


















SPECIAL REPORT



Swinging the pendulum: lessons learned from public discourse concerning hydroxychloroquine and COVID-19

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ABSTRACT

Introduction: Several months into the COVID-19 pandemic, safe and effective treatments against this global health disaster have yet to be identified. Clinical research trials around the world are underway testing a wide array of possible medications. In particular, the off-label use of hydroxychloroquine for COVID-19 prophylaxis and treatment has created many unprecedented challenges for the scientific community and the public.

Areas covered: We critically assessed major events from February – May 2020 that contributed to widespread use of hydroxychloroquine for the treatment and prophylaxis of COVID-19. We aimed to explore how opinions toward hydroxychloroquine may shift from early enthusiasm (based on *in vitro* and preliminary clinical data) to the hope for a miracle cure (through communication and promotion of questionable results) and, finally, to a rise of skepticism as more in-depth analyses are emerging.

Expert opinion: Mindful and rigorous acquisition of data, as well as its interpretation, are essential to an effective pandemic response. The rapid and premature promotion of results has had major implications for global crisis management, even creating distrust among the public. It is crucial for the medical and scientific community to incorporate the lessons learned from this situation.

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1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has disrupted all aspects of society including the economy, health care, and scientific research. In the midst of a global health disaster, there has been a collective race to find safe and effective treatments. The use of preprints as a medium of rapid scientific communication has surged in recent months in order to expedite the availability of study results, though not without peril. Preprints have not been peer-reviewed at the time of online distribution, vary in quality, and some may never be published in a peer-reviewed scientific journal. The use of chloroquine (CQ) and hydroxychloroquine (HCQ) for COVID-19 exemplifies the risks of both overinterpreting and amplifying preliminary data by those outside of the scientific community and was followed by swift corrective measures by

researchers. This may represent the most rapid medical reversal in recent history, a full ‘pendulum swing’ from early enthusiasm to wide skepticism. In this report, we analyze the evolving waves of discourse regarding CQ/HCQ in relation to COVID-19, lessons learned, and implications for the future (Figure 1).

2. Waves of discourse

2.1. Initial movement: Early adopters of HCQ (February to mid-March 2020)

Based on previous evidence of the *in vitro* antiviral effects of CQ and HCQ against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), both medications were used for the treatment of COVID-19 in China [1]. On February 4 *in vitro* data on

Article highlights

- The COVID-19 pandemic has resulted in the rapid dissemination of research, both through scientific and non-scientific channels.
- We highlight the narrative of antimalarial therapy for the treatment of COVID-19 over the course of the pandemic from February through June 2020.
- Researchers and clinicians should be mindful of the public's uptake of both pre-print and published data and provide meaningful interpretations.
- Premature use of unstudied therapies can delay clinical trial enrollment and potentially harm recipients.
- Well-designed rigorous clinical trials are possible and necessary during a public health emergency.

the antiviral effect of CQ on SARS-CoV-2 was published, showing biological plausibility [2]. This data was announced by the State Council of China on February 17 regarding possible efficacy of CQ in the treatment of COVID-19 pneumonia [3]. As reported by Gao et al, this resulted in the development of multiple trials in CQ [4]. The authors also alluded to successful treatment of over 100 patients using CQ, however, no data was published at that time. Similar *in vitro* efficacy against SARS-CoV-2 was demonstrated with HCQ shortly thereafter [5].

Raoult and colleagues in France reported these findings as 'hot topics' in a showcase of their group's research interests [6]. This was also promoted on social media by Raoult in late February [7]. By early March, interest in HCQ abruptly transitioned from mechanistic plausibility that would support its study in a clinical trial setting to rapid off-label use in patients with COVID-19, primarily fueled by promotion on social media, lay press, and celebrity influence [8].

