligence involving OLDU but will not be held liable for nondisclosure.[38,42](#)

The results of a 2006 nationwide poll on the public's view of OLDU may precipitate concerns for future court challenges not fully appreciated by previous legal opinion. Half of the poll's respondents falsely believed that a drug could be prescribed only for its primary FDA-approved use.[43](#) An almost similar percentage felt that physicians should be prohibited from prescribing drugs for off-label use. Nearly two-thirds of those responding felt that except for use in clinical trials, OLDU should be completely banned.[43](#) This is a remarkable aggregate response given that a considerable fraction of those responding negatively to OLDU had likely benefited from the practice at some point in their lives (although they were probably unaware).

Although many courts do not require physicians to disclose OLDU, patients may have a different belief and concern regarding their use. Whether these matters will develop into a greater expectation for adequate disclosure remains unknown. Some physicians have suggested that providing patients with information about OLDU may afford greater protection from future liability suits.[38](#)

#### Medical Malpractice: Negligence

Medical malpractice is a broad term that includes the action of negligence. In fact, 4 elements of tort law dealing with negligence must be proved before liability can be found to exist: (1) the prescribing physician must have a duty to the patient, (2) that duty must be breached, (3) there must be some injury requiring compensation, and (4) there must be a causal link between the breach and that injury.

A physician's duty of care is defined as the same degree of care provided by other physicians practicing under similar circumstances. Use of off-label medication alone does not result in liability under negligence standards.[44](#) When a patient believes that he or she was harmed by an off-label use of a medication, it must be established that the prescribing physician deviated from the standard of practice.[38](#) Because the FDA prohibits manufacturers from sponsoring physician education for off-label use of their medications, physicians may find it difficult to establish how others in their field are using medications outside their FDA-approved uses.[37](#) As peer-reviewed published evidence focusing on a drug's off-label use grows over time, new standards of practice involving the off-label use of a drug begin to develop.[38](#)

To help determine whether the standards of practice are being met when prescribing medications for OLDU, physicians should first ask themselves several questions[38,45,46](#): (1) Does the native drug have FDA approval? (2) Has the off-label use been subjected to substantial peer review? (3) Is the off-label use medically necessary for treatment? (4) Is the use of the medication nonexperimental? To mitigate the risk of liability, physicians should always prescribe off-label drugs in “good faith, in the best interest of the patient, and without fraudulent intent.”[45](#) This 3-pronged approach to prescribing medications will also ensure that the tenets of the FDA’s requirement are met; specifically, physicians prescribing medications for off-label use should “be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.”[47](#)

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Question 7: Will Indexed Medical Journals Publish Articles on OLDU?



Reports on OLDU, particularly original observations, are not only tolerated by indexed medical journals but also may actually be encouraged. The most welcomed reports may follow several patterns, the 2 most common of which are described in the following subsections.

#### Reports to Evaluate New Drug Therapies Seeking FDA Approval

Before a drug use can be approved by the FDA, drug utilization for this specific application must undergo extensive studies of efficacy and safety in humans. The data from multiple phases of study are needed for the drug's proprietor to file a New Drug Application to the FDA. Studies of new drugs or studies involving expanded use of an existing drug are, by definition, "off-label" indications until FDA approval is obtained. These studies may take the form of phase 0 (pharmacokinetic and pharmacodynamic studies of subtherapeutic drug doses in small numbers of patients), phase 1 (small studies of drug pharmacodynamic properties in healthy volunteers), phase 2 (larger studies of drug pharmacology, safety, and efficacy in volunteers and patients), and phase 3 (large, randomized, multicenter trials of drug safety and efficacy; drug compared with a placebo or an existing treatment standard) trials.<sup>48</sup> In addition, phase 4 trials are completed after FDA approval to further delineate the drug's effects and adverse reactions.<sup>48</sup>

Although preliminary research on drug pharmacology and safety intended to support a petition for FDA approval may be important to the proprietor and the FDA, articles based on these data may be difficult to publish in competitive biomedical journals because the data may not be of interest to the journal's target audience. As such, initial research may not pass peer review because of journal priorities. However, as subsequent trials evaluate drug efficacy and safety using methods that mimic the drug's use in clinical practice, journals' interest in the research will be piqued. The more novel the therapy (eg, a new class of drug for a common application, in contrast to a "me too drug"), the more likely the research data will be competitive for publication in better-quality medical journals. In fact, journals may introduce the reports with editorials and engage in media promotion of the discoveries, both testaments to the value the journals place on the research.

#### Reports to Evaluate Off-label Uses, or Describe Adverse Effects, of Drugs Approved for Other Indications

As previously described, a large fraction of drug use is off-label, and these indications may even become the standard of care (see Question 3). In these instances, the FDA will have previously approved the drug for clinical practice but for an indication other than the one under question. Medical journals and their readers may have a keen interest in original observations related to this form of drug use. Articles may not only become accepted for publication but may also get journal promotion (editorials and media promotion) reserved for the highest-priority articles. Clearly, a journal's enthusiasm for these types of articles is coupled with the quality and statistical power of the data, the novelty of the observation, the generalizability of the results, and the relevance of the observations to the intended audience's interests. As such, a journal may publish OLDU articles on drugs' effects and adverse effects related to indications for which FDA approval may never be sought.

Prospective trials of drug use in humans must conform to federal regulations, be approved by the institutional review boards of all participating institutions, and be registered in one of many appropriate registries (eg, [ClinicalTrials.gov](https://clinicaltrials.gov)) to be considered for publication in biomedical journals.<sup>49,50</sup> Retrospective OLDU observations in patients, whether of a drug's effects or adverse effects, also must have accompanying institutional review board approval before reporting the

observations to a biomedical journal. However, the standards of approval for retrospective observations are much less stringent than for prospective research.

Indexed biomedical journals are less likely to publish review articles on drugs that are seeking FDA approval for a first use. Reviews with the best probability of getting published are those that describe novel drug mechanisms or success in treating conditions in which other drugs have limited efficacy. Articles primarily intended to support a marketing angle for the proprietor (ie, seeding reports)<sup>51</sup> have difficulty getting published in the most competitive medical journals. In contrast, journals may welcome review articles that address a widely applied OLDU. As information on a given OLDU grows, journals may even welcome updated reviews or new reviews that address novel aspects of the OLDU experience (eg, new information on a drug's effects or adverse effects, updates on the operant mechanisms of action, and articles on drug-use adherence and economics).

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Question 8: Can Speakers Discuss OLDU During Accredited CME Courses?

Speakers at accredited CME courses are allowed to discuss OLDU during their presentations. The Accreditation Council for Continuing Medical Education historically required that all discussions of OLDU be disclosed during the CME presentation. However, current Accreditation Council for Continuing Medical Education requirements state that all clinical presentations should be based on “evidence that is accepted within the profession of medicine.”<sup>52</sup> If the discussion of OLDU conforms to this mandate, no specific disclosure is required.

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Question 9: Can Drug Companies Promote OLDU?

The 1938 Food, Drug, and Cosmetic Act gave the FDA the power to regulate promotional materials on medications.<sup>53</sup> Two provisions from the FDA prohibit most promotion of off-label uses of medications by pharmaceutical manufacturers and marketers. First, the FDA requires approval before distribution into interstate commerce of all medication labeling (including the package insert, print and broadcast advertisements, brochures, and patient education materials).<sup>53</sup> Second, the FDA prohibits “misbranding” of medications. Misbranding includes labeling a medication with misleading information, including off-label uses.<sup>53</sup>

Although pharmaceutical manufacturers are not allowed to promote off-label uses of medications, they are allowed to respond to unsolicited questions from health care professionals about off-label use and to distribute peer-reviewed publications regarding off-label use.<sup>53</sup> Responses to questions regarding off-label use must be completed by the manufacturer's medical affairs office and not their sales representatives, and interactions with the questioner must be documented.<sup>53</sup>

Historically, the 1997 FDA Modernization Act allowed manufacturers to distribute to health care providers peer-reviewed journal articles about unapproved uses of medications.<sup>54,55</sup> If a given drug company chose to engage in distribution of this type of information, it was required to submit an application for approval of that indication within a rigid and prespecified period. These requirements were subsequently revised in 2009 with the approval of new FDA guidelines.<sup>53</sup> The new guidelines clarified existing rules and allowed distribution of information on off-label uses by pharmaceutical

manufactures if specific regulations were followed.<sup>53</sup> After 2009, pharmaceutical manufacturers could distribute information, including journal articles and textbook chapters, describing unapproved uses for their medications. The FDA demanded that the information in these OLDU publications be accurate, the relationship between the distribution of information and the sponsoring drug manufacturer be disclosed, and the published material not be edited or presented in an abridged form.<sup>53</sup> In addition, the manufacturer is no longer required to submit an application for approval for that indication.<sup>53</sup>

With the increase in direct-to-consumer marketing by pharmaceutical manufacturers, in 2010 the FDA introduced the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program. This program provides a mechanism by which health care professionals and patients can report illicit OLDU promotion to the FDA.

Despite regulations that ban pharmaceutical manufacturers and marketers from promoting OLDUs, some have ignored this mandate. In fact, one study found that off-label marketing by drug companies was one of the most common causes of Medicaid fraudulent claim investigations.<sup>2,56</sup> In addition, marketing of off-label uses has been the source of costly lawsuits and out-of-court penalties for pharmaceutical manufacturers. In 2012, GlaxoSmithKline paid a record \$3 billion to settle a dispute, including alleged illegal off-label marketing involving paroxetine in children (approved only for use in adults), the antidepressant bupropion as a weight loss aid, and failure to report safety information about the antidiabetes medication rosiglitazone.<sup>5</sup> In 2012, Abbott paid \$1.6 billion in penalties for alleged off-label marketing of valproic acid.<sup>7</sup> In 2009, Eli Lilly paid \$1.4 billion in a settlement for alleged off-label marketing of olanzapine for dementia.<sup>3</sup> That same year, Pfizer paid \$2.3 billion for alleged off-label marketing of 4 of its medications.<sup>4</sup>

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Question 10: What is the Difference Between OLDU and Orphan Use of Drugs?

Orphan drugs are medications that are developed and used for rare, or orphan, diseases. Owing to a drug's limited clinical use for an orphan indication, it will typically generate insufficient profitability for the drug's sponsor to seek FDA approval for the narrow indication. As such, practitioners are typically forced to use medications in an off-label manner to treat orphan diseases. Therefore, orphan drugs are often a subtype of OLDU. However, in 1983, the FDA implemented the Orphan Drug Act, which offered incentives to pharmaceutical manufacturers that developed and marketed new drugs for rare diseases.<sup>57</sup> Incentives include tax breaks, exclusive marketing rights, and reduced drug application fees. In addition, the FDA has offered grants for the development of drugs for rare diseases. These measures have been successful in increasing the development of new, FDA-approved (ie, "on-label") drugs for orphan diseases.<sup>57</sup> Examples of off-label uses of medications for orphan disease include aspirin for Kawasaki disease and rituximab for Behçet disease.<sup>16,20</sup>

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OLDU Summary

Off-label drug use involves prescribing medications for an indication, or using a dosage or dosage form, that has not been approved by the FDA. Since the FDA does not regulate the practice of medicine, OLDU has become common. It occurs in every specialty of medicine, but it may be more common in areas of medicine in which the patient population is less likely to be included in clinical trials (eg, pediatric,

pregnant, or psychiatric patients). Pharmaceutical companies are not allowed to promote their medications for an off-label use, which has led to several large settlements for illegal marketing. To limit liability, physicians should prescribe medications only for indications that they believe are in the best interest of the patient on the basis of the most credible available evidence. In an era of global exchange of medical information, this approach to physician prescribing practices may have greater utility than restricting practices solely to indications approved by a US-based pharmaceutical labeling system. Health care professionals should continually educate themselves about OLDU to weigh the risks and benefits and provide the best possible care for their patients.

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Regulating Off-Label Drug Use — Rethinking the Role of the FDA

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The Food and Drug Administration (FDA) provides a barrier to market entry and use of unproven and unsafe products. For prescription drugs, the FDA approval process requires substantial evidence of efficacy and safety for specific clinical situations. Although approval is indication-specific, the FDA has a limited role once a drug is on the market. Recent draft guidelines covering manufacturers' promotion of drugs through the distribution of journal articles suggest that the FDA is moving toward an even more minimal role.<sup>1</sup>

Although off-label prescribing — the prescription of a medication in a manner different from that approved by the FDA — is legal and common, it is often done in the absence of adequate supporting data. Off-label uses have not been formally evaluated, and evidence provided for one clinical situation may not apply to others. As an area of controversy, off-label use is subject to the contradictory expectations of various stakeholders, including health care payers, the pharmaceutical industry, physicians, and consumers. The FDA has a role in balancing these expectations, but it currently does so primarily through regulating corporate marketing. Although there is a strong rationale for greater FDA involvement in off-label use, it is moving toward relinquishing control in its new draft guidelines.

Off-label use arises through many pathways but usually entails the use of drugs for unapproved clinical indications (e.g., the antipsychotic agent quetiapine [Seroquel] prescribed for depression) or in

unapproved subpopulations (e.g., paroxetine [Paxil] for depression in children). Off-label use may originate from a presumed drug class effect, extension to milder forms of an approved indication, extension to related conditions (the use of the antiasthmatic montelukast [Singulair] for chronic obstructive pulmonary disease), expansion to distinct conditions sharing a physiological link (the use of the antidiabetic drug metformin to treat polycystic ovarian syndrome), or extension to conditions whose symptoms overlap with those of an approved indication.

The spectrum of off-label use includes guideline-recommended practice (aspirin in diabetes for prophylaxis against cardiovascular disease), last-resort therapy (tacrolimus [Prograf] for autoimmune diseases, in addition to transplantation), and first-line therapy (gabapentin [Neurontin] for painful diabetic neuropathy, in addition to its use in herpes zoster). Though new indications may be added to a drug's label through a supplemental new drug application, this occurs infrequently: generic drugs lack a corporate sponsor to bear the required expenses, and for brand-name drugs that are already widely used off-label, conducting costly clinical trials that could produce nonsupportive evidence is a potentially risky business decision.

Evaluations have shown that off-label use is common (see [graph](#)) but often not supported by strong evidence.<sup>2</sup> A 2003 report showed that for the 3 leading drugs in each of the 15 leading drug classes, off-label use accounted for approximately 21% of prescriptions.<sup>3</sup> The highest rates of off-label use were for anticonvulsants (74%), antipsychotics (60%), and antibiotics (41%). In an examination of off-label prescribing of 160 common drugs, off-label use was also found to account for 21% of all prescriptions, and most off-label drug uses (73%) were shown to have little or no scientific support.<sup>2</sup> Atypical antipsychotics and antidepressants were particularly likely to be used off-label without strong evidence.<sup>2</sup> Off-label use is also common for many biologics (such as epoetin alfa [Procrit] and bevacizumab [Avastin]).

Physicians' freedom to prescribe drugs off-label carries important advantages. It permits innovation in clinical practice, particularly when approved treatments have failed. It offers patients and physicians earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence. And it can provide the only available treatments for "orphan" conditions. At the same time, off-label use has potentially negative consequences. It undercuts expectations that drug safety and efficacy have been fully evaluated. When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies — and instead subtly encourages them to game the system by seeking approval for secondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.

During the past decade, there have been numerous conflicts about off-label use. Payers increasingly question the need to pay for products that are not proven. Physicians desire the autonomy to prescribe drugs that match individual patient needs regardless of label, but they face difficulties staying abreast of rapidly evolving evidence. The pharmaceutical industry seeks to enlarge its markets to ensure future profits and sustain drug development. The public wants drugs that are safe, evidence-based, and affordable; although consumers want the newest therapies, they may also want the level of supporting evidence to be disclosed. Recent indications suggest that the FDA is unlikely to strengthen its role in balancing these disparate expectations. I believe that the agency is making a mistake, particularly given the faith that physicians and consumers place in it.

The FDA influences the prescribing of all available drugs in several limited ways. Initial and subsequent changes in drug labeling, including black-box warnings, can alert physicians that special caution is required. Specific restrictions on drug availability constrain use to specific settings. Most important, the FDA regulates the industry's marketing practices. Current FDA policy on marketing for off-label uses follows the FDA Modernization Act of 1997 (even though these regulations formally expired in 2006). This legislation greatly eased restrictions on drug promotions. FDA policy currently prohibits the direct promotion of products for unapproved uses.

The drug industry, however, may facilitate off-label use by exploiting areas of ambiguity where policy is permissive, undefined, or not enforced. Besides sponsorship of continuing medical education programs, a key promotional strategy is providing physicians with journal articles about off-label uses. This practice does educate physicians, but it is problematic because the trials reported are too often of limited quality, industry-sponsored, and placebo-controlled (rather than comparisons with approved therapies). Although it has not been well enforced, FDA policy also limits such promotion to drugs and indications for which a supplemental new drug application is under way and requires advance FDA review of any articles to be used in this fashion. But more and more frequently, it is not FDA action but litigation that raises important questions about off-label drug prescribing, as in the examples of the off-label promotion of gabapentin for chronic pain and olanzapine (Zyprexa) for dementia.

The FDA's recently published draft guidelines address the distribution of journal articles by pharmaceutical sales representatives.<sup>1</sup> Although the guidelines nearly nullify themselves by emphasizing their nonbinding nature, they also suggest a more permissive attitude toward the promotion of off-label uses of drugs. Though they carry forward many provisions of the FDA Modernization Act, there are two glaring omissions. First, manufacturers need no longer limit their promotion of off-label uses to drugs and indications for which they are working toward FDA evaluation; and second, there is no requirement for advance FDA review of the journal articles to be distributed.

Although such a relaxation of oversight may merely formalize the FDA's de facto policies, some observers had been expecting the agency to seek a greater role in moderating off-label use. This backward shift seems oddly incongruous with current pressures aimed at improving postmarketing drug evaluation. If there are substantial safety concerns about approved indications, there is even greater uncertainty with regard to off-label uses. The harms associated with rofecoxib (Vioxx) that were recognized only after the drug's widespread use among patients who were unlikely to receive incremental benefits<sup>4</sup> represent but one of many cautionary examples.

There are several reasons why the FDA may be reluctant to take a more active role in diminishing non-evidence-based off-label use. Historically, restrictions on marketing that is not misleading have been successfully challenged as infringements of commercial free speech. The FDA may be conceding to drug manufacturers the responsibility for regulating their own off-label marketing practices. The agency may also believe that its limited resources can be put to better or more effective use in confronting other ongoing challenges. Nevertheless, I believe that the FDA must take an active role in fostering evidence-based practice, eliminating subversion of the approval process, and requiring a balanced and fair presentation of scientific evidence.

The FDA might consider undertaking a range of new activities in regulating off-label use, including systematically collecting postmarketing data to quantify the harms and benefits of common off-label uses; synthesizing evidence regarding off-label uses and disseminating its reports; scrutinizing marketing

efforts to restrict materials on off-label uses that don't have strong support; increasing the use of active drugs as comparators in postmarketing clinical trials; and requiring information about anticipated off-label uses to be presented at the time of a drug's review for initial approval.

The FDA is accepting comments on its draft guidelines through April 21, 2008. Comments may be submitted through [Regulations.gov. opens in new tab](#), under Docket No. FDA-2008-D-0053, using the "send a comment" option.

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### Off-label prescribing among office-based physicians

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#### Abstract

**Background:** Unlike medicines prescribed for Food and Drug Administration-approved indications, off-label uses may lack rigorous scientific scrutiny. Despite concerns about patient safety and costs to the health care system, little is known about the frequency of off-label drug use or the degree of scientific evidence supporting this practice.

**Methods:** We used nationally representative data from the 2001 IMS Health National Disease and Therapeutic Index (NDTI) to define prescribing patterns by diagnosis for 160 commonly prescribed drugs. Each reported drug-diagnosis combination was identified as Food and Drug Administration-approved, off-label with strong scientific support, or off-label with limited or no scientific support. Outcome measures included (1) the proportion of uses that were off-label and (2) the proportion of off-label uses supported by strong scientific evidence. Multivariate analyses were used to identify drug-specific characteristics predictive of increased off-label use.

**Results:** In 2001, there were an estimated 150 million (95% confidence interval, 127-173 million) off-label mentions (21% of overall use) among the sampled medications. Off-label use was most common among cardiac medications (46%, excluding antihyperlipidemic and antihypertensive agents) and anticonvulsants (46%), whereas gabapentin (83%) and amitriptyline hydrochloride (81%) had the greatest proportion of off-label use among specific medications. Most off-label drug mentions (73%; 95% confidence interval, 61%-84%) had little or no scientific support. Although several functional classes were associated with increased off-label use ( $P < .05$ ), few other drug characteristics predicted off-label prescription.

**Conclusions:** Off-label medication use is common in outpatient care, and most occurs without scientific support. Efforts should be made to scrutinize underevaluated off-label prescribing that compromises patient safety or represents wasteful medication use.

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### **Pediatric antidepressant medication errors in a national error reporting database**

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#### **Abstract**

**Objective:** To describe inpatient and outpatient pediatric antidepressant medication errors.

**Methods:** We analyzed all error reports from the United States Pharmacopeia MEDMARX database, from 2003 to 2006, involving antidepressant medications and patients younger than 18 years.

**Results:** Of the 451 error reports identified, 95% reached the patient, 6.4% reached the patient and necessitated increased monitoring and/or treatment, and 77% involved medications being used off label. Thirty-three percent of errors cited administering as the macrolevel cause of the error, 30% cited dispensing, 28% cited transcribing, and 7.9% cited prescribing. The most commonly cited medications were sertraline (20%), bupropion (19%), fluoxetine (15%), and trazodone (11%). We found no statistically significant association between medication and reported patient harm; harmful errors involved significantly more administering errors (59% vs 32%,  $p = .023$ ), errors occurring in inpatient care (93% vs 68%,  $p = .012$ ) and extra doses of medication (31% vs 10%,  $p = .025$ ) compared with nonharmful errors. Outpatient errors involved significantly more dispensing errors ( $p < .001$ ) and more errors due to inaccurate or omitted transcription ( $p < .001$ ), compared with inpatient errors. Family notification of medication errors was reported in only 12% of errors.

**Conclusions:** Pediatric antidepressant errors often reach patients, frequently involve off-label use of medications, and occur with varying severity and type depending on location and type of medication prescribed. Education and research should be directed toward prompt medication error disclosure and targeted error reduction strategies for specific medication types and settings.



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<https://www.wsj.com/articles/SB116422408807730936>

### **Adults Are Divided On Off-Label Use Of Prescription Drugs**

The Wall Street Journal Online Updated Nov. 23, 2006 12:01 am ET U.S. adults are divided on whether doctors should be allowed to prescribe drugs to treat diseases or conditions other than those for which they have been approved, a WSJ.com/Harris Interactive healthcare poll found. Off-label use of prescription drugs is legal in the U.S. However, there are strict rules governing the marketing of a drug for treatment of a disease for which it hasn't been approved. Forty-five percent of those surveyed say doctors "should be allowed to decide which prescription drug treatments to use with their patients regardless of what diseases they have or have not been approved for by the FDA," compared with 46% who said this shouldn't be allowed. But more than two-thirds believe drug companies shouldn't be allowed to encourage off-label use vs. 12% who disagree and 20% who aren't sure.

