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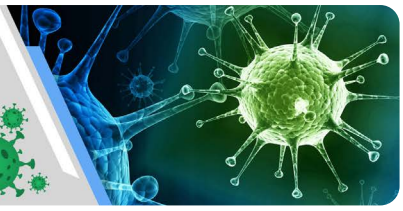

To Put an End to Misinformation and Medical and Scientific Malpractice Concerning Hydroxychloroquine A Loss of Chance for Patients Faced with SARS-Cov-2

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Abstract

Hydroxychloroquine, initially perceived as a promising treatment for the Covid-19 pandemic, sparked intense debate. Early studies conducted in China and later at the IHU in Marseille under Professor Raoult highlighted its efficacy. A retrospective study involving more than 30,000 patients treated at the IHU fully confirmed its effectiveness. However, the story of this molecule was overshadowed by biased or low-quality studies, where the treatment was often administered too late, at inappropriate and sometimes toxic doses. Despite decades of proven use, the scientific evaluation of hydroxychloroquine resembled sabotage, fueled by conflicts of interest and controversies. Key actors in the crisis, including physicians and prominent media figures in France, played a significant role in its discreditation, often at the expense of a rigorous and objective approach. The saga of this molecule underscores issues that go beyond the medical field, raising questions about the integrity of science and the decisions made during a major health crisis.

Keywords: Hydroxychloroquine, HCQ, COVID-19, SARS-CoV-2, azithromycin, Drug doses, Adverse drug reactions, Drug safety, Randomized clinical trials, Observational studies, Mathematical models

Article

Biased science or absence of foolproof scientific studies led to a questionable management of the covid situation. Scientific discourse has found its way on prime-time television which is not most appropriate forum as science requires debates that is often better held within the scientific communities. Hence rightful or wrongful evaluation based on incomplete information have polarized opinions and the voice of the subsidized media have overcome that of science. Controversies were numerous from the origin of the virus, the effectiveness of lockdowns, the wearing of masks outdoors, ultra rapid vaccines developments beyond what was the agreed standards in the scientific community, to the actual patient care and associated the treatment strategy. For centuries, patients have treated according to the best knowledge available of the medical community with medications that are more or less effective (under the "*primum non nocere*" duty of the doctor) combined with the psychological support. However, these approaches have been challenged most recently with an attempt to codify mathematically and statistically medical science to form the evidence-based medicine with a pyramid of proof commonly accepted in the community, where the extremely cumbersome controlled randomized trials sit on top of the pyramid in order to generate "scientific proof". At the highest level is the meta-analyze that combines

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data from different clinical trials in order to reach statistical significance. But meta-analyses have themselves their own problems has they rely on very powerful statistical measures and techniques with one in going hypothesis: "*garbage in garbage out*". It implies that you have a homogeneous set of trials and the term homogenous is term that is far too often ignored by doctors or does not bear the same meaning among doctors and statisticians. For example, two trials, one on early patients and the second one of hospitalized patients with the same molecule may not bear the same input into the analysis but the way the patient is codified early/late in itself creates a bias. Same for the dosage, where one cannot control for the sub dosage or over dosage of a molecule and its biochemical interaction. That was the case for hydroxychloroquine (HCQ) as we will see at a later point. Combining non homogeneous data sets and assuming that statistical methods/techniques are capable of coping for the inbuilt biases requires a thorough analysis of each of the variable, its distribution, its interaction with other variables – it is a complex system of information, more complex than the parameters of any flight simulator as it relies on physiological data that differs from one person to the other. Our views are that the way categorical data are treated in multivariate analyses requires significant care to avoid biased results as we are operating in an incomplete information data set: i.e. the data that is codified in most clinical trial is a reduction of what should be codified in order to cater for other random event or unexplained phenomenon. A simple example is the distance calculation that one would use in a propensity score model using categorical variable. They may appear close but in reality, they are not. Let me take an example, in the calculation of the proximity of points A, **B** and **C** (Figure 1). On the left side, the distance between **A** and **C** appears to be 1 unit. However, if there are no roads from **A** to **C** as for example you have to go through point **B** to go to **C** then the actual distance on the left-hand side is a theoretical distance that has no bearing with reality. So, any propensity score would say that **C** is distant of one unit of distance from **B** – same from the graph on the right. However, in reality if you measure the true distance that one would have to cover to go from **A** to **C** (i.e. 2 units of distance) then you would not be able to say that **C** is equidistant from A or from **B**.