2.2. Swift upswing: HCQ as a miracle cure (March 19 to mid-April 2020)

On March 17, results of the first study from the IHU-Méditerranée Infection on the use of HCQ and azithromycin (AZM) were revealed on Raoult's YouTube channel (video no longer available). On March 19, President Trump endorsed HCQ for the treatment of COVID-19 in a press conference and commented on the drug's presumed safety in this setting as 'if things don't go as planned, it's not going to kill anybody' [9]. The study by Raoult and colleagues was published as a preprint on March 20 and received immediate and at times uncritical media attention, as well as criticism from the scientific medical community regarding the study design and outcomes [10,11]. Following this, Trump posted on Twitter on March 21 describing the combination of HCQ and AZM potentially being 'one of the biggest game-changers in the history of medicine', also mentioning the Federal Drug Administration (FDA) efforts to approve combination and quoting data presented in the International Journal of Antimicrobial Agents [12]. Concurrently, new HCQ prescriptions for COVID-19 surged for both therapeutic and prophylactic use [13]. Without prior stockpiling, drug shortages quickly ensued [11,14]. Patients with rheumatic diseases appeared on news outlets and social media to shed

light on the implications of HCQ and CQ drug shortages. In the same week, multiple state public health agencies and regulatory boards attempted to protect the HCQ supply chain by restricting prescriptions, for both COVID-19 and rheumatic diseases [15]. Multiple rheumatology organizations and governmental institutions also released guiding statements regarding scarce resource allocation during the pandemic [16–19].

With the enthusiasm around HCQ came reports of toxic ingestions, including at least one fatality, from chloroquine phosphate containing aquarium products as well as inappropriate prescriptions by healthcare providers possibly for hoarding purposes [20,21]. By late March, two new studies became publicly available: a second study from the group of IHU-Méditerranée Infection using HCQ and AZM in 80 patients with mild COVID-19 infection released on their webpage, and a preprint of the first randomized controlled trial of 62 patients from Wuhan reporting a difference in clinical time to recovery and radiologic findings with HCQ treatment [22,23]. With the increasing interest and examples of the irrational use of HCQ, physicians and rheumatologists raised concerns about the increasing use of HCQ and the inevitable impact on patients who rely on this medication [24–26]. However, the FDA issued an emergency use authorization (EUA) for the use of HCQ and CQ in hospitalized patients with COVID-19 on March 28 [27]. On March 31, HCQ was added to the FDA drug shortage list with several companies reporting limited supplies [28].

2.3. Momentum begins to shift: The rise of skepticism of HCQ (mid to late April 2020)

During a White House Press Conference on April 4, Trump suggested that a study had shown lupus patients were not contracting COVID-19; this hypothesis was unfortunately echoed by some scientists without supporting data [29,30]. These assertions that lupus patients were protected against COVID-19 were swiftly countered with emerging data from the Global Rheumatology Alliance and emerging data from Italy [31–33].

There were concerns that the use of HCQ, particularly in combination with AZM, might induce arrhythmias, as new onset cardiomyopathy had been reported with severe COVID-19. Lane et al released a preprint in MedRxiv on April 10, in which they used claims data from multiple international sources to study HCQ with or without AZM versus active comparators [34]. Although their study did not find a difference in short-term outcomes with 30-day follow-up, they did detect a concerning safety signal: HCQ combined with AZM was associated with an increased risk of cardiovascular death, angina, and heart failure. Further studies assessing HCQ with or without AZM on QT prolongation in COVID-19 patients emerged [35]. Several observational studies were published on the potentially arrhythmogenic impact of HCQ and azithromycin [36–38].

On April 21, Magagnoli et al. released a preprint of their study from the Veterans Health Administration that showed an increased risk of death from any cause in those who had been treated with HCQ for COVID-19 versus those who did not [39].