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<https://aapsonline.org/judicial/aaps-v-fda-hcq-6-2-2020.pdf>

IN THE UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF MICHIGAN ASSOCIATION OF AMERICAN PHYSICIANS & SURGEONS, Plaintiff, v. FOOD & DRUG ADMINISTRATION; DR. STEPHEN M. HAHN, Commissioner of Food & Drugs, in his official capacity; BIOMEDICAL ADVANCED RESEARCH & DEVELOPMENT AUTHORITY; GARY L. DISBROW, Ph.D., Acting Director, Biomedical Advanced Research & Development Authority, in his official capacity; DEPARTMENT OF HEALTH & HUMAN SERVICES; and ALEX AZAR, Secretary of Health & Human Services, in his official capacity, Defendants. No. 1:20-cv-0493 COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

The Association of American Physicians & Surgeons ("AAPS" or "Plaintiff") seeks declaratory and injunctive relief against the federal Department of Health & Human Services ("HHS"), two of its constituent agencies – the Food and Drug Administration ("FDA") and the Biomedical Advanced Research & Development Authority ("BARDA") – and their respective lead officers (collectively, "Defendants"), based on the following allegations. NATURE OF THE ACTION 1. AAPS brings this action on behalf of its members and their patients to end the irrational interference by the FDA with timely access to hydroxychloroquine ("HCQ"), which has been donated in large quantities to the federal government for prompt distribution. Specifically, AAPS seeks an injunction against the FDA's Emergency Use Authorization dated March 28, 2020 ("EUA"), which prohibits use of the donated HCQ except for already-hospitalized patients for Case 1:20-cv-00493 ECF No. 1 filed 06/02/20 PageID.1 Page 1 of 24 2 whom clinical trials are unavailable. 2. Through a biased, unlawful process described in greater detail below, FDA officials from prior administrations acted contrary to the wishes of President Donald Trump, by arbitrarily limiting use of HCQ from the Strategic National Stockpile (SNS) "to prescribe to adolescent and adult patients hospitalized with COVID-19, as appropriate, when a clinical trial is not available or feasible." 3. Specifically, a Barack Obama-appointed official who is outspokenly critical of President

Trump, Rick Bright, personally opposed making HCQ widely available to the public from the federal SNS,<sup>2</sup> and distorted the agency process to arbitrarily and unjustifiably limit access by patients to HCQ received as donations by the federal government for the purpose of making it available promptly to the public. 4. HCQ has been approved as safe by the FDA for sixty-five (65) years,<sup>3</sup> and is safer than numerous medications that are widely available over the counter (“OTC”) without requiring a prescription, including anti-depressants (St John’s Wort), sleeping pills (diphenhydramine), bronchodilators (ephedrine), many pain medications including ibuprofen, acetaminophen (Tylenol®), and even aspirin. HCQ is not addictive in any way. 5. President Donald Trump himself has repeatedly praised HCQ, and he announced on May 18, 2020 that on his own initiative and with his physician’s advice and prescription, Trump took a full regimen of HCQ himself as a prophylaxis against COVID-19, as other world leaders have reportedly been doing. 6. The arbitrary, irrational, and unjustifiable interference by Defendants with the use of HCQ as a prophylaxis interferes with the political process by which the United States selects its president: national political conventions. For nearly two centuries, thousands of delegates attend a national political convention together to nominate their candidate for president and to present their slate to the American public. Continued, irrational interference by Defendants with a safe prophylaxis for COVID-19 has the effect of infringing on the right of the people to hold national political conventions, which have been an essential part of our presidential elections since at least 1832. 7. Efforts to persuade the FDA to remove its irrational limitations of hospitalization and non-availability of a clinical trial have been unsuccessful and petitioning the FDA amid the conflicts of interests among its officials would be futile on this issue. 8. These arbitrary, irrational, and unjustifiable limitations by the FDA in its EUA prevents the use of HCQ as a prophylaxis in nursing homes and when in the best interests of nonhospitalized patients. 9. HCQ, like most medications, loses its efficacy over time, particularly at warmer temperatures which are occurring now as summer approaches. Most of the HCQ doses in the SNS will be discarded for their loss in efficacy if the FDA restrictions on its use are not promptly lifted. 10. There will be irreparable, immediate harm to AAPS members and their patients if the arbitrary, irrational, and unjustifiable restrictions by FDA on use of HCQ from the SNS are not enjoined and declared invalid immediately. PARTIES 11. Plaintiff AAPS was founded in 1943 and is a nonprofit membership organization of physicians in virtually all specialties. AAPS is incorporated under the laws of Indiana and headquartered at 1601 N. Tucson Blvd., Suite 9, in Tucson, Arizona. AAPS membership includes physicians practicing in this Western District of Michigan. Members of AAPS, including at least one in this district, have been and continue to be harmed irreparably by the FDA’s restrictions in its EUA. 12. Defendant HHS is a federal executive agency, and defendants FDA and BARDA are constituent agencies within HHS. 13. Defendant Stephen M. Hahn is the Commissioner of Food & Drugs, who is the lead officer within the FDA. 14. Defendant Gary L. Disbrow is BARDA’s Acting Director, who is the lead officer within BARDA. 15. Defendant Alex Azar is the Secretary of Health & Human Services, who is the lead officer within HHS. JURISDICTION AND VENUE 16. This action arises out of Defendants’ ongoing violations of the equal protection component of the Due Process Clause, U.S. CONST. amend. V, cl. 4, Section 564 of the Federal Food, Drug and Cosmetic Act (“FDCA”), 21 U.S.C. § 360bbb-3, and the Administrative Procedure Act (“APA”), 5 U.S.C. §§ 701-706, and thus raises federal questions over which this Court has jurisdiction pursuant to 28 U.S.C. § 1331. 17. Venue is proper in this United States District Court for the Western District of Michigan, under 28 U.S.C. § 1391(e)(1), because Defendant FDA resides in this district by virtue of having an office at 410 W. Michigan Ave, Kalamazoo, Michigan 49007, and Plaintiff has at least one member here who has been injured by virtue of Defendants’ actions at issue. If necessary for venue, Plaintiff’s members could become named plaintiffs.

18. An actual and justiciable controversy exists between Plaintiffs and Defendants. 19. As set forth in more detail below, members of Plaintiff AAPS have suffered injury in the form of the denial by the FDA of access to HCQ for AAPS members to prescribe to patients. This causes economic injury to AAPS members by interfering with their ability to care for patients who have COVID-19 or who are at risk for it. 20. Because this Court has jurisdiction as a threshold matter, the Declaratory Judgment Act, 28 U.S.C. §§ 2201-2202, provides this Court the power to “declare the rights and other legal relations of any interested party ..., whether or not further relief is or could be sought.” 28 U.S.C. § 2201; accord FED. R. CIV. P. 57 advisory committee note (“the fact that another remedy would be equally effective affords no ground for declining declaratory relief”). CONSTITUTIONAL AND STATUTORY BACKGROUND 21. The Due Process Clause of the Fifth Amendment includes an equal-protection component that is coextensive with the equal-protection guarantees of the Equal Protection Clause of the Fourteenth Amendment. 22. At a minimum, under those equal protection guarantees, the government cannot treat similarly situated groups or persons differently without a rational basis for doing so. 23. Upon finding an equal-protection violation, a reviewing court’s remedy can “level up” the disparate treatment of the disfavored class (e.g., provide greater access to HCQ). 24. Congress enacted the Pure Food and Drugs Act, ch. 3915, 34 Stat. 768 (1906), under its Commerce Power. In 1938, Congress amended and replaced that Act with the FDCA. PUB. L. NO. 75 -717, 52 Stat. 1040 (1938) (codified, as amended, at 21 U.S.C. §§ 301-399i). 25. In enacting the FDCA, Congress was clear that the FDCA does not define the practice of medicine. See S. REP. NO. 74-361, at 3 (1935) (FDCA is “not intended as a medical practices act and [would] not interfere with the practice of the healing art[s]”).

26. FDA has expressly recognized the freedom that health care professionals possess to use and prescribe approved drugs off-label: “[O]nce a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling.” 59 Fed. Reg. 59, 820, 59, 821-22 (Nov. 18, 1994) (internal quotation marks omitted, alterations in original). 27. Health care professionals may lawfully prescribe or use an FDA-approved drug both for any uses suggested on the labeling itself (i.e., “on-label uses”) and in ways that are not prescribed, recommended, or suggested on the FDA-approved labeling (i.e., “off-label uses”). 28. Off-label use of prescription drugs accounts for roughly 20% of all prescriptions, and in some medical specialties it accounts for a majority of prescriptions. Many off-label uses have become the standard of medical care.<sup>4</sup> For generic medication such as HCQ, on which any patent rights have long since expired, there is no financial incentive for any entity to fund expensive studies to seek approval by the FDA for off-label uses, and such approval is not customarily sought or granted. 29. Section 4(a) of the Project Bioshield Act of 2004, PUB. L. NO. 108-276, §4(a), 118 Stat. 835, 853-859, added Section 564 to the FDCA, codified as 21 U.S.C. § 360bbb-3. Under that section, the Secretary of HHS can authorize the emergency use of either or both unapproved medical products and/or unapproved uses of approved medical products, 21 U.S.C. § 360bbb3(a)(1)-(4), upon recognizing or declaring an emergency under the criteria outlined in 21 U.S.C. § 360bbb-3(b)(1)(A)-(D). 30. In such an emergency, the statutory criteria for granting an emergency use application are that the Secretary of HHS concludes the following: (1) that an agent referred to in a declaration under subsection (b) can cause a serious or life-threatening disease or condition; (2) that, based on the totality of scientific evidence available to the Secretary, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that— (A) the product may be effective in diagnosing, treating, or preventing— (i) such disease or condition; or (ii) a serious or life-threatening disease or condition caused by a product authorized under this section, approved or cleared under this chapter, or licensed under section 351 of the Public Health Service Act

[42 U.S.C. 262], for diagnosing, treating, or preventing such a disease or condition caused by such an agent; and (B) the known and potential benefits of the product, when used to diagnose, prevent, or treat such disease or condition, outweigh the known and potential risks of the product, taking into consideration the material threat posed by the agent or agents identified in a declaration under subsection (b)(1)(D), if applicable; (3) that there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such disease or condition; (4) in the case of a determination described in subsection (b)(1)(B)(ii), that the request for emergency use is made by the Secretary of Defense; and (5) that such other criteria as the Secretary may by regulation prescribe are satisfied. 21 U.S.C. § 360bbb-3(c)(1)-(5). 31. Neither FDA nor HHS nor any other federal agency has promulgated a regulation pursuant to 21 U.S.C. § 360bbb-3(c)(5) to establish criteria that Defendants may consider in granting an EUA under 21 U.S.C. § 360bbb-3(c). 32. Section 1557 of the Affordable Care Act prohibits discrimination in health programs and activities by not only recipients of federal funds but also federal agencies: [A]n individual shall not, on the ground prohibited under title VI of the Civil Rights Act of 1964 ..., the Age Discrimination Act of 1975 ..., or section 504 of the Rehabilitation Act of 1973 ..., be excluded from participation in, be denied the benefits of, or be subjected to discrimination under, any health program or activity, any part of which is receiving Federal financial assistance, including credits, subsidies, or contracts of insurance, or under any program or activity that is administered by an Executive Agency or any entity established under this title[.] 42 U.S.C. § 18116(a). 33. The entity Defendants – HHS, FDA, and BARDA – are “Executive Agencies” within the meaning of Section 1557 of the Affordable Care Act, and the SNS is a “health program or activity” within the meaning of that section. 34. As relevant here, the judicial-review provisions of the APA proscribe agency action that is “arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.” 5 U.S.C. § 706(2)(A). The APA further bars agency action that is “in excess of statutory jurisdiction, authority, or limitations,” *Id.* at § 706(2)(C), and directs courts to “hold unlawful and set aside agency action, findings, and conclusions found to be ... contrary to constitutional right, power, privilege or immunity.” 5 U.S.C. § 706(2)(B). ALLEGATIONS RELEVANT TO ALL COUNTS 35. COVID-19 has reportedly caused the death of more than 100,000 Americans in merely a few months this year, roughly half of whom have contracted and died from this disease while residing in nursing homes. 36. By denying elderly nursing-home patients access to HCQ when COVID-19 affects those patients more severely than younger patients, the EUA disparately impacts the elderly and thus discriminates on the basis of age within the meaning of Section 1557 of the Affordable Care Act, 42 U.S.C. § 18116, and the Age Discrimination Act of 1975. 37. By the end of May 2020, pharmaceutical companies donated more than 150 million doses of hydroxychloroquine (HCQ) – enough to fully treat more than 15 million people – to the federal government for immediate use in treating COVID-19, and as part of their efforts for the “prevention and treatment of the coronavirus outbreak.”<sup>5</sup> 38. Yet the vast majority of these 150 million doses of HCQ have not been distributed to the public and are in imminent danger of spoilage due to the passage of time amid the increasing temperatures as summer approaches. 39. Multiple foreign governments, including China, India,<sup>6</sup> South Korea, Costa Rica, United Arab Emirates, and Turkey, successfully recommend use of HCQ for effective early treatment of COVID-19, and for use as a prophylaxis for the disease. Multiple studies confirm the effectiveness of HCQ as an early treatment of COVID-19. 40. For example, a recent study in India, where HCQ is being widely used as a prophylaxis, concluded that: The pivotal finding of our study was the noteworthy benefits of HCQ prophylaxis. ... [T]he National Task Force for COVID-19 in India recommended once a week maintenance dose for seven weeks (400 mg once weekly), following the loading dose (400 mg bd).<sup>7</sup> 41. There are no peer-reviewed or meritorious

studies showing a lack of HCQ safety for COVID-19 patients. The retrospective studies cited in the media to the contrary are too flawed to inform rational decisionmaking because they compare outcomes without involving like patient populations (e.g., the HCQ patients may have been more sick than the non-HCQ patients or may have come from geographic areas with more acute exposures, which would explain higher rates of negative outcomes without showing in any way that HCQ caused or contributed to those outcomes). 42. There is dramatic difference in saving lives in countries allowing early and prophylactic use of hydroxychloroquine compared with the United States, as of the third week in May 2020:

43. As explained by experts in a recent article published by the New York Times: Acting before or very soon after an infection is the best way to handle most acute viral diseases. Why aren't we focusing on that with Covid-19? ... [W]e believe that trials of prophylactic and therapeutic drugs for asymptomatic and mild cases of Covid-19 have a greater chance of success than does administering drugs to critically ill patients — as well as greater long-term potential to benefit more people overall. Richard Malley and Marc Lipsitch, "Acting before or very soon after an infection is the best way to handle most acute viral diseases. Why aren't we focusing on that with Covid-19?" New York Times (May 23, 2020). IIG An eminent Professor of Epidemiology in the Department of Epidemiology and Public Health at the Yale School of Public Health and Yale School of Medicine, Harvey A. Risch, stated likewise in a peer-reviewed medical journal: An outpatient treatment that prevents hospitalization is desperately needed[for COVID-19]. ... Hydroxychloroquine+azithromycin has been widely misrepresented in both clinical reports and public media .... Evidence about use of hydroxychloroquine alone, or of hydroxychloroquine+azithromycin in inpatients, is irrelevant concerning efficacy of the pair in early high-risk outpatient disease. Five studies, including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy. Hydroxychloroquine+azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20% 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians. Harvey A Risch, Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients That Should Be Ramped-Up Immediately as Key to the Pandemic Crisis, \_\_ AM. J. EPIDEMIOLOGY \_\_ (May 27, 2020) (forthcoming 2020) (emphasis added).<sup>8</sup> 45. The BBC reported on the success of Turkey in keeping its mortality low from COVID-19: Chief doctor Nurettin Yiyit ... says it's key to use hydroxychloroquine early. "Other countries are using this drug too late," he says, "especially the United States. We only use it at the beginning. We have no hesitation about this drug. We believe it's effective because we get the results." Orla Guerin, Coronavirus: How Turkey took control of Covid-19 emergency, BBC News (May 29, 2020).<sup>9</sup> 46. National Public Radio recently quoted the expert Dr. Jon Giles, an epidemiologist and rheumatologist at Columbia University Department of Medicine, about the safety of HCQ: "It's a very, very safe drug; it's been used for over 75 years. When I give someone hydroxychloroquine, I don't get an ECG or do blood monitoring."<sup>10</sup> 47. More than 25 articles since 1982 published in peer-reviewed medical journals have reported on the safety of HCQ, and these articles are included in the PubMed database as maintained by the United States National Library of Medicine at the National Institutes of Health. 48. The Centers for Disease Control and Prevention ("CDC"), which is a division within Defendant HHS, declares the safety of HCQ in one of its publications posted on its website: How long is it safe to use hydroxychloroquine? CDC has no limits on the use of hydroxychloroquine for the prevention of malaria. When hydroxychloroquine is used at higher doses for many years, a rare eye condition called

retinopathy has occurred. People who take hydroxychloroquine for more than five years should get regular eye exams.<sup>11 49</sup>. The President of El Salvador, Nayib Bukele, announced that he is taking hydroxychloroquine as a prophylaxis against COVID-19, and that most world leaders were doing likewise: “I use it as a prophylaxis. President Trump uses it as a prophylaxis. Most of the world’s leaders use it as a prophylaxis,” said President Bukele.<sup>12 50</sup>. On May 31, 2020, the United States and Brazil issued a joint statement regarding health cooperation, which is posted on the White House’s website and provides in part the following: The American and Brazilian people stand in solidarity in the fight against the coronavirus. Today, as a demonstration of that solidarity, we are announcing the United States Government has delivered two million doses of hydroxychloroquine (HCQ) to the people of Brazil. ... HCQ will be used as a prophylactic to help defend Brazil’s nurses, doctors, and healthcare professionals against the virus. It will also be used as a therapeutic to treat Brazilians who become infected.<sup>13</sup> Disregard of President Trump’s Policy by Agency Officials <sup>51</sup>. Rick Bright, Ph.D., an outspoken critic of President Trump, was the Director at BARDA as appointed by prior President Barack Obama. <sup>52</sup>. Bright strongly favors vaccination for COVID-19, even though no such vaccine is available, and some experts doubt the feasibility of developing a timely vaccine for this novel virus.<sup>14 53</sup>. At all relevant times Bright has opposed making HCQ widely available for physicians to prescribe to patients in connection with COVID-19. <sup>15 54</sup>. According to a whistleblower complaint against the Trump Administration submitted by Bright, FDA Director of the Center for Drug Evaluation and Research Janet Woodcock also played a pivotal role in pushing for the EUA. <sup>55</sup>. Woodcock also occupied a top position in a public-private operation designed to approve new vaccines for COVID-19, and she reportedly communicated with a Wall Street analyst concerning such development. <sup>56</sup>. Prophylactic use of HCQ is a rival approach to vaccination, but Woodcock did not recuse herself from the decision-making at the FDA concerning the EUA restrictions on access to HCQ. <sup>57</sup>. After an advocacy group objected to a conflict of interest by Woodcock in her various roles, she recused herself from the review process for vaccination<sup>16</sup> but remains nonrecused from decision-making that sharply and unjustifiably limits access to HCQ. <sup>58</sup>. Bright and agency officials working with him have been biased by their opposition to President Trump and/or their support of rival treatments other than HCQ, such as remdesivir as advocated by Bright and vaccination as sought by Woodcock. <sup>59</sup>. Specifically, Bright favors an expensive, proprietary antiviral medication developed by Gilead Sciences (“Gilead”). Bright formed the following pre-conceived opinion in favor of Gilead which should have caused his recusal from the decision-making process about HCQ: Gilead’s supply of the drug [i.e., remdesivir] was low – it had only a few thousand doses of the drug on hand and the timeline to manufacture more was lengthy. [Bright] repeatedly advised Dr. Kadlec and other HHS officials of the urgent need to acquire the existing doses and to secure future doses as they were produced. He also strongly recommended that HHS work with Gilead to “on-shore” all steps of the Remdesivir supply chain to ensure an uninterrupted supply in the United States.<sup>17 60</sup>. At the improper insistence of Bright, before he was relieved of his HCQ-related duties by the Trump Administration, on March 28, 2020 the FDA arbitrarily limited use of HCQ from the SNS as follows. The EUA <sup>61</sup>. The FDA issued its EUA as a Letter from Denise M. Hinton, Chief Scientist, Food & Drug Admin., to Rick Bright, Ph.D., Director, Biomedical Advanced Research & Development Authority, Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease (Mar. 28, 2020). The disputed portion of the EUA are the hospitalization and clinical-trial restrictions in its “Scope of Authorization” as follows: The hydroxychloroquine sulfate may only be used to treat adult and adolescent patients who weigh 50 kg or more hospitalized with COVID-19 for whom a clinical trial is not

available, or participation is not feasible. EUA, at 4 (emphasis added).<sup>18</sup> 62. These restrictions deny patients the use of HCQ for its prophylactic effect (i.e., the “with COVID-19” limit requires that the patient have COVID-19), deny non-hospitalized patients (such as nursing home residents and patients who visit physicians’ offices) access to HCQ, and even deny or restrict access to hospitalized patients for whom clinical trials are available. 63. In the EUA, Defendants state that the criteria for an EUA are met with respect to the existence of an emergency for the COVID-19 pandemic under 21 U.S.C. § 360bbb-3(b), that the COVID-19 virus can cause serious or life-threatening diseases or conditions under § 360bbb3(c)(1), that HCQ is or may be effective in treating or preventing the COVID-19 virus under § 360bbb-3(c)(2)(A)(i), and that there is no adequate, approved, and available alternative to HCQ under § 360bbb-3(c)(3).<sup>19</sup> 64. Neither the EUA itself nor Defendants invoked the scarcity of HCQ as a basis for rationing access to HCQ. Nor could they, given the plentiful supply of the easy-to-manufacture HCQ which has limited shelf life in the SNS amid warming temperatures. 65. The EUA-related criterion in dispute is whether the limitations in the EUA’s “Scope of Authorization” is necessary under § 360bbb-3(c)(2)(A) with respect to patients who are not “hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.” Defendants give two rationales for these restrictions in the EUA: (1) “The safety profile of these drugs has only been studied for FDA approved indications, not COVID-19;” and (2) “FDA encourages the conduct and participation in randomized controlled clinical trials that may produce evidence concerning the effectiveness of these products in treating COVID-19.” EUA, at 2. 66. Defendants’ first rationale is a strawman, because safety is determined with respect to patients, not diseases. HCQ has been proven to be safe for 65 years and has been fully approved by the FDA as safe throughout this entire period. 67. The EUA misleads the public with its first rationale by falsely pretending that a medication approved as safe for treating one disease can somehow not be safe for treating another disease. 68. The EUA further misleads the public with its first rationale by falsely implying that medication approved as safe for one use requires time-consuming additional studies of safety before it may properly be used to treat a new disease. 69. In fact, the “safety profile” with respect to new uses of a medication previously approved by the FDA is virtually never studied, and there is no rational basis for delaying new uses of previously approved medication by requiring such studies. 70. With respect to patients with COVID-19 who are not hospitalized, the FFDA, the Constitution’s federalist structure, and the presumption against preemption all suggest that Congress did not intend Defendants to supersede a prescribing medical professional’s judgment for off-label uses of FDA-approved drugs for patients. 71. With respect to patients not infected with COVID-19 for whom HCQ is prescribed or sought for HCQ’s prophylactic effect, EUA’s stated safety concern about HCQ’s effect on patients infected with COVID-19 does not apply to patients not infected with COVID-19. 72. With respect to the EUA’s seeking to push patients into clinical trials in lieu of having their medical professional prescribe the drug, Defendants lack the authority to limit access that way. Significantly, not everyone who participates in a “randomized controlled clinical trial” even receives the drug in question, as usually half of participants in a clinical trial receive a placebo and thus would not receive any HCQ. 73. The EUA discriminates against everyone who is outside of a hospital: residents of nursing homes, physicians who care for nursing home patients, physicians having office practices, and patients who are treated in connection with office visits. 74. The EUA also discriminates against those who would receive only a placebo, and not HCQ, in a clinical study arbitrarily required by the EUA. 75. The discrimination against these millions of people threatens to cause the unnecessary loss of life and unnecessary illness and thereby injures AAPS members and their patients. 76. Multiple studies suggest that HCQ is more effective if used early in the progression of COVID-19, as other antiviral medication like oseltamivir

(Tamiflu®) is, and the blanket federal limitations in the EUA are arbitrary, irrational, and unjustified in interfering with early treatment by HCQ. 77. There is no need to ration or restrict access to HCQ, as the stockpile contains enough to serve 15 million Americans and it is feasible for manufacturers to produce a million new doses of HCQ daily. 78. These arbitrary, irrational, and unjustifiable limitations by the FDA prevent the use of HCQ as a prophylaxis, as President Trump and other world leaders are using it, and prevent nursing home residents from receiving it, where more than half of the COVID-19 mortalities have reportedly occurred.<sup>20</sup> 79. Never before in the history of the United States has an “emergency use authorization” been issued to restrict the use of an old and safe medication, as Defendants have improperly done with respect to HCQ. The EUA restrictions on the use of the long-approved medications is outside the scope of any statutory authorization. 80. As is customary, state regulatory officials have imitated or relied upon the unjustified FDA policy,<sup>21</sup> as commanded by the Federation of State Medical Boards (“FSMB”). 81. The FSMB – which directs state medical boards that wield complete authority over licenses to practice medicine – relied on the EUA to order that: Physicians, nurses, pharmacists, pharmacies and hospitals have an ethical duty to put the needs of patients first, and this includes observing strict prescribing guidelines. On March 28, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for use of oral formulations of chloroquine phosphate and hydroxychloroquine sulfate. The authorization allows these medications to be prescribed by clinicians for hospitalized adult and adolescent patients “for whom a clinical trial is not available, or participation is not feasible.” Clinicians should avoid prescribing for themselves or their family members and should be aware that deviating from the standard of care could put their license at risk. 22

Ripeness 82. The EUA is “final agency action for which there is no other adequate remedy.” 5 U.S.C. § 704. The EUA represents FDA’s consummated decision-making process to grant Bright’s request with his limitations. Further, the EUA was a decision from which rights or obligations were determined and from which legal consequences (e.g., access to HCQ from the SNS) flowed. 83. Plaintiff has no adequate or available administrative remedy; in the alternative, any effort to obtain an administrative remedy would be futile. 84. Plaintiff has no adequate remedy at law. Injury to AAPS Members 85. Defendant FDA’s unlawful action has caused injury to a physician member of Plaintiff AAPS (“Dr. John Doe”). 86. Physician Dr. John Doe has been unable to successfully prescribe a full regimen of HCQ for patients in need of it, due to the FDA’s unlawful and irrational EUA. 87. Patients of Dr. John Doe have been additionally harmed by the FDA’s EUA by being denied access to a full regimen of the potentially lifesaving HCQ. 88. Dr. John Doe practices within the Western District of Michigan and has patients who reside in Kalamazoo, Michigan. 89. Another physician member of AAPS was prevented from successfully prophylactically treating his nursing home patients with HCQ by virtue of the FDA’s EUA. 90. Numerous physician members of AAPS, including Dr. John Doe, reasonably fear retaliation against them by state medical boards based on the irrational restrictions in the EUA along with their incorporation into the directive made to state medical boards by the FSMB. Disparate Impact of FDA Policy on Religious Services 91. Access to a prophylaxis and early treatment of COVID-19 is particularly important to reopening religious services without a chilling effect which denial of timely access to treatment causes. 92. About a quarter (25%) of weekly attendees of all kinds of religious services are over 65 years old,<sup>23</sup> who are thereby at higher risk from COVID-19 than other demographic groups, such as young and healthy adults. 93. Clergy are often in contact with people who particularly vulnerable to contagion, such as those suffering from other medical conditions. 94. The withholding and denial of access to prophylactic and early treatment by HCQ has a disparate impact on attendance at religious services, which AAPS members and their patients have a constitutional right to attend. 95. A lawsuit is pending in



Beemer v. Whitmer, 1:20-cv-00323-PLM-PJG (W.D. Mich.), which challenges on constitutional grounds the closure of churches in Michigan. 96. Like arguments made in that lawsuit, those at high risk for COVID-19 (including AAPS members) who attend church services should not be arbitrarily denied access by Defendants to prophylactic and early treatment by HCQ. CAUSES OF ACTION COUNT I (EQUAL PROTECTION) 97. Plaintiff AAPS incorporates herein all statements and allegations contained in this Complaint.