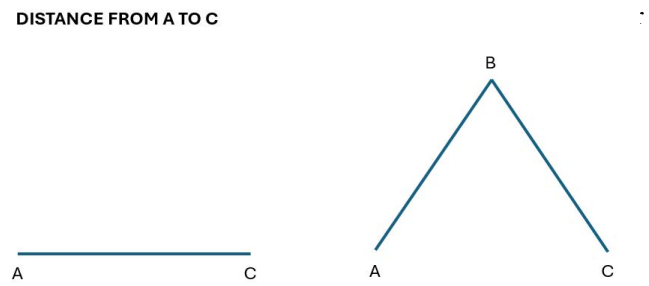

Figure 1

in most multivariate analysis with categorical data. It is the same issue for most statistical tests when one does not appreciate the actual distribution of the variables (continuous, discontinuous, linear, nonlinear, U shape….) and then apply a statistical test. Hence the reason for having observational studies as well as randomized controlled trial. However, the pyramid of proof may have to be reconsidered in a crisis situation in order to have data to inform policies.

Let's come back to the pandemic and the usefulness or lack thereof of HCQ. During the infectious disease pandemic, initial political decisions led to patients being left at home until their conditions deteriorated with breathing difficulties. It is only at that point that they were taken care off. So, without any simple individual oximetric monitoring (an oximetric measurement tool costs a few euros), and a disease that could worsen rapidly (in a few days) without their knowledge they faced the risk of silent hypoxia. This way of managing patients was contrary to the management of most infectious diseases – early treatments have always shown to improve conditions of patients and reduce the risks of worsening or progressing to hospitalization. Meanwhile, expensive, toxic, and difficult-to-administer drugs (particularly the intravenous route) were proposed via the decisions of health authorities that are more than questionable. In many hospitalized patients, when the viral phase was nearly over, and that the inflammatory phase was beginning, these drugs were therefore unsuitable. After observation on a few early cases combined with its long-standing knowledge and handling of infectious diseases, the Doctors at "l'Institut hospitalo-universitaire" (IHU) Méditerranée (a research center specifically built for infection diseases), on the other hand, proposed HCQ and azithromycin (AZI) as a treatment of the early phase of the disease, two molecules that has been known for decades and very well tolerated. After diagnosis, combining knowledge shared by the Chinese and the own expertise of the IHU top notch scientific team, the IHU Méditerranée infection chose to treat the early symptoms of patients based on the corpus of available science. In the emergency situation, they decided based on controlled observations (they measured viral loads through PCR, conducted other patients' data analyses such as QT intervals…) to treat their patients. As recognized scientists and doctors with the highest level of clearance in terms of research, ethics code of conduct, they administered levels of HCQ and AZI that were known to work in other conditions. They collected and codified the data to provide an observational study. This was done in a few days under pressure, and time was not available for conducting randomized controlled studies. As per the code of conduct of pandemic handling or any emergency situation, they considered that such studies would have wasted valuable time during an epidemic and hence endangered patients. Indeed, the time to organize properly an RCT and obtain results from

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such a randomized study would have meant that the results would only have been available after the epidemic peak. In an emergency situation, their decision was sound and in the best interest of the patients that were at risk with a observed lethal rate of 2% at the time. So, a small-scale observational study demonstrating the decrease in viral load had two benefits: treating the patients that had early symptoms and preventing them from having to go to hospital that would have had the consequences of saturation of the ICU.

Let's imagine that despite numerous tests a plane loses its cabin pressure whilst in the air and at the same time the O2 masks in the plane fail to function, there is no time to test what is the cause – and the pilot has to descend as rapidly as possible where the mix of oxygen in the air is breathable. No one would say that the captain did not do is job. The IHU Méditerranée infection observed the likely loss of oxygen due to the respiratory infectious disease and used the tools they had available to prevent the patients from progressing to a more serious stage of the disease. Moreover, using a placebo in a control group seemed inappropriate, especially since HCQ has been known for many years, is well-tolerated, and has very low toxicity at the doses prescribed. The decrease in viral load was sufficient as a reliable indicator to favorably validate the use of both drugs. The IHU team therefore decided to carry out some preliminary studies before treating patients. We will see that, in addition to the problems and discussions that may be related to the type of randomized or observational studies, most scientists have made a double confusion. They confused the viral and inflammatory phases. They also confused the HCQ administered dose (loading dose and plasma concentration) with the HCQ impregnation (increase in HCQ concentration in the phagolysosome).

