EDITORIAL

Contested effects and chaotic policies: the 2020 story of (hydroxy) chloroquine for treating COVID-19

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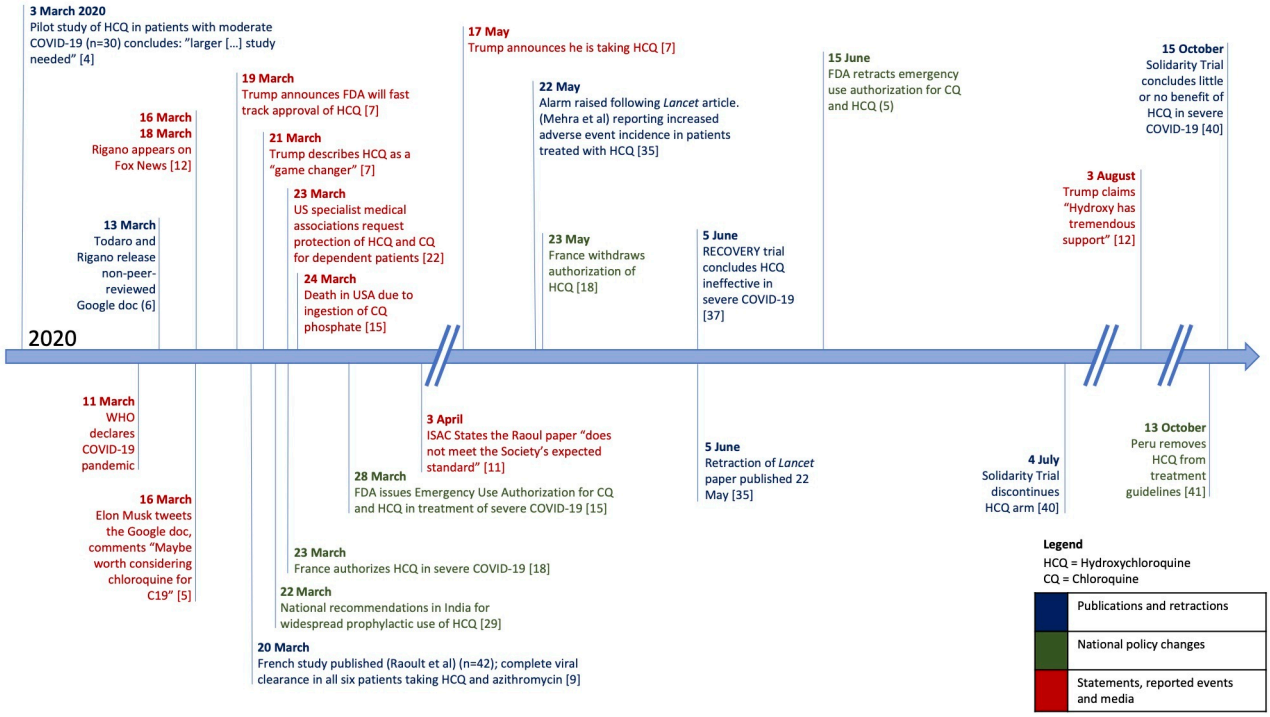
During the past 12 months chloroquine and hydroxychloroquine have been touted as miracle cures for COVID-19 and introduced into COVID-19 treatment protocols in Asia, Africa, and North and South America (see Figure 1). This has led to massive increases in demand such that patients with rheumatoid arthritis and lupus have been deprived of effective treatments.

A Cochrane Review by Bhagteshwar Singh and colleagues definitively concludes that hydroxychloroquine has no clinical benefit in treating COVID-19 in hospitalized patients.[1] The dissemination of information on these drugs in the scientific press and other media has been rapid and tumultuous with strong and polarized opinions among scientists, politicians, and the general public, building a climate of mistrust. Potential resulting harms included wasted resources (including research capacity) and drug shortages for evidence-based indications. The false hope instilled may have also led to unsupervised use of potentially harmful medications. While most national and health system-level guidance is evidence based, how did we get into such a chaotic and confusing situation with the assessment of chloroquine and hydroxychloroquine efficacy?

Figure 1. Timeline of key events in the story of chloroquine/hydroxychloroquine and COVID-19



Chloroquine was proposed as a potential treatment for severe acute respiratory syndrome (SARS) in 2003, but transmission of SARS was stopped before trials were started.[2] As cases of COVID-19 exploded in China in early 2020 some small studies of treatment with hydroxychloroquine reported benefit.[3][4] Speculation regarding these two drugs began in January 2020, spreading globally from China (including statements issued by Chinese state media) and South Korea via Facebook and Instagram, reaching, for example, Nigeria, Vietnam, and France by February.[5]

On 13 March 2020 a Google document on hydroxychloroquine was released by two cryptocurrency investors (Greg Rigano and James Todaro), and Elon Musk tweeted a link to the Google document to more than 40 million followers.[6] Within days, President Trump made his first public comments in support of hydroxychloroquine.[7] US-based searches for online sale of chloroquine or hydroxychloroquine surged after these endorsements from Musk and Trump.[8]

On 20 March 2020 a small study from France was published, reporting 100% cure of COVID-19 in people treated with hydroxychloroquine and azithromycin.[9] The primary outcome reported was time to virological clearance, assessed by daily PCR of nasopharyngeal swabs; all six patients receiving the two drugs had a negative PCR by day 6 of treatment. The paper was heavily criticized (but not corrected or retracted), with one review describing it as “fully irresponsible”.[10] On 3 April, the journal's society owners stated that “the article does not meet the Society's expected standards”.[11]

