Hydroxychloroquine and COVID-19:

Lack of Efficacy and the Social Construction of Plausibility

-Preprint-

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Structured Abstract

Background

Severe acute respiratory syndrome coronavirus 2 SARS- Cov2 has taken the world by surprise. Among the first promising repurposing agents proposed for treatment and prophylaxis, two antimalarial agents came into limelight: chloroquine and its less toxic derivative, hydroxychloroquine. Intense research and public debates have followed.

Areas of Uncertainty

As hydroxychloroquine is still used and studied, future research may bring novel evidence, modifying the state-of-the-art. Despite the lack of a single randomized control trial (RCT) with positive results, there are currently (as for the search on 30th of August 2020) more than 250 RCT registered on ClinicalTrials.gov with HCQ in COVID patients, and more than 150 of them are “still recruiting” or “not yet recruiting” patients.

Data Sources

Our study combines a therapeutic evaluation of RCT data with a sociological analysis of related controversies, examining scientific and public arena discourses.

Results

While any hope of a positive effect was brought exclusively by some and not all of the observational studies, none of the following 7 RCT published until now have found any benefit. From a sociological perspective, the HCQ controversy is a useful case study for understanding the construction of plausibility in a cultural context polarized into mirroring versions of reality, with different epistemologies and ideologies.

Conclusions

The results of the first RCTs have been published, and they are disappointing: beneficial effects of HCQ could not be proven either for negative conversion on Polymerase Chain Reactions (PCR) of COVID patients, or for post-exposure prophylaxis. The question to be asked is: how many studies do we need until HCQ is abandoned? Argumentative time work, appealing to temporal properties of HCQ including its historical use, accumulation of evidence, alternative therapeutic scenarios, and sensationalist tempo for rhetorical purpose, plays a significant role in its continuing legitimation.

Background

Severe acute respiratory syndrome coronavirus 2 SARS- Cov2 has taken the world by surprise, both at individual and public health community level, when the number of infected cases reached over 200,000 cases in March 2020 and the severe pneumonia-like disease that it triggered, named coronavirus disease 2019 (COVID-19), was declared a global pandemic by World Health Organization (WHO).

Facing the continuous rising numbers of both infected people and death from COVID-19, with limited therapeutic options, researchers all over the world have been driven by the same goal, the desire to discover a safe and effective treatment. As the process of transition from a promising molecule to its approval as a new drug is an extremely costly and complex process which usually takes more than 10 to 14 years, it seems to be an unrealistic option during a pandemic. Under the pressure of an urgently needed drug, a much more reasonable and therefore attractive option for shortening the transition from bench to bedside, is that of “drug repurposing”, finding an “old” drug (approved for another indication) for a new disease.

Among the first promising repurposing agents, two antimalarial agents came into limelight: chloroquine and its less toxic derivative, hydroxychloroquine, approved also for lupus and rheumatoid arthritis treatment. This was based on in vitro studies, which have shown they have potent inhibitory activity against SARS-Cov2 (Wang *et al.*, 2020). We will discuss the recent evolution of scientific and public assessments of this potential treatment against COVID-19.

Data Sources

Our study combines a therapeutic evaluation of recent randomized control trial (RCT) data on HCQ effectiveness with a sociological overview and analysis of surrounding controversies, in order to move forward the debate and contribute to a harmonization of conflictual points of view.

Therapeutic Opinion

First report of possible benefits in clinical studies came from China, in a Letter to the editor published on 16th of March in BioScience Trends, claiming apparent efficacy in clinical studies registered in China [1]. Of those, the results were published (posted only as preprint on medRxiv) for a single study, on 62 patients, in which Chen and co-authors reported significant improvement of clinical symptoms and chest CT images after 5 days of treatment with HQ (N=31 patients) compared to standard of care [2]. The wind of hope has further spread to western part of the world after a group of researchers in France have published the results of a non-randomized trial on 26 patients treated with hydroxychloroquine and 16 control patients [3] which lead the authors to conclude that hydroxychloroquine monotherapy and hydroxychloroquine in combination with azithromycin reduced viral load.

Even shortly after its publication, many researchers raised concerns about methodological caveats of the study: poor design, conclusions not supported by the data, lack of clinical outcomes, evaluation on the 6th days of the study instead of on the 10th day, as planned by the protocol, excluding from analysis 6 patients (four transferred to intensive care, one died, one refused to continue treatment) lost to follow-up from the HCQ group, among other (Lenzer, 2020) [4].