The first studies on hydroxychloroquine

The first study by the IHU Méditerranée infection was thus an observation study that led to a preliminary article conducted urgently to evaluate the efficacy of HCQ and AZI on viral load in the nasopharynx (1). This study was carried out knowing the preliminary results from China with chloroquine that had been codified and published in a few articles (2, 3). Four years later, under unprecedented pressure from a group of people, the study by Gautret et al. (1) was retracted for "methodological inadequacy". Apparently, this is as stupid as if pilot Raoult had saved all his passengers by increasing the pitch of the plane to reach acceptable altitude more quickly, and had been criticized for not putting on his turn signal. The IHU approach was sound considering the emergency situation at reducing patients risks of progressing to a more serious stage of the disease. In France, health authorities had suggested slowing the epidemic curve by leaving people at home, with the risk of their condition deteriorating, and preventing them from coming into contact with one another. The early treatment of the IHU Méditerranée infection should have been as complementary. It was by some to the dislike of others that only wanted to obey to state of the art statistical medical science that would lead them the say that point **C** is as close to point **A** without taking into consideration the other factor such as the elevation (Figure 1). This is the major difference in scientific approach.

Some Chinese studies suggested the efficacy of HCQ against COVID-19 (2, 3). A randomized study from Wuhan People's Hospital involved 62 patients with COVID-19 (2). The patients were divided into two groups: one received HCQ (400 mg/day) in addition to standard treatment, and the other received only standard treatment. The results showed a faster improvement in clinical symptoms, such as fever and cough, as well as an improvement in lung images among patients treated with HCQ. Let us also mention this study which showed very early, at the very beginning of the COVID epidemic, that low-dose HCQ (2400 mg over 5 days, i.e., 480 mg per day) was associated with lower mortality among hospitalized patients treated within 5 days, and even after 5 days following the onset of symptoms (4). These preliminary studies sparked global interest in the use of HCQ for the treatment of COVID-19. HCQ, like AZI, has published antiviral effects through various mechanisms (5-11), including alkalinization of the phagolysosome or increased production of interferons. Often, the studies have been conducted in vitro. Nevertheless, these are facts to consider, potentially translating into clinical efficacy. HCQ has been studied for its potential against COVID-19 due to its antiviral and immunomodulatory properties. Its proposed mechanisms of action include:

a) Inhibition of viral entry: HCQ increases the pH of phagolysosomes, intracellular compartments essential for the fusion of SARS-CoV-2 with host cell membranes. This may prevent the virus from entering host cells (12, 13).

b) Interference with viral replication (14): HCQ may inhibit certain viral or cellular enzymes necessary for viral replication, although this mechanism is not fully understood.

c) Modulation of the immune response: As an immunomodulator, HCQ can reduce the activation of pro-inflammatory cytokines, such as interleukin-6 (IL-6) (15). This could mitigate the "cytokine storm," an excessive immune response observed in severe cases of COVID-19.

d) Effect on ACE2 receptors: Some studies have suggested that HCQ may interfere with the interaction between the virus and ACE2 receptors, which SARS-CoV-2 uses to infect cells (16, 17).

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e) Antithrombotic properties: While secondary, HCQ may also influence blood coagulation, potentially reducing thromboembolic complications associated with COVID-19 (18).

Subsequently, numerous articles and meta-analyses were conducted, with seemingly discordant results regarding the efficacy of this treatment, which combines HCQ and AZI, but the conditions under which the treatment was used were very different. We propose to provide a synthesis and a critical analysis of what was conducted during the pandemic.

Studies on HCQ and AZI have suffered from several different biases.

a) The first bias was that many studies were often retrospective, highly heterogeneous, and involved groups that were difficult to compare (19).

b) The second bias was studying the efficacy of these drugs in already hospitalized patients, thus too late, during the inflammatory phase, whereas these drugs should be used early during the initial viral multiplication phase.

c) The third bias was to mix results from treatments with very different doses.

The biased studies on hydroxychloroquine: a treatment administered too late and often at the wrong dosage, sometimes at toxic dosages

On March 13, the World Health Organization (WHO), in partnership with various collaborators, established the SOLIDARITY Response Fund to support research on COVID-19 (19). Following this initiative, the French Institut National de la Santé et de la Recherche Médicale (INSERM) spearheaded a European clinical trial known as Discovery. The Discovery study was a large European clinical trial launched to evaluate the efficacy of various treatments against COVID-19, including HCQ.