98. In issuing the EUA's restrictions to limit access to HCQ to patients who are hospitalized without feasible access to a clinical trial, Defendants violated the equal protection guarantee implicit in the Due Process Clause of the Fifth Amendment to the U.S. Constitution. The EUA impermissibly discriminates based on a patient's hospitalization status, illness status, and access to clinicals trial, without a rational basis for this discrimination. 99. The doctrine of administrative exhaustion does not apply to constitutional violations. 100. With respect to patients who wish to use HCQ, and medical professionals who wish to prescribe HCQ for its prophylactic effect to prevent becoming infected with the COVID-19 virus, the EUA's limitation to hospitalized patients with COVID-19 lacks a rational basis for a drug that FDA already has found to be safe. 101. With respect to hospitalized patients with COVID-19 who have feasible access to clinical trials, Defendants lack the authority to compel participation in randomized controlled clinical trials that might not provide particular patients any access to HCQ at all. 102. With respect to non-hospitalized patients with COVID-19, Defendants lack the authority to override the discretion of a duly licensed medical professional to prescribe off-label uses of FDA-approved drugs. 103. The EUA's unlawful discrimination against the elderly under Section 1557 of the Affordable Care Act, 42 U.S.C. § 18116, per se lacks a rational basis. 104. Inherent in the constitutional right to attend religious services is a right to equal access to prophylactic and early treatment for a disease which may be transmitted during such services. 105. For the foregoing reasons, the challenged EUA violates the equal-protection component of the Fifth Amendment's Due Process Clause and is contrary to the constitutional authority of Defendants. COUNT II (ADMINISTRATIVE PROCEDURE ACT) 106. Plaintiff AAPS incorporates herein all statements and allegations contained in this Complaint. 107. In addition to violating constitutional equal protection guarantees as alleged above and incorporated herein, the EUA is also arbitrary and capricious and exceeds Defendants' lawful authority under the APA. 108. Defendants lack authority under FFDCa Section 564 or any other provision to limit access to a drug based on the patient's ability to participate in a clinical trial. 109. The decision-making underlying the EUA was tainted by bias, and thus it is arbitrary and capricious. 110. The EUA's unlawful discrimination against the elderly under Section 1557 of the Affordable Care Act, 42 U.S.C. § 18116, per se constitutes arbitrary and capricious action and action not otherwise in accordance with the law. 111. For the foregoing reasons, the challenged EUA is arbitrary, capricious, not otherwise in accordance with the law, and in excess of authority granted by law. COUNT III (FIRST AMENDMENT ASSOCIATIVE RIGHTS) 112. Plaintiff AAPS incorporates herein all statements and allegations contained in this Complaint. 113. Plaintiff AAPS's members have First Amendment rights of association that depend on access to safe prophylaxis medication during a pandemic, because otherwise they are prohibited from or instructed not to gather in large groups.

114. Defendants have infringed on these associative rights of Plaintiff AAPS's members by denying them access to HCQ, which has been proven to be safe for more than 65 years. 115. Defendants do not have a compelling or even a rational basis for impeding access to HCQ as a potential prophylaxis for COVID-19. 116. As a result of Defendants' actions, AAPS has already had to cancel one of its scheduled conferences

and its annual conference is in jeopardy; the Republican National Convention is also unnecessarily jeopardized to the detriment of members of AAPS and the entire Nation. 117. Defendants' foregoing infringement on associative rights has caused, and continues to cause, irreparable harm to Plaintiff AAPS. PRAYER FOR RELIEF 118. WHEREFORE, Plaintiff AAPS respectfully asks this Court to grant the following relief: A. Enter judgment in favor of Plaintiff AAPS and against Defendants on all counts. B. Pursuant to 28 U.S.C. §§ 1331, 2201-2202, and FED. R. CIV. P. 57, issue a Declaratory Judgment that the restrictions in the EUA that currently require being hospitalized, having COVID-19, and facing the non-availability of a clinical trial prior to obtaining HCQ from the SNS are invalid. C. Pursuant to 28 U.S.C. §§ 1331, 2201-2202, and FED. R. CIV. P. 57, issue an Injunction providing that: (i) All Defendants are enjoined from enforcing the restrictions in the EUA that currently require being hospitalized, having COVID-19, and facing the nonavailability of a clinical trial prior to obtaining HCQ from the SNS; (ii) All Defendants are enjoined to make available and distribute promptly, and for the benefit of the public holding valid prescriptions, the HCQ being stored in the SNS; and (iii) All Defendants are enjoined from impeding the distribution, sale or purchase of HCQ by adult members of the public during the COVID-19 pandemic. D. Pursuant to 28 U.S.C. § 2412 and any other applicable provisions of law or equity, award Plaintiffs' costs and reasonable attorneys' fees. E. Such other relief as may be just and proper. Dated: June 2, 2020

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<https://www.healthy.arkansas.gov/programs-services/topics/covid-19-guidance-about-chloroquine>

### **COVID-19 GUIDANCE ABOUT CHLOROQUINE**

On June 15, 2020 the Food and Drug Administration (FDA) revoked the Emergency Use Authorization (EUA) for the use of chloroquine (CQ) and hydroxychloroquine (HCQ) to treat COVID-19 after concluding it was “no longer reasonable to believe that oral formulations of HCQ and CQ may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks”. The latter included serious cardiac adverse events. Based on this information, the Arkansas Department of Health (ADH) updated its guidance related to HCQ and CQ indicating that their use for treatment of COVID-19 should be avoided in both outpatient and hospitalized settings.

CQ and HCQ can continue to be administered, prescribed, and dispensed for FDA approved medical conditions under supervision of a patient’s healthcare provider. Unapproved use (i.e. “off label use”) of these medications is left to the discretion of individual clinicians and their patients. However, the ADH wants clinicians to be aware that coadministration of HCQ or CQ with remdesivir, an FDA EUA approved medication for treatment of COVID-19, is not recommended based on data showing an antagonistic effect of these medications on the antiviral activity of remdesivir.

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<https://content.govdelivery.com/accounts/CODORA/bulletins/2833740>

### **Guidance for COVID-19 drug prescribing**

*Colorado Department of Regulatory Agencies sent this bulletin at 03/26/2020 09:38 AM MDT*

**DENVER (March 26, 2020)** - The Colorado State Board of Pharmacy, the Colorado Medical Board and the Colorado Nursing Board are concerned about the inappropriate prescribing of hydroxychloroquine, chloroquine, azithromycin, Kaletra, and potentially other medications, often in large quantities with a high number of refills, to respond to the COVID-19 pandemic.

The Boards are hearing of instances where abnormally high quantities of these drugs are being dispensed/prescribed in situations that don’t merit the drug, or quantities do not warrant the indication. These actions are causing a shortage of these drugs for people who need them for legitimate medical reasons.

The drugs are commonly used to treat malaria, lupus, rheumatoid arthritis and other conditions. According to the Centers for Disease Control, [there are no US Food and Drug Administration \(FDA\)-approved drugs specifically for the treatment of patients with COVID-19.](#)

There is, at this date, only anecdotal evidence of their potential usefulness. Public health authorities are working to obtain better data on their potential – and most appropriate use in the pandemic.

Here are recommendations, first distributed by The American Society of Health-System Pharmacists (ASHP) to its membership, which may serve as a general guide for healthcare professionals regarding the receipt and dispensing of prescriptions for hydroxychloroquine, which can be applied to other COVID-19 investigative medications.

1. Continue to fill prescriptions for existing patients who are being prescribed these medications for FDA-approved indications on chronic therapy.
2. For new prescriptions, prescribers should be cognizant that hydroxychloroquine use in COVID-19 patients [is not the standard of care](#). Pharmacists should verify and document diagnosis with the prescriber or prescriber's agent and limit to a 30-day supply of medication with the drug frequently on back order at this time for prescriptions with an FDA-approved indication.
3. Due to limited supply, reserve hydroxychloroquine for patients with known autoimmune disorders and those ill enough to be hospitalized for COVID-19.

***Please note that the Colorado State Board of Pharmacy, the Colorado Medical Board and the Colorado Nursing Board have the authority to discipline their corresponding licensees who fail to meet their corresponding generally accepted standards of practice.***

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<https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/Facility-Licensing--Investigations/Blast-Faxes/Blast-Fax-2020-29-Updated-Guidance-for-COVID-19.pdf?la=en>

**STATE OF CONNECTICUT**  
DEPARTMENT OF PUBLIC HEALTH



Renée D. Coleman-Mitchell, MPH  
Commissioner

Ned Lamont  
Governor  
Susan Bysiewicz  
Lt. Governor

**HEALTHCARE QUALITY AND SAFETY BRANCH**

**BLAST FAX 2020-29**

TO: All Healthcare Facilities

FROM: Commissioner Renée D. Coleman-Mitchell, MPH *RCM*

CC: Deputy Commissioner Heather Aaron, MPH, LNHA  
Barbara Cass, RN., Branch Chief, Healthcare Quality and Safety Branch  
Donna Ortelle, Section Chief, Facility Licensing and Investigations Section

DATE: April 6, 2020

SUBJECT: Updated Guidance for COVID-19

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Please see the Updated Guidance regarding Healthcare Personnel.

## Updated Guidance for COVID-19 – April 4, 2020

Connecticut is in the acceleration phase of the COVID-19 pandemic, and the challenge of caring for an increasing number of patients with limited personal protective equipment (PPE) is expected to continue for weeks to come. We recognize that the conditions you are working under are extraordinarily difficult, and we applaud your efforts to maintain a high level of care for your patients.

With growing evidence for pre-symptomatic shedding of SARS-CoV-2 and the growing prevalence of COVID-19 in our state, the **Connecticut Department of Public Health (DPH) is now recommending that all healthcare personnel (HCP) wear surgical masks (facemasks) while in healthcare facilities.** Some healthcare organizations have already instituted a “universal masking” policy that requires this.

### **Universal Masking of Healthcare Personnel (HCP)**

Masking all HCP when PPE is otherwise not indicated can help protect HCP from pre-symptomatic transmission in the healthcare setting. Universal masking can also prevent pre-symptomatic HCP from transmitting the virus to other HCP and patients.

HCP who provide direct patient care should wear a medical-grade/FDA-regulated surgical mask, and follow CDC recommendations for extended use and re-use.<sup>1</sup> Those who do not provide direct patient care can wear a cloth or homemade mask to conserve surgical masks for direct patient care.

Wearing a mask must not replace social distancing. All staff and patients should continue to maintain distances of 6 feet apart from others as much as possible during all interactions, and with physical barriers between people when possible. It is vitally important for HCP to avoid touching their face or their facemask. Inappropriate technique during the doffing (taking off) process of facemasks can lead to contamination. Surgical masks should be carefully removed without touching the outer surface of the mask, and the mask should be folded with the outer surface facing inward, then stored in a clean sealable paper bag or breathable container if it is to be reused.<sup>1</sup>

### **Return-to-Work Recommendations for Healthcare**

DPH’s return-to-work recommendations for healthcare workers and first responders was distributed on 3/30/20.<sup>2</sup> At this time, the test-based criteria in CDC guidance<sup>3</sup> is not feasible for widespread use in Connecticut due to limited testing resources. When testing resources allow, CDC’s test-based criteria can be used to determine when HCP can return to work. DPH guidance will be updated as needed.

### COVID-19 Testing Updates

The testing landscape in Connecticut continues to change as new modalities are becoming available. As hospital laboratories take on testing and turn-around-times for commercial testing decrease, many Connecticut hospitals are now using testing resources other than the State Public Health Laboratory (SPHL). **SPHL continues to prioritize residents of congregate settings, hospital healthcare workers, and hospitalized patients who have a fever and lower respiratory disease.** SPHL is now supporting much of the testing for nursing homes and other congregate settings.

For outpatient providers evaluating patients who do not meet any of the above criteria, DPH recommends using clinical judgement and testing stewardship when deciding whether to order a COVID-19 test. If a patient can safely isolate at home<sup>4</sup> and the test result would not change management of the illness, they should self-isolate at home without testing. Patients without symptoms consistent with COVID-19 should also NOT be tested. When testing becomes more widely available and turn-around-time shortens, we can take a broader approach to testing.

At this time, DPH recommends clinicians **prioritize testing for people who interact with others while providing essential services<sup>5</sup> AND have symptoms consistent with COVID-19.** A positive test result in this group of people can lead to public health containment measures that can impact essential services. A negative test result could allow the worker to return to essential work, however a second negative test ( $\geq 24$ h between specimens) is recommended if COVID-19 is suspected.<sup>3</sup> Symptomatic household contacts of people who provide essential services can be considered for testing.

### Atypical Presentations of COVID-19

The potential for COVID-19 to initially present without respiratory symptoms adds to the challenges of diagnosis and containment. There are reports suggesting loss of olfactory (smell) and taste senses could be presenting symptoms. Gastrointestinal symptoms might also present before respiratory symptoms. Clinical judgement and testing stewardship should be used when deciding to test patients with these symptoms, taking into consideration the testing guidance above.

### Off-Label Use of Hydroxychloroquine and Azithromycin

The U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) allowing hydroxychloroquine sulfate and chloroquine phosphate products donated to the Strategic National Stockpile (SNS) to be distributed and prescribed by doctors to hospitalized teen and adult patients with COVID-19, as appropriate, when a clinical trial is not available or feasible.

**DPH strongly advises against off-label use of hydroxychloroquine and azithromycin in the outpatient setting for COVID-19 prophylaxis or treatment, as there is not enough safety and efficacy data at this time.** It is important to note that both hydroxychloroquine and azithromycin can cause QT prolongation (cardiac risks), and both these medications should be conserved for those who require them for indicated purposes.

### Reporting confirmed COVID-19 to CT DPH

CT DPH receives positive test results directly from testing laboratories. Where possible, ordering providers should enter the patient's home address on test requisition forms, so town of residence can be reported with positive results.

Laboratory-confirmed COVID-19 cases are provider-reportable, and the reporting requirement involves completion of a COVID-19 Case Report Form (CRF). There are two options for completing a CRF:

- Fax fillable PDF: [https://portal.ct.gov/-/media/DPH/EEIP/Forms/nCoV\\_PUI\\_Form.pdf](https://portal.ct.gov/-/media/DPH/EEIP/Forms/nCoV_PUI_Form.pdf)
- Complete form online: <https://dphsubmissions.ct.gov/Covid/InitiateCovidReport>

## References

This guidance memo supplements the prior CT DPH provider guidance memos issued on March 16<sup>6</sup> and March 23<sup>7</sup>, which provided more detail about PPE stewardship and conservation and procedures for submitting specimens to SPHL.

Note that COVID-19 websites are updated regularly.

1. CDC Strategies for Optimizing the Supply of Facemasks, Crisis Capacity Strategies: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/face-masks.html#crisis-capacity>
2. CT Facility Licensing and Investigations Section Blast Fax 2020-24: Guidance for Use of Isolation Orders, Return-to-work: <https://portal.ct.gov/-/media/Departments-and-Agencies/DPH/Facility-Licensing--Investigations/Blast-Faxes/Blast-Fax202024-Guidance-for-Use-of-Isolation-Orders-ReturntoWork.pdf>
3. CDC Return-to-Work Criteria for Healthcare Workers: <https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/hcp-return-work.html>
4. CDC Discontinuation of Home Isolation for Persons with COVID-19 (Interim Guidance): <https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html>
5. CT Business Exemptions for Coronavirus – Executive Order 7H: <https://portal.ct.gov/DECD/Content/Coronavirus-Business-Recovery/Business-Exemptions-for-Coronavirus>
6. CT Important Information for Connecticut Physicians, APRNs, PAs, and RNs About COVID-19 – Guidance: <https://portal.ct.gov/-/media/Coronavirus/20200316-DPH-Important-Information-for-Connecticut-Physicians.pdf>
7. CT Guidance on PPE Conservation and Testing Strategies: [https://portal.ct.gov/-/media/Coronavirus/20200324-Update\\_PPE\\_Testing\\_Info.pdf](https://portal.ct.gov/-/media/Coronavirus/20200324-Update_PPE_Testing_Info.pdf)

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<https://www.oplc.nh.gov/pharmacy/documents/dhhs-emergency-order-04-03-2020.pdf>

DEPARTMENT OF HEALTH AND HUMAN SERVICES ORDER TO RESPOND TO CORONAVIRUS DISEASE 2019 IN NEW HAMPSHIRE WHEREAS, since December 1, 2019, there have been over 952,171 people worldwide diagnosed with a novel coronavirus disease now known as coronavirus disease 2019 (COVID19); WHEREAS, on March 13, 2020, His Excellency, Governor Christopher T. Sununu, issued Executive Order 2020-04 declaring a state of emergency due to COVID-19; WHEREAS, there are now more than 540 people who have tested positive in New Hampshire for COVID-19 and numerous other suspected cases are under investigation; WHEREAS, the Department has been monitoring reported drug shortages and finds that there is a statewide shortage and/or threatened shortage of the following medications that may be used to treat COVID-19: chloroquine, hydroxychloroquine, and albuterol inhalers; and WHEREAS, the Commissioner has determined individuals diagnosed with lupus or rheumatoid arthritis, those hospitalized patients with COVID-19, and those patients with COVID-19 enrolled in a clinical trial are high risk or critical needs groups that shall receive priority for chloroquine and hydroxychloroquine; and WHEREAS, the Commissioner has determined individuals diagnosed with COVID-19 and individuals already established on albuterol inhalers are high risk or critical needs groups that shall receive priority for albuterol inhalers; and WHEREAS, to ensure individuals in the high risk or critical needs group have access to necessary medications, and to avoid any disruptions to current treatments, the Commissioner finds it is necessary to control, restrict, and ration chloroquine, hydroxychloroquine, and albuterol inhalers. Now therefore, in consultation and with concurrence of His Excellency, Governor Christopher T. Sununu, and pursuant to RSA 21-P:53, III, it is hereby ordered, effective immediately, that: 1. Chloroquine, hydroxychloroquine, and albuterol inhalers shall be subject



to the following controls, restrictions, and rationing: a) Outpatient prescriptions for patients not already established on chloroquine and hydroxychloroquine shall be limited to a 30-day supply. b) No prescriptions of chloroquine or hydroxychloroquine shall be issued or dispensed as prophylaxis treatment for COVID-19. c) Prescribing providers, when issuing a prescription in any form for chloroquine or hydroxychloroquine, must document an indication for all patients, including patients already established on these medications. d) For albuterol inhalers, prescribing providers shall limit prescriptions to one inhaler with up to three refills for all new prescriptions to treat respiratory symptoms of COVID-19. e) For all prescriptions of albuterol inhalers, pharmacists shall conduct a prospective drug utilization review to ensure adherence to asthma controller or maintenance medications, and counsel patients that are non-compliant and over-utilizing rescue inhalers. 2. This Order shall remain in effect until the State of Emergency declared by the Governor is terminated, or this Order is rescinded, whichever shall happen first. Signed by DHHS Commissioner Lori A. Shibinette on April 3, 2020. Pending receipt of PDF copy of signed order, text of approved order provided by NH Board of Pharmacy

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<https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency>

MARCH 23, 2020

Albany, NY

No. 202.10: Continuing Temporary Suspension and Modification of Laws Relating to the Disaster Emergency

### **Continuing Temporary Suspension and Modification of Laws Relating to the Disaster Emergency**

**WHEREAS**, on March 7, 2020, I issued Executive Order Number 202, declaring a State disaster emergency for the entire State of New York;

**WHEREAS**, both travel-related cases and community contact transmission of COVID-19 have been documented in New York State and are expected to be continue;

**WHEREAS**, ensuring the State of New York has adequate bed capacity, supplies, and providers to treat patients affected with COVID-19, as well as patients afflicted with other maladies, is of critical importance; and

**WHEREAS**, eliminating any obstacle to the provision of supplies and medical treatment is necessary to ensure the New York healthcare system has adequate capacity to provide care to all who need it;

**NOW, THEREFORE**, I, Andrew M. Cuomo, Governor of the State of New York, by virtue of the authority vested in me by Section 29-a of Article 2-B of the Executive Law to temporarily suspend or modify any statute, local law, ordinance, order, rule, or regulation, or parts thereof, of any agency during a State disaster emergency, if compliance with such statute, local law, ordinance, order, rule, or regulation would prevent, hinder, or delay action necessary to cope with the disaster emergency or if necessary to assist or aid in coping with such disaster, I hereby temporarily suspend or modify, for the period from the date of this Executive Order through April 22, 2020 the following:

- Section 2803 of the Public Health Law, and Parts 400, 401, 405, 409, 710, 711 and 712 of Title 10 of the NYCRR, to the extent necessary to permit and require general hospitals to take all measures necessary to increase the number of beds available to patients, in accordance with the directives set forth in this Executive Order;
- Section 3001, 3005-a, 3008, and 3010 of the Public Health Law to the extent necessary to modify the definition of “emergency medical services” to include emergency, non-emergency and low acuity medical assistance; to eliminate any restrictions on an approved ambulance services or providers operating outside of the primary territory listed on such ambulance service’s operating certificate with prior approval by the Department of Health; to permit the Commissioner of Health to issue provisional emergency medical services provider certifications to qualified individuals with modified certification periods as approved; and to allow emergency medical services to transport patients to locations other than healthcare facilities with prior approval by Department of Health;
- Section 3002, 3002-a, 3003, and 3004-a of Public Health Law to the extent necessary to allow any emergency medical treatment protocol development or modification to occur solely with the approval of the Commissioner of Health;
- Sections 405.13 and 755.4 of Title 10 of the NYCRR to the extent necessary to permit an advanced practice registered nurse with a doctorate or master's degree specializing in the administration of anesthesia administering anesthesia in a general hospital or free-standing ambulatory surgery center without the supervision of a qualified physician in these health care settings;
- Paragraph 1 of Section 6542 of the Education Law and Subdivisions (a) and (b) of Section 94.2 of Title 10 of the NYCRR to the extent necessary to permit a physician assistant to provide medical services appropriate to their education, training and experience without oversight from a supervising physician without civil or criminal penalty related to a lack of oversight by a supervising physician;
- Paragraph 1 of Section 6549 of the Education Law and Subdivisions (a) and (b) of Section 94.2 of Title 10 of the NYCRR to the extent necessary to permit a specialist assistant to provide medical services appropriate to their education, training and experience without oversight from a

supervising physician without civil or criminal penalty related to a lack of oversight by a supervising physician;