However, one day after the publication of the study, hydroxychloroquine had already became the "rising star" in the fight against COVID-19. US President cited the study, declaring HCQ as a "game changer" which showed "tremendous promise" in the COVID treatment [5]. One day after, FDA issued an Emergency Use Authorization (EUA) for prescription of both chloroquine and HCQ in the treatment of COVID-19, based on "limited in-vitro and anecdotal clinical data" [6] statement acknowledging in fact the lack of evidence, positive results from randomized clinical trials.

Nevertheless, guidelines or national protocols in various countries allowed or recommended HCQ for the treatment of COVID patients [5]. Many clinical trials started worldwide comparing HCQ to placebo or other treatment regimes, including SOLIDARITY[1], the largest global trial to compare the four most promising therapies.

Paralleling the search for scientific evidence of its efficacy, hydroxychloroquine has become the subject of national headlines all over the world for the next months, and a subject of controversy. While scientific advisers were concerned about the negative effects of unstained positive publicity might have to the general population, high profiles have endorsed it as beneficial. A study, published in JAMA Internal Medicine end of April 2020 found that searches for buying hydroxychloroquine increased by 1,389 percent, from 494 Feb. 1, to 871 March 16, and to 9,006 March 22, the spike in searches being found by the authors to be directly related to the Elon Musk's tweet and US President televised endorsements [7].

Many challenges were posed by the increased prescribing of a drug with unproven benefits and known adverse reactions. Some scientists pointed out that widespread off-label use endorsed by governmental agencies, as was the case of FDA authorization of HCQ use in COVID, might hinder the proper research process in many ways, including the difficulty of recruiting patients in controlled clinical trials were they would be randomly assigned (or not) to a drug they strongly believe is efficient [8]. The complexity of ethical aspects to be taken into account in a case where media and social factors, driven by/associated with the general strong wish to

[1] The SOLIDARITY trial: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

find a treatment, have decisively influenced the clinical decisions and research all over the world warrants to be distinctly analyzed in a future paper.

On April 24, 2020 FDA launched a safety warning on serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine and advised against the use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting (FDA) and in June the EUA for HCQ use in COVID was rescinded. In June WHO announced it withdrawn hydroxychloroquine SOLIDARITY trial, followed by the The National Institutes of Health in USA, which stopped their hydroxychloroquine trial.

Meanwhile, the results of the first RCTs have been published, and they were disappointing; beneficial effects of HCQ could not be proven either for negative conversion on Polymerase Chain Reaction test of COVID patients[9], or for post-exposure prophylaxis [10]. While any hope of a positive effect was brought exclusively by some [3] and not all (Geleris *et al.*, 2020) of the observational studies, and those were with methodological faults, none of the following 7 RCT published until now[2 9 10 11 12 13 14], summarized in **Table 1**, have found any benefit. RCT are well-known, established "gold standard" for proving a drug efficacy and for influencing evidence-based clinical guidelines. The main reason why this is not the case for observational studies, is related to the lack of randomization: while in a well-designed RCT the results are expected to be the consequence of the true drug effect, in a non-randomized, observational study, the results might be the result of the selection process, as well. A clear explanation of this difference and how the lack of randomization can strongly influence the results of an observational study was done in particular on the data from the first Gautret study [15]. However, despite the lack of a single RCT with positive results, there are currently (as for the search on 30th of August 2020) more than 250 RCT registered on ClinicalTrials.gov with HCQ in COVID patients, and more than 150 of them are "still recruiting" or "not yet recruiting" patients. The question to be asked is: how many studies do we need until HCQ is abandoned? What are the factors that drove the decision of researchers conducting the RCT which started after the negative results of other RCT were published?

Insert Table 1 here.

Sociological Opinion

Since the early days of the COVID-19 pandemic, hydroxychloroquine (HCQ) and, to a lesser extent, chloroquine (CQ) have become the focus of intense scientific, public and political controversies across the globe, regarding their potential use for the prevention or treatment of COVID-19. These controversies offer useful insights on the relationships between scientific evidence, public debate, and the social construction of plausibility in diverging political worldviews.

Starting in the fields of clinical practice, pharmaceutical industry, and scientific research, controversies have soon spread to wider media and public debate arenas, increasingly drawing the attention of more participants with wider areas of expertise and interests [16]. At the time of the completion of our study, in August 2020, controversies persist [17] and the uses, evaluations and regulation of HCQ as intervention against the new coronavirus are uneven, dynamic, politically and commercially charged, and often conflictual. At the same time, we are witnessing an increasing consensus in the area of evidence-based medicine (EBM) to the effect that HCQ has not been proven to be an effective treatment against COVID-19. The WHO and regulating agencies in countries such as the US, Canada, the UK, and France have taken note of these conclusions in their recommendations, significantly limiting the possibilities of clinical HCQ-based interventions.

