To: Ravalli County Board of Commissioners and the Ravalli County Health Board
From: James R. Olsen
Date: 20 August 2020
Subject: **Food and Drug Administration (FDA) Decision on Chloroquine**

A lot of people who showed up at the Health Board meeting a month or so ago were adamant about the effectives in Chloroquine (CQ) in treating COVID-19; I thought I would look at the FDA's rationale for revoking its emergency use in a decision on 15 June.

What I thought would take a day or so turned out to be a lot more work because, once I got into reviewing the FDA decision, I began to think they made a mistake. What I found is in the attached paper: "Comments on FDA Notice."

Hydroxychloroquine (HCQ), a compound that incorporates Chloroquine, has fewer side effects and was nearly always the drug used in trials. So, the rest of this letter will focus on HCQ. What I found was that trails of HCQ have different implications for these categories of people:

- Hospitalized with many or all Intensive Care Unit (ICU) patients.
- Hospitalized with mild or moderated symptoms.
- Trial groups which include the two categories above.
- People who have been recently exposed.

In the last category, HCQ is used as a prophylaxis — that is to try to prevent the infection.

For seriously ill patients some trials show a negative effect — there may be a case for stopping the use of HCQ for seriously ill and ventilated patients.

However, the FDA revoked the all used of HCQ in spite of the fact the FDA based their decision on a small group of studies, most with small sample sizes, using phrases such as "very similar" outcomes.

But that doesn't mean that the data showed it didn't work. What the studies showed was either *no difference* or *an improvement* with a much wider confidence interval. The only mention of "no significant difference" statistically was a study the FDA caveated as having limitations on how the trial was set up. These are the studies *the FDA* chose.

The FDA cited the risks for HCQ, even though this drug has been used by people for decades for long term use at prescribed doses. The primary study they relied upon *used a higher dose* and experienced higher adverse (but not fatal) effects.

In the view of the FDA Revocation, there was no improvement with the drug and there were attendant risks — so its emergency authorization was revoked.

It is when I got to this study that I decide to take the time for a thorough review. Failing to achieve a 95% confidence that HCQ is effective — very possibly due to the small sample size — does not mean that one could not say it is effective at a 67% confidence.

What I found was that there were tens-of-thousands papers, trials, and studies on COVID-19 — which means no one can read them all. Reading the ones cited by the FDA, and adding few

others, I found that for 1) mild to moderated symptoms, 2) general hospitalized populations, and 3) recently exposed people HCQ COVID-19 treatment trials show:

- No difference compared to the normal "standard of care" or an improved outcome.
- No side effects that are not already known and managed.

I concluded that the revocation was improper and seems arbitrary. The revocation does not appear to be consistent with the criteria specified in Food Drug and Cosmetics law cited by the FDA as the authority for revocation.

So, with the FDA and CDC running full speed at getting treatments and vaccines through, why did the FDA revoke Chloroquine? One cannot deny that it has become a political. Was real reason the fear unsupervised use? Or, were may there be other "nonmedical" pressures at work?[1]

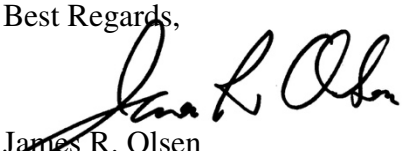
If there is the unstated reason, it is very unfortunate. Yes, there are apparently more effective treatments for hospitalized patients — antiviral remdesivir, and the steroid dexamethasone, in addition to several other treatments depending on signs and symptoms.[2]

But there is nothing approved for someone who knows they have been exposed but have not had a positive test or symptoms. There are compelling trials — although imperfect — that say HCQ should be given a hard look for this application as well as for mild to moderated symptoms at the doses provided for Malaria.

The data is clear. There are risks with HCQ in for treating COVID-19. Some of the side effects, including the change in an electrocardiogram (ECG), may overlap with the signs and symptoms of COVID-19.[3] The HCQ side effects have been around a long time.

The data suggests that these can be mitigated significantly with a baseline ECG and follow-ups and physicians who are aware for the other rare, but serious side effects — just like other prescription drugs — which is the practice in most settings described in the literature I have read.

Best Regards,



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[1] It is also a wildly available and inexpensive drug — and claims have been made about this, versus pharmaceutical industry profits. I have not looked into this and have no comment.

[2] Welsman, Nicole. "Doctors are better at treating COVID-19 patients now that they were in March." (a news item) 8 Jul 2020. *The Verge*. https://www.theverge.com/2020/7/8/21317128/improved-covid-treatment-hospitals-remdesivir-dexamethasone

ECG = Electrocardiogram = EKG — Elektrokardiographie (German)

A symptom is felt by the patient; a sign is some other measure such the result of a blood test or ECG.

[3] Kincaid, Ellie. "COVID-19 Daily: Fauci Testifies, HCQ Trials Lack ECG." (News item). Medscape, 25 Aug 2020.
McLaren, Jesse, "ECG Cases 8 Cardiovascular Emergencies During The COVID-19 Pandemic." (Show EKGs). (Peer reviewed). *Emergency Medicine Cases*. Apr 2020.

COMMENTS ON FDA NOTICE TO REVOKE USE OF CHLOROQUINE FOR TREATING COVID-19[1]

JAMES R. OLSEN • 25 AUGUST 2020

CONTENTS

Preamble.

A guide to find the truth behind the "science driven" politics.

• Trust the science. You don't have to be an expert to read studies. You will run into technical language and lingo which you will find runs through the industry. After taking the time to understand about a half dozen technical terms and what they really mean, after making yourself go through this painful process through a half dozen studies written by experts, you will be on your way to becoming a "citizen expert" — on your way to holding your own with those experts, asking the hard questions that show you cannot simply be dismissed because you are not a member of their guild.

You will soon learn that there is a virus and there is a disease:

SARS-CoV-2 (Severe Acute Respirator Syndrome Coronavirus – 2) is the virus;
COVID-19 (2019 Novel Coronavirus) is the disease caused by the virus.

• Question the scientist. The authors of a paper seldom have a nefarious intent – the errors are human, subject to human limitations, and subject to institutional biases that have creeped into their thinking – unavoidable frailties even for me, which requires self-examination every step of the way.

My rule for PhDs when I was managing engineering projects was, "I am reasonably intelligent. If you cannot explain it to me, you probably don't understand it yourself."

You can always look for common sense no matter what subject area you are reading — but I try to subject myself to the discipline to stick to the data in front of me and not add my own fuzzy logic:

1) Are the assumptions valid; are there assumptions you can think of that are not accounted for?
2) Do the conclusions match the data?
3) Did the author take uncertain raw results and declare unjustified certainty in their conclusion?
4) Or, are conclusions drawn, such as "it does not do…" when, in fact, the study simply did not have sufficiently large data set to show a premise one way or the other.
5) Does the industry have a bias due to a commonly held belief system or biases due to "what will be funded."