- Subdivision (3) of Section 6902 of Education Law, and any associated regulations, including, but not limited to, Section 64.5 of Title 10 of the NYCRR, to the extent necessary to permit a nurse practitioner to provide medical services appropriate to their education, training and experience, without a written practice agreement, or collaborative relationship with a physician, without civil or criminal penalty related to a lack of written practice agreement, or collaborative relationship, with a physician;|
- Subdivision (15) of section 3001, and Sections 800.3, 800.15 and 800.16 of Title 10 of the NYCRR with approval of the department, to the extent necessary to define “medical control” to include emergency and non-emergency direction to all emergency medical services personnel by a regional or state medical control center and to permit emergency medical services personnel to operate under the advice and direction of a nurse practitioner, physician assistant, or paramedic, provided that such medical professional is providing care under the supervision of a physician and pursuant to a plan approved by the Department of Health;
- Subdivision (2) of section 6527, Section 6545, and Subdivision (1) of Section 6909 of the Education Law, to the extent necessary to provide that all physicians, physician assistants, specialist assistants, nurse practitioners, licensed registered professional nurses and licensed practical nurses shall be immune from civil liability for any injury or death alleged to have been sustained directly as a result of an act or omission by such medical professional in the course of providing medical services in support of the State’s response to the COVID-19 outbreak, unless it is established that such injury or death was caused by the gross negligence of such medical professional;
- Any healthcare facility is authorized to allow students, in programs to become licensed in New York State to practice as a healthcare professional, to volunteer at the healthcare facility for educational credit as if the student had secured a placement under a clinical affiliation agreement, without entering into any such clinical affiliation agreement;
- Notwithstanding any law or regulation to the contrary, health care providers are relieved of recordkeeping requirements to the extent necessary for health care providers to perform tasks as may be necessary to respond to the COVID-19 outbreak, including, but not limited to, requirements to maintain medical records that accurately reflect the evaluation and treatment of patients, or requirements to assign diagnostic codes or to create or maintain other records for billing purposes. Any person acting reasonably and in good faith under this provision shall be afforded absolute immunity from liability for any failure to comply with any recordkeeping requirement. In order to protect from liability any person acting reasonably and in good faith under this provision, requirements to maintain medical records under Subdivision 32 of Section 6530 of the Education Law, Paragraph (3) of Subdivision (a) of Section 29.2 of Title

8 of the NYCRR, and Sections 58-1.11, 405.10, and 415.22 of Title 10 of the NYCRR, or any other such laws or regulations are suspended or modified to the extent necessary for health care providers to perform tasks as may be necessary to respond to the COVID-19 outbreak;

- Section 405.45 of Title 10 of the NYCRR to the extent necessary to permit the Commissioner of Health to designate a health care facility as a trauma center, or extend or modify the period for which a health care facility may be designated as a trauma center, or modify the review team for assessment of trauma center;
- Sections 800.3, 800.8, 800.9, 800.10, 800.12, 800.17, 800.18, 800.23, 800.24, and 800.26 of Title 10 of the NYCRR to the extent necessary to extend all existing emergency medical services provider certifications for one year; to permit the Commissioner of Health to modify the examination or recertification requirements for emergency medical services provider certifications; to suspend or modify, at the discretion of the Commissioner of Health, any requirements for the recertification of previously certified emergency medical services providers; and, at the discretion of the Commissioner of Health, develop a process determined by the Department of Health, to permit any emergency medical services provider certified or licensed by another State to provide emergency medical services within New York state; at the discretion of the Commissioner of Health, to suspend or modify equipment or vehicle requirements in order to ensure sustainability of EMS operations;
- Paragraph (6) of subdivision (b) of part 405.4 of Title 10 of the NYCRR to the extent necessary to remove limits on working hours for physicians and postgraduate trainees;
- Subparagraph (ii) of paragraph (2) of subdivision (g) of 10 N.Y.C.R.R. section 405.4, to the extent necessary to allow graduates of foreign medical schools having at least one year of graduate medical education to provide patient care in hospitals, is modified so as to allow such graduates without licenses to provide patient care in hospitals if they have completed at least one year of graduate medical education;
- Subdivision (e) of section 405.2 of Title 10 of the NYCRR, to the extent necessary to permit general hospitals affected by the disaster emergency to maintain adequate staffing;
- Subdivision (b) of section 405.3 of Title 10 of the NYCRR, to the extent necessary to allow general hospitals to use qualified volunteers or personnel affiliated with different general hospitals, subject to the terms and conditions established by the Commissioner of Health;
- Section 3507 of the Public Health Law and Part 89 of Title 10 of the NYCRR to the extent necessary to permit radiologic technologists licensed and in current good standing in New York State but not registered in New York State to practice in New York State without civil or criminal

penalty related to lack of registration;

- Sections 3502 and 3505 of the Public Health Law and Part 89 of Title 10 of the NYCRR to the extent necessary to permit radiologic technologists licensed and in current good standing in any state in the United State to practice in New York State without civil or criminal penalty related to lack of licensure;
- Sections 8502, 8504, 8504-a, 8505, and 8507 of the Education Law and Subpart 79-4 of Title 8 of the NYCRR, to the extent necessary to allow respiratory therapists licensed and in current good standing in any state in the United States to practice in New York State without civil or criminal penalty related to lack of licensure;
- Section 6502 of the Education Law and 8 NYCRR 59.8, to the extent necessary to allow physician’s assistants licensed and in current good standing in New York State but not registered in New York State to practice in New York State without civil or criminal penalty related to lack of registration;
- Section 6502 of the Education Law and 8 NYCRR 59.8, to the extent necessary to allow registered professional nurses, licensed practical nurses and nurse practitioners licensed and in current good standing in New York State but not registered in New York State to practice in New York State without civil or criminal penalty related to lack of registration;
- Subdivision (2-b) of Section 4002 of the Public Health Law to the extent necessary to allow a hospice residence to designate any number of beds within such facility as dually certified inpatient beds;
- Title V of Article 5 of the Public Health Law and subparts 19 and 58 of Title 10 of the NYCRR, to the extent necessary to allow laboratories holding a Clinical Laboratory Improvement Acts (CLIA) certificate and meeting the CLIA quality standards described in 42 CFR Subparts H, J, K and M, to perform testing for the detection of SARS-CoV-2 in specimens collected from individuals suspected of suffering from a COVID-19 infection;
- Article 139 of the Education Law, Section 576-b of the Public Health Law and Section 58-1.7 of Title 10 of the NYCRR, to the extent necessary to permit registered nurses to order the collection of throat or nasopharyngeal swab specimens from individuals suspected of being infected by COVID-19, for purposes of testing; and
- Subdivision (1) of Section 6801 of the Education Law, Section 6832 of the Education Law and Section 29.7(a)(21)(ii)(b)(4) of Title 8 of the NYCRR, to the extent necessary to permit a certified or registered pharmacy technician, under the direct personal supervision of a licensed

pharmacist, to assist such licensed pharmacist, as directed, in compounding, preparing, labeling, or dispensing of drugs used to fill valid prescriptions or medication orders for a home infusion provider licensed as a pharmacy in New York, compliant with the United States Pharmacopeia General Chapter 797 standards for Pharmaceutical Compounding – sterile preparations, and providing home infusion services through a home care agency licensed under Article 36 of the Public Health Law.

**IN ADDITION**, by virtue of the authority vested in me by Section 29-a of Article 2-B of the Executive Law to issue any directive during a disaster emergency necessary to cope with the disaster, I hereby issue the following directives for the period from the date of this Executive Order through April 22, 2020:

- Any healthcare facility is authorized to allow students, in programs to become licensed in New York State to practice a healthcare professional, to volunteer at the healthcare facility for educational credit as if the student had secured a placement under a clinical affiliation agreement, without entering into any such clinical affiliation agreement;
- The Commissioner of Health is authorized to direct, and shall so direct, all general hospitals, ambulatory surgery centers, office-based surgery practices and diagnostic and treatment centers to increase the number of beds available to patients, including by canceling all elective surgeries and procedures, as the Commissioner of Health shall define. General hospitals shall comply with such order by submitting COVID-19 Plans to the New York State Department of Health (NYSDOH), on a schedule to be determined by NYSDOH, to accomplish this purpose;
- The Commissioner of Health is authorized to suspend or revoke the operating certificate of any general hospital should they be unable to meet the requirements of the necessary capacity directives; and notwithstanding any law to the contrary the Commissioner may appoint a receiver to continue the operations on 24 hours' notice to the current operator, in order to preserve the life, health and safety of the people of the State of New York.
- No pharmacist shall dispense hydroxychloroquine or chloroquine except when written as prescribed for an FDA-approved indication; or as part of a state approved clinical trial related to COVID-19 for a patient who has tested positive for COVID-19, with such test result documented as part of the prescription. No other experimental or prophylactic use shall be permitted, and any permitted prescription is limited to one fourteen day prescription with no refills.
- Any licensed health insurance company shall deliver to the Superintendent, no later than March 24, 2020 a list of all persons who have a professional licensure or degree, whether physician's assistant, medical doctor, licensed registered nurse, licensed nurse practitioner or licensed practical nurse, and whether or not the person has a currently valid, or recently (within past five years) expired license in the state of New York. The Department of Financial Services shall poll such individuals to determine whether or not such professionals would serve in the COVID-19

response effort.

- Non-essential gatherings of individuals of any size for any reason (e.g. parties, celebrations or other social events) are canceled or postponed at this time.

G I V E N under my hand and the Privy Seal of the State in the City of Albany this twenty-third day of March in the year two thousand twenty.

BY THE GOVERNOR

Secretary to the Governor

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<https://secure.sos.state.or.us/oard/viewReceiptPDF.action?filingRsn=44884>

TEMPORARY ADMINISTRATIVE ORDER INCLUDING STATEMENT OF NEED & JUSTIFICATION BP 7-2020  
CHAPTER 855 BOARD OF PHARMACY

FILING CAPTION: Prohibits dispensing of certain drugs for COVID19 prevention and treatment EFFECTIVE DATE: 06/15/2020 THROUGH 09/20/2020 AGENCY APPROVED DATE: 06/15/2020 CONTACT: Rachel Melvin 971-673-0001 [pharmacy.rulemaking@oregon.gov](mailto:pharmacy.rulemaking@oregon.gov)

800 NE Oregon St., Suite 150 Portland,OR 97232 Filed By: Rachel Melvin Rules Coordinator

NEED FOR THE RULE(S): On 6/15/2020, the FDA revoked the emergency use authorization (EUA) that allowed for chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalized patients with COVID-19 when a clinical trial was unavailable, or participation in a clinical trial was not feasible. The agency determined that the legal criteria for issuing an EUA are no longer met. Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious side effects, the known and potential benefits of chloroquine and hydroxychloroquine no longer outweigh the known and potential risks for the authorized use. Furthermore, hydroxychloroquine continues to remain on the FDA's drug shortage list.

JUSTIFICATION OF TEMPORARY FILING: New clinical evidence has determined that there are potential serious patient health risks associated with the inappropriate use of these drugs. DOCUMENTS RELIED UPON, AND WHERE THEY ARE AVAILABLE: FDA News Release - <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fdarevokes-emergency-use-authorization-chloroquine-and> ADOPT: 855-007-0085 SUSPEND: Temporary 855-007-0085 from BP 3-2020 RULE TITLE: Prescriptions for Chloroquine and Hydroxychloroquine during COVID-19 Public Health Emergency RULE SUMMARY: Related to dispensing chloroquine/hydroxychloroquine prescriptions during COVID-19 public health emergency. RULE TEXT: Prescription orders for chloroquine or hydroxychloroquine for the

prevention or treatment of COVID-19 infection may only be dispensed if written for a patient enrolled in a clinical trial by an authorized investigator. STATUTORY/OTHER AUTHORITY: ORS 689.205  
STATUTES/OTHER IMPLEMENTED:

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1232869/>

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Chloroquine is a potent inhibitor of SARS coronavirus infection and spread

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Background

Severe acute respiratory syndrome (SARS) is an emerging disease that was first reported in Guangdong Province, China, in late 2002. The disease rapidly spread to at least 30 countries within months of its first appearance, and concerted worldwide efforts led to the identification of the etiological agent as SARS coronavirus (SARS-CoV), a novel member of the family *Coronaviridae* [1]. Complete genome sequencing of SARS-CoV [2,3] confirmed that this pathogen is not closely related to any of the previously established coronavirus groups. Budding of the SARS-CoV occurs in the Golgi apparatus [4] and results in the incorporation of the envelope spike glycoprotein into the virion. The spike glycoprotein is a type I membrane protein that facilitates viral attachment to the cellular receptor and initiation of infection, and angiotensin-converting enzyme-2 (ACE2) has been identified as a functional cellular receptor of SARS-CoV [5]. We have recently shown that the processing of the spike protein was effected by furin-like convertases and that inhibition of this cleavage by a specific inhibitor abrogated cytopathicity and significantly reduced the virus titer of SARS-CoV [6].

Due to the severity of SARS-CoV infection, the potential for rapid spread of the disease, and the absence of proven effective and safe *in vivo* inhibitors of the virus, it is important to identify drugs that can effectively be used to treat or prevent potential SARS-CoV infections. Many novel therapeutic approaches have been evaluated in laboratory studies of SARS-CoV: notable among these approaches are those using siRNA [7], passive antibody transfer [8], DNA vaccination [9], vaccinia or parainfluenza virus expressing the spike protein [10,11], interferons [12,13], and monoclonal antibody to the S1-subunit of the spike glycoprotein that blocks receptor binding [14]. In this report, we describe the identification of chloroquine as an effective pre- and post-infection antiviral agent for SARS-CoV. Chloroquine, a 9-aminoquinoline that was identified in 1934, is a weak base that increases the pH of acidic vesicles. When added extracellularly, the non-protonated portion of chloroquine enters the cell, where it becomes protonated and concentrated in acidic, low-pH organelles, such as endosomes, Golgi vesicles, and lysosomes. Chloroquine can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes endosomes for entry. Chloroquine has been



widely used to treat human diseases, such as malaria, amoebiasis, HIV, and autoimmune diseases, without significant detrimental side effects [15]. Together with data presented here, showing virus inhibition in cell culture by chloroquine doses compatible with patient treatment, these features suggest that further evaluation of chloroquine in animal models of SARS-CoV infection would be warranted as we progress toward finding effective antivirals for prevention or treatment of the disease.

#### Preinfection chloroquine treatment renders Vero E6 cells refractory to SARS-CoV infection

In order to investigate if chloroquine might prevent SARS-CoV infection, permissive Vero E6 cells [1] were pretreated with various concentrations of chloroquine (0.1–10  $\mu\text{M}$ ) for 20–24 h prior to virus infection. Cells were then infected with SARS-CoV, and virus antigens were visualized by indirect immunofluorescence as described in Materials and Methods. Microscopic examination (Fig. (Fig.1A)1A) of the control cells (untreated, infected) revealed extensive SARS-CoV-specific immunostaining of the monolayer. A dose-dependant decrease in virus antigen-positive cells was observed starting at 0.1  $\mu\text{M}$  chloroquine, and concentrations of 10  $\mu\text{M}$  completely abolished SARS-CoV infection. For quantitative purposes, we counted the number of cells stained positive from three random locations on a slide. The average number of positively stained control cells was scored as 100% and was compared with the number of positive cells observed under various chloroquine concentrations (Fig. (Fig.1B).1B). Pretreatment with 0.1, 1, and 10  $\mu\text{M}$  chloroquine reduced infectivity by 28%, 53%, and 100%, respectively. Reproducible results were obtained from three independent experiments. These data demonstrated that pretreatment of Vero E6 cells with chloroquine rendered these cells refractory to SARS-CoV infection.

#### Postinfection chloroquine treatment is effective in preventing the spread of SARS-CoV infection

In order to investigate the antiviral properties of chloroquine on SARS-CoV after the initiation of infection, Vero E6 cells were infected with the virus and fresh medium supplemented with various concentrations of chloroquine was added immediately after virus adsorption. Infected cells were incubated for an additional 16–18 h, after which the presence of virus antigens was analyzed by indirect immunofluorescence analysis. When chloroquine was added after the initiation of infection, there was a dramatic dose-dependant decrease in the number of virus antigen-positive cells (Fig. (Fig.2A).2A). As little as 0.1–1  $\mu\text{M}$  chloroquine reduced the infection by 50% and up to 90–94% inhibition was observed with 33–100  $\mu\text{M}$  concentrations (Fig. (Fig.2B).2B). At concentrations of chloroquine in excess of 1  $\mu\text{M}$ , only a small number of individual cells were initially infected, and the spread of the infection to adjacent cells was all but eliminated. A half-maximal inhibitory effect was estimated to occur at  $4.4 \pm 1.0 \mu\text{M}$  chloroquine (Fig. (Fig.2C).2C). These data clearly show that addition of chloroquine can effectively reduce the establishment of infection and spread of SARS-CoV if the drug is added immediately following virus adsorption.

Electron microscopic analysis indicated the appearance of significant amounts of extracellular virus particles 5–6 h after infection [16]. Since we observed antiviral effects by chloroquine immediately after virus adsorption, we further extended the analysis by adding chloroquine 3 and 5 h after virus adsorption and examined for the presence of virus antigens after 20 h. We found that chloroquine was still significantly effective even when added 5 h after infection (Fig. (Fig.3);3); however, to obtain equivalent antiviral effect, a higher concentration of chloroquine was required if the drug was added 3 or 5 h after adsorption.

## Ammonium chloride inhibits SARS-CoV infection of Vero E6 cells

Since chloroquine inhibited SARS-CoV infection when added before or after infection, we hypothesized that another common lysosomotropic agent,  $\text{NH}_4\text{Cl}$ , might also function in a similar manner. Ammonium chloride has been widely used in studies addressing endosome-mediated virus entry. Coincidentally,  $\text{NH}_4\text{Cl}$  was recently shown to reduce the transduction of pseudotype viruses decorated with SARS-CoV spike protein [17,18]. In an attempt to examine if  $\text{NH}_4\text{Cl}$  functions similarly to chloroquine, we performed infection analyses in Vero E6 cells before (Fig. (Fig.4A)4A) and after (Fig. (Fig.4B)4B) they were treated with various concentrations of  $\text{NH}_4\text{Cl}$ . In both cases, we observed a 93–99% inhibition with  $\text{NH}_4\text{Cl}$  at  $\geq 5$  mM. These data indicated that  $\text{NH}_4\text{Cl}$  ( $\geq 5$  mM) and chloroquine ( $\geq 10$   $\mu\text{M}$ ) are very effective in reducing SARS-CoV infection. These results suggest that effects of chloroquine and  $\text{NH}_4\text{Cl}$  in controlling SARS CoV infection and spread might be mediated by similar mechanism(s).

## Effect of chloroquine and $\text{NH}_4\text{Cl}$ on cell surface expression of ACE2

We performed additional experiments to elucidate the mechanism of SARS-CoV inhibition by chloroquine and  $\text{NH}_4\text{Cl}$ . Since intra-vesicular acidic pH regulates cellular functions, including N-glycosylation trimming, cellular trafficking, and various enzymatic activities, it was of interest to characterize the effect of both drugs on the processing, glycosylation, and cellular sorting of SARS-CoV spike glycoprotein and its receptor, ACE2. Flow cytometry analysis was performed on Vero E6 cells that were either untreated or treated with highly effective anti-SARS-CoV concentrations of chloroquine or  $\text{NH}_4\text{Cl}$ . The results revealed that neither drug caused a significant change in the levels of cell-surface ACE2, indicating that the observed inhibitory effects on SARS-CoV infection are not due to the lack of available cell-surface ACE2 (Fig. (Fig.5A).5A). We next analyzed the molecular forms of endogenous ACE2 in untreated Vero E6 cells and in cells that were pre-incubated for 1 h with various concentrations of either  $\text{NH}_4\text{Cl}$  (2.5–10 mM) or chloroquine (1 and 10  $\mu\text{M}$ ) and labeled with  $^{35}\text{S}$ -(Met) for 3 h in the presence or absence of the drugs (Fig. (Fig.5B5B and and5C).5C). Under normal conditions, we observed two immunoreactive ACE2 forms, migrating at  $\sim 105$  and  $\sim 113$  kDa, respectively (Fig. (Fig.5B,5B, lane 1). The  $\sim 105$ -kDa protein is endoglycosidase H sensitive, suggesting that it represents the endoplasmic reticulum (ER) localized form, whereas the  $\sim 113$ -kDa protein is endoglycosidase H resistant and represents the Golgi-modified form of ACE2 [19]. The specificity of the antibody was confirmed by displacing the immunoreactive protein bands with excess cold-soluble human recombinant ACE2 (+ rhACE2; Fig. Fig.5B,5B, lane 2). When we analyzed ACE2 forms in the presence of  $\text{NH}_4\text{Cl}$ , a clear stepwise increase in the migration of the  $\sim 113$ -kDa protein was observed with increasing concentrations of  $\text{NH}_4\text{Cl}$ , with a maximal effect observed at 10 mM  $\text{NH}_4\text{Cl}$ , resulting in only the ER form of ACE2 being visible on the gel (Fig. (Fig.5B,5B, compare lanes 3–5). This suggested that the trimming and/or terminal modifications of the N-glycosylated chains of ACE2 were affected by  $\text{NH}_4\text{Cl}$  treatment. In addition, at 10 mM  $\text{NH}_4\text{Cl}$ , the ER form of ACE2 migrated with slightly faster mobility, indicating that  $\text{NH}_4\text{Cl}$  at that concentration might also affect core glycosylation. We also examined the terminal glycosylation status of ACE2 when the cells were treated with chloroquine (Fig. (Fig.5C).5C). Similar to  $\text{NH}_4\text{Cl}$ , a stepwise increase in the electrophoretic mobility of ACE2 was observed with increasing concentrations of chloroquine. At 25  $\mu\text{M}$  chloroquine, the faster electrophoretic mobility of the Golgi-modified form of ACE2 was clearly evident. On the basis of the flow cytometry and immunoprecipitation analyses, it can be inferred that  $\text{NH}_4\text{Cl}$  and chloroquine both impaired the terminal glycosylation of ACE2, while  $\text{NH}_4\text{Cl}$  resulted in a more dramatic effect. Although ACE2 is expressed in similar quantities at the cell surface,

the variations in its glycosylation status might render the ACE2-SARS-CoV interaction less efficient and inhibit virus entry when the cells are treated with NH<sub>4</sub>Cl and chloroquine.

To confirm that ACE2 undergoes terminal sugar modifications and that the terminal glycosylation is affected by NH<sub>4</sub>Cl or chloroquine treatment, we performed immunoprecipitation of <sup>35</sup>S-labeled ACE2 and subjected the immunoprecipitates to neuraminidase digestion. Proteins were resolved using SDS-PAGE (Fig. (Fig5D).5D). It is evident from the slightly faster mobility of the Golgi form of ACE2 after neuraminidase treatment (Fig. (Fig5D,5D, compare lanes 1 and 2), that ACE2 undergoes terminal glycosylation; however, the ER form of ACE2 was not affected by neuraminidase. Cells treated with 10 μM chloroquine did not result in a significant shift; whereas 25 μM chloroquine caused the Golgi form of ACE2 to resolve similar to the neuraminidase-treated ACE2 (Fig. (Fig5D,5D, compare lanes 5 and 6). These data provide evidence that ACE2 undergoes terminal glycosylation and that chloroquine at anti-SARS-CoV concentrations abrogates the process.