Fox News Channel, a US-based news broadcaster, interviewed Rigano (on 16 and 18 March), and hosts and guests made frequent reference to chloroquine and hydroxychloroquine between 23 March and 6 April: 275 of these references were positive and 29 were negative or doubtful.[12][13] Dr Oz, a television personality and cardiothoracic surgeon, appeared on the network supporting the 100% cure claim multiple times over the same period, and on 23 March he echoed Trump's description of hydroxychloroquine as a “game changer”.[13][14][15]

The US Food and Drug Administration (FDA) was criticized by former leadership for issuing an Emergency Use Authorization for chloroquine and hydroxychloroquine on 28 March 2020 in response to Trump's endorsement of hydroxychloroquine.[16] In France, a former Minister for Health and cardiologist led those demanding wider access to hydroxychloroquine.[17] France authorized the use of hydroxychloroquine in hospitalized patients on 26 March.[18] President Macron formally visited the institute of Dr Raoult, who led the French study referred to above, on 9 April.[19] By 6 April, 98% of the French population had heard about chloroquine-based treatment regimens for patients infected with SARS-CoV-2, and 59% of the French population believed that chloroquine-based regimens were effective against this virus.[20]

A significant increase in prescriptions of hydroxychloroquine or chloroquine above expected levels was seen between February and May 2020 in France. This peaked between 23 and 29 March with the volume of prescriptions for hydroxychloroquine or chloroquine alone and hydroxychloroquine in combination with azithromycin respectively 145% and 7000% higher than predicted.[19][21] On 23 March, a joint statement from US medical specialist associations, including rheumatologists and dermatologists, requested protected supplies for those reliant on hydroxychloroquine treatment.[22] These patients had been impacted by major shortages as demand for hydroxychloroquine also rose in the United States, with associated reports of prescription fraud.[23] In the Dominican Republic, reduced availability drove such patients to solicit the drug via social media from those who had stockpiled it for COVID-19.[23] New manufacturers and suppliers quickly emerged, leading to concerns regarding quality control.[25]

Countries around the world introduced chloroquine or hydroxychloroquine into guidelines.[26][27][28] For example, India quickly directed all frontline healthcare workers and household contacts to take prophylactic hydroxychloroquine.[29] A few days after Trump's initial hydroxychloroquine promotion, President Bolsonaro ordered an increase in production of chloroquine in Brazil.[30]

Those expressing caution regarding the early use of hydroxychloroquine outside of clinical trials included Stephen Hahn, US FDA Commissioner, and Anthony S Fauci, director of the US National Institute of Allergy and Infectious Diseases, who described the evidence as “anecdotal” (20 March 2020).[15][31] Concern arose about already known potential side effects of chloroquine and hydroxychloroquine, including cardiac arrythmias.[28][32]

More than 100,000 COVID-19 related papers and preprints were published by December 2020.[33] A preprint released on 11 May 2020 suggested that hydroxychloroquine and azithromycin might reduce hospital morbidity in COVID-19 patients.[34] It was withdrawn 10 days later but had already been referenced by Fox News. A paper in *The Lancet* describing a high incidence of adverse events in hospitalized patients treated with hydroxychloroquine provoked alarm before retraction following controversy about the reliability of the data source.[35] In an attempt to expose poor practice by a suspected predatory journal, a ‘Trojan horse’ article was submitted, published and only retracted once the nature of it was identified by readers.[36]

Criticisms and retractions of widely disseminated publications engendered confusion and distrust. More robust data were released from large, randomized control trials in June and October 2020.[37][38]

By July 2020 one in six COVID-19 treatment trials included chloroquine or hydroxychloroquine, potentially at the expense of other drug candidates.[39] Meanwhile, following authorizations by national agencies such as the US FDA, an unknown number of people received hydroxychloroquine outside of trials, with potentially useful data going unrecorded.[39] Difficulties recruiting to studies during the initial enthusiasm for hydroxychloroquine were reported. Many patients in France reportedly declined randomization to any other treatment arm when approached for recruitment to the large DISCOVERY trial.[17] After the tide of opinion turned, concern regarding adverse effects or perceived inefficacy restricted recruitment to trials addressing outstanding questions regarding pre- or post-exposure prophylaxis.[39]

The intense global discussion of the role of chloroquine-based treatments in the management of COVID-19 has highlighted the

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risks and repercussions of misunderstanding and politicization of the uncertainties which can arise in clinical medicine and public health. Uncertainties arise particularly when the need for effective treatments is urgent, information and evidence is scant and rapidly evolving, and the scenario highly complex. Challenges for the scientific community included the efficient prioritization of potential novel or repurposed treatments, the execution and publication of valid and generalizable research studies in short periods of time, and the effective communication of study findings and any attendant uncertainties with a diverse and global audience.

Scientists achieving control of the narrative, rather than politicians, seems improbable, but could provide clearer distinction between facts and subjective interpretation. Efforts should be made to identify substandard studies prior to dissemination, and consideration given to whether a change in approach to preprints is necessary, to incentivize researchers to avoid premature publication. High-quality peer review using such principles as those underpinning Cochrane Reviews is vital. However, although Cochrane has done much to expedite this process, sifting through the data to produce a careful systematic review, even when rapid, nonetheless requires time.

With the urgent need for solutions to a global catastrophe, researchers responded with immense efforts, producing and sharing new ideas and information at an unprecedented rate. Scientific research was under a spotlight and politicians, and traditional and social media showed their power to expedite the spread of both information and disinformation. However, there was never a greater need for critical appraisal, peer review, clear communication of facts and any uncertainties in the data and evidence, and a distinction between evidence and its interpretation.

Scientists, politician and media organizations share a responsibility to combat 'fake news' and to promote rational discourse, access to reliable information, and discussion of uncertainties. This will help to ensure the credibility of the scientific community and, most importantly, benefit individual and population health.

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