These are the most common mistakes I find in peer reviewed literature from forest wildfire science to highway safety and capacity to biosafety to alternative theories of government… and the list goes on.

• Don't trust the scientist's boss. Scientific institutions, government entities, and activist movements that present a counter narrative — always have a bias. There are instances where participants have the self-discipline to account for their own biases – bias cannot be eliminated, only managed — but that self-discipline is rarer than one would hope.

[1] Hinton, Denise RADM, Chief Scientist, Food and Drug Administration. Letter to Gary Disbrow, Dept. Asst. Secretary, US Dept. of Health and Human Services dated 15 Jun 2020 and attached "Memorandum Explaining Basis for Revocation of Emergency Use Authorization for Emergency Use of Chloroquine Phosphate and Hydroxychloroquine Sulfate" — https://www.fda.gov/media/138945/download. Hereinafter referred to as "FDA Revocation."

The Promise of Chloroquine to treat COVID-19.

Conclusion: The FDA revoked the use of Chloroquine for treating COVID-19 without waiting to see if at least one of several mechanisms that have shown promise would work.

Discussion: On June 15, the FDA revoked the emergency use authorization (EUA) of Chloroquine (CQ) and Hydroxychloroquine (HCQ) for Covid-19 — this letter and attachments is referred to the *FDA Revocation*.[2]

CQ and HCQ have been authorized and continue to be used for Malaria and other disorders — they have a similar effect to Quinine in treating Malaria.[3] Quinine occurs naturally in the bark some species of flowering trees and shrubs of the Chinchona genus; it can also be synthesized — it has centuries long history of traditional use and is still used today.[4]

The FDA Revocation (noted that the EUA was granted because studies of CQ and HCQ interacting with SARS-CoV-2 in vials showed promise, suggesting human trials were justified.

The promise was multifold as illustrated in figures below. [5]

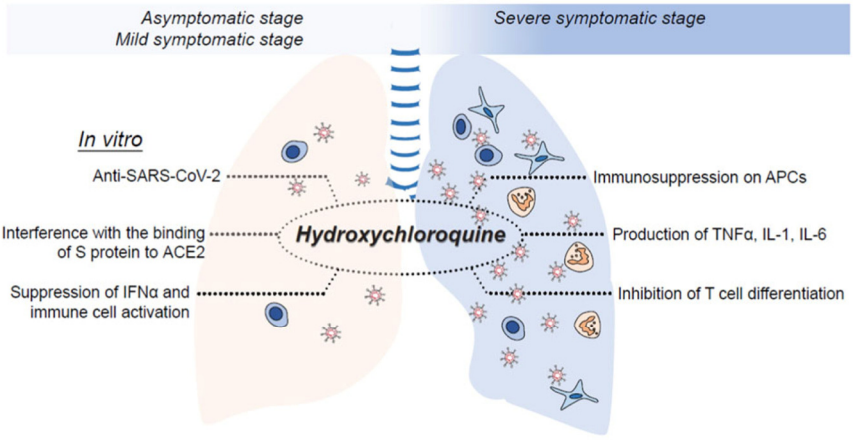

Fig. 1 Hydroxychloroquine (HCQ) shows several potential effects against COVID-19 disease. While HCQ is likely to have the ability to control the CRS, suppress hyperactive immune responses and subsequently promote tissue repair, which leads to significantly improved severe symptoms in late-stage of COVID-19.

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[2] Ibid.

[3] Watt, George, et. al. "Chloroquine and quinine: A randomized, double-blind comparison of efficacy and side effects in the treatment of *Plasmodium falciparum* malaria in the Philippines." *Transactions of The Royal Society of Tropical Medicine and Hygiene*, Volume 82, Issue 2, March-April 1988, Pages 205–208, https://doi.org/10.1016/0035-9203(88)90411-7

[4] Encyclopedia Britannica. "Cinchona." https://www.britannica.com/plant/Cinchona

[5] {Written in May, published 8 July, having been submitted in May. Figures shown are from pages 2 and 4 respectively} Li, X., Wang, Y., Agostinis, P. *et al.* "Is hydroxychloroquine beneficial for COVID-19 patients?" *Cell Death and Disease,* (Published by *Nature Research* – which also publishes *Nature* and *Scientific American)* **11,** 512 (2020). https://doi.org/10.1038/s41419-020-2721-8

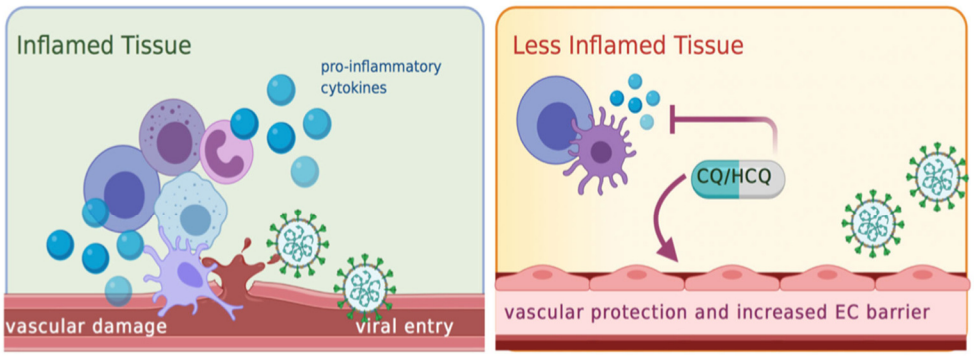

Fig. 2 Speculative dual role exerted by HCQ/CQ on calming tissue inflammation and protecting the endothelium against SARS-CoV-2 mediated injury.

It is not clear that the mechanisms that held out hope have been fully explored.

> There have been studies that suggest some of the mechanisms don't work but, because of the short time during which COVID-19 has been a subject of study, there appears that there is no comprehensive study that dismisses all of the possible mechanisms; some that suggest a benefit — although none that I can find that document Chloroquine as "the silver bullet."

For example, on 10 July, *Science News* came out with the headline, "Why lopinavir and hydroxychloroquine do not work on COVID-19", a non-peer review journalism site, the article submitted by the University of Basel, Switzerland.[6] It references a peer reviewed paper from the same university, "Effect of Systemic Inflammatory Response to SARS-CoV-2 on Lopinavir and Hydroxychloroquine Plasma Concentrations."[7]

But this study was limited to looking at the amount of HCQ in plasma from COVID-19 patients — drawing conclusions based on other insights that there was not enough present in the lungs to kill of SARS-CoV-2 — certainly not a comprehensive study on the effectiveness of Chloroquine (CQ) or its sister, Hydroxychloroquine (HCQ) for an impact on the immune system.