The study aimed to test four potential treatments in hospitalized patients with severe COVID-19:

1. Remdesivir.
2. Lopinavir/ritonavir (with or without interferon beta).
3. HCQ.
4. Standard care (control group)

Each treatment was administered according to a rigorous protocol to compare their efficacy and safety. After several months of analysis, the data from Discovery showed a benefit, but not statistically significant, of HCQ in the treatment of hospitalized COVID-19 patients. The study revealed that HCQ did not improve survival chances or clinical progression compared to standard care due to the undersizing of the HCQ group. Indeed, in June 2020, HCQ was excluded from the Discovery study following the publication of the study by Mehra et al. (now withdrawn) in The Lancet suggesting risks associated with HCQ on the basis of false data (21). This decision followed recommendations from the trial's International Steering Committee, based on data indicating that these treatments resulted in little to no reduction in mortality among hospitalized COVID-19 patients compared to standard care. In fact, the treatment showed efficacy that had not yet reached statistical significance for the abrupt interruption of the trial, and therefore did not allow for a conclusion to be drawn. The Discovery study on HCQ was therefore halted because of this study containing erroneous data, which was quickly retracted in a resounding scandal now known as "LancetGate". We will discuss this study in more detail later in this article. French researchers concluded that HCQ was not effective for treating COVID-19 in hospitalized patients and could even cause adverse cardiac effects. The conclusions of the Discovery study contributed to the global abandonment of HCQ as a recommended treatment for COVID-19. However, this decision was controversial, as some argued that large studies like Discovery did not adequately explore its efficacy in the early stages of the disease or as a prophylactic measure. Indeed, most researchers refused to acknowledge that it was absurd to test a treatment effective during the viral phase, on hospitalized patients already in the inflammatory phase. This can only reflect an incompetence and misunderstanding of the disease's pathophysiology. Antiviral treatment can only be truly effective when administered very early, at the onset of the disease. While some efficacy in hospitalized patients might still be observed, it would more likely be due to other effects, such as immunomodulatory or anti-inflammatory properties.

(c) A third bias was incorrect HCQ dosing. The dose proposed by the IHU Méditerranée infection was 600 mg per day, a common dosage of the molecule in several known pathologies such as rheumatoid arthritis or solar lucite. Some studies evaluated the efficacy of HCQ using lower doses, while others used toxic doses, such as the Recovery trial. We had already written about it in an article, which addressed the pulmonary consequences of HCQ overdose (22).

The calculations here concern the doses of sulfate and base in the Borba and Recovery studies (23, 24).

For tablets:

- In the Borba et al. study, the doses are 241.9 mg of chloroquine sulfate, corresponding to 150 mg of chloroquine base.
- In the Recovery study, the doses are 200 mg of HCQ sulfate, corresponding to 155 mg of HCQ base.

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Regarding the doses:

- In the Borba et al. study, the dose is 967.6 mg of chloroquine sulfate, or 600 mg of chloroquine base (4 tablets of 150 mg of chloroquine base) twice a day, which totals 1935.2 mg of HCQ sulfate or 1200 mg of chloroquine base per day.
- In the Recovery study, the dose is 800 mg of HCQ sulfate, or 620 mg of HCQ base (4 tablets of 200 mg of HCQ sulfate) once a day.

In the Recovery study, an 800 mg loading dose of HCQ sulfate was administered at the start of the treatment, followed by 800 mg six hours later, and then 400 mg every 12 hours, totaling 2400 mg on the first day, which is equivalent to 1860 mg of HCQ base. The total dose of HCQ over three days is 2790 mg in base form and 3600 mg in sulfate form.

The toxicity of HCQ in adults is well-documented. According to medical literature, the toxic dose is estimated to be 20 to 25 mg/kg in base form for an adult. For a 70 kg individual, a total dose of 1400 to 1750 mg of HCQ in base form may cause severe toxic effects, including cardiac and neurological disturbances. In sulfate form, this corresponds to a total dose of approximately 1806 to 2258 mg of HCQ sulfate, which is equivalent to approximately 9 to 11 tablets of 200 mg HCQ sulfate (25). HCQ is primarily eliminated through the liver and kidneys. It undergoes partial metabolism in the liver, producing active metabolites. A significant portion of the drug is excreted unchanged in the urine by the kidneys. Its elimination is influenced by its long half-life, which can span several weeks due to its accumulation in tissues such as the lungs, liver, spleen, and kidneys. Therefore, the elimination of HCQ depends on both hepatic and renal function of patients. The clearance rate of the drug is variable and can change depending on the pathological condition of the patient.