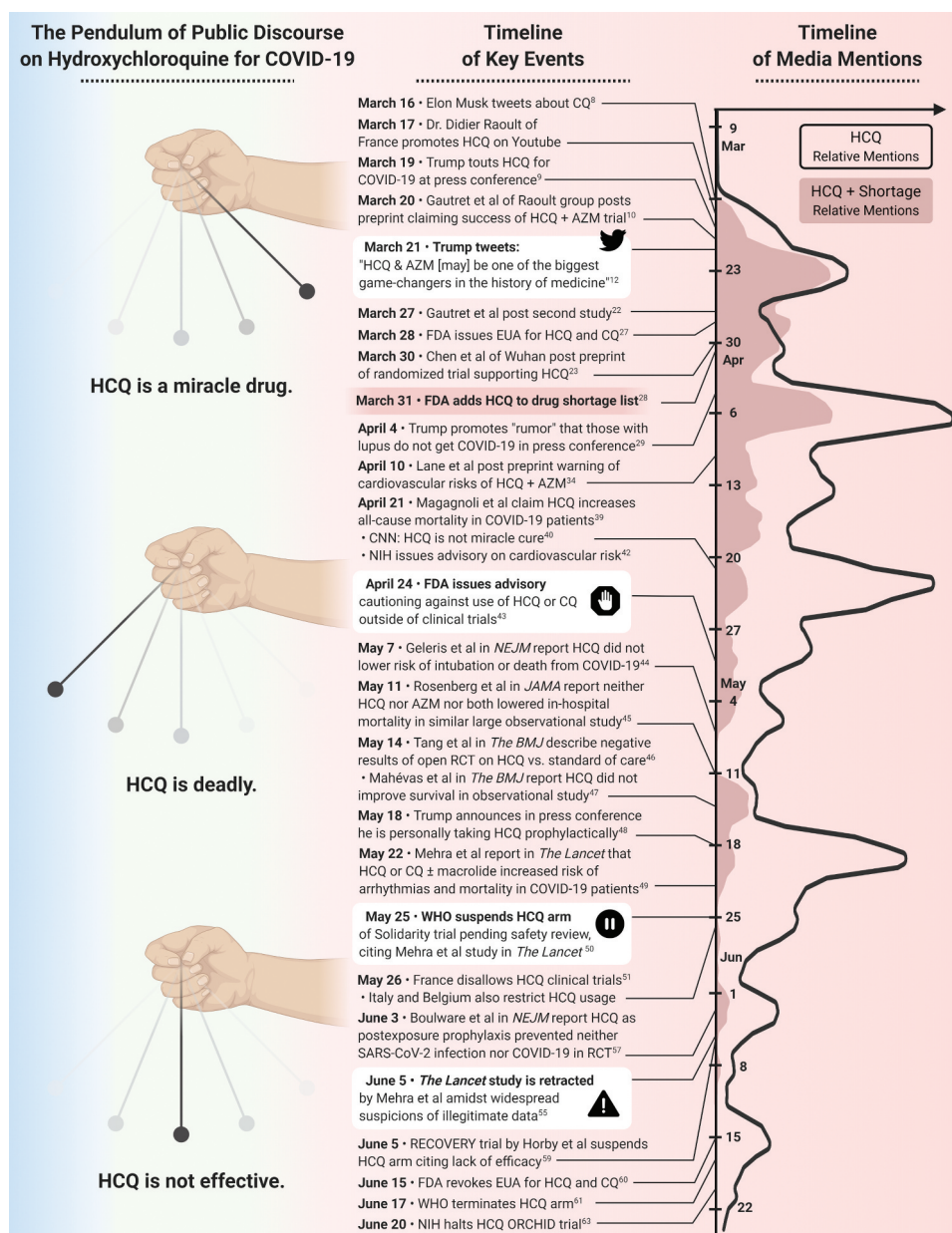


Figure 1. The swinging pendulum. Each swing of the pendulum (left column) illustrating changes in the discourse on HCQ use in COVID-19 as a result of key events (middle column). Timeline on the amount of media mentions of HCQ and HCQ + shortage (data extracted from www.mediacloud.org, source U.S. Top Sources 2018* collection) are presented graphically in right column. Curves show a 4-day mean of leading.

Although the observational design had limitations, its release was followed by articles in the press highlighting concerns of harm with HCQ use [40]. Additionally, Silva-Borba et al. published a study demonstrating that high dose CQ was associated with a higher risk of mortality versus low dose [41]. With mounting evidence, the National Institute of Health (NIH) made an advisory on April 21, followed by an FDA advisory on April 24 [42,43].

2.4. What goes up must come down: The pendulum swings back (May-June 2020)

By May, the pendulum's return swing gained force as multiple studies were published in high impact journals. On May 7 and 11, two large observational studies of hospitalized COVID-19 patients in New York found nonsignificant associations between

the use of HCQ and major outcomes such as intubation or death, or in-hospital mortality [44,45]. Two studies were published on May 14: a negative open-label RCT of HCQ versus standard of care on the outcome of seroconversion at 28 days, and an observational study of patients requiring supplemental oxygen for COVID-19 that did not demonstrate a significant association between the use of HCQ versus no HCQ on the outcome of survival without ICU transfer within 21 days [46,47]. Counter to this new evidence, on May 18 Trump announced at a press conference that he was personally taking HCQ for the prevention of COVID-19. He cited anecdotes that frontline healthcare workers were doing the same [48].