The authors of the study worked with a hospital in Basel, Switzerland — their work was driven the rather urgent need to figure out the best was to treat severely ill COVID-19 patients, which was the population they studied. This study was focused on inflammation, looking at the correlation with inflammation indicators with two drugs, Lopinavir and HCQ — HCQ which was, "For comparison, we measured hydroxychloroquine (HCQ) concentrations, because HCQ is characterized by a different metabolism."[8]

The study was confounded by presence of other interventions and the population being given other drugs (which were checked for known drug interactions). One was Tocilizumab (mostly

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[6] University of Basel. "Why lopinavir and hydroxychloroquine do not work on COVID-19." *ScienceDaily*., 10 July 2020. www.sciencedaily.com/releases/2020/07/200710112108.htm.

[7] Marzolini, Catia, et. al. "Effect of Systemic Inflammatory Response to SARS-CoV-2 on Lopinavir and Hydroxychloroquine Plasma Concentrations," *Antimicrobial Agents and Chemotherapy,* American Society of Microbiology. 2020. DOI: 10.1128/AAC.01177-20.

[8] Ibid, Page 2.

prescribed for rheumatoid arthritis) was given for inflammation. But inflammation was the subject of the study.

The conclusion of the study itself was far from the headline. Its results are focused on the correlation of the drugs administered and inflammation indicators – and there are plenty of caveats related to the population, age, and whether or not they were in the Intensive Care Unit (ICU) as well as number of side observations. The study does not look for whether there was any reduced mortality or time with severe symptoms.[9]

Of course, there is nothing wrong with making a judgement with this data when the clock is ticking and people are dying — a decision of how to treat based on the study and other factors is certainly useful and necessary. The problem is that the news release headlines with a statement that goes well beyond the conclusion of the study.

Another study, which found no benefit for HCQ in intubated patients, got to the practical point of decision making: "Clinical guidance at our medical center has been updated to remove the suggestion that patients with Covid-19 be treated with hydroxychloroquine."[10]

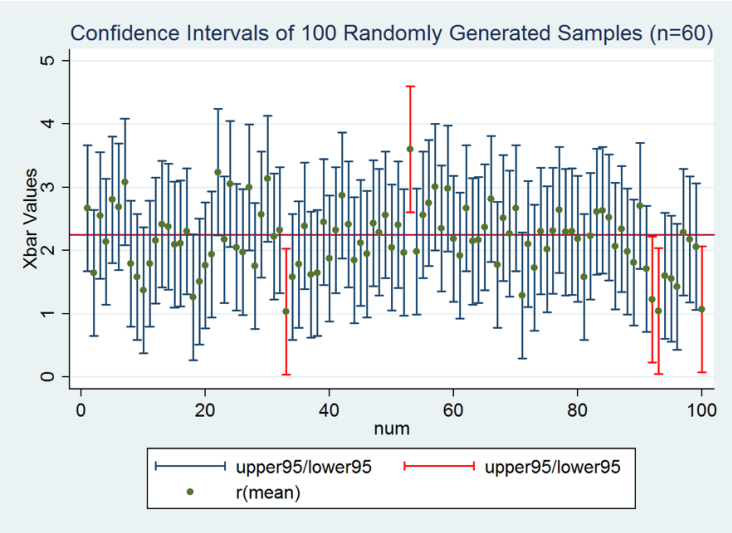
The number of studies and papers on COVID-19 bloomed into the thousands, 23,000 by the middle of May.[11] In the rush to find answers, studies are often pre-published, referenced, and become news items — too many going through the process illustrated here. So, this paper, as well as the FDA decision, deals with a small sample a very large body of work.

A Note on Statistics and Epidemiology.

The data and analysis we are discussing is called Epidemiology — the study of disease and health in populations, which invariably involves identifying a population, taking measurements, and collecting data — get one in the math-world of statistics. Things like "confidence interval" are statement about the data — regardless where it came from.

The math and the underlying rules of statistics are the same for political polling, engineering, and epidemiology. A confidence interval is the lower and upper bound of actual value if were could measure it precisely, with a … confidence, usually 95% — meaning you are 95% confident that the real value of what you are measuring is between the two values. Of course, for a particular trial, the real value is either inside the interval or not. The idea of random sampling and confidence intervals is show in the graphic below – the red samples and their confidence intervals do not include the actual real value.

[9] Note also, "These calculations are supported by studies failing to demonstrate a benefit of HCQ both in hospitalized patients with COVID-19 (37) and as prophylaxis after SARS-CoV-2 exposure (38). " Ibid, Page 7.
[10] Geleris, Joshua, et. a. "Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19." *New England Journal of Medicine,* 2020: 382:2411-2418. DOI: 10.1056/NEJMoa2012410, page 2418.
[11] Brainard, Jeffery. "Scientists are drowning in COVID-19 papers. Can new tools keep them afloat?" *Science Magazine.* 13 May 2020. https://www.sciencemag.org/news/2020/05/scientists-are-drowning-covid-19-papers-can-new-tools-keep-them-afloat



So, the scientists do their study and collect the data — say a group of patients tested positive for SARS-CoV-2: Did patients who took HCQ have a better chance of testing negative than people who did not take it over some period?

The scientists run the results through statistics equations. It could be that they cannot say with 95% confidence that HCQ improved the odds for shedding the virus; *and* they cannot say with 95% confidence that HCQ *didn't* improve the odds. This is a common result with small sample sizes — the precisely accurate answer is "we don't know with any certainty."

"The X was not *shown to* Y" (since it did not do so at a 95% confidence). Therefore, one occasionally finds reverse statement X does *not do* Y — this is *a false statement* unless the study also showed that X did not do Y with 95% confidence. Sometimes the authors of papers will do this as well.

This happens in many disciplines from forestry to highways by those "for" and "against," whatever the issue it may be. Unfortunately, the whole concept of risk management may get lost in the process. There is a great popular book on the subject, *The Signal and Noise — why so many predictions fail but some don't* — in fact, it has a commentary on the epidemiology of flu predictions.[12]

So far, we have only talked about the math of sampling. But there is even more dangerous ground when the nature of the data and the setup of the experiment is considered. Many peer reviewed studies do what they should do — recognized this in a section titled something like "limitations." Here the setup of the study, the characterizations of the population and data collection are noted. It is *critical* to note these possible or probable biases or additional uncertainty are *in addition* to any statement about a confidence interval.