#### Effect of chloroquine and NH<sub>4</sub>Cl on the biosynthesis and processing of SARS-CoV spike protein

We next addressed whether the lysosomotropic drugs (NH<sub>4</sub>Cl and chloroquine) affect the biosynthesis, glycosylation, and/or trafficking of the SARS-CoV spike glycoprotein. For this purpose, Vero E6 cells were infected with SARS-CoV for 18 h. Chloroquine or ammonium chloride was added to these cells during while they were being starved (1 h), labeled (30 min) or chased (3 h). The cell lysates were analyzed by immunoprecipitation with the SARS-specific polyclonal antibody (HMAF). The 30-min pulse results indicated that pro-spike (proS) was synthesized as a ~190-kDa precursor (proS-ER) and processed into ~125-, ~105-, and ~80-kDa proteins (Fig. (Fig.6A,6A, lane 2), a result identical to that in our previous analysis [6]. Except for the 100 μM chloroquine (Fig. (Fig.6A,6A, lane 3), there was no significant difference in the biosynthesis or processing of the virus spike protein in untreated or chloroquine-treated cells (Fig. (Fig.6A,6A, lanes 4–6). It should be noted that chloroquine at 100 μM resulted in an overall decrease in biosynthesis and in the levels of processed virus glycoprotein. In view of the lack of reduction in the biosynthesis and processing of the spike glycoprotein in the presence of chloroquine concentrations (10 and 50 μM) that caused large reductions in SARS-CoV replication and spread, we conclude that the antiviral effect is probably not due to alteration of virus glycoprotein biosynthesis and processing. Similar analyses were performed with NH<sub>4</sub>Cl, and the data suggested that the biosynthesis and processing of the spike protein were also not negatively affected by NH<sub>4</sub>Cl (Fig. (Fig.6A,6A, lanes 7–12). Consistent with our previous analysis [6], we observed the presence of a larger protein, which is referred to here as oligomers. Recently, Song et al. [20] provided evidence that these are homotrimers of the SARS-CoV spike protein and were incorporated into the virions. Interestingly, the levels of the homotrimers in cells treated with 100 μM chloroquine and 40 and 20 mM NH<sub>4</sub>Cl (Fig. (Fig.6A,6A, lanes 3, 9, and 10) were slightly lower than in control cells or cells treated with lower drug concentrations.

The data obtained from a 30-min pulse followed by a 3-h chase (Fig. (Fig.6B,6B, lanes 2 and 8) confirmed our earlier observation that the SARS-CoV spike protein precursor (proS-ER) acquires Golgi-specific modifications (proS-Golgi) resulting in a ~210-kDa protein [6]. Chloroquine at 10, 25, and 50 μM had no substantial negative impact on the appearance of the Golgi form (Fig. (Fig.6B,6B, compare lane 2 to lanes 4–6). Only at 100 μM chloroquine was a reduction in the level of the Golgi-modified pro-spike observed (lane 3). On the other hand, NH<sub>4</sub>Cl abrogated the appearance of Golgi-modified forms at ≥10 mM (compare lane 8 with 9–11) and had a milder effect at 1 mM (lane 12). These data clearly demonstrate that the biosynthesis and proteolytic processing of SARS-CoV spike protein are not affected

at chloroquine (25 and 50  $\mu$ M) and  $\text{NH}_4\text{Cl}$  (1 mM) doses that cause virus inhibitory effects. In addition, with 40, 20, and 10 mM  $\text{NH}_4\text{Cl}$ , there was an increased accumulation of proS-ER with a concomitant decrease in the amount of oligomers (Fig. [Fig.6B,6B](#), lanes 9–11). When we examined the homotrimers, we found that chloroquine at 100  $\mu$ M and  $\text{NH}_4\text{Cl}$  at 40 and 20 mM resulted in slightly faster mobility of the trimers (Fig. [Fig.6B,6B](#), lanes 3, 9, and 10), but lower drug doses, which did exhibit significant antiviral effects, did not result in appreciable differences. These data suggest that the newly synthesized intracellular spike protein may not be a major target for chloroquine and  $\text{NH}_4\text{Cl}$  antiviral action. The faster mobility of the trimer at certain higher concentration of the drugs might be due the effect of these drugs on the terminal glycosylation of the trimers.

We have identified chloroquine as an effective antiviral agent for SARS-CoV in cell culture conditions, as evidenced by its inhibitory effect when the drug was added prior to infection or after the initiation and establishment of infection. The fact that chloroquine exerts an antiviral effect during pre- and post-infection conditions suggest that it is likely to have both prophylactic and therapeutic advantages. Recently, Keyaerts et al. [\[21\]](#) reported the antiviral properties of chloroquine and identified that the drug affects SARS-CoV replication in cell culture, as evidenced by quantitative RT-PCR. Taken together with the findings of Keyaerts et al. [\[21\]](#), our analysis provides further evidence that chloroquine is effective against SARS-CoV Frankfurt and Urbani strains. We have provided evidence that chloroquine is effective in preventing SARS-CoV infection in cell culture if the drug is added to the cells 24 h prior to infection. In addition, chloroquine was significantly effective even when the drug was added 3–5 h after infection, suggesting an antiviral effect even after the establishment of infection. Since similar results were obtained by  $\text{NH}_4\text{Cl}$  treatment of Vero E6 cells, the underlying mechanism(s) of action of these drugs might be similar.

Apart from the probable role of chloroquine on SARS-CoV replication, the mechanisms of action of chloroquine on SARS-CoV are not fully understood. Previous studies have suggested the elevation of pH as a mechanism by which chloroquine reduces the transduction of SARS-CoV pseudotype viruses [\[17,18\]](#). We examined the effect of chloroquine and  $\text{NH}_4\text{Cl}$  on the SARS-CoV spike proteins and on its receptor, ACE2. Immunoprecipitation results of ACE2 clearly demonstrated that effective anti-SARS-CoV concentrations of chloroquine and  $\text{NH}_4\text{Cl}$  also impaired the terminal glycosylation of ACE2. However, the flow cytometry data demonstrated that there are no significant differences in the cell surface expression of ACE2 in cells treated with chloroquine or  $\text{NH}_4\text{Cl}$ . On the basis of these results, it is reasonable to suggest that the pre-treatment with  $\text{NH}_4\text{Cl}$  or chloroquine has possibly resulted in the surface expression of the under-glycosylated ACE2. In the case of chloroquine treatment prior to infection, the impairment of terminal glycosylation of ACE2 may result in reduced binding affinities between ACE2 and SARS-CoV spike protein and negatively influence the initiation of SARS-CoV infection. Since the biosynthesis, processing, Golgi modification, and oligomerization of the newly synthesized spike protein were not appreciably affected by anti-SARS-CoV concentrations of either chloroquine or  $\text{NH}_4\text{Cl}$ , we conclude that these events occur in the cell independent of the presence of the drugs. The potential contribution of these drugs in the elevation of endosomal pH and its impact on subsequent virus entry or exit could not be ruled out. A decrease in SARS-CoV pseudotype transduction in the presence of  $\text{NH}_4\text{Cl}$  was observed and was attributed to the effect on intracellular pH [\[17,18\]](#). When chloroquine or  $\text{NH}_4\text{Cl}$  are added after infection, these agents can rapidly raise the pH and subvert on-going fusion events between virus and endosomes, thus inhibiting the infection.

In addition, the mechanism of action of  $\text{NH}_4\text{Cl}$  and chloroquine might depend on when they were added to the cells. When added after the initiation of infection, these drugs might affect the endosome-mediated fusion, subsequent virus replication, or assembly and release. Previous studies of chloroquine have demonstrated that it has multiple effects on mammalian cells in addition to the elevation of endosomal pH, including the prevention of terminal glycosylation of immunoglobulins [22]. When added to virus-infected cells, chloroquine inhibited later stages in vesicular stomatitis virus maturation by inhibiting the glycoprotein expression at the cell surface [23], and it inhibited the production of infectious HIV-1 particles by interfering with terminal glycosylation of the glycoprotein [24,25]. On the basis of these properties, we suggest that the cell surface expression of under-glycosylated ACE2 and its poor affinity to SARS-CoV spike protein may be the primary mechanism by which infection is prevented by drug pretreatment of cells prior to infection. On the other hand, rapid elevation of endosomal pH and abrogation of virus-endosome fusion may be the primary mechanism by which virus infection is prevented under post-treatment conditions. More detailed SARS CoV spike-ACE2 binding assays in the presence or absence of chloroquine will be performed to confirm our findings. Our studies indicate that the impact of  $\text{NH}_4\text{Cl}$  and chloroquine on the ACE2 and spike protein profiles are significantly different.  $\text{NH}_4\text{Cl}$  exhibits a more pronounced effect than does chloroquine on terminal glycosylation, highlighting the novel intricate differences between chloroquine and ammonium chloride in affecting the protein transport or glycosylation of SARS-CoV spike protein and its receptor, ACE2, despite their well-established similar effects of endosomal pH elevation.

The infectivity of coronaviruses other than SARS-CoV are also affected by chloroquine, as exemplified by the human CoV-229E [15]. The inhibitory effects observed on SARS-CoV infectivity and cell spread occurred in the presence of 1–10  $\mu\text{M}$  chloroquine, which are plasma concentrations achievable during the prophylaxis and treatment of malaria (varying from 1.6–12.5  $\mu\text{M}$ ) [26] and hence are well tolerated by patients. It recently was speculated that chloroquine might be effective against SARS and the authors suggested that this compound might block the production of  $\text{TNF}\alpha$ , IL6, or  $\text{IFN}\gamma$  [15]. Our data provide evidence for the possibility of using the well-established drug chloroquine in the clinical management of SARS.

## Conclusion

Chloroquine, a relatively safe, effective and cheap drug used for treating many human diseases including malaria, amoebiasis and human immunodeficiency virus is effective in inhibiting the infection and spread of SARS CoV in cell culture. The fact that the drug has significant inhibitory antiviral effect when the susceptible cells were treated either prior to or after infection suggests a possible prophylactic and therapeutic use.

[Go to:](#)

## Methods

### SARS-CoV infection, immunofluorescence, and immunoprecipitation analyses

Vero E6 cells (an African green monkey kidney cell line) were infected with SARS-CoV (Urbani strain) at a multiplicity of infection of 0.5 for 1 h. The cells were washed with PBS and then incubated in OPTI-MEM (Invitrogen) medium with or without various concentrations of either chloroquine or  $\text{NH}_4\text{Cl}$  (both from

Sigma). Immunofluorescence staining was performed with SARS-CoV-specific hyperimmune mouse ascitic fluid (HMAF) [8] followed by anti-mouse fluorescein-coupled antibody.

Eighteen hours after infection, the virus-containing supernatants were removed, and the cells were pulsed with  $^{35}\text{S}$ -(Cys) for 30 min and chased for 3 h before lysis in RIPA buffer. Clarified cell lysates and media were incubated with HMAF, and immunoprecipitated proteins were separated by 3–8% NuPAGE gel (Invitrogen); proteins were visualized by autoradiography. In some experiments, cells were chased for 3 h with isotope-free medium. Clarified cell supernatants were also immunoprecipitated with SARS-CoV-specific HMAF.

#### ACE2 flow cytometry analysis and biosynthesis

Vero E6 cells were seeded in Dulbecco's modified Eagle medium (Invitrogen) supplemented with 10% fetal bovine serum. The next day, the cells were incubated in Opti-MEM (Invitrogen) in the presence or absence of 10  $\mu\text{M}$  chloroquine or 20 mM  $\text{NH}_4\text{Cl}$ . To analyze the levels of ACE2 at the cell surface, cells were incubated on ice with 10  $\mu\text{g}/\text{mL}$  affinity-purified goat anti-ACE2 antibody (R&D Systems) and then incubated with FITC-labeled swine anti-goat IgG antibody (Caltag Laboratories). Labeled cells were analyzed by flow cytometry with a FACSCalibur flow cytometer (BD Biosciences). For ACE2 biosynthesis studies, Vero E6 cells were pulsed with 250  $\mu\text{Ci}$   $^{35}\text{S}$ -(Met) (Perkin Elmer) for 3 h with the indicated concentrations of chloroquine or  $\text{NH}_4\text{Cl}$  and then lysed in RIPA buffer. Clarified lysates were immunoprecipitated with an affinity-purified goat anti-ACE2 antibody (R&D systems), and the immunoprecipitated proteins were separated by SDS-polyacrylamide gel electrophoresis.

The author(s) declare that they have no competing interests.

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[https://www.legifrance.gouv.fr/jo\\_pdf.do?id=JORFTEXT000041400024](https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000041400024)

Décrets, arrêtés, circulaires TEXTES GÉNÉRAUX MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ Arrêté du 13 janvier 2020 portant classement sur les listes des substances vénéneuses NOR : SSAP2001007A La ministre des solidarités et de la santé, Vu le code de la santé publique, notamment les articles L. 5132-1, L. 5132-6, L. 5132-7 et R. 5132-1 ; Vu l'arrêté du 22 février 1990 modifié portant inscription sur les listes I et II des substances vénéneuses définies à l'article L. 5132-6 du code de la santé publique ; Vu l'avis du directeur général de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail en date du 12 novembre 2019 ; Sur proposition du directeur général de l'Agence nationale de sécurité du médicament et des produits de santé en date du 13 décembre 2019, Arrête : Art. 1er. – Est classée sur la liste II des substances vénéneuses l'hydroxychloroquine sous toutes ses formes. Art. 2. – Le directeur général de la santé et le directeur général de l'Agence nationale de sécurité du médicament et des produits de santé sont chargés, chacun en ce qui le concerne, de l'exécution du présent arrêté, qui sera publié au Journal officiel de la République française. Fait le 13 janvier 2020. Pour la ministre et par délégation : Le directeur général de la santé, J. SALOMON

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<https://www.cnn.com/2020/05/27/politics/anthony-fauci-hydroxychloroquine-trump-cnntv/index.html>

## Fauci: Science shows hydroxychloroquine is not effective as a coronavirus treatment

By [Devan Cole](#), CNN

Updated 3:43 PM ET, Wed May 27, 2020

Dr. Anthony Fauci said Wednesday that data shows [hydroxychloroquine is not an effective treatment](#) for the coronavirus, disputing use of the drug to fight the deadly virus even as [President Donald Trump touts it as a potential cure](#) and says he has taken it himself.

"The scientific data is really quite evident now about the lack of efficacy for it," Fauci, a key medical adviser on the White House coronavirus task force, told CNN's Jim Sciutto on "Newsroom" of the drug, adding that there's likelihood of "adverse events with regard to cardiovascular."

Fauci, the nation's top infectious disease expert, is the first Trump administration official to say the drug is not effective in treating the virus based on scientific data. Medical experts and the US Food and Drug Administration, though, have questioned its efficacy and warned of potentially harmful side effects as the President has promoted the treatment.

France earlier Wednesday [moved to ban doctors in the country from prescribing](#) the drug to coronavirus patients. Asked by Sciutto if the US should similarly outlaw the drug for its patients, Fauci replied: "I'm not so sure it should be banned."

Trump has been a frequent cheerleader for a combination of the antimalarial hydroxychloroquine and the antibiotic azithromycin as a Covid-19 treatment. He promoted the drugs nearly 50 times, despite pleas from scientists to let studies decide if the treatment worked or not. Earlier this month, [the President said he was taking hydroxychloroquine](#) to prevent coronavirus infection, although there's no evidence it can do that.

The World Health Organization said on Monday it had temporarily halted the study of hydroxychloroquine as a potential Covid-19 treatment in its Solidarity Trial, due to safety concerns.

The WHO's decision was made after an observational study, published last week in the medical journal The Lancet, described how seriously ill Covid-19 patients who were treated with hydroxychloroquine and chloroquine were more likely to die or develop irregular heart rhythms.

Despite the warnings from health experts, [retail sales of the decades-old drug have soared in recent weeks](#) amid the growing public attention on the medication.

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[https://omnij.org/Gilead: Twenty-one billion reasons to discredit hydroxychloroquine \(ORIGINAL ARTICLE\)](https://omnij.org/Gilead: Twenty-one billion reasons to discredit hydroxychloroquine (ORIGINAL ARTICLE))

## Gilead: Twenty-one billion reasons to discredit hydroxychloroquine (ORIGINAL ARTICLE)

### Introduction

In the history of medicine, no single drug has been so singularly attacked by the media, World Health Organization, government officials and institutional health experts as hydroxychloroquine. Approved as a “safe and cost-effective” essential medicine by the WHO, CDC and regulatory authorities across Europe, hydroxychloroquine has been prescribed to millions of patients over the past 65 years. Despite decades of known safety, hydroxychloroquine was labelled “dangerous” and a “poisonous substance” after showing promise as a therapeutic for COVID-19.

Many attribute this negative publicity to anti-Trump sentiment from mainstream media outlets including CNN, MSNBC, Washington Post, New York Times and Huffington Post. This thesis does not entirely hold up to scrutiny though. President Trump named both hydroxychloroquine and Gilead’s remdesivir as a “game changer” in his breaking March 19th press conference.

*There are promising therapies produced by Gilead, and that’s remdesivir. Remdesivir. And that’s a drug used for other purposes that’s been out and has had very good results for other purposes, but it seems to have a very good result, having to do with this virus...So you have remdesivir and you have chloroquine and hydro- — hydroxychloroquine. So those are two that are out now, essentially approved for prescribed use. And I think it’s going to be very exciting. I think it could be a game changer...Very powerful. They’re very powerful.*

- President Donald J. Trump, March 19th, 2020. 11:31 AM EDT <sup>[1]</sup>

At the time of the press conference, there was only in vitro evidence of remdesivir’s effectiveness against SARS-CoV-2. No clinical trial existed showing remdesivir to be effective. <sup>[2]</sup> The preliminary results from the NIH clinical trial were not available until over a month later on April 29. <sup>[3]</sup> The evidence of its efficacy primarily stemmed from a few in vitro studies that included an article published in the Nature-owned journal *Cell Research*. Interestingly, the Nature publication demonstrated that both remdesivir and chloroquine were effective against SARS-CoV-2, stating “remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro.” <sup>[4]</sup> While there was only in vitro evidence of successes with remdesivir, there was both in vitro and clinical evidence of hydroxychloroquine’s efficacy. <sup>[5]</sup> Nevertheless, scientists, including Dr. Fauci, as well as the WHO and media outlets worldwide criticized Trump for providing false hope on the therapeutic effect of hydroxychloroquine while staying quiet about remdesivir.

The effort to undermine hydroxychloroquine appears to have begun months prior to Trump’s announcement. Chloroquine was first shown to have strong antiviral effects on SARS-CoV infection in primate cells back in the 2005 publication *Chloroquine is a potent inhibitor of SARS coronavirus infection*. <sup>[6]</sup> Pharmaceutical companies were likely aware that if hydroxychloroquine was shown to be effective against SARS-CoV-2 it would diminish the value of patented therapeutics or vaccines. Through



lobbying efforts, regulation may have been the first step to control the availability of hydroxychloroquine.

This may have been what occurred in France. Hydroxychloroquine was available without prescription in France for years. This came to an end on January 13, 2020, when hydroxychloroquine was classified “in all its forms” as a “list II poisonous substance.” <sup>[7]</sup> After decades of widespread use, hydroxychloroquine quickly became a restricted substance in France in the earliest days of the COVID-19 pandemic. Just several weeks later, Dr. Didier Raoult in the South of France would report his landmark clinical trial demonstrating hydroxychloroquine’s efficacy against COVID-19. <sup>[8]</sup>

Why was hydroxychloroquine—a drug safely used for over half a century—aggressively labeled dangerous while a medication that proved ineffective for hepatitis C with an unknown safety profile got a pass? Herein I outline the evidence showing hydroxychloroquine to be a direct threat to Gilead’s success as well as the massive sphere of influence Gilead has over government taskforces, the World Health Organization, medical journals, academic institutions and research scientists. These organizations provided ammunition for the media’s war on doctors prescribing hydroxychloroquine.

### **Remdesivir vs hydroxychloroquine**

Gilead’s stock rises and falls based on the successes and failures of both hydroxychloroquine and remdesivir. Immediately before Trump first announced hydroxychloroquine as a promising therapeutic for COVID-19, GILD traded at a local high of \$85 per share, a price unattained since early 2018. Hours after Trump’s press conference, GILD dropped 8.7%, and then continued to plummet to \$69 per share the following week—erasing \$21 billion from its market cap in mere days. Immediately after Dr. Fauci announced the success of remdesivir in the NIH trial, GILD stock surged back to \$85 per share. Compared to the largest pharmaceutical companies by revenue, Gilead has consistently outperformed in this pandemic with GILD gaining over 20% YTD while most of its competition struggled with losses or meager gains. This growth is almost certainly attributed to remdesivir’s promise as an effective treatment for COVID-19.

Gilead has a direct financial incentive for hydroxychloroquine to fail. Actually, based on its share price, Gilead has 21 billion reasons to discredit hydroxychloroquine. Perhaps no other company has more to gain in the immediate future from hydroxychloroquine’s failure than Gilead.

### **Medical journals**

Medical journals have increasingly become marketing machines for big pharma. This has been openly stated by editors of even the highest impact medical journals. Back in 2003, Richard Horton, editor-in-chief of *The Lancet* wrote, “The business climate for most modern medical journals, whether in the for-profit or non-profit sector, is strongly pro-pharmaceutical industry...In this environment, I know that it can be difficult for editors to raise questions about the ethics and marketing tactics of pharmaceutical companies...” <sup>[9]</sup> The following year Horton again bemoaned the influence of big pharma stating, “Journals have devolved into information laundering operations for the pharmaceutical industry.” <sup>[10]</sup> Similarly, Marcia Angell, former editor of the *New England Journal of Medicine*, excoriated the industry in her book *The Truth About the Drug Companies* saying, “Now primarily a marketing machine to sell drugs of dubious benefit, this industry uses its wealth and power to co-opt every institution that might stand in its way, including the U.S. Congress, the Food and Drug Administration,

academic medical centers, and the medical profession itself. (Most of its marketing efforts are focused on influencing doctors, since they must write the prescriptions.)" <sup>[10]</sup>

Although written in 2004, Marcia Angell's comments are especially prescient in the current setting of the promotion of remdesivir over hydroxychloroquine. In marketing alone, the situation has only worsened over the past two decades. According to researchers at Dartmouth College, the US pharmaceutical industry increased total spending on marketing from \$17.7 billion in 1997 to nearly \$30 billion in 2016. The strategy was successful with US spending on prescription drugs ballooning from \$117 billion to \$329 billion during this time. <sup>[11]</sup> Advertising and sponsorships are a substantial source of revenue for most medical journals comprising up to 80% of publishing revenue for some journals. <sup>[12]</sup> Likely less publicly vocal today than over a decade ago due to growing control of big pharma, editors still secretly complain about the influence of big pharma. Just recently, Philippe Douste-Blazy, former French Minister of Health and Under-Secretary-General of the United Nations, reported a leaked conversation from a conference where editors-in-chief of both *The Lancet* and *NEJM* bemoaned big pharma's control over publishing, "These meetings that are completely behind closed doors, only with experts. No one can record, no one is taking any pictures...but still, there was a meeting the other day of the directors of scientific journals like *The Lancet*, *The New England Journal of Medicine*...and it ended up leaked. The *Lancet's* boss, Horton, said 'Now we are not going to be able to, basically, if this continues publish any more clinical research data because the pharmaceutical companies are so financially powerful today and are able to use such methodologies, as to have us accept papers which are apparently methodologically perfect, but which, in reality, manage to conclude what they want to conclude.'" <sup>[13]</sup> The reality is that without advertising revenue, most medical journals would go bankrupt. The unfortunate downside is that the very survival of journals relies on keeping big pharma happy at the expense of scientific truths.

**The *Lancet* may have chosen satisfying Gilead over scientific truths when it published a fraudulent study showing that hydroxychloroquine increased mortality and lethal arrhythmias in COVID-19 patients.**

On May 22, 2020, *The Lancet* published a peer-reviewed, observational study comparing hydroxychloroquine to standard therapy in 96,032 hospitalized COVID-19 patients. <sup>[14]</sup> Almost immediately afterwards, the WHO suspended all clinical trials on hydroxychloroquine because of safety concerns. <sup>[15]</sup> Dr. Fauci also commented on the dangers of hydroxychloroquine, telling CNN's Jim Sciutto that it likely causes "adverse events with regard to cardiovascular." <sup>[16]</sup>

Independent researchers not beholden to big pharma quickly recognized the study to be predicated on a likely fraudulent dataset that included an impossible number of COVID-19 patients or deaths and an improbable number of partnerships with hospitals. Almost laughable if not for the gravity of the malfeasance, the dataset was provided by the unknown corporation Surgisphere with only five employees that included a science fiction writer and erotic model-for-hire posing as the Director of Sales. <sup>[17]</sup> Facing overwhelming evidence that the study was fraudulent, the authors retracted the study in less than two weeks from the date of publication. <sup>[18]</sup>

One could argue that the publication of this study was a mere oversight by *The Lancet*. That is, a study that slipped through the peer-review process. Let's speculate for a moment, however, on what the strategy would be to publish a fraudulent study discrediting hydroxychloroquine.