On May 22, an observational study using purported de-identified international registry data on nearly 100,000

patients with COVID-19 found an increased risk of mortality and new arrhythmias for HCQ or CQ alone, and either anti-malarial in combination with a macrolide, versus comparators, receiving neither an antimalarial nor a macrolide [49].

These findings prompted near immediate safety reviews of multiple international trials involving HCQ use. Less than 24 hours after publication, enrollment in the HCQ arm of the Solidarity trial was suspended pending an interim Data Safety Monitoring Board (DSMB) review [50]. Within days, France's public health agency recommended against HCQ's use as treatment for COVID-19 treatment and revoked authorization for its use in clinical trials [51,52]. Similar measures were taken simultaneously by drug safety agencies in Italy and Belgium [53].

However, the plausibility of Surgisphere's data was soon questioned by the scientific community. For example, the study contained electronic data derived from the digital hospital records of almost a third of all COVID-19 cases and 70% of COVID-19 related deaths in Africa at the time [54]. Clinicians and researchers working in Africa found it implausible that these extensive digital platforms existed and that this proportion of COVID-19 cases across the continent were admitted to hospitals with these digital facilities. Multiple other questions were raised, including the lack of a data availability statement and the lack of ethical approval. After third party reviewers were not given access to verify the data, this study and a related NEJM study by the same group were retracted [55,56].

2.5. Returning to center: The resting pendulum (June 2020 and beyond)

In addition to friction from scientific dissent, results from multiple large RCTs on HCQ for prevention or treatment of COVID-19 provided a restoring force to the pendulum's swing. On June 3, a double blind placebo controlled RCT for HCQ as post-exposure prophylaxis against COVID-19 infection involving 821 subjects showed no significant differences in subsequent infection rates between the treatment and control groups [57]. Most subjects were healthcare workers and infections were self-reported by participants as either PCR-confirmed or symptomatically compatible due to limited testing availability in the US. No arrhythmias or deaths were reported. The authors also included data on concurrent zinc use which has been a topic of considerable interest amongst the general public [58].

On June 5, the lead investigators of the RECOVERY trial announced the suspension of the HCQ arm in a statement citing lack of efficacy [59]. An interim DSMB review showed no significant difference comparing those treated with HCQ alone to those who received supportive care regarding the primary endpoint of 28-day mortality or secondary outcomes such as length of hospitalization or mechanical ventilation. These data were also cited by the FDA in a detailed memorandum which revoked the EUA for CQ/HCQ on June 15 [60]. Shortly thereafter, the WHO announced that the HCQ arm of the Solidarity trial, which included the French Discovery trial data, had been stopped due to inefficacy on June 17 [61,62]. Following an interim DSMB review on June 19 involving 470 enrolled subjects, the NIH suspended the ORCHID study due to lack of efficacy between the HCQ arm and placebo in hospitalized patients [63].

3. The patient perspective

The discourse surrounding COVID-19 in the US has forced patients to disseminate accurate information to the public and combat the politicization of the narrative. It has been extremely frustrating for patients to ensure that the general public, and especially patients with rheumatic diseases, have been receiving correct information. Patients, especially those with chronic illness, tend to latch on to any hope they find. Public support for the use of HCQ as a cure for COVID-19 has put patients on these medications in danger as a massive influx of people tried to access HCQ who did not have prior prescriptions. Patients already on HCQ were facing shortages and some were questioning if they should alter their doses. Some wanted to decrease the risks that they would contract COVID-19 while others were seeking to lower their doses in the face of obstacles to receiving their prescriptions. These actions have important consequences, as this increased their risk of worsening disease activity.

Two things stand out to patients: 1) the need to combat misinformation and 2) coordination of physician-researchers, patient advocacy groups, and patient care partners. It is expected that some people will take the media, scientists, and politicians at their word with no further search for the truth. Others will seek to read the published data, but when the data is uninterpretable due to study design or methodological issues, patients are left in a difficult position. Most rheumatic disease patients go to advocates and patient-oriented organizations as their source for information related to their health, sources that are outside of their care team. For these people, it is imperative that the groups have a wealth of accurate information. This is not only where precise lay summaries are helpful, but also references to the sources of this information. If nothing else, we are taught that going forward we need to have better systems in place and infrastructure to work together to disseminate factual and transparent scientific information to the public in a comprehensible way. This best helps us to avoid instances of people taking matters into their own hands.