[12] Silver, Nate. *The Signal and Noise — why so many predictions fail but some don't*. NY: The Penguin Press. 2012. This book introduces Bayesian probability theory — conditional probability — which we used a lot in the engineering systems I worked on. Silver gives an example of applying Bayes's Theory to mammograms on pages 245-246.

FDA's flawed analysis of effectiveness of Chloroquine to treat COVID-19.

The FDA Revocation than precedes to a "*Review of New Information to Assessing Whether CQ and HCQ May Be Effective in Treating COVID-19.*"[13]

Conclusion: The FDA arbitrarily dismissed positive results of HCQ, one showing statistically significant improvement. The FDA magnified the negative side effects without taking into account that these occurred when doses well over the norm for Malaria were used. The data provided in the papers referenced in this section of the FDA Revocation suggests that HCQ does improve mild to moderate cases with normal doses when done under a physician's care who checks for side effects.

This section cites 8 studies, declaring one as most relevant (Tang)[14] and the others not very relevant because of inconsistencies, small sample sizes, or observational (not randomized).

- Tang, the "relevant study" that uses a high dose of HCQ, shows a minor, non-significant difference from standard care and has the expected magnified side effects.
- *One study cited by the FDA, with sample size on par with Tang, shows a significant improvement in shedding the virus with a normal dose and few side effects.*[15]
- Four studies had small sample sizes (22 to 45, split into two or three groups), two showing no difference, one showing standard care better than HCQ, the third showing improved outcomes with HCQ.
- A non-peer review report with 93 subjects showed not difference.
- One was withdrawn by the authors.

The selection of one study as relevant and dismissing a study showing HCQ improvement appears arbitrary – as no specific rationale was given.

Justification: Proceeding point-by-point in this section:

"Clinical Pharmacology Assessment Regarding Dosing"

- The first paragraph deals with experiment "in vitro," in essence in a test tube — suggesting that these were not valid since the dosage to have the same effect in a cell would require excessive dosage to the person — UNLESS they CQ/HCQ had "immunomodulatory," that is effects on the immune system. This should be no surprise, since HCQ is known to affect the immune system when it is used for autoimmune diseases.[16]

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[13] FDA Revocation. Page 4 of Memo.

[14] Tang, Wei, et. al. "Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial." *BMJ (Previously the British Medical Journal),* 2020. 369:m1849. http://dx.doi.org/10.1136/bmj.m1849

[15] Huang, Mingxing, et. al. "Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19," 4 May 2020, *National Science Review*, Oxford. https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa113/5848167

[16] {Toxicity of Long-Term Use Of HCQ} Wolfe, F. and Marmor, M.F. "Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus." 2010. *Arthritis Care Res*, 62: 775-784. doi:10.1002/acr.20133.

"Published Literature Regarding Viral Shedding."

- Viral shedding means that the virus has reproduced in a cell and left the cell. In this case the evidence is one of the varieties of molecular tests.
- The FDA Revocation goes on to provide a brief narrative regarding eight studies shown in Table 1.[17] The narrow subject of viral shedding is misleading since some studies went further than measure the effect on symptoms.
- The first entry in Table 1, by Tang, is characterized by the FDA as the most compelling — being a randomized trial — that is the population that gets HCQ is chosen randomly. The FDA Revocation, on page 7, states that:

> Only randomized controlled trials can answer the question of whether HCQ or CQ is of clinical benefit in hospitalized patients with COVID-19, and the RECOVERY Trial results offer persuasive evidence of a lack of benefit of HCQ in the treatment of hospitalized patients with COVID-19.

But decisions are made on what to do about COVID-19 all the time without a randomized study — including mask mandates, whose justification is based upon mechanical experiments and retrospective and observational analysis.[18]

Randomization as *a* major criterion for a quality study makes sense, although there is much more to it than randomization, including bias, how the population is selected, how the information is collected, and so on. Tang falls short of the "gold standard,"[19] a randomized study where the subjects and providers do not know who they are — "closed label." Tang is an open label study.

{One of many articles dealing with the beneficial effect of changing Ph as a optional or additional therapy} C. Ponticelli & G. Moroni, "Hydroxychloroquine in systemic lupus erythematosus (SLE)," *Expert Opinion on Drug Safety,* 16:3, 411-419, 2017. DOI: 10.1080/14740338.2017.1269168

[17] FDA Revocation Memo, pages 4 and 4. On pages 4 and 5 of the FDA Revocation, eight studies are cited.

A number of the studies in Table 1 originate from the People's Republic of China (PRC).

The science literature in the PRC is on par with other industrialized countries, and they frequently publish in Western peer-reviewed journals. (This was certainly true of the translated Soviet Union engineering papers I had occasion read during the Cold War). The reports of China "bungling the job," becoming secretive, and accusations of disfunction because of their relationship with the World Health Organization (WHO) are driven by Chinese political officials, and possibly by the senior management of institutions – all nations, including the United States, suffer from "dichotomy of truth" to some degree – as illustrated in this report.

It appears that the PRC's managed capitalism initiative has depended upon the importation of science from other countries as well as creating an innovative intellectual environment in their own country – and engagement with the West — than the old Cold War Soviet block and Moa's China.

So far, I have noted no instances of suppressed science in the international press – and it would have been noted if it went on to any extent. It seems to me that if the West engages in an encirclement policy to the extent of the Cold War with the Soviet Russia and the Eastern Communist Block then it would be unsurprising to see the PRC move to a more science suppression and secretiveness than exists now.

[18] Chu, Derek, et. al. "Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis." The Lancet. 1 June 2020. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31142-9/fulltext

[19] Zacci, J. H. "How to assess epidemiological studies." Postgraduate Medical Journal, 80:941, March 2004. https://pmj.bmj.com/content/80/941/140

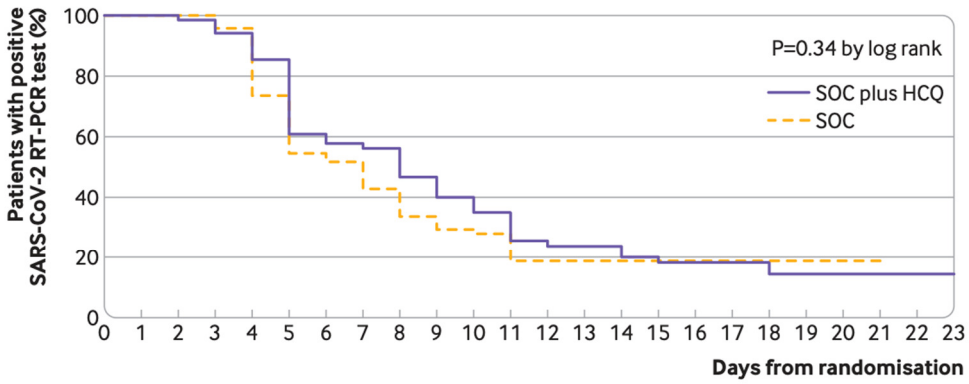
Of course, given the time factor, very few of the studies for COVID-19 meet this standard — none for the citations in the FDA Revocation. While the quality of the trials and studies vary widely, a retrospective study — that looks at "what happened in the past" can provide extremely useful information if done correctly — as can be seen with ventilation and the medical community's attempt to optimize why, how, and when.[20]

- Table 1, paper 1: Tang, "Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease ...."[21] This study had a population of 150 who tested positive and had at least some symptoms. People with severe underlying conditions were excluded. The patients and doctors knew who was in which group (called "open label").