We can trace the recent history of CQ and HCQ use against the infection with SARS-CoV-2 to February 2020 publications by Chinese scientists concerning its in-vitro efficacy [18], and apparent clinical usefulness [1]. Still, its relevant history is much longer, involving numerous in vitro and in vivo research programs for investigating and repurposing this proven antimalarial drug for a large-spectrum antiviral uses, most notably against SARS-CoV, MERS, Ebola, Zika, Chikungunya, or Influenza A [19]. However, the most famous research is probably the one conducted by professor Didier Raoult and his collaborators at Institut hospitalo-universitaire (IHU) Méditerranée Infection Aix-Marseille University [20]. Professor Raoult has become one of the most active proponents of HCQ as treatment against COVID-19, both in the scientific and public arenas. He is a key figure in the HCQ controversies because of his bridging character, being one of the very few scientists who are

simultaneously involved in HCQ research [21] and public advocacy. Most participants are only involved in one role or the other - including highly visible figures such as the president of the USA, Donald J. Trump, and the president of Brazil, Jair Bolsonaro, USA public administrators such as Peter Navarro, assistant to the US President, and Anthony Fauci, advisor to the US President for the COVID-19 pandemic, the famous tech entrepreneur Elon Musk, and the cartoonist Scott Adams, among many others.

We can broadly distinguish, analytically, several arenas of controversy, each operating with specific institutional logics, though interlinked through flows of information and influence:

- **The scientific research arena** on HCQ effectiveness, including empirical studies taking place in hospitals and other research centers, and syntheses of available evidence; research articles are published in various preprint platforms and peer-reviewed publications.
- **The policy arena**, in which regulatory bodies at global, national and local levels assess available evidence and decide on the possible uses of HCQ in the COVID pandemic; this is also the arena in which **political** and **commercial** interests are most relevant, since policies can greatly impact large scale consequences for corporations and political organizations.
- **The public debate arena** of detailed, argumentative public evaluations of HCQ, in which people from various professional fields and areas of expertise publish their syntheses, evaluations and supported points of view, mostly through the medium of long-form journalism and blogs.
- An ever-broader **media arena**, in which news, opinions, fights, satires, memes and many other signals are constantly published through mass media and social media, shaping public opinion, and impacting political and commercial interests.

The first evaluations that fueled the HCQ controversies appeared in the scientific arena, prompted by the Chinese and French studies and, later, by the Surgisphere fraud leading to the retraction of the Lancet article [22] and the NEJM article [23] that were documenting fatality risks of HCQ treatment. Still, the controversy's global scale and persistence can be better understood through the **emergence of polarized repertories of arguments**, combining the evidence generated in the arena of scientific research, the narrative sensemaking in the arena of public debates, the official decisions in the policy arena, and the broad sensemaking and sensationalism

created through mass-media and social-media communication, similar to the structure of the anti-vaccination controversy[24]. Mathematical models have been both used and critiqued for their role in the production of knowledge[25], and technology has played a role in the collective moral agency[26] of defending or accusing HCQ. We currently witness the consolidation of **two mirroring realities.** In one of them, HCQ is a long-tried remedy for malaria and lupus among others, with documented risks, which has proven ineffective against SARS-CoV-2 in clinical research, through a cumulative body of evidence. In this view, centered on the current EBM consensus, continuing efforts to promote it as cure against COVID-19 are unethical [15], driven by populism and by the political interests of shifting blame for deficient management of the pandemic. While its prophylactic use is still explored [27], the HCQ toxicity and the difficulties of population-scale monitoring for adverse effects make its large scale preventive use very risky. In the alternative, contrarian reality, HCQ is a long-tried drug whose risks can be completely contained, with high plausibility and increasingly proven effectiveness against SARS-CoV-2 both for prevention and for treatment, especially early outpatient treatment. The international RCT's (Solidarity, Discovery and Recovery) have been designed to suppress it in order to promote the commercially profitable Remdesivir, and/or to undermine the legitimacy of President Trump and his government of the pandemic. In this view, disallowing HCQ use for COVID-19 prevention and treatment is a profit driven criminal act responsible for thousands of deaths.

The fault line between what has emerged as the mainstream and contrarian view on HCQ is assembled through:

1. Interpretations of empirical evidence produced in the scientific arena;
2. Epistemological divides and narrative sensemaking in the public debate arena.