*Step 1.* Establish plausible deniability by relying on an external corporation to provide the dataset. **Surgisphere.**

*Step 2.* Delete any digital footprint that could jeopardize the integrity of the data source. **Surgisphere's website is not included in the Internet Archives.**

*Step 3.* Establish a track record of publications in high impact journals that would lend legitimacy to the Surgisphere dataset. **The authors had just enough time to publish in *NEJM* the study *Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19* using the Surgisphere dataset.** (This study was later retracted as well.) [\[19\]](#)

*Step 4.* Select a lead author with impeccable credentials. **Dr. Mandeep Mehra is a professor of medicine at Harvard Medical School, the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine and the medical director of the Brigham Heart and Vascular Center in Boston.** [\[20\]](#)

*Step 5.* Obfuscate the dataset as much as possible so that its integrity would be difficult to definitively invalidate. **Patient data in *The Lancet* study was categorized by continent such that even the countries supposedly participating in the dataset were hidden.**

*Step 6.* Publish the study in a prestigious medical journal with the comfort of knowing that it will immediately garner the support of the WHO, Dr. Fauci and influential scientists worldwide. ***The Lancet.***

**Despite all the above hypothetical steps, through the power of social media platforms such as Twitter, independent researchers were able to collaborate to quickly debunk the study.**

The motivation for the above actions is admittedly still unclear. The connection between Gilead and the study authors is tenuous. What is known is that both Dr. Mehra and Dr. Sapan Desai (founder of Surgisphere) have openly praised remdesivir in various interviews and tweets. Of note though, Dr. Mehra was one of just a few experts selected to speak at a Gilead sponsored COVID-19 conference live-streamed by thousands of experts worldwide in early April. [\[21\]](#) Without a formal investigation into this affair, it is likely the motivation—be it attention seeking or the meddling of big pharma—will never be fully revealed.

The authors and *Lancet* were not the only involved parties though. The WHO suspended worldwide clinical trials on hydroxychloroquine based on this study.

### **World Health Organization**

Gilead helps fund the WHO. Gilead Sciences provided 0.12% of the WHO's funding for the biennium of 2018-19—more than doubling its contribution from the prior biennium. [\[22\]](#) This may seem like an insignificant percentage, but it's important to note that China contributed just 0.21%, Italy 0.48% and Spain 0.06% of the WHO's funding. With the exception of Sanofi, Gilead gave more to the WHO than any other pharmaceutical company. With remdesivir approved as a standard therapy for COVID-19, I suspect Gilead will further increase its contributions to become the largest pharmaceutical donor in the 2020-2021 biennium. While Gilead may appear philanthropic, one must wonder how ethical it is for organizations making global recommendations on therapeutics to receive substantial funding from big pharma.

This conflict of interest is suspicious considering the WHO's dogged criticism of hydroxychloroquine while praising remdesivir. In late February 2020, WHO assistant director-general Bruce Aylward said: "There is only one drug right now that we think may have real efficacy and that's remdesivir." [23] This statement is peculiar because just two weeks prior on February 5, an article was published in *Cell Research* titled "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV)." [4] Despite only in vitro evidence of efficacy for both medications, remdesivir was touted as a potential therapeutic while hydroxychloroquine and chloroquine were completely disregarded. It was only after grassroots investigators James Todaro, MD and Gregory Rigano published an article on chloroquine/hydroxychloroquine as a treatment for COVID-19 that caught the attention Elon Musk and President Trump did the WHO begin clinical exploration of hydroxychloroquine. [24]

Through various actions and inactions, the WHO provided little support for clinical trials on hydroxychloroquine. The WHO did nothing to dispel the myth that hydroxychloroquine was dangerous throughout April and May. We now know that the WHO was collaborating with Oxford University researchers, who were giving patients doses of hydroxychloroquine exceeding four times that of treatment courses administered by Drs. Raoult and Zelenko. [25] Surely if hydroxychloroquine was dangerous, these high doses would not have been administered with the WHO's blessing. Nevertheless, the WHO remained quiet allowing the narrative of hydroxychloroquine's harmful effects to grow resulting in diminishing enrollment in clinical trials.

Inaction turned into action when the WHO aggressively suspended its clinical trials of hydroxychloroquine in May 2020, after *The Lancet* published its fraudulent observational study. This bombshell announcement was splashed across media headlines reaching millions of patients and healthcare providers alike and deterring not just enrollment in its own SOLIDARITY trial, but also clinical trials outside the purview of the WHO. The WHO made this decision without any independent assessment of the study's veracity. Soumya Swaminathan, chief scientist for the WHO, openly admitted the WHO's mistake by stating, "It is [very] difficult for us to check data quality of each published paper & we trust authors to adhere to basic [standards]. HCQ restarted today after data safety committee approval." [26] It's very surprising that an organization such as the WHO employing over 7000 people and receiving over \$2 billion annually to investigate potential therapeutics for COVID-19 issued guidance based on a study that unpaid independent researchers debunked just a few days later.

## **US Government**

The pharmaceuticals and health products spent \$295 million in lobbying efforts in the United States which places it in 1st place in money spent on lobbying. For comparison, the insurance industry and automotive industry only spent \$155 million and \$69 million in 2019, respectively. [27] In 2019, Gilead spent nearly \$6 million in political lobbying efforts. This number is on track to reach record highs in 2020 as Gilead has spent already nearly \$2.5 million on lobbying in just Q1 of 2020. [28] The money appears to be well spent. The exclusive NIH COVID-19 Treatment Guidelines Panel that informs US clinicians how to care for patients is occupied by 8-9 experts who have received financial support from Gilead. [29]

## **Academic medical centers and scientists**

To compile all of the thousands of scientists and research institutions who have received funding from Gilead would take weeks of effort. However, it is noteworthy that some of the most vehement critics of hydroxychloroquine have conflicts of interest with Gilead. Just for example, in the New York Times

feature *He Was a Science Star. Then He Promoted a Questionable Cure for Covid-19*, <sup>[30]</sup> all three scientists (Karine Lacombe, Christine Rouzioux, and Jean-Michel Molina) criticizing Dr. Raoult and his study are either on Gilead's advisory board and/or received funding from Gilead. <sup>[31]</sup> <sup>[32]</sup> <sup>[33]</sup> Notably, the New York Times article fails to mention these conflicts of interest.

Some other notable examples include **Stanford University School of Medicine** that conducted two clinical trials on remdesivir (one funded by the NIH and the other by Gilead); **University of Alabama at Birmingham** who received funding from the NIAID to develop remdesivir (of note, Dr. Richard Whitley, principal investigator of the \$37.5 million dollar NIAID grant, is on the board of directors for Gilead).

## Conclusion

Gilead's influence over the process of clinical investigation and approval of therapeutics is undeniable. A direct threat to remdesivir, hydroxychloroquine has likely been in Gilead's crosshairs for months.

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<https://www.thedenverchannel.com/news/national/these-are-the-50-most-dangerous-drugs-on-the-market>

### List: The 50 most dangerous drugs

By: Sabrina Perry

*Posted at 12:23 PM, Apr 11, 2016 and last updated 4:08 PM, Apr 11, 2016*

While [overdose deaths](#) from prescription opioids have nearly quadrupled since 1999, some of the most dangerous drugs don't require a prescription.

Using data from the [Food and Drug Administration](#) for 2004 through 2015, [HealthGrove](#) looked at the 150 drugs that are involved in the highest number of adverse reactions and ranked them by the percent of these reactions classified as serious. For many of these reactions, the FDA database uses medical terminology, such as pyrexia and dyspnoea for fever and labored breathing, respectively.

The top 50 drugs with the most serious adverse reactions are considered the most dangerous. Though most on the list require a prescription and treat serious diseases, those like [Advil](#) and [acetaminophen](#) don't.

It's important to note that these medicines may not be inherently dangerous, but improper dosage, combining medicines or taking them with substances like alcohol can dramatically increase risk.

One-third of Americans say they "combine medications when treating multiple symptoms," according to the [National Council on Patient Information](#), cited in a New York Times [report](#) on over-the-counter medicines. The same source also claims that only one in ten people read the labels entirely and one in five admits to using medication more than the label indicates. This creates an environment primed for unintended drug interactions and overdoses.

Additionally, people over 65 years old — those most likely to take multiple drugs for chronic health issues — account for approximately 40 percent of over-the-counter drug usage. This puts this group at greater risk for trouble with these drugs by way of adverse side effects and interactions.

Despite the potential for negative consequences of drug use and misuse, modern pharmaceuticals have greatly contributed to the health and longevity of people around the world. Though many are regarded as safe, as more drugs become available over the counter and [prescriptions of others rise](#), consumer awareness becomes increasingly important.

*Note: In the case of ties, the drug with the highest number of total reported reactions is ranked higher.*

#50. Losartan

**Percent of Reactions That Were Serious:** 70%

**Number of Serious Reactions:** 24,242

**Total Number of Reported Reactions:** 34,571

**Therapeutic Class:** Cardiovascular Agent

**Brand Names:** Cozaar

#49. Alprazolam

**Percent of Reactions That Were Serious:** 70%

**Number of Serious Reactions:** 51,950

**Total Number of Reported Reactions:** 73,606

**Therapeutic Class:** Antianxiety

**Brand Names:** Gabazolamine-0.5, Niravam, Xanax, Xanax Xr, Alti-Alprazolam

#48. Tramadol

**Percent of Reactions That Were Serious:** 71%

**Number of Serious Reactions:** 26,278

**Total Number of Reported Reactions:** 36,867

**Therapeutic Class:** Analgesic

**Brand Names:** Conzip, Fusepaq Synapryn, Rybix Odt, Ryzolt, Ultram, Ultram Er

#47. Venlafaxine

**Percent of Reactions That Were Serious:** 71%

**Number of Serious Reactions:** 33,623

**Total Number of Reported Reactions:** 47,132

**Therapeutic Class:** Antidepressant

**Brand Names:** Effexor, Effexor-Xr

#46. Sertraline

**Percent of Reactions That Were Serious:** 71%

**Number of Serious Reactions:** 45,622

**Total Number of Reported Reactions:** 64,182

**Therapeutic Class:** Antidepressant

**Brand Names:** Zoloft

#45. Metoprolol

**Percent of Reactions That Were Serious:** 71%

**Number of Serious Reactions:** 71,979

**Total Number of Reported Reactions:** 100,829

**Therapeutic Class:** Cardiovascular Agent

**Brand Names:** Lopressor, Toprol XL

#44. Aspirin

**Percent of Reactions That Were Serious:** 71%

**Number of Serious Reactions:** 134,402

**Total Number of Reported Reactions:** 187,836

**Therapeutic Class:** Analgesic

**Brand Names:** Ascriptin, Aspergum, Aspirin, Bayer, Easprin, Ecotrin, Ecpirin, Enterocote, Genacote, Halfprin, Ninoprin, Norwich Aspirin

#43. Atenolol

**Percent of Reactions That Were Serious:** 72%

**Number of Serious Reactions:** 45,374

**Total Number of Reported Reactions:** 62,930

**Therapeutic Class:** Cardiovascular Agent

**Brand Names:** Tenormin

#42. Prednisone

**Percent of Reactions That Were Serious:** 72%

**Number of Serious Reactions:** 60,187

**Total Number of Reported Reactions:** 83,321

**Therapeutic Class:** Endocrine-Metabolic Agent

**Brand Names:** Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred Ds

#41. Fluoxetine

**Percent of Reactions That Were Serious:** 73%

**Number of Serious Reactions:** 36,722

**Total Number of Reported Reactions:** 50,213

**Therapeutic Class:** Antidepressant

**Brand Names:** Prozac, Prozac Weekly, Rapiflux, Sarafem, Selfemra, Phl-Fluoxetine

#40. Fentanyl

**Percent of Reactions That Were Serious:** 74%

**Number of Serious Reactions:** 29,996

**Total Number of Reported Reactions:** 40,444

**Therapeutic Class:** Analgesic

**Brand Names:** Abstral, Actiq, Fentora, Onsolis, Subsys

#39. Acetaminophen

**Percent of Reactions That Were Serious:** 74%

**Number of Serious Reactions:** 119,389

**Total Number of Reported Reactions:** 160,481

**Therapeutic Class:** Analgesic

**Brand Names:** Ofirmev

#38. Amlodipine

**Percent of Reactions That Were Serious:** 75%

**Number of Serious Reactions:** 95,694

**Total Number of Reported Reactions:** 126,505

**Therapeutic Class:** Cardiovascular Agent

**Brand Names:** Norvasc

#37. Cyclosporine

**Percent of Reactions That Were Serious:** 76%

**Number of Serious Reactions:** 24,422

**Total Number of Reported Reactions:** 31,881

**Therapeutic Class:** Immune Suppressant

**Brand Names:** Gengraf, Neoral, Sandimmune, Apo-Cyclosporine

#36. Risperidone



**Percent of Reactions That Were Serious:** 76%  
**Number of Serious Reactions:** 34,023  
**Total Number of Reported Reactions:** 44,415  
**Therapeutic Class:** Antipsychotic  
**Brand Names:** Risperdal, Risperdal M-Tab, Risperidone M-Tab

#35. Warfarin

**Percent of Reactions That Were Serious:** 76%  
**Number of Serious Reactions:** 79,961  
**Total Number of Reported Reactions:** 104,230  
**Therapeutic Class:** Anticoagulant  
**Brand Names:** Coumadin, Jantoven

#34. Lorazepam

**Percent of Reactions That Were Serious:** 77%  
**Number of Serious Reactions:** 42,737  
**Total Number of Reported Reactions:** 54,873  
**Therapeutic Class:** Antianxiety  
**Brand Names:** Ativan, Lorazepam Intensol

#33. Valsartan

**Percent of Reactions That Were Serious:** 77%  
**Number of Serious Reactions:** 46,987  
**Total Number of Reported Reactions:** 60,639  
**Therapeutic Class:** Cardiovascular Agent  
**Brand Names:** Diovan

#32. Pantoprazole

**Percent of Reactions That Were Serious:** 77%  
**Number of Serious Reactions:** 48,736  
**Total Number of Reported Reactions:** 62,968  
**Therapeutic Class:** Gastric Acid Secretion Inhibitor  
**Brand Names:** Protonix, Protonix Iv

#31. Oxycodone

**Percent of Reactions That Were Serious: 77%**

**Number of Serious Reactions: 56,165**

**Total Number of Reported Reactions: 72,020**

**Therapeutic Class: Analgesic**

**Brand Names: Dazidox, Eth-Oxydose, Oxaydo, Oxycontin, Oxycontin Cr, Oxydose, Oxyfast, Oxy Ir, Roxicodone, Roxicodone Intensol, Apo-Oxycodone Cr, Co Oxycodone Cr, Oxycodone, Oxy-Ir, Oxyneo, Pms-Oxycodone**

#30. Drospirenone And Ethinyl Estradiol

**Percent of Reactions That Were Serious: 78%**

**Number of Serious Reactions: 31,921**

**Total Number of Reported Reactions: 40,426**

**Therapeutic Class: Monophasic Contraceptive Combination**

**Brand Names: Gianvi, Loryna, Nikki, Ocella, Syeda, Vestura, Yasmin, Yaz, Yaz 28, Zarah**

#29. Citalopram

**Percent of Reactions That Were Serious: 78%**

**Number of Serious Reactions: 42,147**

**Total Number of Reported Reactions: 53,752**

**Therapeutic Class: Antidepressant**

**Brand Names: Celexa**

#28. Diclofenac

**Percent of Reactions That Were Serious: 79%**

**Number of Serious Reactions: 27,921**

**Total Number of Reported Reactions: 35,286**

**Therapeutic Class: Central Nervous System Agent**

**Brand Names: Cambia, Cataflam, Voltaren, Voltaren-Xr, Zipsor, Zorvolex**

#27. Conjugated Estrogens

**Percent of Reactions That Were Serious: 79%**

**Number of Serious Reactions: 40,659**

**Total Number of Reported Reactions: 51,272**

**Therapeutic Class: Female Reproductive Agent**

**Brand Names: Premarin, Premarin Vaginal**

#26. Olanzapine

**Percent of Reactions That Were Serious: 80%**

**Number of Serious Reactions: 32,222**

**Total Number of Reported Reactions: 39,957**

**Therapeutic Class: Antipsychotic**

**Brand Names: Zyprexa, Zyprexa Zydis**

#25. Diazepam

**Percent of Reactions That Were Serious: 81%**

**Number of Serious Reactions: 31,794**

**Total Number of Reported Reactions: 38,978**

**Therapeutic Class: Anticonvulsant**

**Brand Names: Diastat, Diastat Pediatric**

#24. Rivaroxaban

**Percent of Reactions That Were Serious: 81%**

**Number of Serious Reactions: 33,317**

**Total Number of Reported Reactions: 41,114**

**Therapeutic Class: Anticoagulant**

**Brand Names: Xarelto**

#23. Alendronate

**Percent of Reactions That Were Serious: 82%**

**Number of Serious Reactions: 39,257**

**Total Number of Reported Reactions: 47,769**

**Therapeutic Class: Calcium Regulator**

**Brand Names: Fosamax**

#22. Clopidogrel

**Percent of Reactions That Were Serious: 82%**

**Number of Serious Reactions: 70,205**

**Total Number of Reported Reactions: 85,447**

**Therapeutic Class: Platelet Aggregation Inhibitor**

**Brand Names: Plavix**

#21. Furosemide

**Percent of Reactions That Were Serious:** 82%  
**Number of Serious Reactions:** 102,865  
**Total Number of Reported Reactions:** 124,020  
**Therapeutic Class:** Cardiovascular Agent  
**Brand Names:** Furocot, Lasix

#20. Digoxin

**Percent of Reactions That Were Serious:** 83%  
**Number of Serious Reactions:** 30,355  
**Total Number of Reported Reactions:** 36,506  
**Therapeutic Class:** Cardiovascular Agent  
**Brand Names:** Digitek, Digox, Lanoxicaps, Lanoxin, Lanoxin Pediatric, Digitaline Nativelle

#19. Spironolactone

**Percent of Reactions That Were Serious:** 84%  
**Number of Serious Reactions:** 28,871  
**Total Number of Reported Reactions:** 34,336  
**Therapeutic Class:** Cardiovascular Agent  
**Brand Names:** Aldactone

#18. Allopurinol

**Percent of Reactions That Were Serious:** 84%  
**Number of Serious Reactions:** 30,921  
**Total Number of Reported Reactions:** 36,755  
**Therapeutic Class:** Antigout  
**Brand Names:** Alopriam

#17. Morphine

**Percent of Reactions That Were Serious:** 84%  
**Number of Serious Reactions:** 37,986  
**Total Number of Reported Reactions:** 44,906  
**Therapeutic Class:** Analgesic  
**Brand Names:** Avinza, Kadian, Kadian Er, Morphabond, Ms Contin, Msir, Oramorph Sr, Roxanol, Roxanol-T

#16. Ondansetron

**Percent of Reactions That Were Serious: 85%**

**Number of Serious Reactions: 31,005**

**Total Number of Reported Reactions: 36,133**

**Therapeutic Class: Antiemetic**

**Brand Names: Zofran, Zofran Odt, Zuplenz**

#15. Ramipril

**Percent of Reactions That Were Serious: 85%**

**Number of Serious Reactions: 32,374**

**Total Number of Reported Reactions: 37,895**

**Therapeutic Class: Antihypertensive**

**Brand Names: Altace**

#14. Rosiglitazone

**Percent of Reactions That Were Serious: 85%**

**Number of Serious Reactions: 87,352**

**Total Number of Reported Reactions: 101,873**

**Therapeutic Class: Antidiabetic**

**Brand Names: Avandia**

#13. Medroxyprogesterone

**Percent of Reactions That Were Serious: 89%**

**Number of Serious Reactions: 34,018**

**Total Number of Reported Reactions: 38,079**

**Therapeutic Class: Endocrine-Metabolic Agent**

**Brand Names: Provera, Alti-Mpa**

#12. Lenalidomide

**Percent of Reactions That Were Serious: 89%**

**Number of Serious Reactions: 69,123**

**Total Number of Reported Reactions: 77,417**

**Therapeutic Class: Immune Modulator**

**Brand Names: Revlimid**

#11. Methylprednisolone

**Percent of Reactions That Were Serious:** 90%  
**Number of Serious Reactions:** 30,040  
**Total Number of Reported Reactions:** 33,095  
**Therapeutic Class:** Endocrine-Metabolic Agent  
**Brand Names:** Medrol, Medrol Dosepak, Methylpred-Dp

#10. Metoclopramide

**Percent of Reactions That Were Serious:** 91%  
**Number of Serious Reactions:** 32,757  
**Total Number of Reported Reactions:** 35,623  
**Therapeutic Class:** Antiemetic  
**Brand Names:** Metozolv Odt, Reglan

#9. Infliximab

**Percent of Reactions That Were Serious:** 91%  
**Number of Serious Reactions:** 68,167  
**Total Number of Reported Reactions:** 74,738  
**Therapeutic Class:** Immunological Agent  
**Brand Names:** Remicade

#8. Tacrolimus

**Percent of Reactions That Were Serious:** 92%  
**Number of Serious Reactions:** 27,964  
**Total Number of Reported Reactions:** 30,262  
**Therapeutic Class:** Antipsoriatic  
**Brand Names:** Protopic

#7. Zoledronic Acid

**Percent of Reactions That Were Serious:** 93%  
**Number of Serious Reactions:** 35,581  
**Total Number of Reported Reactions:** 38,016  
**Therapeutic Class:** Calcium Regulator  
**Brand Names:** Reclast, Zometa

#6. Dexamethasone

**Percent of Reactions That Were Serious: 93%**

**Number of Serious Reactions: 38,966**

**Total Number of Reported Reactions: 41,636**

**Therapeutic Class: Endocrine-Metabolic Agent**

**Brand Names: Baycadron Elixer, Decadron, Dekpak 13 Day Taperpak, Dexamethasone Intensol, Dexpak, Dexpak 10 Day Taperpak, Dexpak Jr, Zema-Pak**

#5. Clozapine

**Percent of Reactions That Were Serious: 95%**

**Number of Serious Reactions: 29,470**

**Total Number of Reported Reactions: 30,914**

**Therapeutic Class: Antipsychotic**

**Brand Names: Clozaril, Fazaclor, Versacloz**

#4. Rituximab

**Percent of Reactions That Were Serious: 96%**

**Number of Serious Reactions: 30,014**

**Total Number of Reported Reactions: 31,157**

**Therapeutic Class: Antineoplastic Agent**

**Brand Names: Rituxan**

#3. Bevacizumab

**Percent of Reactions That Were Serious: 96%**

**Number of Serious Reactions: 39,957**

**Total Number of Reported Reactions: 41,281**

**Therapeutic Class: Immunological Agent**

**Brand Names: Avastin**

#2. Prednisolone

**Percent of Reactions That Were Serious: 96%**

**Number of Serious Reactions: 42,323**

**Total Number of Reported Reactions: 43,817**

**Therapeutic Class: Endocrine-Metabolic Agent**

**Brand Names: Bubbli-Pred, Cotolone, Flo-Pred, Millipred, Millipred Dp, Orapred, Orapred Odt, Pediapred, Prelone, Veripred 20, Pms-Prednisolone**

#1. Cyclophosphamide

**Percent of Reactions That Were Serious: 97%**  
**Number of Serious Reactions: 33,128**  
**Total Number of Reported Reactions: 34,076**  
**Therapeutic Class: Antineoplastic Agent**  
**Brand Names: Cytozan, Cytozan Lyophilized**

fn73 (see fn14)

<https://www.aspph.org/yale-dr-harvey-risch-wins-50000-ruth-leff-siegel-award/>

fn76 (see fn60)