  Half were given HCQ (1200 mg for 3 days followed by 800 mg. The Mayo Clinic gives the standard dose as 800 mg followed by 400 mg for active malaria – lower doses for other purposes[22]) and standard care and half standard care alone. 63% of the subjects were also given some other antiviral as part of the standard care, 59% were given antibiotics. The time in the study was two weeks, unless the disease was severe than the time was three weeks.

  "Adverse effects" 3% (two people) reported as serious for HCQ, one a return to the hospital and one an upper respiratory infection. 10% had diarrhea and 17% other mild side effects for the HCQ group and 9% for the standard care group.

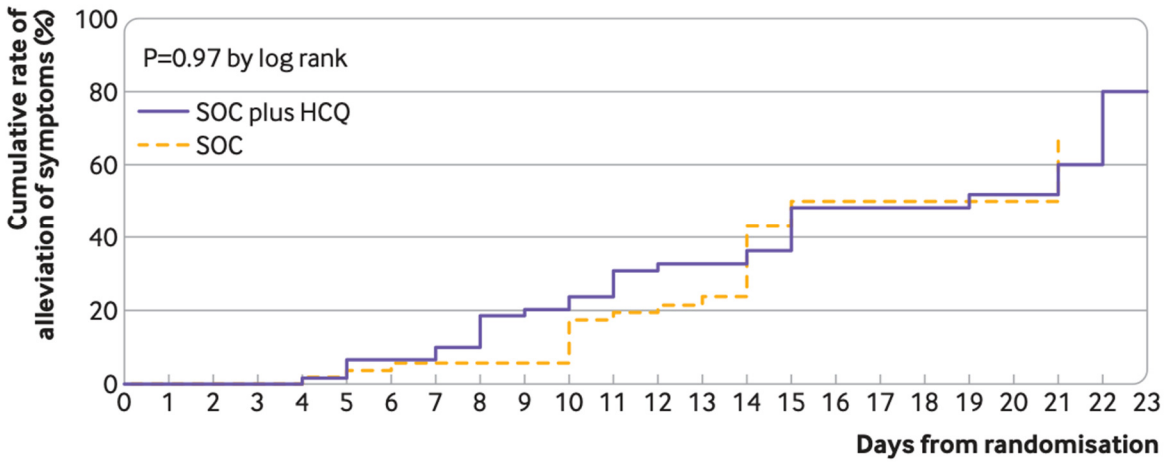
  The results for both groups for eliminating the virus and alleviating symptoms were considered the same given the sample size – although the data show some difference in favor of HCQ of eliminating the virus in test sample by 4.1%, even though it took bit longer, and alleviation symptoms — the charts are from the paper (SOC = Standard of Care).



[20] Anesi, Goerge. "Coronavirus disease 2019 (COVID-19): Critical care and airway management issues." July 2020. UpToDate. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-critical-care-and-airway-management-issues

[21] Tang, Wei, et. al. "Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial." *BMJ,* 2020; 369:m1849. http://dx.doi.org/10.1136/bmj.m1849

[22] "Hydroxychloroquine (Oral Route)," Mayo Clinic. Acessed 23 Aug 2020. https://www.mayoclinic.org/drugs-supplements/hydroxychloroquine-oral-route/proper-use/drg-20064216

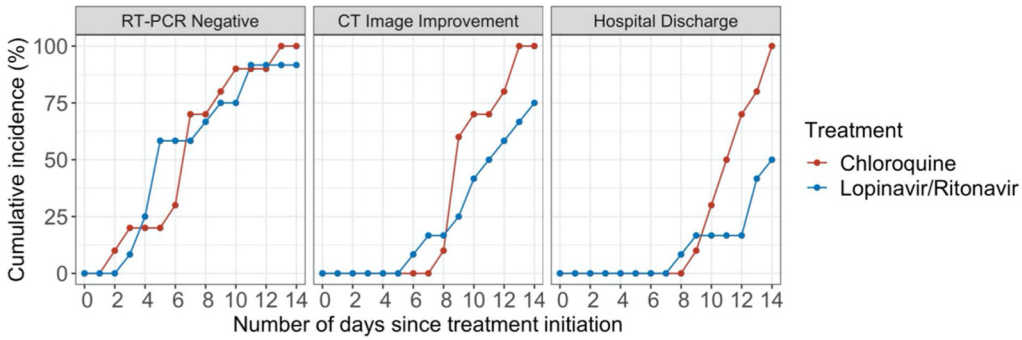


The conclusion of the study is that HCQ did not show additional benefits and more frequent side effects — although with open label the accurate reporting of side effects could well have been affected by patient expectations. While at a 95% confidence the study showed no improvement, a 65% confidence interval would probably be derived from the data. If there were no difference in side effects, one would come to a different conclusion — it is not a magic bullet, but, along with other treatments, HCQ tends to relieve symptoms sooner in mild cases.

On the other hand, HCQ is a drug that is taken for years with known side effects at recommended doses — side effects that can be monitored by a physician.

Based on this study it is hard to justify revoking the use HCQ to treat COVID-19 — although it could be a reason for a revision by the FDA to specify a lower dose than was used in this trial.

- Table 1, paper 2: Huang, "Treating COVID-19 with Chloroquine."[23] This is a study of 22 patients who tested positive and had moderate to severe symptoms. The trial was a comparison between HCQ (500 mg) and Lopinavir/Ritonavir. The conclusion was that the small sample suggests the HCQ could be an inexpensive option compared to other therapies. This result was with a lower dose than the Tang study and there were no serious side effects. *This result was dismissed in the narrative and apparent decision making by the FDA.*



[23] Huang, Mingxing, et. al. "Treating COVID-19 with Chloroquine," *Journal of Molecular Cell Biology*, Volume 12, Issue 4, April 2020, Pages 322–325, https://doi.org/10.1093/jmcb/mjaa014

- Table 1, paper 3: Chen, "… clinical characteristics and antiviral drugs … in patients with COVID-19…" (Non peer reviewed).[24] This is a "retrospective" study — that is, there was no designed trial but a review of the data using specified criteria — the data was a review of electronic records of 284 patients.