1. The fault lines of empirical evidence

In the arena of **empirical evidence**, among the many studies dedicated to HCQ, EBM prioritizes large scale RCTs and emerging meta-analyses which indicate no significant therapeutic efficacy of HCQ. Such studies include the large scale RCT's against HCQ effectiveness: Brazil study [13], and the Solidarity, Discovery and Recovery trials [28]. On the reverse side, the mirroring reality in which HCQ is a savior molecule is constructed by invoking evidence from several large scale observational studies supporting HCQ, such as IHU Marseille studies [29,30], Henry Ford Hospital study [31]; NYC retrospective cohort study (N=6493) [32], or the large scale case-

control study on preventive efficacy for healthcare workers in India [33]. Experts advocating the use of HCQ also propose it for early outpatient treatment of symptomatic high-risk patients [34] rather than later use for hospitalized patients in severe condition.

2. The epistemological divide and narrative sensemaking

The HCQ public controversy is also increasingly building on a **longstanding epistemological debate** about the relative merits and demerits of RCTs in comparison to other studies, such as large **observational** research with statistical controls, and especially in comparison to **clinical wisdom and insight**. The epistemological debate may seem even more remote from the general public than the evidence-focused one, but it is very powerful for medical practitioners [35] and it functions as an argumentative infrastructure of the contrarian positions to the emerging scientific consensus [36]. A strong valuation of medical practitioners' clinical wisdom against RCTs and mathematical models [37], and a serious consideration of large scale observational studies lead to the possibility of an optimistic synthesis of available evidence as regards HCQ effectiveness in general [38] or for specific scenarios of use [34]. This opposes the EBM scientific consensus that, according to the pyramid of evidence, discounts clinicians' opinions as weak evidence and privileges the evidentiary force of the RCT against observational and case study research [15] which do not account for placebo effectiveness and residual confounding factors.

Hydroxychloroquine is not the only controversial treatment of the COVID-19 pandemic. Remdesivir, Lopinavir / Ritonavir, convalescent plasma or vitamin D have also been subject to conflicting scientific and public assessments. Convalescent plasma is currently caught in a similar trap of high use and low efficacy evidence, though for different historical reasons [39]. Remdesivir has a special place in these controversies because it is a patented medicine produced by Gilead Sciences, which stands to profit considerably from its global use in the pandemic – while the other treatments are much less if at all a source of profits. This strong **asymmetry of commercial interests** in Remdesivir vs. HCQ has played an important role in the public controversy, with HCQ pitted by its defendants as a costless (yet safe and effective) alternative to the expensive, profit-driven (yet risky) Remdesivir and future vaccines. To illustrate, the French sociologist Laurent Mucchielli has articulated this perspective both in his public stances [40] and his research [41].

With the wisdom of hindsight, HCQ has elicited so much political, public and consequently scientific attention because it has specific **temporal profiles** which makes it an ideal ingredient for the discursive construction of alternative political realities. On the right, people see people on the left deny a useful past and ignore a helpful present of HCQ in an effort to prevent or undermine a political future they find abhorrent (including the re-election of President Donald J. Trump). On the left, people see people on the right misrepresenting an irrelevant past and ignoring evidence of a medically problematic present of HCQ in an effort to substantiate the unscientific claims of President Trump. Both sides make claims to scientific evidence. From the right, there is a claim to large scale observational and case control studies as well as clinical, personal, anecdotal, or ethnographic evidence. From the left, there is a claim to RCTs and meta-analyses that would distill the therapeutic effects of HCQ, or lack thereof, against confounding factors.

Unlike other controversial remedies, the specific HCQ temporal profiles sustain the narrative consolidation of a contrarian reality in which past, present and future are adjusted through argumentative time work [42] [43]: a reality in which profit-driven elites, together with experts and academics distanced from clinical and human realities of the present, suppress a century-old and proven remedy in order to assert their control in a regime of urgency and panic. These profiles include:

- **A historical profile**: HCQ has been **used for decades** at population scale, with an established long-term safety and risk profile [27]; it thus contrasts with anti-COVID19 vaccines which are being developed with unprecedented speed and, some people fear, with increased risks [38].
- **An evidentiary profile**: during the pandemic, there has been **constant accumulation** of scientific evidence on both sides of the controversy [17], though the evidence is heterogeneous in terms of design and quality. This evidence has been both boosted and hampered by the fast growth of HCQ therapeutic use. Its popularity has proven auspicious for observational research and for attracting scholars' attention, but it has raised difficulties for recruiting participants in RCTs, since patients were often already using HCQ or unwilling to be randomized to other treatments [44]. Also, the relatively low-speed temporality of science has been challenged by the urgency of the pandemic, leading to the proliferation of preprint publications reaching public attention through mass media.