<https://aapsonline.org/judicial/aaps-v-fda-hcq-6-2-2020.pdf>

fn77

CFR by Country

Country	# of deaths	# of cases	CFR use	Deaths per 100k policy	Source
<b>All of June 31, 2020 - countries with major news announcements only</b>					
Qatar	0	86,883	0.11%	encourages HCQ Qatar's health minister says country uses HCQ and not Remdesivir	<a href="https://www.foxnews.com/health/qatar-health-minister-says-country-uses-hydroxychloroquine">https://www.foxnews.com/health/qatar-health-minister-says-country-uses-hydroxychloroquine</a>
Saudi Arabia	60	21,261	0.28%	encourages HCQ Saudi Arabia says that countries to use Hydroxychloroquine	<a href="https://www.foxnews.com/health/saudi-arabia-health-minister-says-countries-use-hydroxychloroquine">https://www.foxnews.com/health/saudi-arabia-health-minister-says-countries-use-hydroxychloroquine</a>
Oman	128	28,566	0.45%	encourages HCQ Oman has approved the antimalarial drug, HCQ, as one of the medications to be used in	<a href="https://www.foxnews.com/health/oman-has-approved-antimalarial-drug-hydroxychloroquine">https://www.foxnews.com/health/oman-has-approved-antimalarial-drug-hydroxychloroquine</a>
Costa Rica	12	2,127	0.56%	encourages HCQ use	<a href="https://www.foxnews.com/health/costa-rica-health-minister-says-country-uses-hydroxychloroquine">https://www.foxnews.com/health/costa-rica-health-minister-says-country-uses-hydroxychloroquine</a>
Bahrain	343	57,945	0.59%	encourages HCQ Bahraini doctor: HCQ/500 chloroquine helps to fight COVID	<a href="https://www.foxnews.com/health/bahraini-doctor-hcq-500-chloroquine-helps-fight-covid">https://www.foxnews.com/health/bahraini-doctor-hcq-500-chloroquine-helps-fight-covid</a>
UAE	201	44,523	0.45%	31 encourages HCQ use UAE says it is successfully treating patients with hydroxychloroquine	<a href="https://www.foxnews.com/health/uae-says-it-is-successfully-treating-patients-with-hydroxychloroquine">https://www.foxnews.com/health/uae-says-it-is-successfully-treating-patients-with-hydroxychloroquine</a>
Israel	118	10,779	0.76%	encourages HCQ Israeli doctor: HCQ/500 chloroquine helps to fight COVID	<a href="https://www.foxnews.com/health/israeli-doctor-hcq-500-chloroquine-helps-fight-covid">https://www.foxnews.com/health/israeli-doctor-hcq-500-chloroquine-helps-fight-covid</a>
Saudi Arabia	120	154,233	0.80%	"Saudi Arabia's treatment plan from March which shows HCQ use falling back to March"	<a href="https://www.foxnews.com/health/saudi-arabias-treatment-plan-from-march-which-shows-hcq-use-falling-back-to-march">https://www.foxnews.com/health/saudi-arabias-treatment-plan-from-march-which-shows-hcq-use-falling-back-to-march</a>
Singapore	1,620	107,712	1.51%	encourages HCQ Singapore's health minister says HCQ is one of the drugs to be used for COVID-19	<a href="https://www.foxnews.com/health/singapores-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19">https://www.foxnews.com/health/singapores-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19</a>
Russia	862	576,922	1.36%	56 Russia recommends PEP use of HCQ. Post contact prevention in individuals with a single contact with con	<a href="https://www.foxnews.com/health/russia-recommends-pei-use-of-hcq-post-contact-prevention-in-individuals-with-a-single-contact-with-con">https://www.foxnews.com/health/russia-recommends-pei-use-of-hcq-post-contact-prevention-in-individuals-with-a-single-contact-with-con</a>
Malaysia	121	8,826	1.41%	encourages HCQ Malaysia's Health Minister says HCQ is one of the drugs to be used for COVID-19	<a href="https://www.foxnews.com/health/malaysias-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19">https://www.foxnews.com/health/malaysias-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19</a>
Senegal	62	5,763	1.42%	encourages HCQ Senegal will continue use of HCQ, hydroxychloroquine, says Professor Moussa Diallo	<a href="https://www.foxnews.com/health/senegal-will-continue-use-of-hcq-hydroxychloroquine-says-professor-moussa-diallo">https://www.foxnews.com/health/senegal-will-continue-use-of-hcq-hydroxychloroquine-says-professor-moussa-diallo</a>
Iran	205	20,623	1.49%	33 encourages HCQ Iran's Health Minister says HCQ is one of the drugs to be used for COVID-19	<a href="https://www.foxnews.com/health/irans-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19">https://www.foxnews.com/health/irans-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19</a>
China	4,006	220,764	1.81%	234 "14 China, a combination of Hydroxychloroquine and Chloroquine, says Professor Moussa Diallo	<a href="https://www.foxnews.com/health/china-a-combination-of-hydroxychloroquine-and-chloroquine-says-professor-moussa-diallo">https://www.foxnews.com/health/china-a-combination-of-hydroxychloroquine-and-chloroquine-says-professor-moussa-diallo</a>
Pakistan	3,082	17,886	1.97%	"Pakistan will use Hydroxychloroquine to control coronavirus outbreak"	<a href="https://www.foxnews.com/health/pakistan-will-use-hydroxychloroquine-to-control-coronavirus-outbreak">https://www.foxnews.com/health/pakistan-will-use-hydroxychloroquine-to-control-coronavirus-outbreak</a>
South Africa	1,677	10,881	2.02%	33 "New South Africa HCQ is used widely for patients as the last three weeks have been using it exclusively	<a href="https://www.foxnews.com/health/new-south-africa-hcq-is-used-widely-for-patients-as-the-last-three-weeks-have-been-using-it-exclusively">https://www.foxnews.com/health/new-south-africa-hcq-is-used-widely-for-patients-as-the-last-three-weeks-have-been-using-it-exclusively</a>
Serbia	200	12,833	2.02%	Serbia and Romania's Health Minister says HCQ is one of the drugs to be used for COVID-19	<a href="https://www.foxnews.com/health/serbia-and-romaniyas-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19">https://www.foxnews.com/health/serbia-and-romaniyas-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19</a>
Morocco	215	6,839	2.18%	encourages HCQ Morocco's Health Minister says HCQ is one of the drugs to be used for COVID-19	<a href="https://www.foxnews.com/health/moroccos-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19">https://www.foxnews.com/health/moroccos-health-minister-says-hcq-is-one-of-the-drugs-to-be-used-for-covid-19</a>
S. Korea	280	14,421	2.26%	5 encourages HCQ use	<a href="https://www.foxnews.com/health/s-korea-says-it-is-successfully-treating-patients-with-hydroxychloroquine">https://www.foxnews.com/health/s-korea-says-it-is-successfully-treating-patients-with-hydroxychloroquine</a>
Argentina	392	41,204	2.41%	Severe reports of patients in Argentina using they treated HCQ	<a href="https://www.foxnews.com/health/severe-reports-of-patients-in-argentina-using-they-treated-hcq">https://www.foxnews.com/health/severe-reports-of-patients-in-argentina-using-they-treated-hcq</a>
Nigeria	108	18,868	2.50%	"Nigeria will continue use Hydroxychloroquine to treat COVID-19 patients" Also in C	<a href="https://www.foxnews.com/health/nigeria-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/nigeria-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Turkey	4,627	186,615	2.49%	38 encourages HCQ use	<a href="https://www.foxnews.com/health/turkey-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/turkey-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Libania	184	10,425	2.77%	encourages HCQ use	<a href="https://www.foxnews.com/health/libania-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/libania-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Honduras	108	12,328	2.91%	"The Honduran government assured that hydroxychloroquine will continue - having verified 'scientific evid"	<a href="https://www.foxnews.com/health/the-honduran-government-assured-that-hydroxychloroquine-will-continue-having-verified-scientific-evid">https://www.foxnews.com/health/the-honduran-government-assured-that-hydroxychloroquine-will-continue-having-verified-scientific-evid</a>
Philippines	780	20,128	3.19%	"Philippines will continue use Hydroxychloroquine to treat patients" Health Minister 'Victor	<a href="https://www.foxnews.com/health/philippines-will-continue-use-hydroxychloroquine-to-treat-patients-health-minister-victor">https://www.foxnews.com/health/philippines-will-continue-use-hydroxychloroquine-to-treat-patients-health-minister-victor</a>
Peru	136	10,448	3.22%	32 Health Ministry permits temporary use of Hydroxychloroquine to hospitalized pts	<a href="https://www.foxnews.com/health/perus-health-ministry-permits-temporary-use-of-hydroxychloroquine-to-hospitalized-patients">https://www.foxnews.com/health/perus-health-ministry-permits-temporary-use-of-hydroxychloroquine-to-hospitalized-patients</a>
India	1,277	41,727	3.22%	10 encourages HCQ use	<a href="https://www.foxnews.com/health/india-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/india-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Colombia	218	8,923	3.24%	Hydroxychloroquine and Chloroquine Can Be Used to Treat COVID-19"	<a href="https://www.foxnews.com/health/hydroxychloroquine-and-chloroquine-can-be-used-to-treat-covid-19">https://www.foxnews.com/health/hydroxychloroquine-and-chloroquine-can-be-used-to-treat-covid-19</a>
Philippines	110	28,420	3.91%	32 Health Ministry permits temporary use of Hydroxychloroquine to hospitalized pts	<a href="https://www.foxnews.com/health/philippines-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/philippines-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Spain	2108	50,778	3.92%	"Hydroxychloroquine in Denmark can only be prescribed for hospital patients"	<a href="https://www.foxnews.com/health/hydroxychloroquine-in-denmark-can-only-be-prescribed-for-hospital-patients">https://www.foxnews.com/health/hydroxychloroquine-in-denmark-can-only-be-prescribed-for-hospital-patients</a>
Portugal	1528	38,841	3.93%	389 Hospital HCQ use in the new coronavirus cases is limited use where allowed	<a href="https://www.foxnews.com/health/portugal-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/portugal-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
England	188	17,223	3.97%	"Malaria drug is used in Austria" hospitalized pts	<a href="https://www.foxnews.com/health/malaria-drug-is-used-in-austria-hospitalized-patients">https://www.foxnews.com/health/malaria-drug-is-used-in-austria-hospitalized-patients</a>
France	1,246	31,265	4.20%	Some use in France use used March 13	<a href="https://www.foxnews.com/health/some-use-in-france-used-march-13">https://www.foxnews.com/health/some-use-in-france-used-march-13</a>
Brazil	58,108	1,071,128	4.46%	used for HCQ use in the process, poor distribution, isolated use	<a href="https://www.foxnews.com/health/used-for-hcq-use-in-the-process-poor-distribution-isolated-use">https://www.foxnews.com/health/used-for-hcq-use-in-the-process-poor-distribution-isolated-use</a>
Germany	861	19,216	4.49%	only 12% of doctors in Germany said they would prescribe HCQ	<a href="https://www.foxnews.com/health/only-12-of-doctors-in-germany-said-they-would-prescribe-hcq">https://www.foxnews.com/health/only-12-of-doctors-in-germany-said-they-would-prescribe-hcq</a>
Iran	8,167	202,884	4.06%	not clear	<a href="https://www.foxnews.com/health/iran-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/iran-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Denmark	300	12,281	4.84%	"Hydroxychloroquine in Denmark can only be prescribed for hospital patients"	<a href="https://www.foxnews.com/health/hydroxychloroquine-in-denmark-can-only-be-prescribed-for-hospital-patients">https://www.foxnews.com/health/hydroxychloroquine-in-denmark-can-only-be-prescribed-for-hospital-patients</a>
USA	121,480	2,530,519	5.20%	389 Hospital HCQ use in the new coronavirus cases is limited use where allowed	<a href="https://www.foxnews.com/health/usa-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients">https://www.foxnews.com/health/usa-will-continue-use-hydroxychloroquine-to-treat-covid-19-patients</a>
Japan	492	17,739	5.30%	Hydroxychloroquine usage amongst COVID-19 patients is 7% in Japan	<a href="https://www.foxnews.com/health/hydroxychloroquine-usage-amongst-covid-19-patients-is-7-in-japan">https://www.foxnews.com/health/hydroxychloroquine-usage-amongst-covid-19-patients-is-7-in-japan</a>
China	4,006	81,278	5.30%	Health Minister HCQ efficacy	<a href="https://www.foxnews.com/health/china-health-minister-hcq-efficacy">https://www.foxnews.com/health/china-health-minister-hcq-efficacy</a>
Greece	100	3,228	5.84%	Greece has increased production of chloroquine to treat cases of coronavirus, but used in hospitalized pts	<a href="https://www.foxnews.com/health/greece-has-increased-production-of-chloroquine-to-treat-cases-of-coronavirus-but-used-in-hospitalized-patients">https://www.foxnews.com/health/greece-has-increased-production-of-chloroquine-to-treat-cases-of-coronavirus-but-used-in-hospitalized-patients</a>
Belgium	498	13,243	6.20%	"Hospitalized COVID-19 patients" i.e. low rate	<a href="https://www.foxnews.com/health/hospitalized-covid-19-patients-i-e-low-rate">https://www.foxnews.com/health/hospitalized-covid-19-patients-i-e-low-rate</a>
Ireland	1710	25,274	6.76%	Apparently HCQ was tested again in Ireland	<a href="https://www.foxnews.com/health/apparently-hcq-was-tested-again-in-ireland">https://www.foxnews.com/health/apparently-hcq-was-tested-again-in-ireland</a>
Sweden	8,410	101,919	8.33%	very low HCQ availability	<a href="https://www.foxnews.com/health/very-low-hcq-availability">https://www.foxnews.com/health/very-low-hcq-availability</a>
Scotland	6108	40,251	8.30%	At least one city in Scotland used it regular access	<a href="https://www.foxnews.com/health/at-least-one-city-in-scotland-used-it-regular-access">https://www.foxnews.com/health/at-least-one-city-in-scotland-used-it-regular-access</a>
Canada	5023	58,542	8.02%	April 6 Several Swedish Hospitals Have Stopped Using Chloroquine	<a href="https://www.foxnews.com/health/april-6-several-swedish-hospitals-have-stopped-using-chloroquine">https://www.foxnews.com/health/april-6-several-swedish-hospitals-have-stopped-using-chloroquine</a>
Spain	28,122	220,916	8.67%	688 Hydroxychloroquine usage amongst COVID-19 patients is 72% in Spain, 40% in Italy, 47% in Brazil, 20% in	<a href="https://www.foxnews.com/health/hydroxychloroquine-usage-amongst-covid-19-patients-is-72-in-spain-40-in-italy-47-in-brazil-20-in">https://www.foxnews.com/health/hydroxychloroquine-usage-amongst-covid-19-patients-is-72-in-spain-40-in-italy-47-in-brazil-20-in</a>
Algeria	1,617	6,164	9.30%	Dr. Ali Boudjellal reports that Algeria of 170 people treated with HCQ + hydroxychloroquine 47% returned to health	<a href="https://www.foxnews.com/health/dr-ali-boudjellal-reports-that-algeria-of-170-people-treated-with-hcq-hydroxychloroquine-47-returned-to-health">https://www.foxnews.com/health/dr-ali-boudjellal-reports-that-algeria-of-170-people-treated-with-hcq-hydroxychloroquine-47-returned-to-health</a>
USA	20,781	175,222	11.80%	very low Trump leadership, poor distribution	<a href="https://www.foxnews.com/health/very-low-trump-leadership-poor-distribution">https://www.foxnews.com/health/very-low-trump-leadership-poor-distribution</a>
Netherlands	6089	49,362	12.30%	389 some hospitals used HCQ, but early use apparently discouraged, prohibited, "After 800H and the Health Ca	<a href="https://www.foxnews.com/health/some-hospitals-used-hcq-but-early-use-apparently-discouraged-prohibited-after-800h-and-the-health-ca">https://www.foxnews.com/health/some-hospitals-used-hcq-but-early-use-apparently-discouraged-prohibited-after-800h-and-the-health-ca</a>
UK	42,989	383,110	14.08%	688 only 12% of GPs, pharmacists said they used it	<a href="https://www.foxnews.com/health/only-12-of-gps-pharmacists-said-they-used-it">https://www.foxnews.com/health/only-12-of-gps-pharmacists-said-they-used-it</a>
Italy	34,410	228,275	14.93%	673 did not realize how about HCQ previously adopted in some areas, also much older population	<a href="https://www.foxnews.com/health/did-not-realize-how-about-hcq-previously-adopted-in-some-areas-also-much-older-population">https://www.foxnews.com/health/did-not-realize-how-about-hcq-previously-adopted-in-some-areas-also-much-older-population</a>
Belgium	4,108	30,822	16.57%	687 Belgium used HCQ, "for the most coronavirus patients"	<a href="https://www.foxnews.com/health/belgium-used-hcq-for-the-most-coronavirus-patients">https://www.foxnews.com/health/belgium-used-hcq-for-the-most-coronavirus-patients</a>
France	28,433	160,893	18.91%	404 France banned HCQ	<a href="https://www.foxnews.com/health/france-banned-hcq">https://www.foxnews.com/health/france-banned-hcq</a>



Country	Mortality # of deaths	# of cases	CFR c/d	Deaths per 100Q policy	As of June 21, 2020 - numbers from <a href="https://www.worldometers.info/">https://www.worldometers.info/</a>
Qatar	94	86488	0.11%		encourages HCQ Qatar's health minister says country uses HCQ and not Remdesivir
Bahrain	60	21,331	0.28%		encourages HCQ Bahrain among first countries to use Hydroxychloroquine
Oman	128	28,866	0.45%		encourages HCQ Oman has approved the antimalaria drug, HCQ, as one of the medications to be used in treating people with COVID-19.
Costa Rica	12	2,127	0.56%	2	encourages HCQ use
Belarus	343	57936	0.59%		encourages HCQ Sandoz will donate potential effective drug for treating COVID-19, hydroxychloroquine, to Belarus
UAE	301	44,533	0.68%	31	encourages HCQ use UAE says it is successfully treating patients with hydroxychloroquine
Kazakhstan	118	16,779	0.70%		encourages HCQ Pakistan donated 700,000 chloroquine tablets to Kazakhstan
Saudi Arabia	1230	154,233	0.80%		"Saudi Arabia's treatment plan from March which shows HCQ use dating back to March"
Bangladesh	1425	108,775	1.31%		encourages HCQ Bangladesh recommends controversial drugs for Covid-19 treatment
Russia	8002	576,952	1.39%	56	Russia recommended PHEP use of HCQ: Post contact prevention in individuals with a single contact with confirmed case of COVID-19
Malaysia	121	8556	1.41%		encourages HCQ "Malaysia Finds Hydroxychloroquine Can Slow Covid-19 Progress. Health director-general Dr Noor Hisham Abdullah said
Senegal	82	5,783	1.42%		encourages HCQ use. Senegal will continue use of HCQ + azithromycin, says Professor Moussa Seydi.
Israel	305	20,633	1.48%	33	encourages HCQ PM Netanyahu thanks Modi for donation of HCQ
Chile	4295	236,748	1.81%	234	* In Chile, a centralized national Protocol was made in which both Public and Private Hospitals treated with Hydroxychloroquine Z Pack.*
Pakistan	3382	171,666	1.97%		"Pakistan asks India for Hydroxychloroquine to combat coronavirus outbreak"
South Africa	1877	92,681	2.03%	33	* here in South Africa HCQ is used widely for malaria so the last three weeks I have been saying to everybody, it is obvious to use HCQ as prophylaxis to corona, since its side effects are well known @ low risk."
Serbia	260	12,803	2.03%		Serbian and Bosnian drugmakers Galekika and Zada Pharmaceuticals said on Monday they had started producing chloroquine and hydroxychloroquine for the treatment of COVID-19 patients
Morocco	213	9,839	2.16%		encourages "Morocco to Receive 6 Million Hydroxychloroquine Tablets from India"
S. Korea	280	12,421	2.25%	5	encourages HCQ use
Argentina	992	41,204	2.41%		Several reports of patients in Argentina noting they received HCQ
Nigeria	506	19,808	2.55%		"Nigerian authorities say they will continue to use hydroxychloroquine in treating Covid-19 patients" Also is OTC
Turkey	4927	186,493	2.64%	59	encouraged HCQ use
Ukraine	964	35,825	2.77%		encourages HCQ use
Honduras	358	12,306	2.91%		"the Honduran government assured that hydroxychloroquine will continue ... having verified "excellent results"
Peru	7861	251,338	3.13%		Peru will continue to use the controversial drug hydroxychloroquine to treat patients, Health Minister Victor Zamora said, adding that it was recommended by a team of experts.
Czechia	338	10,448	3.22%		Czech Health Ministry permits temporary use of hydroxychloroquine to hospitalized pts
India	13277	411,727	3.22%	10	encourages HCQ use
Colombia	2126	65,633	3.24%		"Hydroxychloroquine and Chloroquine Can Be Used to Treat Covid-19"
Philippines	1150	29,400	3.91%		Makati Medical Center (MMC) is using Hcq-Az plus zinc and Vitamin C, which boosts resistance to disease. With the treatment, MMC reportedly achieved 81 percent success rate with Covid-19 patients, four times the discharge rate at other hospitals.
Egypt	2106	53,758	3.92%		Egyptian Health Minister on Hydroxychloroquine: "We put it in the treatment from the first day ... and achieved great results in Egypt"
Portugal	1528	38,841	3.93%		Patients in Portugal with Covid-19 can be treated with malaria and ebola drugs
Austria	688	17,323	3.97%		* Malaria drug is used in Austria* hospitalized pts
Poland	1348	31,620	4.26%		Some use in Poland was noted March 13
Brazil	50,058	1,070,138	4.68%		asked US for HCQ late in the process, poor distribution, isolated use
Germany	8961	191,216	4.69%		only 13% of doctors in Germany said they would prescribe HCQ
Iran	9,507	202,584	4.69%		not clear
Denmark	5	600	12.391	4.84%	"hydroxychloroquine in Denmark can only be prescribed by hospital doctors"
USA	121,980	2,330,578	5.23%	369	blocked HCQ use (a few brave physicians use it), isolated use where allowed
Japan	6	952	17,799	5.35%	Hydroxychloroquine usage amongst COVID-19 treaters is 7% in Japan.
China	4634	83,378	5.56%		didn't know about HCQ initially
Greece	190	3,256	5.84%		Greece has resumed production of chloroquine to treat cases of coronavirus, but used in hospitalized pts
Switzerland	1956	31,243	6.26%		*hospitalised Covid-19 patients* i.e. too late
Ireland	7	1715	25,374	6.76%	Apparently HCQ was frowned upon in Ireland
Canada	8	8,410	10,019	8.33%	very anti-HCQ leadership.
Ecuador	8	4156	49,731	8.36%	At least one city in Ecuador used it reported success
Sweden	9	5053	56,043	9.02%	April 6. Several Swedish Hospitals Have Stopped Using Chloroquine
Spain	10	28,322	29,018	9.67%	606 Hydroxychloroquine usage amongst COVID-19 treaters is 72% in Spain, 49% in Italy, 41% in Brazil, 39% in Mexico, 28% in France, 23% in the US, 17% in Germany, 16% in Canada, 13% in the UK and 7% in Japan.
Algeria	837	8,324	10.06%		Dr. Idr Bitam reports that in Algeria of 170 people treated with HCQ + Azithromycin 97% returned to health.
Mexico	12	20,781	175,202	11.86%	very anti-Trump leadership, poor distribution
Netherlands	12	6089	49,052	12.30%	365 some hospitals used HCQ, but early use apparently discouraged, prohibited, "After RIVM and the Health Care Inspectorate learned of this, he had to discontinue treatment"
UK	15	42,569	30,310	14.05%	628 only 13% of UK physicians said they used it
Italy	15	34,610	238,275	14.53%	573 did not initially know about HCQ (eventually adopted in some areas) also much older population
Belgium	15	9,696	60,590	16.01%	837 Belgium used HCQ "for the sickest coronavirus patients."
France	18	29,633	160,093	18.51%	454 France banned HCQ.

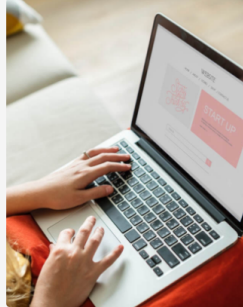
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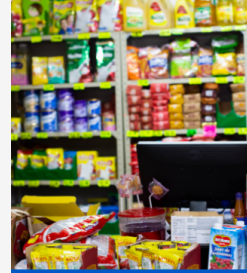
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<https://www.politico.eu/article/former-french-pm-health-ministers-to-be-investigated-for-pandemic-response/>

Former French Prime Minister Edouard Philippe | Ludovic Marin/AFP via Getty Images

### **Former French PM, health ministers to be investigated for pandemic response**

Edouard Philippe, Agnès Buzyn and Olivier Véran are accused of abstaining from fighting a disaster.

By [CARMEN PAUN](#)

7/3/20, 9:16 PM CET

A French court will investigate former French Prime Minister Edouard Philippe and two health ministers following complaints about the government's handling of the coronavirus pandemic, Prosecutor General François Molins said today.

Philippe, former Health Minister [Agnès Buzyn](#) and outgoing Health Minister Olivier Véran will have to respond to accusations of abstaining from fighting a disaster, [Le Figaro reported](#).