Overdosing on HCQ can be toxic or even fatal, leading to a pulmonary shunt effect similar to what is observed during the inflammatory phase of COVID-19. This has potentially led to false conclusions about the effect of HCQ, as there may have been confusion between the effects of overdosing and severe COVID-19 (22). The Recovery study used very high doses of HCQ, doses that were very close to the toxic threshold. The authors claimed that it was important to administer a loading dose to rapidly achieve sufficiently high plasma levels of HCQ for the treatment to be effective. However, this reflects a misunderstanding of pharmacology, as HCQ concentrates thousands of times within the phagolysosome- (« lysosomal trapping »), the site where the virus enters and where the treatment's potential efficacy lies (26, 27). An article reports that the intracellular concentration exceeds 50,000 times that of plasma within the phagolysosome (28). This observation renders absurd the comments of certain pharmacologists regarding in vivo concentrations, deemed unattainable for the molecule to be clinically effective. Additionally, Maisonnasse et al. found that HCQ concentrations in the lung were higher than in plasma, with Lung plasma ratios ranging from 27 to 177 in macaques (29). We mention as well that too a high dose of HCQ may suppress anti-inflammatory cytokines production (30, 31).

Thus, we understand that the in vivo concentration is much higher than what can be studied in vitro because the cell naturally acts as a concentrator of HCQ. Therefore, it is not necessary to administer an excessive loading dose but rather to provide an adequate, non-toxic dose, and most importantly, to do so early—at the very onset of the disease.

This is exactly what is suggested by a fundamental study on the antiviral effect of HCQ: « In our study we noted that the EC50 values for HCQ and chloroquine decreased with longer incubation times. This suggests that incubation time may influence the drug's antiviral activity. Both HCQ and chloroquine have been reported to accumulate in cells » (32). In addition, it was identified by a team from Glaxo in the supplementary analysis of their paper, that the combination of HCQ and AZI reduced by a factor 20 the dosage of HCQ required to achieve the required viral load reduction. They also asserted that "When HCQ is administered without AZI, no safe and suitable HCQ dose can achieve targeted concentrations in (low respiratory tract infection) LRTI and URTI (upper respiratory tract infection) patients (Supplementary Fig. S6)" (33).

Regarding the cardiac safety of hydroxychloroquine

HCQ is one of the oldest drugs for subacute and chronic inflammatory diseases (1955) and the most widely prescribed synthetic antimalarial. In the 17th century, the bitter bark of the cinchona tree was already renowned for its febrifuge properties. However, it wasn't until 1820 that French pharmacists Pelletier and Caventou succeeded in isolating an essential alkaloid: quinine. The first synthetic antimalarial drugs, chloroquine and HCQ, were developed by German chemists between the wars. In the 1960s, the emergence of malaria resistance to synthetic antimalarials was accompanied by the discovery of their anti-inflammatory properties, which were rapidly exploited in the treatment of lupus and rheumatoid arthritis.

From an immunological perspective, HCQ interferes with lysosomal activity, inhibits antigen presentation, and modulates Toll-like receptor (TLR) signaling. Based on its mechanism of action, experimental data suggest that HCQ may provide cardiovascular protection. Its lysosomal activity reduces insulin degradation and blocks cholesterol synthesis. Furthermore, HCQ increases hepatic LDL receptors, enhancing plasma LDL catabolism and lowering total cholesterol concentration (34). HCQ has been accused, in combination with AZI, of causing torsades de pointes by prolonging the QT interval. At the doses used by the IHU

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Méditerranée infection, namely 600 mg of chloroquine sulfate per day, toxicity is absent. This corresponds to approximately 8.57 mg/kg/day for a 70 kg man. Given that 600 mg of chloroquine sulfate is equivalent to approximately 465 mg of chloroquine base, this represents 6.64 mg/kg/day for a 70 kg man. When 115 French physicians, including the President of the COVID-19 Scientific Council in France, Jean-François Delfraissy, published in 2020 on the treatment of arthritis with HCQ for more than six months in 573 patients, they reported no side effects (35)!