4. Lessons learned

4.1. The perils of accessibility

Much of the early enthusiasm for HCQ originated from preprints listed on MedRxiv, a database launched in 2019 with the aims of enhancing scientific collaboration and increasing accessibility of scientific findings. However, unfettered access to preliminary reports has proven to be a double-edged sword with widespread dissemination via social media and the press serving as dangerous substitutes for peer review. Communicating accurate and accessible scientific information, including the limitations of current understanding, is crucial in preserving the public's trust during the uncertainties inherent in public health emergencies.

4.2. Impact on research

Several authors have drawn comparisons between COVID-19 and the 2014–2015 Ebola virus disease outbreak in West Africa

where widespread investigational drug use outside of well-designed clinical trials confounded the search for safe effective treatments [64]. Despite these reminders, close to 200 clinical trials involving HCQ for COVID-19 had been registered on clinicaltrials.gov including 93 which were actively enrolling participants as of late May. Most of the trials are too small to detect a meaningful effect size despite the immeasurable resources required to develop and conduct these trials.

The FDA's EUA, issued prior to the availability of rigorous clinical data demonstrating efficacy or safety, allowed widespread access to HCQ/CQ outside of clinical trials. Consequently, enrollment in large RCTs rapidly decreased, delaying the critical safety and efficacy data necessary to evaluate these treatments in a timely fashion.

5. Conclusion

While the story of HCQ for COVID-19 is unique and has many unprecedented factors, it is also not the first time that humanity has pinned its hopes on this compound. Discovered in the bark of the cinchona tree, high in the mountains of the Andes in the 1600s after the Pope died of malaria, quinine and its derivatives have been an essential weapon in pandemics, wars, politics and empire building throughout history [65,66]. During the 1918 flu, it is reported that 'Londoners refused to be fobbed off with advice to gargle with salt water, and besieged chemists and doctors' surgeries demanding quinine' [67,68].

Although data sharing and dissemination of data are important and enabled now by current forms of communication, the role of peer review is more crucial now than ever. As much as social media plays a role in the dissemination of information and scientific findings, scientists need to adequately direct and discuss these non-scientists, especially in challenging times such as a pandemic. While research is at times difficult to translate to the public, we can improve communication by providing patient-centered summaries at the time of publication.

6. Expert opinion

In many ways, the swift uptake and downfall for the recommended use of antimalarials, particularly HCQ, for COVID-19 serves as a cautionary tale for the conduct of research during a pandemic. The timeline of events has been particularly illustrative of the various types of pitfalls of research and scientific communication. That these events have occurred in a compressed timespan of several months is even more remarkable.

Scientific rigor needs to be upheld even in critical situations, such as pandemics, where there is an urgent need for new and efficacious treatments [69]. Transparency and accessibility in the publication and dissemination of results must remain key parts of research. Data availability, open peer review, and open access are emerging tools to improve scientific integrity. Maintaining these principles of the scientific method is even more vital during critical times, since results and findings will rapidly influence decision making. As observed with the use of antimalarials, rapid clinical implementation was based on data with clear

limitations, without an adequate understanding of either benefits or potential harms. Furthermore, the impact of these decisions was not only restricted to its use in COVID-19 but had repercussions on patients who depended on these medications for other data-driven indications. It also led to inadequate allocation of resources that could have been employed for other vital interventions or equipment.

Effective, timely, and open peer review is critical to the validity of the data and the interpretation of the results. The widespread use of pre-print publications has highlighted the importance of adequate peer review, but also highlighted the value of the 'community review' of pre-prints when formal peer review has failed. With the contracted process from data collection to publication, the continued promotion of publication ethics is important to protect scientific integrity and trust in the system.

Finally, it is important for clinicians and scientists to realize that their role as communicators is now more vital than ever. Media, including social media, are powerful tools of dissemination. As experienced during this crisis, the handling of data dissemination is critical and can have an either positive or negative impact in the public's image of the scientific community. As the COVID-19 pandemic persists in the coming months, the scientific community must reemerge as a reliable source for guidance in interpreting the evolving knowledge base. This should be accomplished in tandem with stakeholders, such as patient advocates and public health officials, to carefully and effectively communicate findings to a wide audience.

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Declaration of interest

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