The news came during a ceremony where Philippe was passing on power to his successor, Jean Castex, [who was appointed today](#) by French President Emmanuel Macron.

There have been 90 complaints lodged against the French government since the beginning of the epidemic, [according to 20Minutes](#). Some accused members of the French government of endangering people's lives, failing to assist people in danger or even of manslaughter.

A commission at the Court of Justice of the Republic, a special court in charge of trying cases of ministerial misconduct, examined 53 of them and retained nine, which were sent to the Prosecutor General. The other 44 were considered inadmissible or were closed.

The complaints, coming from individuals, doctors, associations or prisoners, have been pouring in since the beginning of the confinement in response to the pandemic, in mid-March, according to Le Figaro.

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<https://zelfzorgcovid19.nl/wp-content/uploads/2020/06/voornemen-off-label-gebruik.pdf>

AANGETEKEND en via de fax 088-1205001 Inspectie Gezondheidszorg en Jeugd Postbus 2518 6401 DA HEERLEN

Geachte Inspectie, 1. Deze brief is namens drs. R. Elens, huisarts te Meijel, Limburg, verzoeker sub 1 en drs J.P.Peterse, apotheker te Meijel en Herten-Merum, verzoeker sub 2, opgesteld door gemachtigde mr. P.C. van Houten, advocaat te Dordrecht. Verzoekers kiezen te dezer zake woonplaats te Dordrecht aan de Singel 125, 3311PC Dordrecht ten kantore van mr. P.C. van Houten, gemachtigde. 2.

VOORNEMEN VAN VERZOEKER SUB 1 Verzoeker sub 1 heeft het voornemen over te gaan tot voorschrijven van hydroxychloroquine (HCQ) bij patiënten uit de praktijk van huisarts Elens die lijden aan de COVID-19 ziekte. Verzoeker sub 1 is ermee bekend dat het gaat om off label gebruik van HCQ. VOORNEMEN VAN VERZOEKER SUB 2 Verzoeker sub 2 is voornemens als verzoeker sub 1 HCQ aan een patiënt zou voorschrijven dit middel aan die patiënt te verstrekken. 3. Verzoekers hebben voorwaarden opgesteld waaraan zij zullen gaan voldoen, hun protocol: Alvorens HCQ voor te schrijven zal aan de volgende voorwaarden moeten zijn voldaan: 1. De patiënt behoort tot de volgende categorie: positieve corona (Covid19) -test waarbij één of een combinatie van de volgende symptomen is geconstateerd: kortademigheid, snelle pols, lage saturatie, koorts, hoorbare afwijkingen op de longen, geur- en smaakverlies of diarree. 2. Er zijn geen bekende contra-indicaties bij de inzet van HCQ zoals allergieën of hartritmestoornissen, hetgeen uit ECG en nierfunctie controle is gebleken. 3. Met de patiënt vindt een uitgebreid gesprek plaats inzake het gebruik van HCQ aangevuld met vrij verkrijgbare supplementen, waaronder zink supplementen welke mede ingenomen dienen te worden 4. De patiënt dient uitdrukkelijk toestemming te geven (aan het einde extra check of er nog vragen zijn en of alles is duidelijk is) 5. Het voorschrijven dient in overleg en afstemming met de apotheker plaats te vinden, met een schriftelijke vastlegging van de afspraken. 6. Het gebruik van HCQ wordt voorgeschreven als volgt: 200 mg 3 maal daags, gedurende 4 dagen; dit betreft dus in totaal 12 tabletten van 200 mg, over vier dagen gerekend 2400 mg totaal.

4. Overwegingen van verzoekers 4.1 Op grond van artikel 68 van de Geneesmiddelenwet (hierna: Gmw) is het toegestaan een medicatie buiten de geregistreerde indicaties (off -label) voor te schrijven wanneer protocollen en standaarden nog in ontwikkeling zijn, mits overleg tussen de behandelende arts en apotheker heeft plaatsgevonden. Zie productie 1. 4.2 Op dit moment is er geen eenduidig protocol over de inzet en het gebruik van HCQ bij COVID-19 behandeling. Het RIVM-richtlijn COVID-19 schrijft onder “profylaxe en behandeling” dat er geen profylaxe en/ of behandeling voor handen is. Met andere woorden er is momenteel geen specifieke behandeling voor COVID-19 in de eerstelijnsgezondheidszorg. Zie Productie 2 (RIVM, pag. 29 en bericht Nederlands Huisartsen Genootschap, waar op pag. 2 wordt gesteld dat er momenteel geen specifieke behandeling voor Covid-19 in de eerste lijn bestaat)). Uit hetgeen hierboven is aangegeven kan niet anders afgeleid worden dan dat er in de wetenschap geen consensus is over het off-label gebruik van HCQ. 4.3 Van belang is verder dat er steeds meer aanwijzingen zijn waaruit kan worden afgeleid dat HCQ effectief is bij de behandeling van COVID-19 patiënten in een vroeg stadium van deze ziekte, indien ook gebruik van zink wordt voorgeschreven. Zie voor meer HCQ relevante informatie <https://zelfzorgcovid19.nl/nieuws/>. 4.4 Zie productie 3: De brief van dokter Zelenko, die de inspiratie was voor verzoeker sub 1, waaruit blijkt dat gebruik

van HCQ in een vroeg stadium van de ziekte, als er ook zinksulfaat wordt ingenomen, effectief is. 4.5 Zie productie 4: Het artikel uit American Journal of Epidemiology van Harvey A. Risch over vroegtijdige behandeling met HCQ. 4.6 Zie productie 5: Het artikel van Jean-Pierre Kiekens waarin deze de vroegbehandeling met HCQ beargumenteert. 4.7 Zie productie 6: Vergelijking Verenigde Arabische Emiraten met Nederland. De case fatality rate in de VAE is minder dan 2 %. In Nederland ligt deze boven de 12%. In de VAE is de vroegbehandeling met HCQ standaard. In Nederland wordt het aan de eerste lijn ontraden. Zie ook de geproduceerde nationale handleiding. Op pagina 9: slechts chloroquine en HCQ toegestaan. Op pagina 12 bij vermoeden van covid19 chloroquine en HCQ toepassen. Zie ook pagina 13 en 14. Zie productie 7: India: Uit de grafiek blijkt dat de case fatality rate in India rond de 3% ligt. In Nederland ligt deze iets boven de 12%. In India wordt HCQ in een vroeg stadium voorgeschreven (in Nederland is dit aan de eerstelijns hulp, bij de huisartsen ontraden). Zie pagina 12 en 13 van het bijgevoegde clinical management control: COVID-19 van de regering van India. 4.8 Zie productie 8: Een artikel uit het Leidsch Dagblad d.d. 10 juni 2020 waarvan de conclusie, op basis van een statistisch onderzoek, luidt dat er een goede kans bestaat dat HCQ effectief is in de eerstelijnsgezondheidszorg.

4.9 Zelf heeft verzoeker sub 1 kunnen constateren dat alle door hem in een vroeg stadium met HCQ behandelde patiënten genazen. Dit was niet het geval met zijn patiënten die in het ziekenhuis werden behandeld. Van die patiënten is ongeveer 50% overleden. 4.10 Zie productie 9: informatie verstrekt door het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), d.d. 13 juni 2020, waarvan hier vermeld wordt: Positief geteste personen: 48.640 Overleden personen 6.057 Verder vermeldt het RIVM wel het aantal ziekenhuis opnames namelijk 11.822, maar niet het aantal covid 19 patiënten dat is overleden in het ziekenhuis, of het aantal covid 19 patiënten dat genezen is en is ontslagen uit het ziekenhuis. Is HCQ gevaarlijk voor de gezondheid? 4.11 Zie productie 10: rapport van de WHO waaruit blijkt dat dit middel meer dan 60 jaar wereldwijd in miljoenen gevallen als malariamedicijn wordt toegepast. Op pagina 36: despite hundreds of millions of doses administered in the treatment of malaria, there have been no reports of sudden unexplained death associated with quinine, chloroquine or amodiaquine. Volgens WHO is dit middel op zichzelf niet gevaarlijk. 4.12 Zie productie 11: monografie inzake Chloroquine en hydroxychloroquine Toxisch vanaf 8 gram in één keer. De doses geadviseerd door Zelenko (productie 3): 2 keer 200 mg per dag voor vijf dagen dus totaal 2000mg in vijf dagen. Conclusie: niet gevaarlijk als het Zelenko protocol wordt gevolgd. Zie productie 12: een bericht van Radboudumc te Nijmegen HCQ wordt ook voorgeschreven bij auto-immuunziekten. De hoeveelheid per dag varieert van 200 tot 600 mg. De werking van HCQ treedt op na 3 tot 6 maanden. Zelenko adviseert maximaal 400 mg per dag en een maximale duur van vijf dagen. Elens adviseert maximaal 600 mg per dag en een maximale duur van vier dagen. Conclusie: als HCQ zoals voorgeschreven bij auto-immuunziekten niet gevaarlijk wordt geacht dan is er geen reden om het in het geval van de behandeling door Zelenko of Elens, lagere dosis voor veel kortere periode, wel gevaarlijk te achten. 4.13 Op basis van al deze gegevens is het de overtuiging van verzoekers dat vroegtijdige behandeling met behulp van HCQ in de eerstelijnsgezondheidszorg een veilige behandeling is die een reële kans biedt op genezing en preventie van schade aan longen en andere organen. 5. Subdoel van verzoekers: Met behulp van bovenstaande producties menen verzoekers aannemelijk te hebben gemaakt:

A. Dat gebruik van HCQ indien voorgeschreven als omschreven in het protocol zoals zij dat hanteren (randnummer 3) niet gevaarlijk is. B. Dat hun voornemen niet gebaseerd is op ongegronde en onverantwoorde praktijken, in de woorden van minister De Jonge kwakzalverij, maar op wel degelijk goed te verantwoorden toepassingen voor medische hulp in de eerstelijnszorg, welke aansluiten bij de kerntaak van een goede huisarts. Aan deze taakuitoefening is de prescriptievrijheid van de arts onlosmakelijk verbonden. 6.

**PRESCRIPTIEVRIJHEID VAN ARTSEN** 6.1 Artsen hebben prescriptievrijheid en zijn vrij om op grond van hun deskundigheid en professionele verantwoordelijkheid een middel aan een patiënt voor te schrijven, ook indien dit een ongeregistreerd geneesmiddel of een off-label indicatie betreft. Daarbij dient de arts wel te blijven binnen de grenzen van een redelijk bekwame beroepsuitoefening, rekening houdend met de stand van de wetenschap en hetgeen in de beroepsgroep ter zake als norm of standaard is aanvaard (vgl. art. 40 Wet BIG jo art. 7:448 BW). 6.2 Off label voorschrijven **ARTIKEL 68 LID 1 GENEESMIDDELENWET** Art 68 lid 1: Het buiten de door het College geregistreerde indicaties voorschrijven van geneesmiddelen is alleen geoorloofd wanneer daarover binnen de beroepsgroep protocollen of standaarden zijn ontwikkeld. Als de protocollen en standaarden nog in ontwikkeling zijn, is overleg tussen de behandelend arts en apotheker noodzakelijk. 6.3 Commentaar bij artikel 68 Geneesmiddelenwet: naar schatting 50% van de geneesmiddelen wordt buiten de registratietekst voorgeschreven. Voor veel patiënten betekent dit een behandeling waarbij zij haast hebben en waarvoor geen alternatief voorhanden is. Off-label gebruik voorschrijven blijft volgens dit artikel mogelijk als er standaarden/ protocollen bestaan en die gevolgd worden. Zijn er die niet, dan is overleg met de apotheker nodig (Kamerstukken II 2005/06, 29 359, 57). Zie Tekst en Commentaar Gezondheidsrecht - Wolters Kluwer (achtste druk, 2019) bij artikel 68 Gmw onder 1. Off-label gebruik. Met andere woorden kan het toegestaan off-label gebruik zich in twee situaties voordoen: i. wanneer standaarden en protocollen voor een bepaald middel aanwezig zijn en ii. wanneer zulke standaarden ontbreken, in overleg tussen de voorschrijvende arts en de apotheker. In casu doet zich de tweede situatie voor, conform de reikwijdte en het toepassingsbereik van artikel 68 Gmw. 6.4 De huisarts als poortwachter is één van de hoekstenen van de structuur van de Nederlandse gezondheidszorg. De poortwachtersfunctie van huisartsen moet worden beschouwd binnen hun bredere rol als spil in de eerstelijnszorg en een goed georganiseerde gezondheidszorg. Daarom is het een abnormaliteit dat de behandelrol en wetenschappelijke benadering van patiënten inzake COVID-19 door de IGJ niet wordt toegestaan. Temeer abnormaal daar een effectieve vroege behandeling juist in de eerstelijnszorg mogelijk is. Zie ook Tekst en Commentaar Gezondheidsrecht – Wolters Kluwer (achtste druk, 2019) Art. 68 Gmw onder 2. Standpunt CBG en IGJ - waaruit blijkt dat het College ter beoordeling van geneesmiddelen (CBG) en de IGJ geen bezwaar hebben tegen off-label voorschrijven van medicijnen, op voorwaarde dat het verantwoord gebeurt. Goed off-label gebruik is het voorschrijven van een geneesmiddel voor een indicatie waar al wél wetenschappelijk bewijs voor is, maar die (nog) niet is beoordeeld door het CBG of het Bureau.

**7 STANDPUNT EN VISIE VAN VERZOEKERS** Zoals in randnummer 6.3 aangegeven gaat het om protocollen en standaarden waarin juist het off-label gebruik is vastgelegd 'positieve protocollen' (situatie i). Een protocol of richtlijn waarin het off-label gebruik ontraden wordt, zoals de SWAB-richtlijn bij COVID-19, valt hier onder - 'negatieve protocollen'. Anders gezegd een protocol of richtlijn waarin het off-label gebruik ontraden wordt, kan de werking van artikel

68 niet buitenwerking stellen, nu deze protocollen niet relevant zijn bij de toepassing van artikel 68. Immers uit de laatste zinsnede van artikel 68 volgt dat bij afwezigheid dan wel ontwikkeling van 'positieve protocollen' overleg tussen de behandelend arts en de apotheker noodzakelijk is (situatie ii). Situatie ii is dan ook het enige wettelijk toetsbaar criterium, nu geen nadere definitie inzake 'protocollen en standaarden' is gegeven. Los hiervan doet zich in dit geval een situatie ii voor. 8. Hierboven hebben verzoekers duidelijk gemaakt hoe het artikel 68 Gmw uitgelegd dient te worden. Aanvullend merken de verzoekers nog op dat artikel 68 enkele onduidelijkheden bevat: bijvoorbeeld "geregistreerde indicaties" is geen wettelijke term. Bovendien is het niet duidelijk wat onder "protocollen of standaarden" precies moet worden verstaan. Deze onduidelijkheden kunnen en mogen nooit in het nadeel van verzoeker sub 1, normadressant ex artikel 68 Gmw, worden toegepast. 9. Uit het legaliteitsbeginsel volgt voorts ook, dat een voorschrift dat door bestuurlijke sancties wordt gehandhaafd, voldoende duidelijk, voorzienbaar en kenbaar moet zijn (ook wel het 'lex certa-beginsel'). Het lex certa beginsel, verlangt van de wetgever dat hij met het oog op de rechtszekerheid op een zo duidelijk mogelijke wijze een verboden gedraging omschrijft (Art. 5:4 Awb). 9.1 Verzoekers zijn dan ook van mening dat in het geval zij hun voornemen (zie hierboven randnummer 3) zouden verwerkelijken er van een normoverschrijding als bedoeld in artikel 68 van de Gmw in hun geval geen sprake is. 9.2 De kern van de rechtsregel is dat een arts in de eerste lijn, op grond van zijn bevoegdheid en bekwaamheid off-label medicatie kan voorschrijven, mits overleg met de apotheker heeft plaatsgevonden. 9.3 Verzoekers wijzen verder op de Beleidsregels bestuurlijke boete Ministerie Volksgezondheid Welzijn en Sport 2019. Uit de Bijlage bij de Boetebeleidsregels kan het volgende getraceerd worden namelijk een boetebedrag van maximaal € 150.000. In de toelichting bij artikel 68 staat dat van een overtreding sprake is: indien er geen standaarden en protocollen zijn en er geen overleg heeft plaatsgevonden. Zie productie 13. 10. In het geval van verzoekers doet zich de situatie voor dat er geen vastgestelde standaarden en protocollen bestaan voor het off-label gebruik van HCQ bij COVID-19 terwijl verzoeker sub 1 in het verleden wel degelijk heeft overlegd met zijn apotheker (zijnde verzoeker sub 2). Daarnaast zal hij ook in de toekomst overleg met de apothekers voeren. 11. De noodzaak tot het off-label gebruik in de eerstelijnszorg van HCQ bij COVID-19 patiënten kan gezien de huidige omstandigheden als een verantwoord alternatief dienen. Het gebruik van HCQ indien het hierboven weergegeven voorschrift wordt gevolgd levert geen gevaar voor de gezondheid op. Zie hierboven 4.11 en 4.12. 12. De visie van verzoekers voor wat betreft de belangenafweging is allereerst dat de IGG niet kan volstaan met een enkele belangenafweging op het veilig gebruik. Er dient eveneens een afweging tussen leven en dood gemaakt te worden. Wanneer er aanwijzingen zijn dat het inzetten van HCQ in de eerstelijnszorg de kans op overlijden verkleint, (zie hierboven onder punt 4.3 t/m 4.13) dan moet het mogelijk zijn om medisch verantwoord kortdurend, maximaal vier-vijf dagen, HCQ voor te schrijven in combinatie met andere medicamenten en supplementen die zonder recept verkrijgbaar zijn, zoals zink. 13. De noodzaak van deze mogelijkheid klemt te meer nu er geen enkele (alternatieve) behandeling in de eerstelijnszorg voorhanden is – behalve dan het voorschrijven van paracetamol. Concluderend wijzen verzoekers erop dat uit artikel 68 van de Gmw voortvloeit dat off-label voorschrijven van een medicatie na overleg tussen de arts en de apotheker is toegestaan. Zij hebben middels dit schrijven uitgebreid gemotiveerd waarom en onder welke voorwaarden zij voornemens zijn om in de eerste lijn HCQ bij de behandeling van COVID-19 patiënten in te zetten. 14. Reactie op dit voornemen middels kennisgeving of besluit

Hierboven hebben verzoekers u in kennis gesteld van hun voornemen tot voorwaardelijk en kortdurend off-label gebruik van HCQ (conform het protocol als neergelegd in randnummer 3). 15.1 In het geval u van mening bent dat verzoekers inderdaad geen overtreding zouden plegen zoals neergelegd in artikel 68 Gmw, verzoeken wij u hiervan op korte termijn een schriftelijke bevestiging te sturen. Indien u van mening mocht zijn dat in dit specifieke geval behandeling met HCQ, ondanks overleg met de apotheker, niet zou zijn toegestaan dan dient naar de mening van verzoekers allereerst dit verbod te zijn gebaseerd op een wettelijke grondslag. 15.2 De wettelijke termijn als bedoeld in artikel 4:13 lid 2 AWB

Op 16 april 2020 hebt u aan verzoeker sub 1 een brief geschreven die hierbij wordt geproduceerd als productie 14. In die brief neemt u een standpunt in dat impliceert dat een behandeling in de eerste lijn als hierboven omschreven in randnummers 2 en 3 en 4.4 verboden is althans ontraden moet worden aan de eerste lijn en u kondigt indien verzoeker zich niet aan dat standpunt zou conformeren “passende maatregelen” aan. In dat licht wijzen de verzoekers op een arrest van De Hoge Raad van 27 juni 1986. Daarin heeft zij geoordeeld over de bevoegdheid van de Inspectie. De inspectie mag geen bindende voorschriften geven of normen stellen voor de wijze van beroepsuitoefening. Die bevoegdheid is voorbehouden aan de wetgever en de rechter (HR 27 juni 1986, NJ 1987/898 (Methadonbrief)). Verzoekers hebben recent een brief van u ontvangen, een brief van 17 juni 2020, welke hierbij wordt geproduceerd als productie 15. In die brief neemt u het standpunt in dat in de Geneesmiddelenwet aan u niet de bevoegdheid is toegekend om aan verzoeker sub 1 toe te staan dat hij, in de eerste lijn, HCQ zou voorschrijven aan patiënten die lijden aan Covid-19. Verzoekers nemen dit standpunt over. Verzoekers koesteren de hoop dat u wellicht door de feiten die zich sinds u die brief schreef, sinds 16 april 2020, hebben voorgedaan en/of door de argumenten en feiten als in deze schriftuur gepresenteerd een ander standpunt dan het standpunt dat u innam blijkens uw brief van 16 april (productie 14) bent gaan innemen. Mocht u daarentegen van mening zijn dat verzoekers hun voornemen nog steeds ontraden dienen te worden en/of zelfs hen verboden zou moeten worden hun voornemen te verwerkelijken en/of dat verzoekers indien zij hun voornemen zouden verwerkelijken, zij beboet zouden dienen te worden ex artikel 68 lid 1 Gmw, dan dient u in beginsel binnen de maximale wettelijke termijn van acht weken een gemotiveerd besluit af te geven. Waar u in april 2020 al een duidelijke mening had, zult u, als u, onverhoopt, nu nog steeds diezelfde mening zou zijn toegedaan niet de maximale termijn van acht weken nodig hebben om dat gemotiveerd weer te geven. Vier weken Verzoekers hebben de visie dat met de behandeling in de eerste lijn zoals zij die weergeven mensenlevens gered kunnen worden. Verzoekers hebben er vanuit de taak die zij binnen de gezondheidszorg op zich hebben genomen, kort omschreven in de eerstelijns hulp hun patiënten die lijden aan het coronavirus, zo goed mogelijk behandelen en daarmee bewerkstelligen dat zij niet in het ziekenhuis behoeven te worden opgenomen, een groot belang bij dat u veel sneller, namelijk binnen een redelijke termijn van vier weken beslist. Gelet op de hoogte van de boete zoals beschreven in de beleidsregels, 150.000 euro, van verzoekers niet kan worden verwacht dat zij afwachten of er handhavend zal worden opgetreden als zij uitvoering zouden geven aan hun voornemen.

Verzoekers vinden het van belang dat er geen onduidelijkheid bestaat over de vraag of zij passende maatregelen, op strafrechtelijk terrein of wellicht ook op tuchtrechtelijk terrein, van u te vrezen hebben indien zij hun voornemen zouden verwerkelijken,. Zij vinden het ook belangrijk dat voor u duidelijk is waarom zij een veel kortere termijn dan de wettelijke maximale termijn willen aanhouden. Zij menen dat als zij de therapie als omschreven in randnummer 3 toepassen daarmee mensenlevens gered



worden .Tevens zal de druk op de ziekenhuizen aanzienlijk verminderen. In het geval verzoekers binnen de hierboven genoemde termijn van vier weken na dagtekening geen reactie van u ontvangen zijn verzoekers voornemens beroep wegens niet tijdig beslissen in te stellen bij de bestuursrechter. Indien en voor zover de Inspectie meent dat geen sprake is van enige overtreding bij uitvoeren van het voornemen, volstaat voor verzoekers een simpele schriftelijke bevestiging. Deze schriftuur wordt u als aangetekend stuk toegezonden en ook direct via de fax naar uw faxnummer 088-1205001. Hoogachtend, P.C. van Houten, gemachtigde.

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*Notable & Quotable: Fear for Our Children?*

‘We’re meeting because we adults are afraid.’

July 15, 2020 7:12 pm ET

*Mark McDonald, a psychiatrist who specializes in children and at-risk youth, [testifying](#) at a June 24 hearing of the Orange County, Calif., Board of Supervisors:*

Children are not dying from Covid-19. Children are not passing the disease on to adults. So the only question is, “Why are we even having this meeting tonight?” We’re meeting because we adults are afraid.

As parents, we will face many moments of anxiety: seeing our children off on their first day of kindergarten, their first day of camp, their first year of college. We may want to keep them home to protect them from the world, which can indeed be a frightening place. But let’s be clear, when we do that, we are not really protecting our children. We are only attempting to manage our own anxiety, and we do that at their expense. We are acting as negligent parents. We are harming our children. We are failing them.

We must agree to make decisions in the best interest of the children. If we do not—if, paralyzed by fear, we continue to act purely out of selfinterest—we will ensure an entire generation of traumatized young adults, consigned to perpetual adolescence and residency in their parents’ garages, unable to move through life with independence, courage, and confidence. They deserve better—we owe it to them as parents.