In the retrospective article by Harvey Risch (34), it is reported that HCQ combined with AZI was administered as standard care in the USA to over 300,000 elderly patients with multiple comorbidities, with only 0.047% developing arrhythmia as a result of the treatment. Furthermore, just 9 out of 100,000 patients (0.009%) succumbed to the disease, a figure that stands in stark contrast to the 10,000 Americans dying weekly from the illness. Similarly, Lagier et al. observed QTc prolongation > 600 ms in 0.67% of patients, yet without any cases of torsade de pointes or sudden death (37).

In a cohort study including 52,883 patients with systemic lupus erythematosus, the use of HCQ was associated with a protective cardiovascular effect, and no significant adverse effects were observed. It should be noted that the doses used to treat systemic lupus are usually 200 to 400 mg per day for several months or even years, whereas the doses used by the IHU Méditerranée infection are 600 mg per day for about ten days (38). A study recently published in December 2024 by Hazan et al. (39) shows that outpatients treated with this protocol did not experience an increase in their QT interval compared to the QT interval in the placebo group. Patients treated at the IHU in Marseille had however undergone electrocardiograms. It is likely that the risk is primarily present in patients with severe COVID, renal impairment, and hypokalemia. In such cases, which do not involve early treatment, there is no indication for treatment with AZI and HCQ.

We also remind that COVID-19 can lead to cardiac involvement through various mechanisms, notably thrombosis and myocarditis. Severe cases of COVID-19 can also be associated with renal involvement, characterized by tubulopathy and hypokalemia, the latter potentially causing torsades de pointes. These patients are generally hospitalized, and hypokalemia is identified through blood tests. It should be noted that this is not at all the situation for early cases that could benefit from a few days of treatment with HCQ and AZI. Furthermore, no autopsies were conducted on COVID-19 patients who died from cardiac causes, and these deaths cannot be attributed to HCQ in any way. The Recovery study was therefore an act of sabotage, with the protocol designed as an example of "bad science" to ensure that no evidence of HCQ efficacy could be demonstrated. In addition, the Recovery Trial co head removed the pharmacocinetic models used in V2 of their protocol. It could not be found in the later protocol, most likely as it shows some serious issues with the HCQ dosage calculation.

Publications whose integrity has been called into question

In addition to these low-quality articles, some publications have been issued whose integrity has been called into question. We will mention two of them which have since been retracted.

a) First, the "LancetGate". This refers to the article published in The Lancet in May 2020, that purported to provide a global overview of HCQ prescriptions and their outcomes, concluding an inefficacy of the treatment and a significant increase in mortality (21). This article was not consistent with scientific data, as it was implausible that a treatment with HCQ over a few days could increase mortality. This article has since been retracted 15 days later because it was proven that the data were fabricated. The study by Mehra, et al. caused immense controversy before being retracted a few weeks later. The study claimed that HCQ significantly increased the risk of mortality and cardiac arrhythmias in COVID-19 patients. It led to the temporary suspension of several clinical trials, including the Solidarity trial by the WHO and the Discovery study. The study relied on data collected by Surgisphere, a company that claimed to have access to information from hundreds of hospitals worldwide. However, experts quickly identified major inconsistencies in the data. The number of patients recorded in some countries did not match official epidemic figures. Anomalies in patient demographics and administered treatments were apparent. Some hospitals mentioned in the study denied providing any data to Surgisphere. Surgisphere company refused to share its databases for independent verification, citing confidentiality agreements, which prevented any validation of the results. The statistical analyses used in the study were deemed questionable by several experts. The high number of severely ill COVID-19 patients receiving HCQ seemed unrealistic, and the reported ratios failed to account for numerous confounding variables. Surgisphere also provided no concrete evidence on how the data were obtained, stored, or analyzed, raising questions about ethical practices and data confidentiality. In response to these criticisms, three of the four co-authors, including Professor Mehra, requested the retraction of the article, citing their inability to guarantee the accuracy of the data. The Lancet officially retracted the article on June 4, 2020. This episode had a significant impact on trust in scientific research during the pandemic, highlighting the dangers