- **An intervention profile**: HCQ defendants separate interventions in two temporal scenarios: early-stage outpatient and prophylactic use scenarios are set apart from late stage inpatient treatment scenarios, allowing divergent interpretations of available evidence [34].
- Finally, there is **its sensationalist profile**: through its **fast raise to prominence** and its **rhythmic public scandals**, including the political controversies fueled by President Trump's endorsements, the periodic public interventions of professor Raoult, and the Surgisphere scandal, HCQ has maintained a vivid presence in the public imagination. This sensationalist profile has been accentuated by the accelerated circuits of scientific argument through the preprint platforms [16] [45], and the high hopes for an urgent cure ignited by the tragedy of the pandemic.

To illustrate, we can observe the argumentative time work [46] that positions HCQ as a viable therapeutic option in the following quote:

> *"If you think this year's controversy is bad, consider that hydroxychloroquine is given to relatively few people with COVID-19, all sick, many with nothing to lose. It enters the body, and leaves fairly quickly, and has been known to us for decades. COVID vaccines, which advocates will want to be mandatory and given to all people—healthy and not, young and old—are being rushed past their normal safety precautions and regulations, and the typical five-to-10-year observation period is being waived to get "Operation Warp Speed" done as soon as possible. This is being done with the endorsement of public health officials—the same ones, in many cases who are saying HCQ is suddenly extremely dangerous. Philosophically, and psychologically, it is a fantastic spectacle to behold, a reversal, the magnitude and the chutzpah of which must inspire awe: a public health establishment, showing extraordinary risk aversion to medications and treatments that are extremely well known, and had been used by billions, suddenly throwing caution to the wind and endorsing the rollout of treatments that are entirely novel—and about which we literally can't possibly know anything, as regards to their long-term effects."* [38]

Limitations

Our study captures the state of the art on hydroxychloroquine as treatment and prophylaxis against COVID-19 in August 2020, and the dominant conclusions are likely to change to some extent through future accumulation and synthesis of evidence.

Conclusions

The HCQ controversy is a useful case study for understanding the construction of plausibility in a cultural context increasingly polarized into mirroring versions of reality, structured by different epistemologies and ideologies. HCQ, unlike other controversial treatments, has become a resource in the narrative construction of these polarized versions, because of its temporal profiles and moral connotations. It is a century-long remedy in contrast to vaccines that are being developed faster than ever; it has sprung rapidly to prominence across the globe and fueled a great many studies, with the persistent accumulation of heterogeneous and diverging evidence. It has revived the long-lasting epistemological discussion of the relative value of RCTs when they are opposed by clinical experience and observational studies. Last but not least, it has captured public imagination through rhythmic scandals, becoming the most popular cheap opponent to an expensive and profitable drug, and offering abundant political ammunition in partisan fights in the USA, France, and Brazil among others. Therefore, HCQ has been a useful resource for the argumentative time work required for constructing coherent, polarized worldviews.

At this point, the history of HCQ use against COVID-19 and related research is still recent, measuring months, and there is an emerging scientific and policy consensus concerning its lack of therapeutic effectiveness. At the same time, its continued global use will generate further studies. Thus, the juries are still out on the final formulations of HCQ scientific evaluations for various scenarios of use, let alone their incorporation in public movements and political stances. Researchers across disciplines should be prepared and open for a continuing accumulation of scientific evidence and need for syntheses, a longer controversy, and an even longer work of engagement with the public, concerning the merits of HCQ in the COVID-19 pandemic, or lack thereof.

Table 1 Randomized clinical trials performed with hydroxychloroquine in COVID19

Author, country	Design	Patients	Treatment	Outcome	Results benefits	Adverse effects	Study conclusion on efficacy
Chen et al. [2], China	Open label, randomized controlled trial	30 treatment-naïve patients with confirmed COVID-19	HCQ 400 mg/day for 5 days plus conventional treatments, conventional treatment only in the control group	Negative conversion rate of SARS-CoV-2 nucleic acid in respiratory pharyngeal swab on days 7 after randomization	Negative conversion in 86.7% cases in the HCQ group and 93.3% in the control group (*P*>0.05)	Non-significant differences between groups	No evidence of beneficial effect of HCQ treatment on probability of negative conversion, compared to standard of care alone
Tang et al.[9], China	Open label, randomized controlled trial	150 hospitalized patients with mild to moderate or severe laboratory confirmed covid-19 disease assigned to either HCQ plus standard of care (75 patients), or standard of care alone (75 patients)	HCQ - loading dose 1200 mg daily for 3 days - maintenance dose 800 mg daily Total treatment duration: 2 to 3 weeks for mild/moderate or severe disease form, respectively	Absence of virus PCR on nasal swab at 28 days	85.4% cleared the virus in the HCQ group compared with 81.3% in the standard of care group (difference not statistically significant)	30% in the HCQ group vs. 9% in the usual-care group	No evidence of beneficial effect of HCQ treatment on probability of negative conversion, compared to standard of care alone
Boulware et al. [10] US, parts of Canada	Randomized, double-blind, placebo-controlled trial HCQ tested as post-exposure prophylaxis	821 asymptomatic participants assigned to either HCQ or placebo	Within 4 days after exposure, HCQ: - 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days	The incidence of either laboratory confirmed Covid-19 or illness compatible with Covid-19 at 14 days.	The incidence was not significantly different between subjects receiving HCQ (11.8%) and those receiving placebo (14.3%).	Side effects were more common with HCQ than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.	HCQ did not prevent illness or confirmed infection when used 4 days after exposure