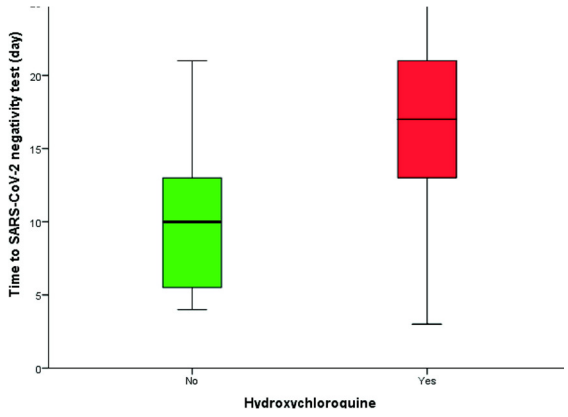
  > "The majority of patients received antibiotic treatment (75.0%) and oxygen therapy (64.8%). Four (1.4%) patients received mechanical ventilation, and 24 (8.5%) patients were admitted to ICU. A total of 25 (8.8%) patients received chloroquine, and 36 (12.7%), 78 (27.5%), 69 (24.3%) patients were treated with the antiviral drugs of oseltamivir, lopinavir/ritonavir, and arbidol, respectively. Thirty-one (10.9%) patients were treated with corticosteroid, 9 (3.2%) patients received immunoglobulin, and 2 (0.7%) patients received ribavirin (Table 1)."[25]

  The study found no difference between any intervention or none. The table entry in the FDA Revocation only deals with CQ and does not report the results for all of the other interventions.

  Doctors choosing treatment options were attempting to optimize the patients outcome which might well be the dominate factor in the "results are all the same."

- Table 1, paper 4: Mallat, "Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease…" (Not peer reviewed).[26] A retrospective study of 34 patients at the *Critical Care Institute, Cleveland Clinic Abu Dhabi*. 55.9% with symptoms, 41.2% with pneumonia. 61.8% received HCQ (400 mg). No side effects were recorded. on treatment options

  The authors admit the small sample size and retrospective nature of the study are issues. *The study did find a large difference in the time patients who tested negatively — people taking HCQ taking longer.*

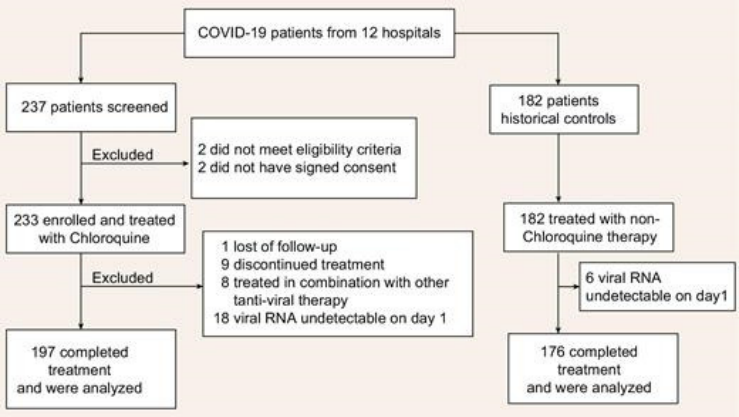


[24] Chen, Zudan, et. al. "Associations of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: a retrospective cohort study." MedRxiv. BMJ. 2020. https://doi.org/10.1101/2020.04.09.20058941

[25] Ibid, page 7.

[26] Mallat, Jihad, et. al. "Hydroxychloroquine is associated with slower viral clearance in clinical COVID-19 patients with mild to moderate disease." MedRxiv. BMJ. 2020. https://doi.org/10.1101/2020.04.27.20082180

- Table 1, paper 5: Huang, "Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19."[27] This study compared HCQ (half with 500 mg and half with 250 mg/day) versus non-HCQ therapy, both getting the standard of care for China, for over 300 patients total.



Most patients had moderate symptoms at the start of the trial. Of those, seven patients experienced "aggravated" symptoms — 1 in the chloroquine group and six in standard care all seven patients eventually tested negative.

There was a statistically significant difference in the time to test negative.

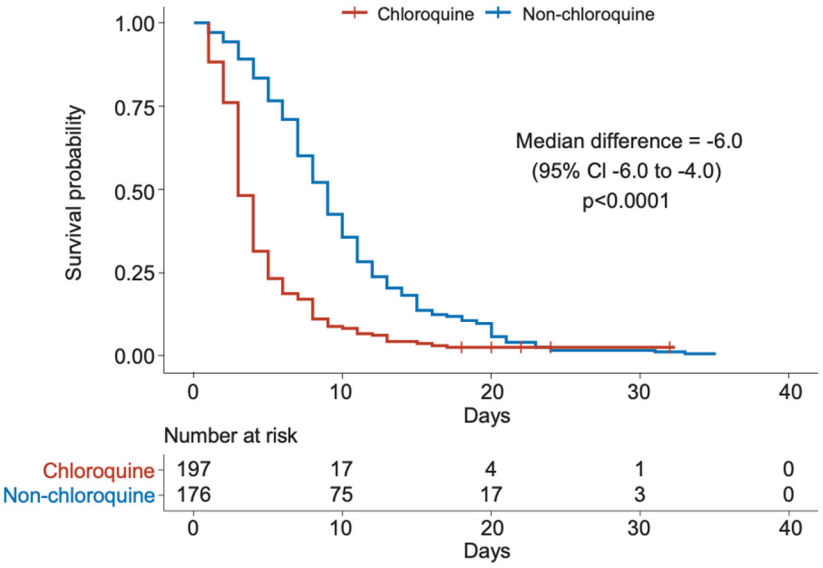


Figure 2. Kaplan-Meier curve for time to undetectable viral RNA comparing treatment groups.

[27] Huang, Mingxing, et. al. "Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19," 4 May 2020, *National Science Review*, Oxford. https://academic.oup.com/nsr/advance-article/doi/10.1093/nsr/nwaa113/5848167. – this reference is for the peer reviewed version. The reference given in the FDA Revocation is for an initial print in medRxiv (https://www.medrxiv.org/content/10.1101/2020.04.26.20081059v1.full.pdf)

This study has one of the large sample sizes reference by the FDA Revocation but is dismissed without any specific comment on this study. Grouped with other studies as "inconsistent." While paper 1 is randomized and this is an enrollment versus an existing unenrolled group, it seems arbitrary that this study is dismissed — especially in light of the flaws in how the FDA Revocation interprets and uses the paper 1, the Tang study.