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of publishing hastily under media and political pressure and the importance of transparency and data validation in large-scale studies. The Surgisphere affair has been described as one of the greatest scientific scandals of the pandemic. The fabricated data and misleading conclusions temporarily discredited HCQ as a potential treatment, even as other studies were still ongoing. This episode also fueled debates about biases and partiality within the scientific community, with some accusing ideological or commercial motives behind the publication. This scandal marked a turning point in the management of research during the pandemic, underscoring that scientific integrity must always prevail, even during times of crisis

b) The second article was that of Pradelle et al., which reported the 3 january 2024 over 17,000 deaths allegedly caused by the prescription of HCQ (40). Once again, this article suffered from significant methodological biases. It was quickly retracted after we issued a letter of concern on 7th January 2024 that Elsevier, the editor failed to publish. The study by Pradelle et al. focused on the effects of HCQ and claimed that nearly 17,000 deaths were attributed to its use in COVID-19 patients. Published in a scientific journal, it quickly sparked controversy due to the scale of the reported figures and the lack of transparency in its methodology. The sources of the data were not clearly explained, and several hospitals mentioned in the study denied their involvement. Experts identified anomalies in the results, including figures incompatible with official data on hospitalizations and deaths related to COVID-19. The authors refused to make their databases accessible for independent analysis. The study lacked rigorous controls and failed to account for numerous confounding factors, such as patients' pre-existing conditions and the problems associated with the HCQ doses actually received by patients. This study was based on a model that was incompatible with the real data, which is the first reason for saying that a model is wrong and should be abandoned. Ultimately, the study was retracted because it did not meet the expected standards of quality and reliability for scientific publications. We identified numerous methodological, mathematical, and medical shortcomings in a letter published in The Archives of Microbiology and Immunology (41). This incident contributed to growing skepticism about studies conducted in haste or by non-expert teams on a subject during the pandemic.

It is surprising that some scientists criticize IHU Méditerranée infection and claim that his entire body of work is discredited by a single retracted preliminary article, while simultaneously referring to the article by Pradelle et al., which has also been retracted, which in this case suffers from a real methodological problem. We also conducted a critique of a meta-analysis by Fiolet et al. (42), which concluded that HCQ was ineffective (43-45). There were numerous issues in this meta-analysis, reflecting a misunderstanding of the treatment. The studies included were of poor quality, and the treatment was often administered too late, during the hospitalization phase. PROSPERO (International prospective register of systematic reviews) is a database designed for the prospective registration of meta-analysis protocols. It is crucial to describe the study protocol beforehand, prior to data extraction, to avoid biases. Fiolet et al., the authors of the analyze registered their work on PROSPERO on June 9 2020, claiming they had not yet started data extraction or bias analysis. However, it is easy to see on the YouTube channel of the first author that the extraction of eligible studies had already begun and had advanced significantly by May 31, including sensitivity analyses—10 days before the PROSPERO registration. PROSPERO was contacted in December regarding this false statement. Their response was delayed, and for a brief period, they even removed the misleading registration. However, this change was short-lived. To everyone's surprise, they ultimately decided to keep the authors' registration, allowing them to make modifications. Interestingly, the list of authors in the preprint (46) is not exactly the same as in the final article that was peer-reviewed and referenced in National Library of Medicine (42). Such variations in authorship between a preprint and its final published version can raise questions about transparency, ethical practices, and the contributions of the individuals involved in the study. It would be important to investigate whether the changes were documented or justified, as authorship adjustments without clear explanations could undermine the credibility of the research process.

However, our revisited meta-analysis, broken down into several subsets, formally concludes that the early treatment with HCQ and AZI is effective against COVID-19 (19). Once again, considering the dose received by patients is essential for drawing conclusions about the efficacy of a treatment. Grouping data in the same meta-analysis from patients who received normal doses with those who received toxic doses is a scientific absurdity, as was shamelessly done in the study by Fiolet et al. (42).

Studies on prophylaxis using HCQ

A study conducted by the IHU Méditerranée Infection team in elderly patients demonstrated that the combination of HCQ and AZI was associated with 50% reduction in mortality rate (47, 48). The COPCOV (chloroquine/ hydroxychloroquine prevention of coronavirus disease) study demonstrated that hydroxychloroquine and chloroquine prophylaxis was safe and well-tolerated (49). Combined with data from other similar trials, these findings provide evidence that laboratory-confirmed symptomatic COVID-19 cases might be reduced. The effect was nevertheless moderate. Specifically:

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- The study found that CQ or HCQ use was associated with a 15% reduction in the risk of symptomatic COVID-19 compared to placebo, with a risk ratio (RR) of 0.85. However, this result was not statistically significant ($p = 0.051$), suggesting a limited protective effect.
- A pre-specified meta-analysis including this study and other randomized controlled trials reported a statistically significant RR of 0.80, indicating a 20% reduction in the risk of symptomatic COVID-19.