Skipper et al.[11], USA and Canada	Randomized, double-blind, placebo-controlled trial	491 non-hospitalized adults with COVID-19 or high-risk exposure were randomized to HCQ or placebo	HCQ 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days	Change in symptom severity at 14 days	No significant difference between the HCQ and placebo group in symptom severity score change: 2.60 in HCQ vs 2.33 in placebo (p=0.117) At 14 days, 24% of HQ arm patients had ongoing symptoms compared with 30% in the placebo group (*P* = 0.21).	43% in the HCQ group and 22% in the placebo group (*P* < 0.001)	No evidence of change in symptom severity at 14 days
Mitja et al. [12], Catalonia, Spain	Multicenter, open label, randomized controlled trial	293 non-hospitalized patients with recently confirmed SARS-CoV-2 infection and less than five days of symptoms: 157 in the control arm and 136 in the HCQ arm	HCQ (800 mg on day 1, followed by 400 mg once daily for 6 days) or no antiviral treatment (not-placebo controlled)	1) reduction of viral RNA load in nasopharyngeal swabs up to 7 days of treatment; 2) disease progression on WHO scale up to 28 days, and 3) time to the complete resolution of symptoms.	No significant differences in: 1) the mean reduction of viral load at day 3 (-1.41 in the control vs. -1.41 in the intervention group); or at day 7 (-3.37 vs. -3.44). 2) risk of hospitalization (7.1%, control vs. 5.9%, intervention 3) the time to complete resolution of symptoms (12 days, control vs. 10 days, intervention; p = 0.38).	No relevant treatment-related AEs were reported.	No evidence of reducing the viral load, the risk of hospitalization, or the time to complete resolution
Cavalcanti et al.[13] 55 hospitals in Brazil	Multicenter, randomized, open-label, 3 arms (random assignment in 1:1:1 ratio),	667 hospitalized patients with suspected or confirmed Covid-19, receiving either no supplemental oxygen or a maximum of 4 liters/minute; 504 patients with	3 arms: 1) standard care, 2) standard care plus HCQ 400 mg bid, 3)standard care plus HCQ 400 mg bid plus azithromycin	Clinical status at 15 days on a seven-level ordinal scale	Proportional odds of having a higher clinical status score at 15 days was not influenced by either HCQ alone (OR, 1.21; 95% CI, 0.69-2.11; P=1.00) or HCQ plus AZT (OR, 0.99; 95% CI, 0.57-1.73; P=1.00), compared to	Prolongation of the corrected QT interval and elevation of liver-enzyme levels more frequent in patients receiving HCQ, alone or with AZT The adverse event rate was 39.3% in	The use of HCQ, alone or with AZT, did not improve clinical status at 15 days as compared with standard care among patients hospitalized with mild-to-moderate Covid-19.

	controlled trial	confirmed Covid-19 included in the modified intention-to-treat analysis	500 mg once daily for 7 days		standard care. There was no significant difference in the outcome rates at day 15 for either of the treatment groups compared with usual care.	the combined-therapy group, 33.7% in the HCQ group, and 22.6% in the standard-care group.	
Horby[14], RECOVERY trial, 176 hospitals UK	Randomized, controlled, open-label, platform trial	1561 patients randomly assigned to receive HCQ plus usual care compared with 3155 patients assigned to usual care alone	HCQ 800 mg loading dose at zero and 6 hours, followed by 400 mg every 12 hours for the next 9 days or until discharge	The primary outcome: all-cause mortality. Secondary outcomes: 1) time to discharge 2) among patients not on invasive mechanical ventilation randomization, invasive mechanical ventilation or death. Subsidiary: cause-specific mortality, use of hemodialysis or hemofiltration, major cardiac arrhythmia, and receipt and duration of ventilation.	No significant difference in the 28-day mortality rate between the two arms (26.8% in the intervention arm vs. 25% in the usual care arm; P=0.18) Longer time until discharge alive in HCQ arm than in usual care arm (median 16 days vs. 13 days) and a lower probability of discharge alive within 28 days (rate ratio 0.92, 95% CI 0.85-0.99) The number of patients progressing to the composite outcome of invasive mechanical ventilation or death was higher in HCQ group (risk ratio 1.12, 95% CI 1.01-0.25).	No excess of new major cardiac arrhythmia in HCQ group	The use of HCQ inpatients hospitalized with COVID-19 was not associated with decrease in 28-day mortality, but with an increased length of hospital stay and increased risk of progressing to invasive mechanical ventilation or death.