The significance of this study seems to arbitrarily dismissed because it is not consistent with the FDA's decision.

- Table 1, paper 6: Hasson, "Hasson, Mohammed, et, al. "Negative nasopharyngeal SARS-CoV-2 PCR conversion in Response to different therapeutic interventions." (not peer reviewed).[28] This study is a retrospective of 93 patients in Mecca. If found no statistical difference between HCQ and non-Chloroquine therapies in the time to achieve a negative test.
- Table 1, paper 7: Kim M. "Treatment Response to Hydroxychloroquine…" (not peer reviewed)[29] *This paper has been withdrawn by the authors.*
- Table 1, paper 8: Hraiech, "Lack of viral clearance by the combination of hydroxychloroquine and azithromycin…"[30] Report on 45 subjects in critical care separated into three groups HCQ and Azithromycin (AZI), Lopinavir and Ritonavir, and no antivirals, leading to small sample sizes. No statistical difference in Acute Respiratory Syndrome. The HCQ and Azithromycin has been found to be a potentially deadly combination.[31]

  The small groups would make any statistical significance for any but the largest different unlikely.

FDA's Analysis of Hospitalized Patients.

Conclusion: The FDA's assessment that there is unlikely to be a benefit for severely ill patients seems justified. However, this should not preclude consideration for mild to moderate symptoms or as a prophylaxis.

The NIH trial, which the FDA Revocation said was ongoing was halted on 20 June — saying HCQ "does no harm, but provides no benefit."[32]

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[28] Hassan, Mohammed, et, al. "Negative nasopharyngeal SARS-CoV-2 PCR conversion in Response to different therapeutic interventions." medRxiv. 2020. https://doi.org/10.1101/2020.05.08.20095679

[29] Kim M. et al. "Treatment Response to Hydroxychloroquine, Lopinavir/Ritonavir, and Antibiotics for Moderate COVID 19: A First Report on the Pharmacological Outcomes from South Korea." medRxiv, 2020. https://www.medrxiv.org/content/10.1101/2020.05.13.20094193v2

[30] Hraiech, S. *et al.* "Lack of viral clearance by the combination of hydroxychloroquine and azithromycin or lopinavir and ritonavir in SARS-CoV-2-related acute respiratory distress syndrome." *Annals of Intensive Care* **10,** 63. 2020. https://doi.org/10.1186/s13613-020-00678-4

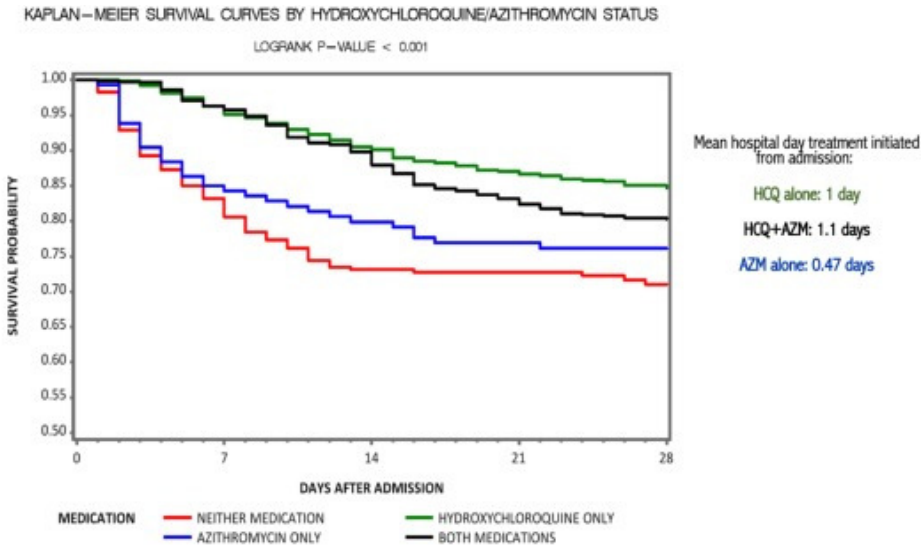
[31] American Hearth Institute, "Serious and potentially lethal impact of hydroxychloroquine and azithromycin." *Medical Press/Diseases, Conditions, and Syndromsl.* 25 May 2020. https://medicalxpress.com/news/2020-05-potentially-lethal-impact-hydroxychloroquine-azithromycin.html

[32] National Institutes of Health, "NIH halts clinical trial of hydroxychloroquine." 20 June 2020. https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine

This is grossly misleading. The Bulletin on the same trial, says that, which they planned to enroll 2,000 people, they had only enrolled 20[33] — certainly too small a sample size noted in their commentary to Table 1 to provide any conclusion whatsoever.

On the other hand, a retrospective review of COVID-19 patients in the Henry Ford Health System showed:

> In a large-scale retrospective analysis of 2,541 patients hospitalized between March 10 and May 2, 2020 across the system's six hospitals, the study found 13% of those treated with hydroxychloroquine alone died compared to 26.4% not treated with hydroxychloroquine. None of the patients had documented serious heart abnormalities; however, patients were monitored for a heart condition routinely pointed to as a reason to avoid the drug as a treatment for COVID-19.[34]



NUMBER AT RISK (IN HOSPITAL)

	ADMISSIONS	DAY 7	DAY 14	DAY 21	DAY 28
BOTH MEDICATIONS	783	751 (498)	675 (219)	593 (87)	490 (37)
HYDROXYCHLOROQUINE ONLY	1202	1144 (564)	999 (176)	786 (60)	463 (15)
AZITHROMYCIN ONLY	147	120 (31)	108 (8)	99 (2)	86 (1)
NEITHER MEDICATION	409	317 (117)	212 (16)	156 (6)	110 (3)

Of course, this is not a randomized, double blind, closed label review — it could have biases, particularly in the selection of patients to receive HCQ. But, it certainly suggests follow-up, not shut down.

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[33] NIAID, NIH. "BULLETIN—NIH Clinical Trial Evaluating Hydroxychloroquine and Azithromycin for COVID-19 Closes Early." 20 June 2020. https://www.niaid.nih.gov/news-events/bulletin-nih-clinical-trial-evaluating-hydroxychloroquine-and-azithromycin-covid-19

[34] Henry Ford Health System, "Treatment with Hydroxychloroquine Cut Death Rate Significantly in COVID-19 Patients, Henry Ford *Health System Study Shows. Henry Health System News*. 2 Jul 2020. https://www.henryford.com/news/2020/07/hydro-treatment-study;

The study refered to is: Arshad, Samai, et. al. "Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19." *International Journal of Infectious Diseases* 97 (2020). pages 396–403. (Published by Elsevier).