The COPCOV study however mainly focused on healthcare professionals and young, healthy individuals: the median age of the participants was 29 years (interquartile range, 23 to 39). The population was generally healthy; 4.8% (225/4,652) reported having a chronic disease. This population is usually free from severe and critical forms of COVID-19 and therefore does not represent the target group for which HCQ might be beneficial, namely older populations with risk factors (e.g., obesity, diabetes). Although achieving impregnation is the intended goal to ensure a sufficient concentration in the intracellular phagolysosome, adequate drug exposure is crucial to ensure effective prevention of the disease and its severe forms. Indeed, the dosing regimen used in the study may have been insufficient to demonstrate efficacy. According to the study protocol, a loading dose of 10 mg/kg base was administered on the first day, followed by a daily dose of 155 mg base (equivalent to a daily dose of 200 mg HCQ sulfate). Additionally, exposure to the SARS-CoV-2 virus was heterogeneous and may have been too low among many participants, making it difficult to detect a protective effect. To demonstrate a true protective effect against the disease, a study focusing specifically on older populations with risk factors and significant exposure to the virus would be required and with appropriate HCQ doses.

Other studies demonstrating the efficacy of hydroxychloroquine on COVID-19

A Spanish study conducted in 24 hospitals analyzed data from COVID-19 patients (50). Among the 5,094 patients included, 17.5% of those treated with HCQ died, compared to 34.1% of untreated patients. This difference in mortality was significant, with an odds ratio (OR) of 0.41 in favor of HCQ. This treatment was particularly associated with reduced mortality in elderly patients and those with severe forms of the disease, characterized by elevated inflammatory markers.

Numerous other studies have demonstrated the effectiveness of this treatment, yet they are never taken into account by its detractors (51-61). Finally, the IHU Méditerranée infection conducted a retrospective analysis of approximately 30,000 patients treated at the IHU in Marseille (62). The data were certified by a bailiff to prevent accusations of manipulation or error. This analysis also concluded that the treatment is effective. The calculations were rechecked by our team, comprising scientists and mathematicians, and they reached the same conclusions (63). It seems necessary to take these data into account and possibly analyze them a third time, which has indeed been requested by the IHU team. Ultimately, HCQ has a non-specific antiviral action on many pathogens, particularly enveloped viruses (64). This stems less from complex molecular mechanisms than from a simple physicochemical property we have already discussed, which occurs at the level of the phagolysosome. To enter the cell, the phagolysosome needs to be acidic, and HCQ raises the pH, thereby blocking the virus's entry and its release into the cytoplasm, which then allows access to the nucleus. This mechanism is well-known and explains the antiviral efficacy of chloroquine or HCQ against numerous viruses, including the coronavirus, as well as the flu, HIV, and other viruses.

Conclusion

In conclusion, the evaluation of HCQ has been scientifically flawed overall, with studies of poor quality, incomparable groups, incorrect dosages, under- or overdosed treatments, and studies prematurely interrupted due to scientific publications with fabricated data that have since been retracted. Stating that there were concerted actions against this molecule to promote more profitable innovative treatments for the pharmaceutical industry is merely a factual observation, not a conspiracy theory. Overall, the studies that concluded that HCQ was ineffective, or failed to show efficacy, were those in which treatment was not given early, and/or in inadequate doses, and/or in patients not at risk of severe forms of the disease. Conversely, numerous articles have concluded that HCQ is effective, particularly the retrospective study on the IHU data, which we independently reanalyzed. It is surprising to see part of the scientific community and the media rely solely on the retraction of the first IHU article, a preliminary study carried out in the emergency of the pandemic to dismiss the efficacy of HCQ. This raises questions about the independence of some scientists and doctors from pharmaceutical companies and their intellectual honesty. We believe that throughout the COVID-19 pandemic, studies were indeed of poor quality, often intellectually dishonest, and there was significant corruption. This is bad science, not science. One of the only consistent studies, whose data was certified by a bailiff, conducted at the IHU, demonstrated that HCQ was effective when administered early.

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The Four Main Misconceptions by Scientists During the Covid-19 Pandemic

Confusion between the viral and inflammatory phases.
Confusion between the administered dose (loading dose and plasma concentration) with the impregnation (increase in hydroxychloroquine concentration in the phagolysosome)
Confusion in the timing between the urgency of an epidemic and the normal timeframe required to conduct studies.
Confusion about the populations that could benefit from hydroxychloroquine treatment: studies conducted on young patients, in whom the disease is almost never severe.

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