AE – Adverse effects
AZT - Azithromycin
HCQ – Hydroxychloroquine

References

1. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;advpub. doi:10.5582/bst.2020.01047
2. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial | medRxiv. Accessed September 11, 2020. https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3
3. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949
4. Machiels JD, Bleeker-Rovers CP, ter Heine R, et al. Reply to Gautret et al: hydroxychloroquine sulfate and azithromycin for COVID-19: what is the evidence and what are the risks? *Int J Antimicrob Agents*. 2020;56(1):106056. doi:10.1016/j.ijantimicag.2020.106056
5. Singh AK, Singh A, Singh R, Misra A. "Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis." *Diabetes Metab Syndr Clin Res Rev*. 2020;14(4):589-596. doi:10.1016/j.dsx.2020.05.017
6. Hinton DM. FDA Emergency use authorization (EUA) of chloroquine and hydroxychloroquine. Published online March 28, 2020. https://www.fda.gov/media/136534/download
7. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6(1):1-4. doi:10.1038/s41421-020-0156-0
8. Lenzer J. Covid-19: US gives emergency approval to hydroxychloroquine despite lack of evidence. *BMJ*. 2020;369. doi:10.1136/bmj.m1335
9. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. 2020;369:m1849. doi:10.1136/bmj.m1849

10. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2020;383(6):517-525. doi:10.1056/NEJMoa2016638

11. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. *Ann Intern Med*. Published online July 16, 2020. doi:10.7326/M20-4207

12. Mitjà O, Corbacho-Monné M, Ubals M, et al. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. *Clin Infect Dis Off Publ Infect Dis Soc Am*. Published online July 16, 2020. doi:10.1093/cid/ciaa1009

13. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med*. 2020;0(0):null. doi:10.1056/NEJMoa2019014

14. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. *medRxiv*. Published online July 15, 2020:2020.07.15.20151852. doi:10.1101/2020.07.15.20151852

15. Wilson FP. Hydroxychloroquine RCTs: "Ethically, the Choice Is Clear." Medscape. Published August 5, 2020. Accessed August 22, 2020. http://www.medscape.com/viewarticle/935058

16. Sattui SE, Liew JW, Graef ER, et al. Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19. *Expert Rev Clin Immunol*. 2020;0(0):1-8. doi:10.1080/1744666X.2020.1792778

17. Somberg J. Science, Politics and Hydroxychloroquine. *Cardiol Res*. 2020;11(5):267-268. doi:10.14740/cr.v0i0.1140

18. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0

19. Rebeaud ME, Zores F. SARS-CoV-2 and the Use of Chloroquine as an Antiviral Treatment. *Front Med*. 2020;7. doi:10.3389/fmed.2020.00184

20. Rolain J-M, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents*. 2007;30(4):297-308. doi:10.1016/j.ijantimicag.2007.05.015

21. Sayare S. He Was a Science Star. Then He Promoted a Questionable Cure for Covid-19. *The New York Times*. https://www.nytimes.com/2020/05/12/magazine/didier-raoult-hydroxychloroquine.html. Published May 12, 2020. Accessed August 23, 2020.

22. Mehra MR, Desai SS, Ruschitzka F, Patel AN. RETRACTED: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet Lond Engl*. Published online May 22, 2020. doi:10.1016/S0140-6736(20)31180-6

23. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *N Engl J Med*. 2020;382(25):e102. doi:10.1056/NEJMoa2007621

24. Toth C. The rational, loving and responsible parent. A discursive construction of the identities of the parents that decided not to vaccinate their children. *J Comp Res Anthropol Sociol*. 2019;10(02):1-14.