There appears to some controversy over the study and

Rationale: Two of the eight studies discussed above for hospitalized patients and shown no significant difference using HCQ. One small retrospective study of critical patients showed improvement. The FDA Revocation, page 7, cites the decision to stop including HCQ/CQ in the Oxford University RECOVERY trail. This focuses on 11,000 hospitalized patients and the trial's focus is on mortality. There was no difference in mortality data to date.[35]

Brief Excursion into Post-Exposure Prophylaxis

(FDA Revocation pages 7-8)

Conclusion: The FDA references one study (Boulware) and incorrectly dismisses it because of "limitations," that shows no "significant difference" of using HCQ as a prophylaxis (preventative) for people who have been exposed to people with COVID-19. Given that there is no approved prophylaxis at this point, the dismissal of HCQ as a prophylaxis is inappropriate.[36] There is evidence that HCQ is effective as a poste-exposure prophylaxis — *This should be pursued.*

Rationale: The Boulware study does have limitations – in particular, people self-select over the internet and the exposure time was 10 minutes of unprotected exposure. The self-selection, as in many, many COVID-19 studies creates the potential for bias based on peoples decision-making process to enter the study. 10 minutes may be too short a duration — especially since the practical problem is often family groups, institutions, or longer term or frequent exposure by health care and other workers.

The results of this study does show a difference, though not significant, due to the sample size and other factor — the graphic shows overlapping confidence intervals with the mean showing a difference at day 14 after the start of the trial — the data showing a relative risk reduction of getting COVID-19 of 17%.[37]

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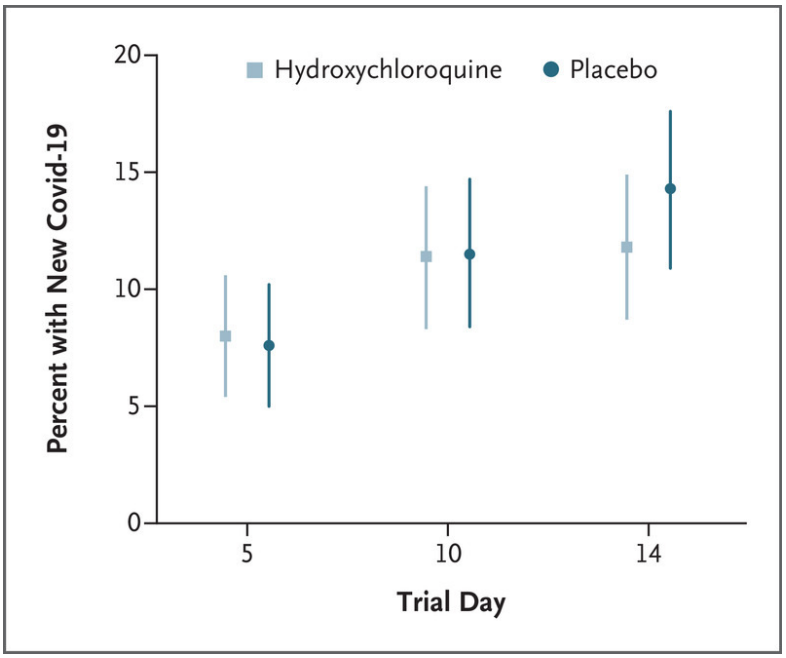
[35] Chief Investigators, "No clinical benefit from use of hydroxychloroquine in hospitalized patients with COVID-19." *Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trail on hydroxychloroquine.* Oxford University. 2020. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19;
ISRCTN registry. "A randomized trial of treatments to prevent death in patients hospitalized with COVID-19 (coronavirus)". http://www.isrctn.com/ISRCTN50189673

[36] Boulware D Ret al. "A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19." [published online ahead of print, 2020 Jun 3]. N Engl J Med. 2020;10.1056/NEJMoa2016638. doi: 10.1056/NEJMoa2016638

[37] Ibid; Llewelyn, Martin and William Schilling. "Down, but not out: hydroxychloroquine couls still have a role against COVID-19. 5 Aug 2020. *The Phamacheutical* Journal. https://www.pharmaceutical-journal.com/news-and-analysis/opinion/insight/down-but-not-out-hydroxychloroquine-could-still-have-a-role-against-covid-19/20208233.article?firstPass=false#fn_3



Another study, with its own limitations, including a retrospective examination of self-selected participants, shows a large, statistically significant, improvement among health care workers who elected to HCQ as a prophylaxis.[38]

FDA Analysis of Known and Potential Risks.

The FDA Revocation reviews information on data bases for adverse effects, listing a summary of 347 HCQ cases and 38 CQ cases, noting serious cardiac events, 73% being QT prolongation, which appears to both a side effect of HCQ and a sign of COVID-19.[39] No conclusion could be reached because the number of people exposed are unknown. Jordon Prutkin, MD, MHS, FHRS in "Coronavirus Disease 2019 (COVID-19): Arrhythmias and conduction disease," provides management recommendations, including creating a baseline and monitoring patients for QT-prolonging medications.[40]

Literature Review.

The findings of "effectiveness endpoints" were inconsistent across all reviewed studies."[41]

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[38] Bhattacharya, Raja. "Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers - a Retrospective cohort." (not peer reviewed). 22 Jun 2020. *medRxiv. BMJ*. https://doi.org/10.1101/2020.06.09.20116806

[39] Prutkin, Jordon. "Coronavirus Disease 2019 (COVID-19): Arrhythmias and conduction disease." UpToDate, UpToDate, Inc. (Articles peer reviewed by a deputy editor for the speciality). 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-arrhythmias-and-conduction-system-disease/print

[40] Ibid. Two withdrawn because the peer review questioned the veracity of the data and was withdrawn: Mandeep R Mehra, Frank Ruschitzka, Amit N Patel. "Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis." The Lancet Published: June 5, 2020 Available at: https://www.thelancet.com/journals/lancet/article/PIIS01406736(20)31324-6/fulltext

[41] FDA Revocation Memo, page 10.

FDA Conclusion

The bulleted determinations contain selective rationale regarding:

- Mortality
- Length of Hospital Stay
- Negative Conversion (a negative test) being no different between HCQ and Standard of Care.

The last of this is inconsistent with at least one compelling trial cited in the FDA Revocation. Further, the rationale does not deal with improvement for mild symptoms or as a prophylaxis.

The rationale does not seem to comply fully with the criteria for assessing the benefits versus the risk provided for in Section 564 of the Food Drug and Cosmetic Act.