25. Matei Ş, Preda M. When social knowledge turns mathematical – The role of formalisation in the sociology of time. *Time Soc*. 2019;28(1):247-272. doi:10.1177/0961463X17752279

26. Matei Ş. Responsibility Beyond the Grave: Technological Mediation of Collective Moral Agency in Online Commemorative Environments. *Des Issues*. 2018;34(1):84-94. doi:10.1162/DESI_a_00478

27. Infante M, Ricordi C, Alejandro R, Caprio M, Fabbri A. Hydroxychloroquine in the COVID-19 pandemic era: in pursuit of a rational use for prophylaxis of SARS-CoV-2 infection. *Expert Rev Anti Infect Ther*. 2020;0(0):1-12. doi:10.1080/14787210.2020.1799785

28. Lowe, Derek. The RECOVERY Trial Reports on Hydroxychloroquine. In the Pipeline. Published June 5, 2020. Accessed August 17, 2020. https://blogs.sciencemag.org/pipeline/archives/2020/06/05/the-recovery-trial-reports-on-hydroxychloroquine

29. Lagier J-C, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. *Travel Med Infect Dis*. 2020;36:101791. doi:10.1016/j.tmaid.2020.101791

30. Million M, Lagier J-C, Gautret P, et al. Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel Med Infect Dis*. 2020;35:101738. doi:10.1016/j.tmaid.2020.101738

31. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020;97:396-403. doi:10.1016/j.ijid.2020.06.099

32. Mikami T, Miyashita H, Yamada T, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. *J Gen Intern Med*. Published online June 30, 2020. doi:10.1007/s11606-020-05983-z

33. Chatterjee P, Anand T, Singh KJ, et al. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. *Indian J Med Res*. 2020;151(5):459-467.

34. Risch HA. Opinion: Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis. *Am J Epidemiol*. Published online May 27, 2020. doi:10.1093/aje/kwaa093

35. Dominus S. The Covid Drug Wars That Pitted Doctor vs. Doctor. *The New York Times*. https://www.nytimes.com/2020/08/05/magazine/covid-drug-wars-doctors.html. Published August 5, 2020. Accessed August 23, 2020.

36. Hernandez J. Fin de partie pour la chloroquine. Futura. Published August 9, 2020. Accessed August 23, 2020. https://www.futura-sciences.com/sante/actualites/coronavirus-fin-partie-chloroquine-80151/

37. Sacré P. COVID-19 - Remdesivir: License to Kill. Hydroxychloroquine: Prohibition to Cure. Global Research. Published July 17, 2020. Accessed August 23, 2020. https://www.globalresearch.ca/covid-19-remdesivir-license-to-kill-hydroxychloroquine-prohibition-to-cure/5718844

38. Doidge N. Hydroxychloroquine: A Morality Tale. Tablet Magazine. Published August 14, 2020. Accessed August 22, 2020. /sections/science/articles/hydroxychloroquine-morality-tale

39. Rogers A. 97,000 People Got Convalescent Plasma. Who Knows if It Works? *Wired*. Published online August 21, 2020. Accessed August 23, 2020. https://www.wired.com/story/97000-people-got-convalescent-plasma-who-knows-if-it-works/

40. Mucchielli L. La dangerosité de l'hydroxychloroquine: une fable politico-médiatique? *Club Mediapart*. Published online May 11, 2020. Accessed August 23, 2020. https://blogs.mediapart.fr/laurent-mucchielli/blog/110520/la-dangerosite-de-l-hydroxychloroquine-une-fable-politico-mediatique
41. Mucchielli L. Behind the French controversy over the medical treatment of Covid-19: The role of the drug industry. *J Sociol*. Published online June 17, 2020:1440783320936740. doi:10.1177/1440783320936740
42. Flaherty MG. Time Work: Customizing Temporal Experience. *Soc Psychol Q*. 2003;66(1):17-33. doi:10.2307/3090138
43. Flaherty MG, Meinert L, Dalsgård AL. *Time Work: Studies of Temporal Agency*. Berghahn Books; 2020.
44. Talpos S. Is Hydroxychloroquine Making COVID-19 Clinical Trials Harder? Medscape. Published April 15, 2020. Accessed August 23, 2020. http://www.medscape.com/viewarticle/928719
45. Dasinieres L. Le Covid-19 a fait basculer la recherche dans le «binge-publishing». korii. Published June 30, 2020. Accessed August 23, 2020. https://korii.slate.fr/et-caetera/recheche-scientifique-medecine-crise-covid-19-preprint-prepublication-revues-points-sigaps
46. Ciocanel A, Rughinis C, Flaherty MG. Argumentative time work for legitimizing homeopathy: Temporal reasons for the acceptance of an alternative medical practice. *Time Soc*. 2020;In Issue (Accepted for publication).